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This article shows how enantioselective organocatalysis can represent a powerful, complementary paradigm to metal-catalysed enantiolselective synthesis in the preparation of single enantiomers of chiral drug molecules for screening and clinical trials.

Enantioselective organocatalysis

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Enantioselective organocatalysis has emerged as a powerful synthetic paradigm that is complementary to metal-catalysed transformations and has accelerated the development of new methods to make diverse chiral molecules. The operational simplicity, ready availability of catalysts and low toxicity associated with organocatalysis makes it an attractive method to synthesise complex structures. Here, we discuss the impact of enamine, iminium, nucleophilic and Brønsted acid catalysts in organic synthesis, and highlight key strategic methods to assemble useful molecules with high enantiomeric purity.

The continually increasing challenges associated with the treatment of new and existing diseases necessitates that potential therapeutics contain higher levels of molecular complexity to achieve potency, selectivity and desirable physical properties. Of particular relevance is the emergence of drug candidates with one or more non-racemic, asymmetric centres. Single-enantiomer drugs are, however, significantly more difficult to synthesize using conventional asymmetric synthesis; new enantioselective methods are thus required to meet this challenge.

The synthetic chemistry community has been revolutionized over the past 20 years by the advent of enantioselective catalysis [1–3]. Paramount to the viability of this technology to synthesise chiral molecules is the use of asymmetric metal complexes as catalysts for a wide variety of processes [4]. In particular, asymmetric hydrogenation has been crucial in the development of many commercial therapeutics [2,3]. Although such transformations are invaluable to the pharmaceutical industry, especially in chemical development and process research, many of these reactions require specific expertise and equipment that is not always available. Ideally, enantioselective catalysis needs to be efficient, facile, reliable and economic if it is to be used widely in pharmaceutical synthesis. Over the past five years, the field of enantioselective organocatalysis has had a significant impact in chemical synthesis [5–8] and has developed into a practical synthetic paradigm since its genesis nearly 30 years ago [9]. Although this field is in its infancy, the breadth of different reactions that can be catalysed make it a complementary discipline to conventional metal catalysis. Of crucial importance is that it offers a mild, practical and, generally, simple method of making small, functionalized molecules with high enantiopurity and, therefore, has great potential in discovery chemistry.

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Having graduated from the University of Birmingham in 1995, Matthew Gaunt moved to the University of Cambridge to carry out his graduate studies with Jonathan B. Spencer, finishing in 1999. Matthew then moved to the University of Pennsylvania to work with Amos B. Smith as a GlaxoWellcome postdoctoral research fellow. He returned to Cambridge in 2001 to work with Steven Ley as a Junior Research Fellow, where he remained for two and a half years. He began his independent research career in October 2003 at the University of Cambridge and was awarded a Royal Society University Research Fellowship in 2004. In October 2006, he was promoted to the position of Lecturer in Synthetic Organic Chemistry. The Gaunt Group currently comprises 18 people and their research interests are focused on the invention of new catalytic strategies for chemical synthesis, in particular, enantioselective organocatylsis, metal catalysed C–H bond activation and the development of cascade processes for the rapid assembly of natural products.

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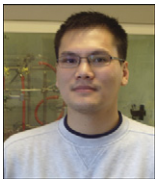

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The number of chiral, non-racemic pharmaceuticals on the market is increasing and it is becoming more important to prepare these compounds using new enantioselective technologies to minimise the losses incurred from making racemic mixtures. Traditionally, enantiopure compounds have been prepared by resolution. However, the time constraints on discovery chemists and the potential wastage associated with racemic-process routes have ensured that enantioselective synthesis be considered as a viable option. Organocatalysis is an emerging area in asymmetric synthesis; here, we highlight enantioselective organocatalytic processes that might be of interest to the pharmaceutical industry. This is a fast-moving field and it is not possible to cover all of the developments of the past five years. Instead, we present a selection that might have useful applications in the synthesis of chiral, non-racemic molecules in the pharmaceutical industry.

Organocatalysis have several significant advantages over conventional metal catalysis. For example, there are usually fewer toxicity issues associated with organocatalysis, although little is known about the toxicity of many organic catalysts. Of particular importance is that most reactions are tolerant of water and air, and are often easy to perform. These factors often affect metal catalysed reactions, and that provides a significant advantage in terms of operational simplicity. Several comprehensive publications are available that give a full account of the organocatalysis area [5–8].

Here, we use five different modes of catalysis to detail the scope of organocatalysis and how it can be applied to the synthesis of pharmaceutically relevant molecules: (i) secondary amine catalysis via enamines; (ii) secondary amine catalysis via iminium ions; (iii) phase transfer catalysis; (iv) nucleophilic catalysis and Brønsted base catalysis; and (v) H-bonding catalysis. For each mode, we include a basic description of the general mechanism, where appropriate, and some reactions that are possible with examples of application to their use in synthesis.

Secondary amine catalysis via enamines

The reaction that alerted the synthetic community to the potential of organocatalysis was a proline-catalysed intramolecular aldol process that was reported simultaneously by Hajos, Parrish, Wiechert, Eder and Sauer during the early 1970s (Figure 1) [9,10]. Central to the success of this aldol transformation is a proposed hydrogen bond between the carboxylic acid motif and the carbonyl electrophile. The proposed mechanism is shown in Figure 1 [11]. This transformation provides a simple method of forming highly advanced, enantiopure, progesterone intermediates that are useful in synthesis.

The catalytic generation of asymmetric enolate equivalents is an area for which there is no general solution and, perhaps, the most surprising factor in the growth of organocatalysis is that it took ~25 years for the significance of this discovery to be realized. It was not until List, Barbas and Lerner published a related intermolecular process that secondary amine catalysis via enamines became *en vogue* in the synthetic community (Figure 2a) [12]. Since this report, there have been many subsequent publications of catalytic reactions via enamines and several of the key reactions are highlighted here.

The closely related Mannich reaction can also be catalysed by proline to form syn β-amino aldehydes and ketones that can be converted to a range of amino acid and alcohol products (Figure 2b) [13,14]. A one-pot imine formation–Mannich reaction is also possible, although, in some cases, the enantiomeric excess is moderate [15]. A powerful application of the aldol reaction is the use of hydroxy ketones as enamine precursors in a reaction with an aldehyde that affords anti-diols and offers a complementary approach to the Sharpless dihydroxylation protocol (Figure 2c) [16]. An impressive development of this process has been reported by MacMillan and co-workers, who describe a cross aldehyde aldol coupling (Figure 2d) [17,18]. A requirement of this reaction is that the aldehyde can be defined clearly as donor and acceptor. This means that only one aldehyde should be able to form an enamine (donor) and the other can act as the acceptor. Thus, chemoselective coupling leads to excellent yields, and diastereo- and enantioselectivities of anti-aldol products. This concept has been extended to the synthesis of carbohydrate derivatives via a simple, two-step, iterative aldol concept (Figure 3) [19,20]. Proline-catalysed coupling of suitably protected hydroxy acetaldehydes form the polyoxygenated aldehyde fragments that undergo subsequent Mukaiyama aldol reaction to form the hexose motif after cyclization. A range of sugars can be produced by this method and it is particularly useful for the synthesis of unnatural sugar-type derivatives and L-hexose.

In addition to reactions that involve C–C bond formation catalysed by proline, several C-heteroatom bond-forming processes have been developed. In particular, the α-functionalization of aldehydes is a particularly versatile process. Conceptually, these

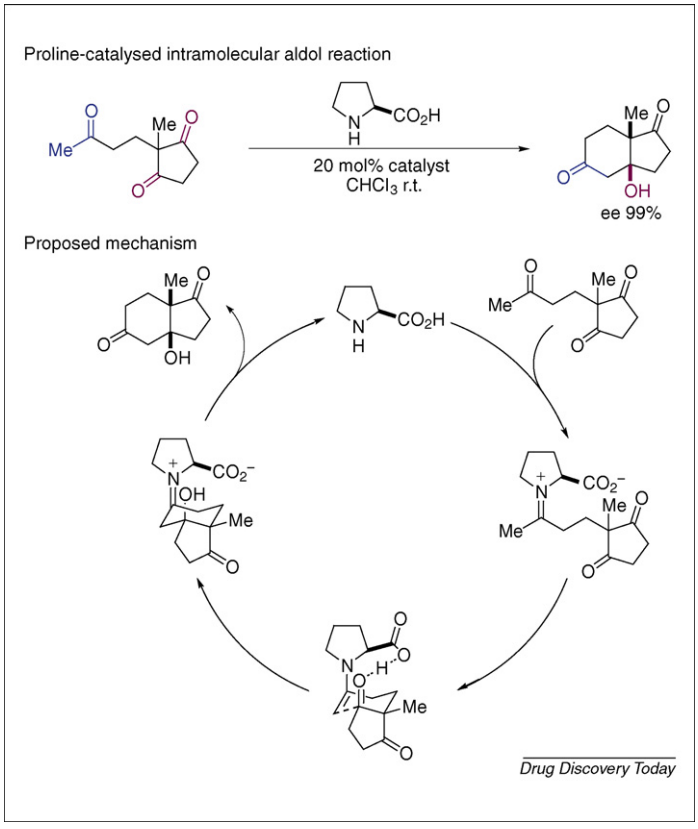

FIGURE 1

Proline-catalysed intramolecular aldol reaction.

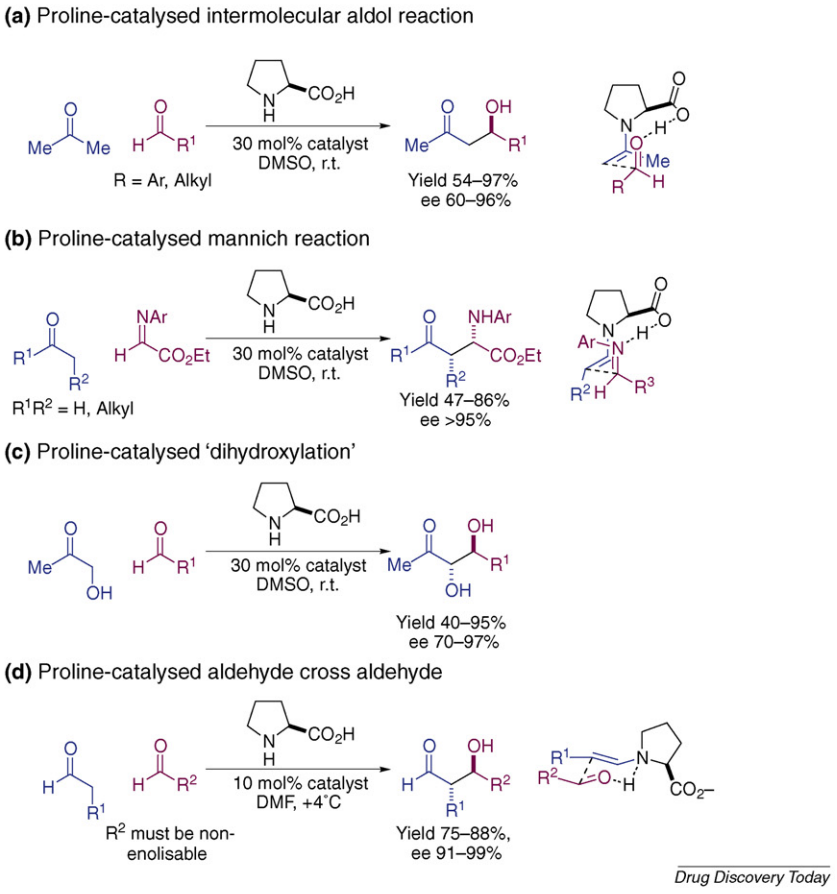

FIGURE 2

Proline-catalysed aldol and Mannich reactions.

reactions work similarly to those described previously and exploit an H-bonded transition state. The reaction that has received the most attention involves the α-oxygenation of aldehydes with nitrosobenzene. Numerous groups have published developments of this reaction after the initial reports from MacMillan and Zhong [21,22]. A broad range of carbonyls work well and this simple oxygenation of aldehydes and ketones provides a convenient method for the rapid synthesis of useful chiral building blocks for natural product synthesis (Figure 4a) [23].

Other electrophiles can also be used to intercept enamines. For example, reaction of enamines with alkyl diazodicarboxylates results in the installation of a nitrogen group in the α-position to the carbonyl and these can be transformed readily into amino acid derivatives (Figure 4b) [24,25]. The installation of sulfur-containing groups can also be made with high enantiomeric excess to form useful thiol-containing molecules [26].

Perhaps the most important α-oxidation reaction involves the α-chlorination of aldehydes (Figure 5) [27]. The products derived from this reaction are versatile intermediates that can be converted to a range of different functional motifs, such as amino acids, and important chiral building blocks, such as epoxides and aziridines. Again, there are many derivatives of this process but MacMillan's process [28] with the oxazolinone catalysts and Jørgensen's C_2-symmetric pyrrolidine reaction [29] provide the best results.

Also important is the asymmetric formation of C–F bonds and catalytically generated enamines can be used to form α-F carbonyls [30]. Jørgensen's and MacMillan's systems provide the most general procedure for the synthesis of these important synthons with excellent enantiomeric excess, and represent one of the most simple and general methods for the asymmetric introduction of C–F bonds (Figure 6) [31,32].

Other reactions that have held persistent interest in the area of asymmetric catalysis are conjugate addition-type reactions. Although early reports of the addition of ketones to nitro olefins via enamines afforded only modest enantiomeric excesses with proline and related catalysts, [33] this reaction probably accelerated the search for proline alternatives [34,35]. The best example of this reaction is the use of a prolinol-derived catalyst that provides excellent yields and enantiomeric excesses for this transformation (Figure 7a) [36]. Notably, the stereochemical control in this reaction seems to be dominated by the steric properties of the catalyst and does not rely on H-bonding. Although the addition of enamines to enones has also been a troublesome reaction, Gellman *et al.* recently showed that a similar pyrrolidine catalyst readily affected the addition of aldehydes to simple enones in excellent enantio-

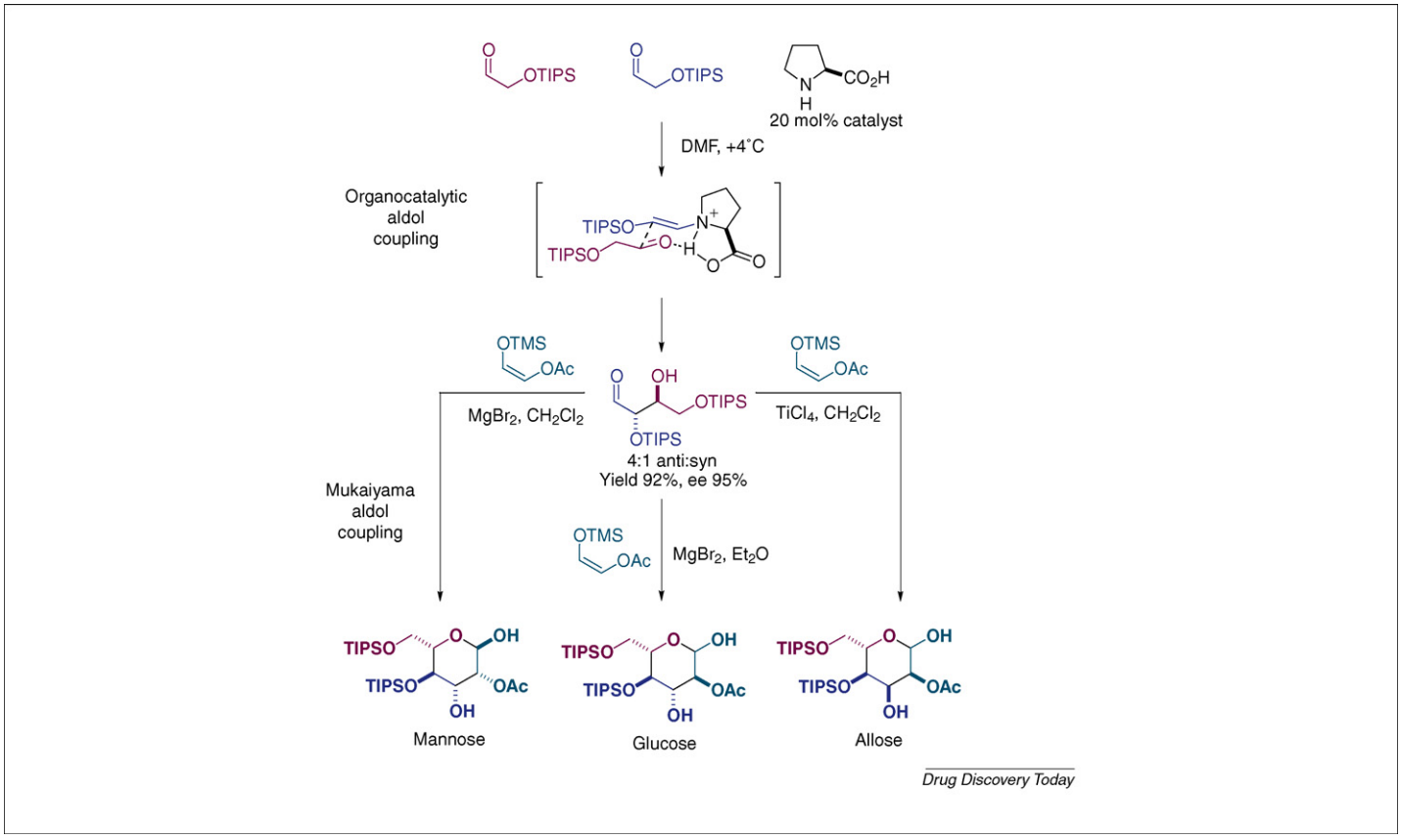

FIGURE 3

An iterative, two-step carbohydrate synthesis.

meric excess, which provides a solution to this long-standing problem (Figure 7b) [37–38]. Intramolecular reactions have also been reported by the groups of List (Figure 7c) [39] and Hayashi (Figure 7d) [40] and effectively form five-membered ring systems, in the latter case with the control of three stereocentres.

A process that makes medicinally useful scaffolds is Jørgensen's intramolecular addition of enamines to quinolinium salts to form chiral heterocyclic compounds (Figure 8) [41]. The catalyst used in this process is a highly reactive C_2 symmetric pyrrolidine. The products of this process are potentially useful in a range of synthetic applications.

Finally, a rare example of enamine alkylation has been reported by List and co-workers in which they describe an intramolecular alkylation process that forms five-membered ring

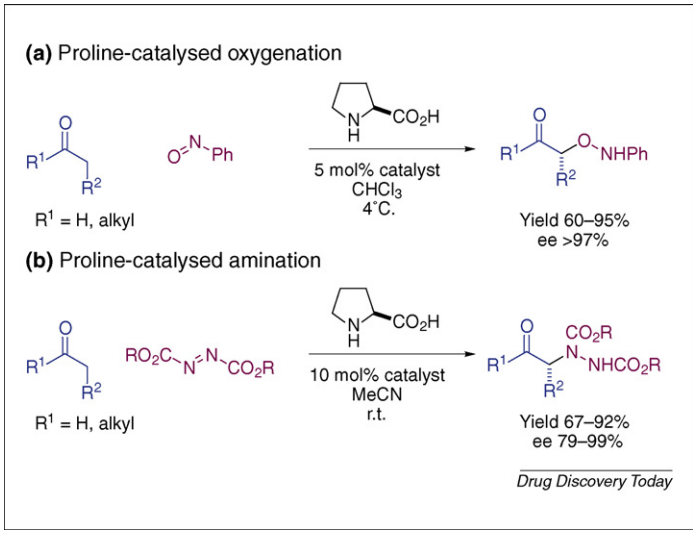

FIGURE 4

Proline-catalysed α-oxidation of carbonyls.

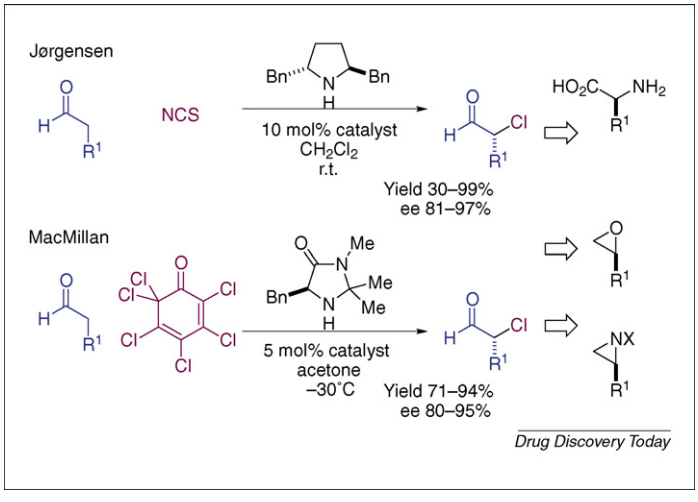

FIGURE 5

Secondary amine-catalysed chlorination of aldehydes.

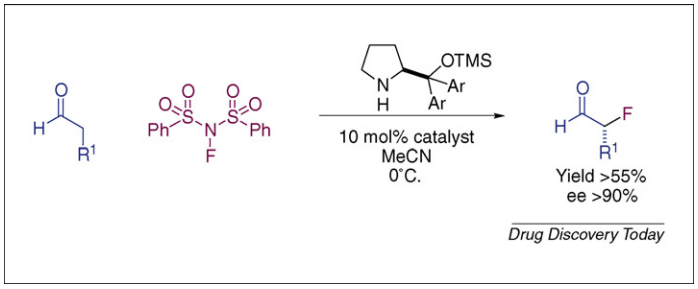

FIGURE 6

Secondary amine-catalysed fluorination of aldehydes.

systems with excellent enantiomeric excesses [42]. A more hindered proline derivative is required as catalyst in this transformation (Figure 9).

Many processes can be catalysed via the formation of enamines and not all are discussed here. However, it is likely that many processes remain to be discovered. To achieve this, a better understanding of the reactions is essential, especially of the kinetic parameters of the processes, which will help in the design of better catalysts for new and existing processes.

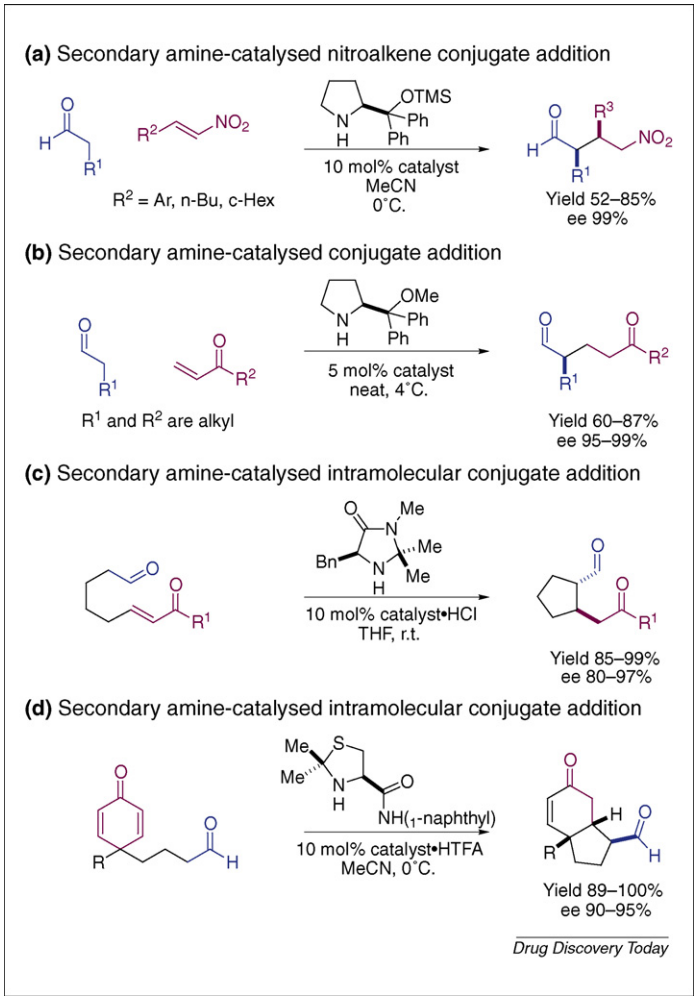

FIGURE 7

Secondary amine-catalysed conjugate addition reactions.

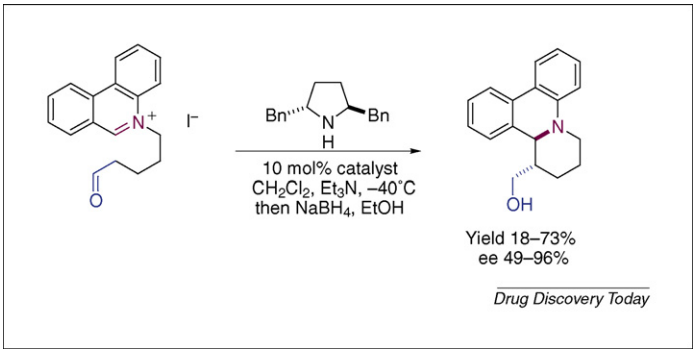

FIGURE 8

Secondary amine-catalysed intramolecular additions to isoquinolines.

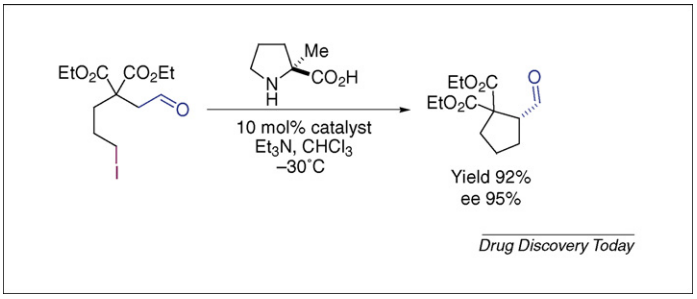

FIGURE 9

Secondary amine-catalysed intramolecular alkylation of aldehydes.

Secondary amine catalysis via iminium ions

The use of chiral secondary amines as catalysts to activate enals via the iminium ion was reported during the late 1990s by MacMillan and co-workers. The almost simultaneous reporting of the initial proline aldol research [12] and MacMillan's iminium ion catalysis concept [43] set the scene for an explosion of organocatalytic research over the next six years. Put simply, iminium ion catalysis provides an organocatalytic alternative to conventional Lewis acid catalysis of α,β-unsaturated compounds (Figure 10). Condensation of a chiral secondary amine with an enal forms the iminium ion. The LUMO orbital of the iminium species is lowered in energy such that it can now interact with suitable coupling partners through either pericyclic reactions or by conjugate addition. The operational simplicity of these processes makes them attractive alternatives to Lewis acid catalysis.

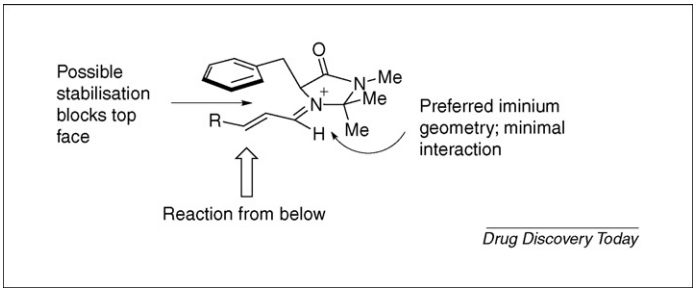

FIGURE 10

Stereocontrol elements in the iminium ion.

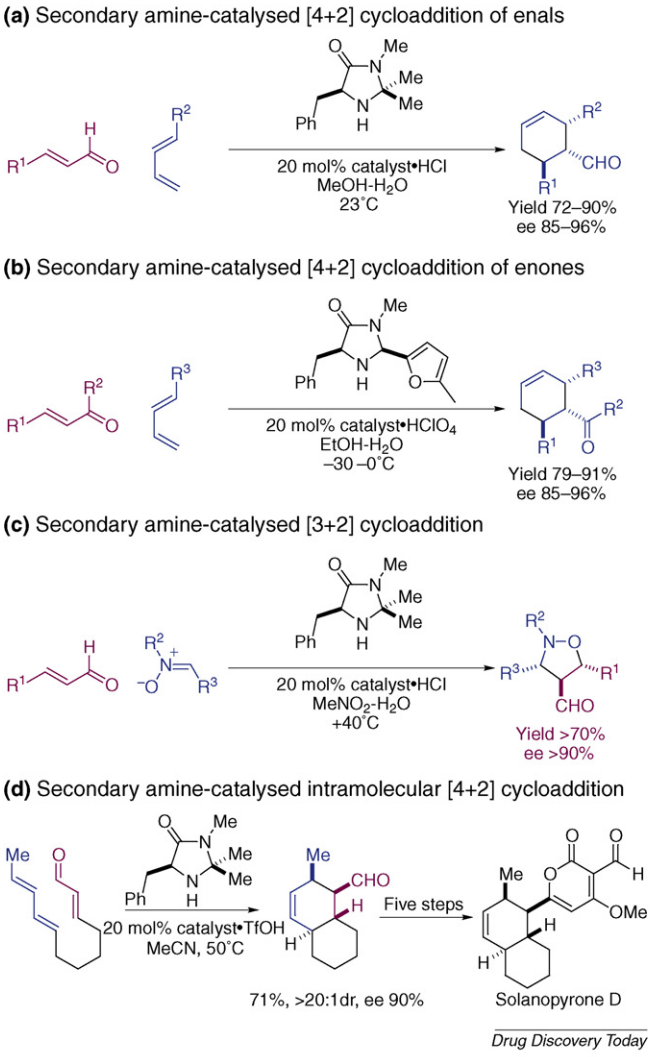

FIGURE 11

Secondary amine-catalysed cycloaddition processes.

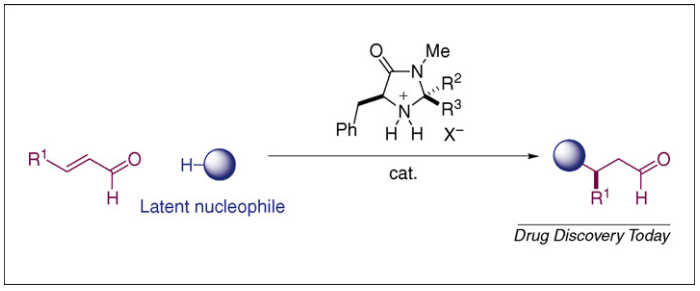

FIGURE 12

Secondary amine-catalysed conjugate addition.

The design of the catalysts is such that in the active species a single iminium ion geometry is formed. The dimethyl substitution forces the bulk of the iminium ion away from this large group and a potential stabilization by a π-interaction with the benzyl group of the phenylalanine unit enforces this conformation and leads to high facial selectivity during attack on the alkene. The reactions on the alkenyl portion of the iminium ion can be split into two groups, cycloaddition processes and conjugate addition. In successful reactions the enantiomeric excesses are usually >90%, they are operationally simple and deliver highly versatile products that are useful building blocks for synthesis. Furthermore, the conjugate addition products can sometimes be intercepted at the enamine stage, undergoing multiple bond forming processes via tandem reactions.

The range of cycloadditions that can be attained through iminium catalysis covers conventional [4 + 2] [44], nitrone [3 + 2] [45] and [4 + 3] [46] processes, as well as intramolecular versions of some of these reactions. In general, the reactions tolerate a range of diene and dienophile components, which provides a reasonably broad scope for these catalytic cycloadditions, and the products are produced in good yields, diastereoselectivities and excellent enantiomeric excesses. MacMillan reported that enals smoothly undergo [4 + 2] cycloadditions with substituted dienes with good endo control (Figure 11a) [43]. Enones are good substrates when a more reactive catalyst is used to provide an elegant solution to the problem of catalytic enantioselective enone cycloadditions (Figure 11b) [44]. 1,3-amino alcohols are readily formed from the products of nitrone cycloaddition with activated enals and can be used to form a range of functionalized products (Figure 11c) [45]. Cycloadditions via an intramolecular Diels Alder process form complex frameworks with high complexity and enantiomeric excess and this process was used in a short synthesis of the natural product solanopyrone D (Figure 11d) [47].

Activation via iminium ion formation also renders facile conjugate addition processes with soft nucleophiles. A range of aromatic and heteroaromatic nucleophiles can be added to enals in high yields and enantiomeric excesses to form many functionalities that are common in pharmaceutical compounds (Figure 12). In particular, the indole and aniline motifs are readily incorporated into an asymmetric framework and modified to synthetically useful compounds (Figure 13) [48,49]. For example, a COX-2 inhibitor was assembled in a few steps from commercially available building blocks. Although not described here, pyrroles [50] and siloxyfurans [51] can also be added to enals with excellent enantiomeric excesses, making this a general strategy.

A useful feature of the aniline additions is that amino moieties can be further transformed to useful products. For example, Birch-type reduction of the corresponding trimethyl ammonium salt results in the unsubstituted aryl motif [49]. However, MacMillan and co-workers also report that these alkylammonium salts can undergo Suzuki coupling with boronic acids, leading to a highly versatile process for the synthesis of complex molecular architectures [52].

MacMillan's group also reported a tandem process that involves attack of a tryptamine derivative through the C3 position to an activated enal. The resulting indole-iminium species can be intercepted intramolecularly to form the pyrroloindoline framework in excellent diastereomeric ratio and enantiomeric excess and represents a highly efficient entry into a key architecture that is present in many natural products (Figure 14) [53].

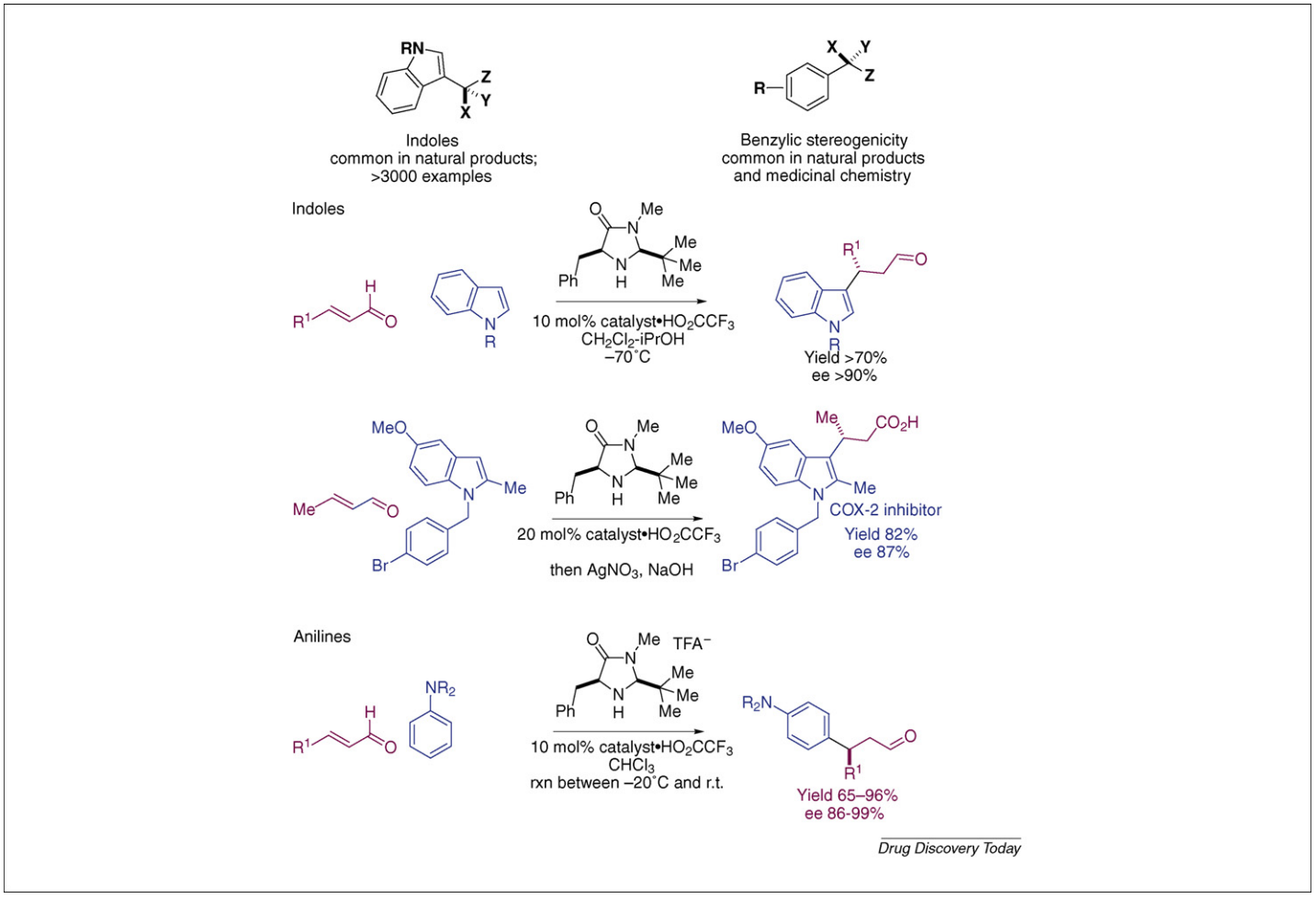

FIGURE 13

Secondary amine-catalysed conjugate addition of indoles and anilines to enals.

The β-stereocentre can also be installed asymmetrically via a catalytic enantioselective conjugate reduction of suitably substituted enals using a Hantzsch ester as a hydride source (Figure 15) [54]. This process is highly versatile as it can be linked with the reliable Wittig olefination for the enal construction to install a range of functionalities at the β and β' positions. Furthermore, MacMillan and coworkers also showed that the E/Z mixtures can be used to deliver the same product, presumably because of a facile isomerisation of the iminium species, making an overall synthesis of a chiral aldehyde from a simple ketone a versatile process.

A closer inspection of the mechanism reveals that the conjugate addition of a nucleophile to iminium-activated enals forms an enamine. If this enamine can be intercepted with a suitable electrophile, then a second functionalization could be achieved in the same overall process. The concept of using catalytic imi-

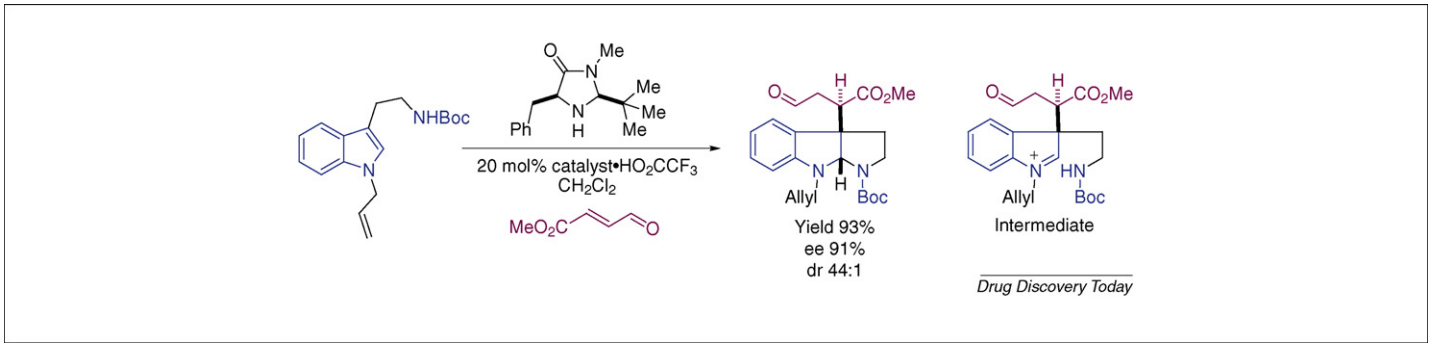

FIGURE 14

Catalytic enantioselective synthesis of pyrroloindolines.

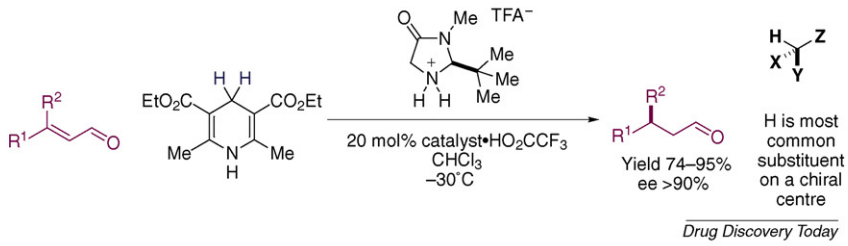

FIGURE 15

Secondary amine-catalysed conjugate reduction of enals.

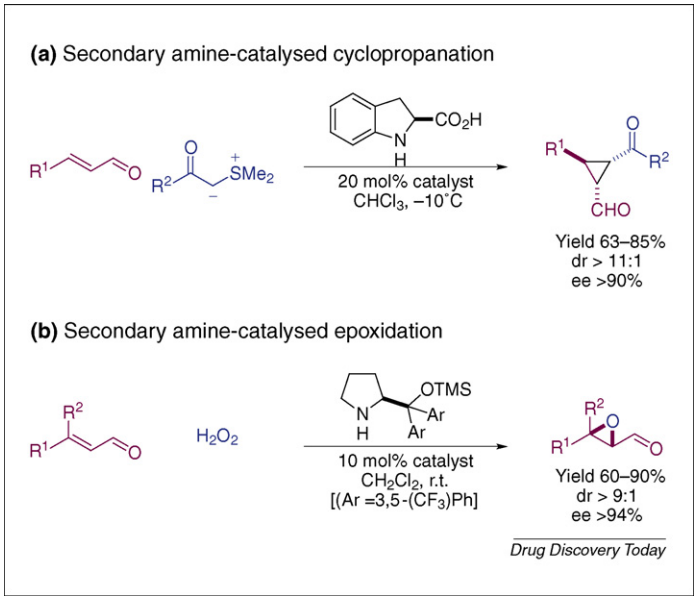

FIGURE 16

Secondary amine-catalysed cyclopropanation and epoxidation reactions.

nium–enamine tandem reactions was first reported through a cyclopropanation process involving the addition of a sulfur ylide to an enal activated by a secondary amine [55]. The ylide adds to the iminium ion in a 1,4-fashion and the resulting enamine displaces the sulfonium group to form a tri-substituted cyclopropane in excellent yield, enantiomeric excess and diastereomeric ratio (Figure 16a). A corresponding oxidation process, using urea–hydrogen peroxide in combination with an enal and secondary amine catalyst, results in the formation of epoxides. Jørgensen and co-workers reported that this elegant method works well for a range of substrates again in good yield, enantiomeric excess and diastereomeric ratio, and provides a complementary and operationally simple alternative to existing epoxidation methods (Figure 16b) [56].

Ideally, a process that involves C–C bond formation as part of the iminium and enamine-mediated steps would be a powerful method in synthesis. Although not yet achieved, it is possible to carry out a range of tandem transformations that give rise to densely functionalized non-racemic molecules in good yields and enantiomeric excesses. In this way, a range of heterocycles can be added to the iminium-activated enal and the resulting

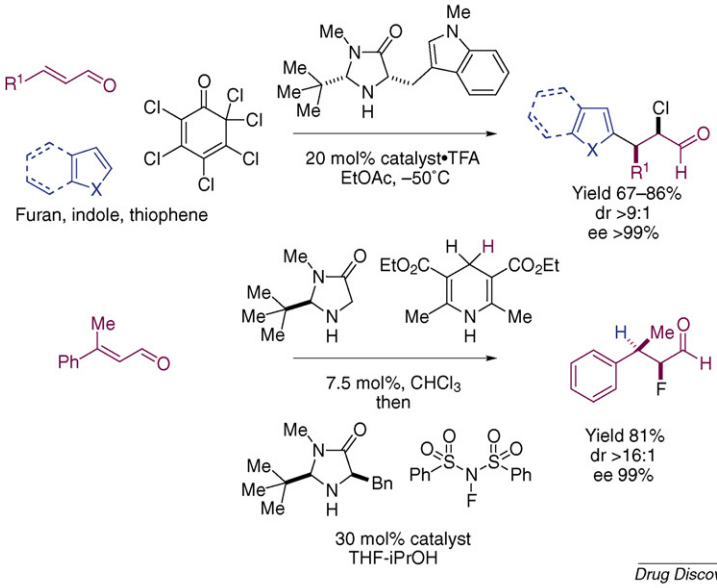

FIGURE 17

Secondary amine-catalysed iminium–enamine tandem reactions.

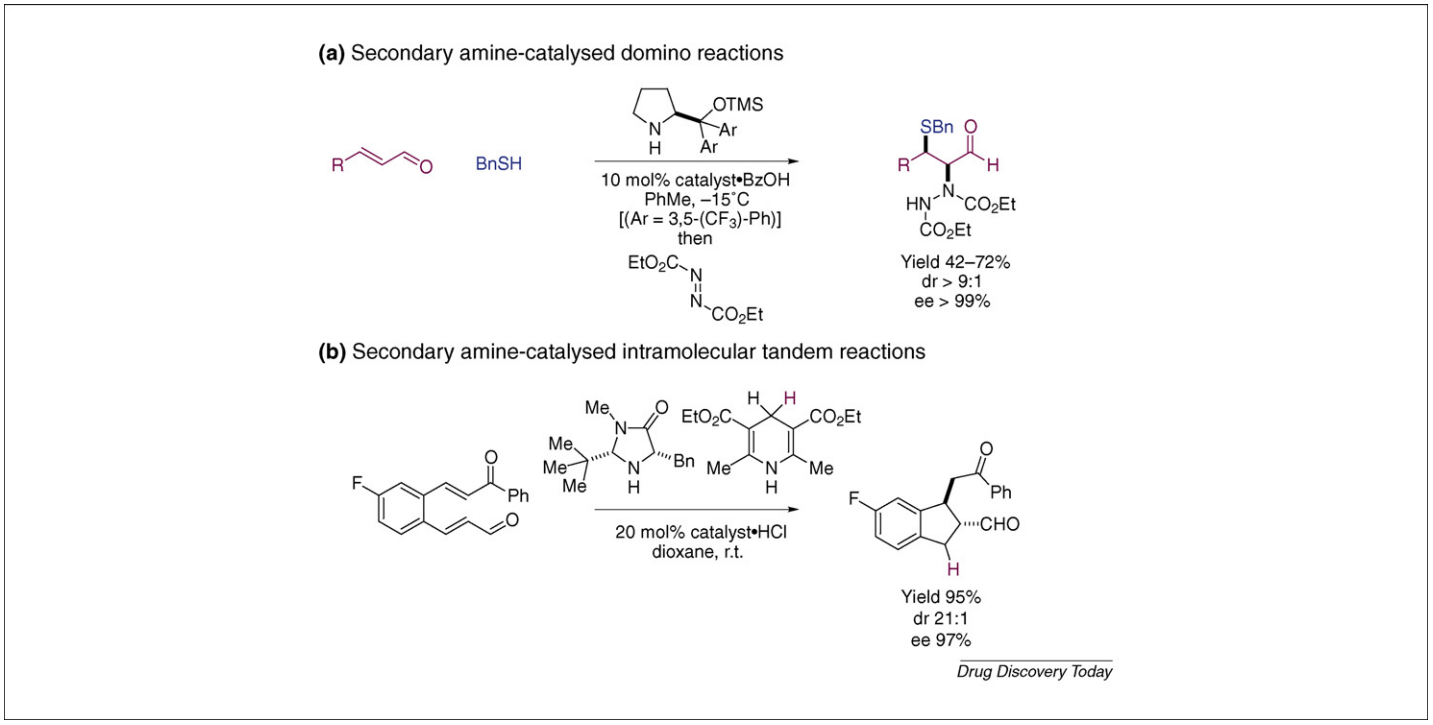

FIGURE 18

Secondary amine-catalysed iminium–enamine domino and tandem reactions.

enamine intercepted with a chlorinating reagent to form useful aldehyde building blocks. Furthermore, a similar process can be performed wherein a Hantzsch ester conjugate reduction of the iminium species followed by either chlorination or fluorination affords valuable compounds that are formally the products of asymmetric HCl or HF addition. It is difficult to see another way that such molecules could be made so simply using conventional organic synthesis (Figure 17) [57].

Jørgensen's group also reported a tandem process involving C–S and C–N bond formation, giving rise to chiral amino thiols that can be readily converted to molecules bearing inhibitory properties towards leukotriene A4-hydrolase (Figure 18a) [58]. List and co-workers have also reported that tandem functionalization can be carried out intramolecularly via a process that involves conjugate iminium reduction followed by interception of the resulting enamine by intramolecular conjugate addition, forming cyclic products in good enantiomeric excesses, yields and diastereomeric ratios (Figure 18b) [59].

Iminium ion catalysis of enals with secondary amines has become a general synthetic paradigm over the past 6 years. Its

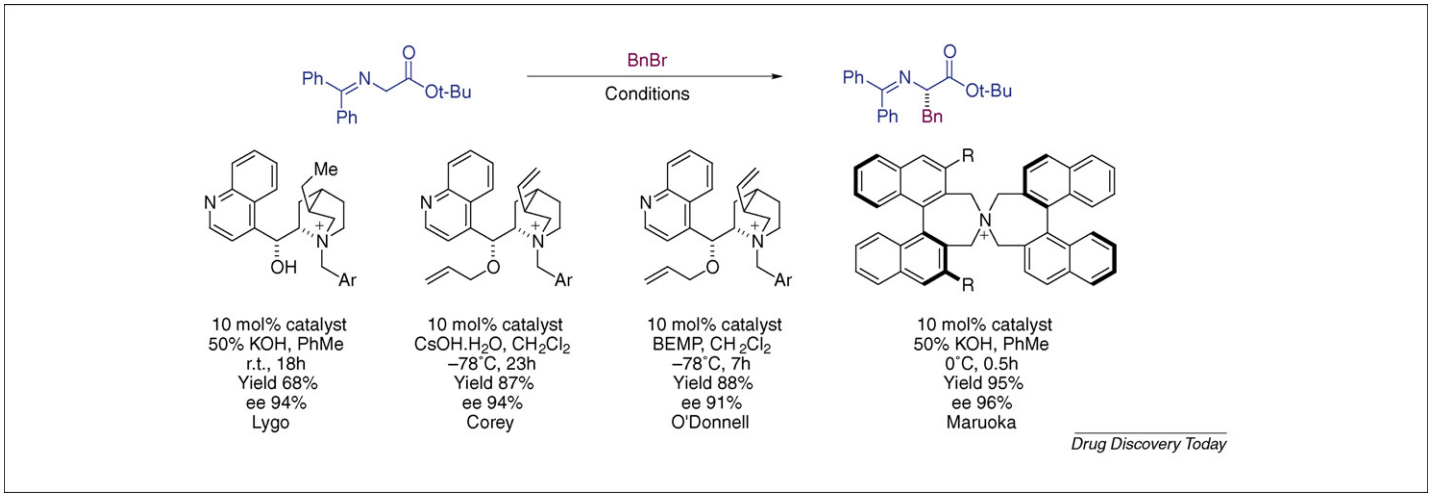

FIGURE 19

Asymmetric phase transfer-catalysed alkylation.

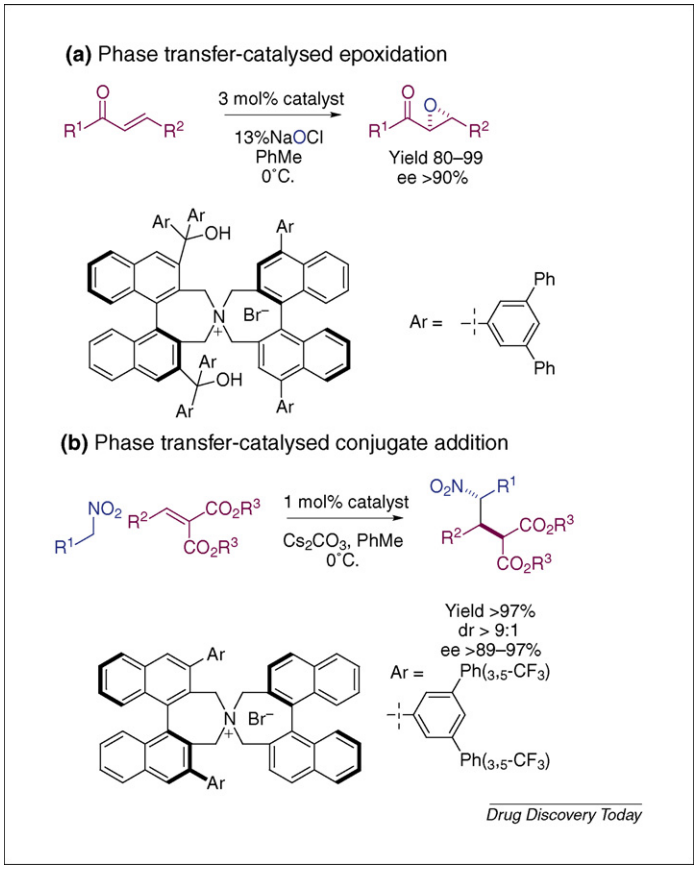

FIGURE 20

Asymmetric phase transfer reactions.

development has accelerated the progression of enantioselective organocatalysis and, although many of the obvious reactions have now been developed, the challenge has been set to design and discover new processes. This exciting area of synthetic chemistry promises the continued development of new and useful methodology.

Phase-transfer catalysis

The use of chiral phase transfer catalysts has had a major impact on synthesis over the years, especially for the synthesis of unnatural amino acid derivatives via asymmetric alkylation reactions (Figure 19). There are many excellent reviews on this subject [60–63], so we do not discuss this process here. Instead, we describe some of the recent new developments that utilize these catalysts.

Recently the range of reactions that can be catalysed by phase transfer molecules has increased significantly. Enone epoxidation can also be affected using the Marouka catalyst [64], which extends further the variety of methods available for asymmetric epoxidation (Figure 20a). Nitroalkanes can also be used as nucleophiles in conjugate addition reactions and imine equivalents (Figure 20b) [65]. These catalysts are highly versatile and enantioselective in their reactions, but their use might be restricted by reasonably lengthy syntheses and their incredibly high-molecular weight. Despite this, the range of reactions that can be achieved is increasing steadily, making them a convenient method to prepare chiral molecules.

Jørgensen reported a ketone α-arylation process based on the addition of stabilized enolates to activated aromatic systems via an S_NAr mechanism that generates quaternary centres in excellent enantiomeric excesses (Figure 21a) [66]. Moreover, this scaffold can be converted into spiro-oxyindole frameworks, providing a facile way to access this common structural motif. Of particular interest in the area of new phase transfer-catalysed reactions is an azãHenry process reported by Palomo and co-workers [67], who have developed an efficient process that displays an impressive substrate scope for this transformation and excellent results with imine equivalents bearing aryl, alkyl, branched and conjugated groups (Figure 21b).

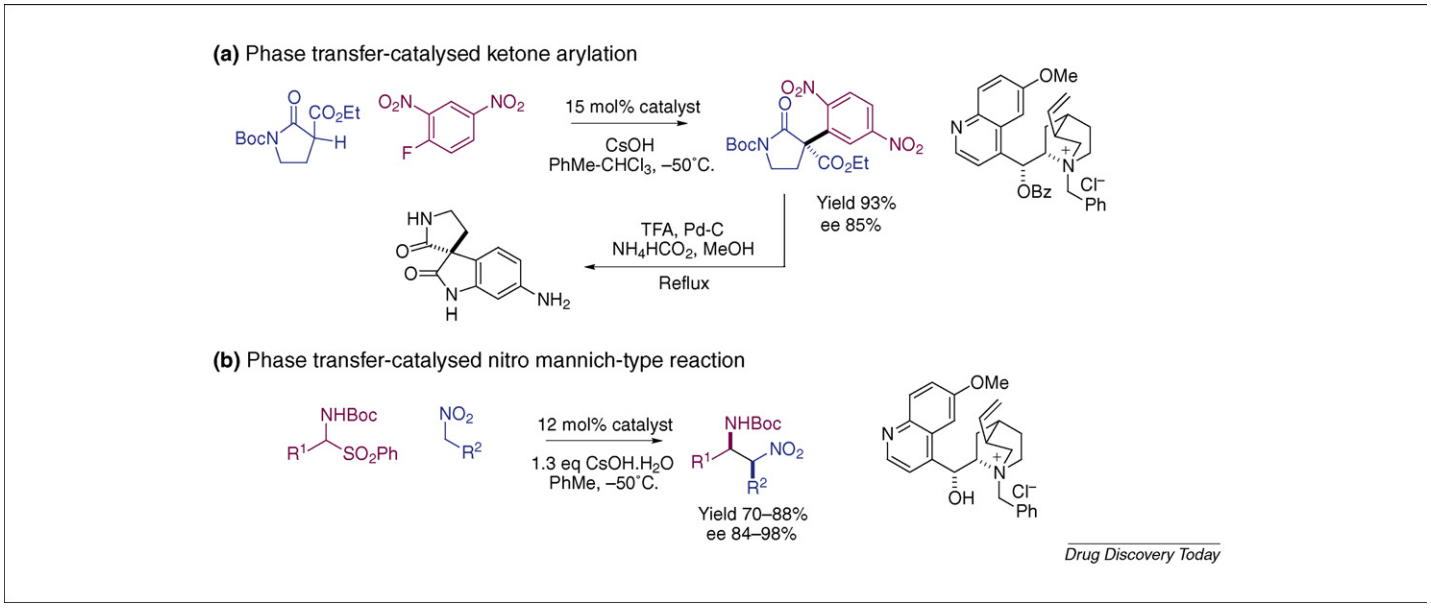

FIGURE 21

Asymmetric phase transfer reactions.

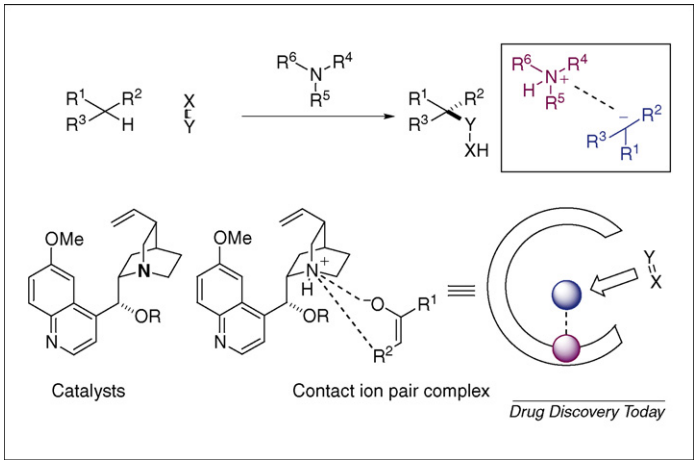

FIGURE 22

Cinchona alkaloids as catalysts for reactions through chiral contact ion pairs.

Nucleophilic and Brønsted base catalysis

Nucleophilic catalysts have had a wide-ranging role in the development of new synthetic methods [68]. In particular, the cinchona alkaloids catalyse many useful processes with high enantioselectivities; of particular note (although not covered in this review) is the use of modified alkaloids in the kinetic resolution of several organic molecules [69]. Cinchona alkaloids can be used as bases to deprotonate substrates with relatively acidic protons (e.g. malonates and thiols), forming a contact ion pair between the resulting anion and protonated amine. This interaction leads to a chiral environment around the anion and permits enantioselective reactions with electrophiles (Figure 22).

Deng *et al.* first showed that thiols could undergo asymmetric 1,4-addition to cyclic enones forming the β-mercaptoketones in excellent enantioselectivities using the $(DHQD)_2PYR$ catalyst (Figure 23a) [70]. Subsequently, they used this concept to develop C–C bond-forming processes including additions of stabilized enolates to nitroalkenes (Figure 23b) and vinyl sulphones

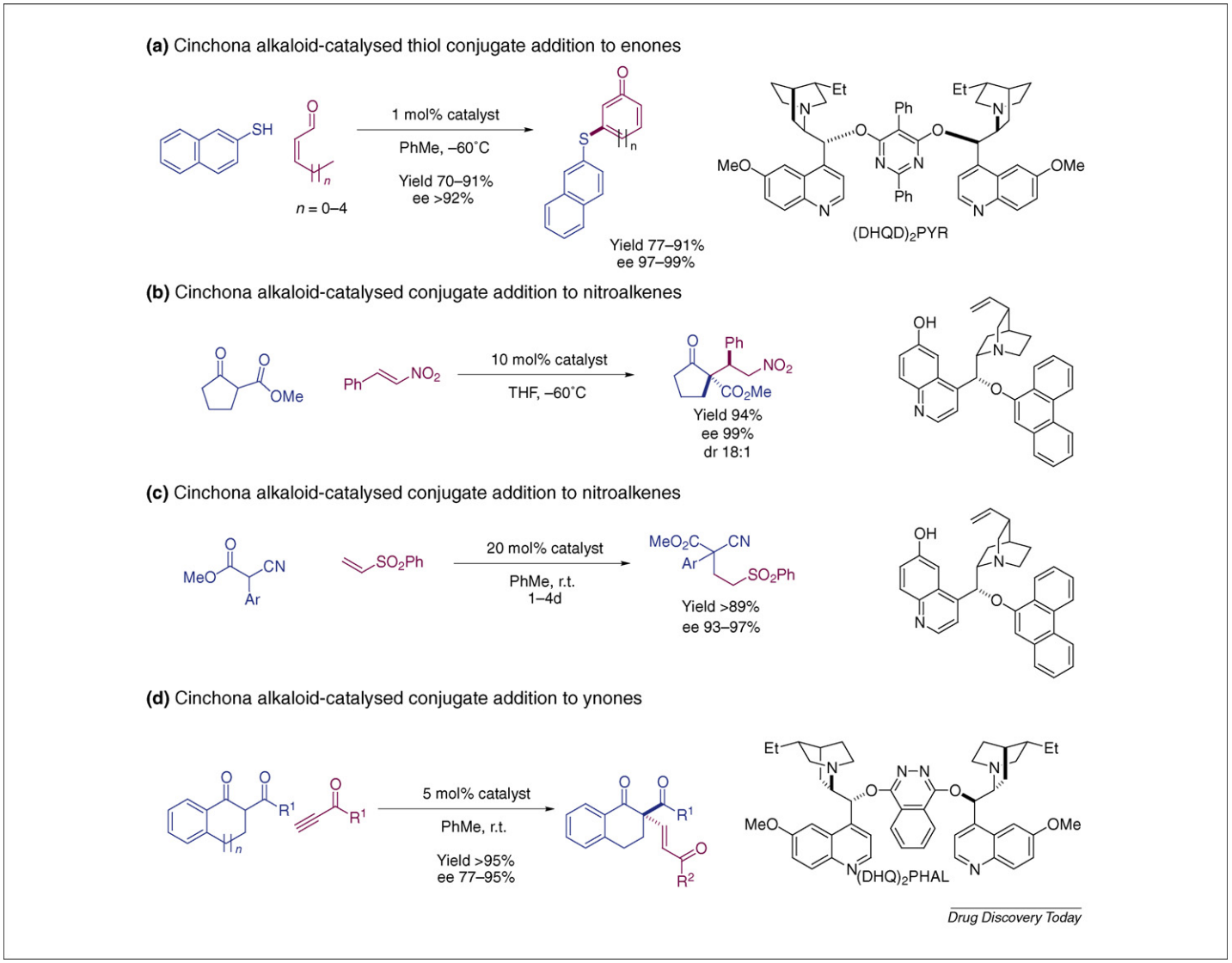

FIGURE 23

Asymmetric processes catalysed by cinchona alkaloids through contact ion pairs.

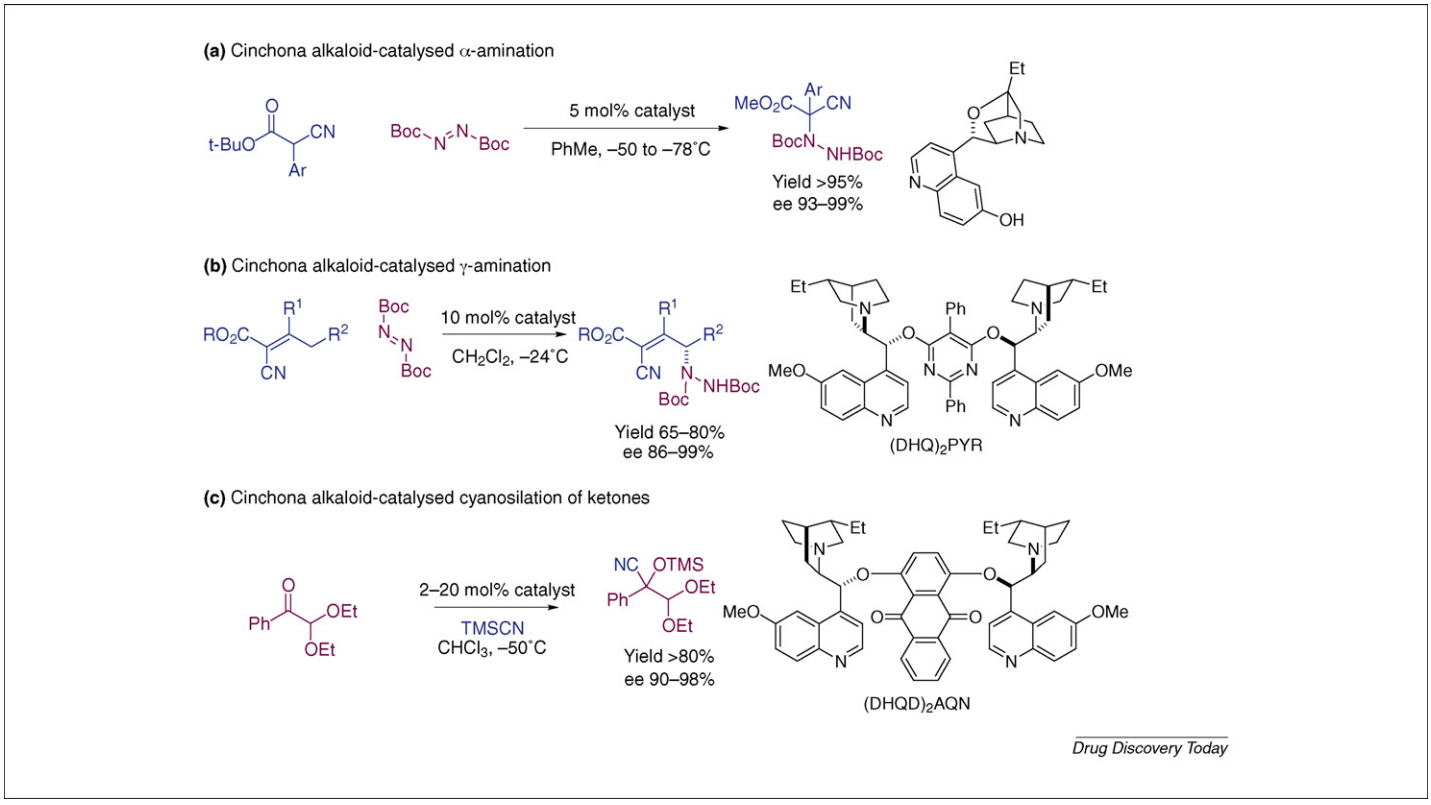

FIGURE 24

Asymmetric processes catalysed by cinchona alkaloids through contact ion pairs.

(Figure 23c) [71,72]. Important in many of these processes is the ability to control the formation of quaternary asymmetric centres with high enantiomeric excesses [73,74].

It is also possible to affect the α-functionalization of suitable anions in a similar fashion (Figure 24). Amination with diimides can also be carried out at either the α-position (Figure 24a) [75] or at the remote γ-position (Figure 24b) [76] to form a diverse range of highly functionalized amine compounds. The latter represents the first, metal-free, allylic amination reaction and provides a useful extension to the conventional palladium catalysed π-allylic methodology. It is also possible to control the addition of TMSCN to ketones forming the corresponding cyanohydrin in excellent yield and enantiomeric excess (Figure 24c) [77].

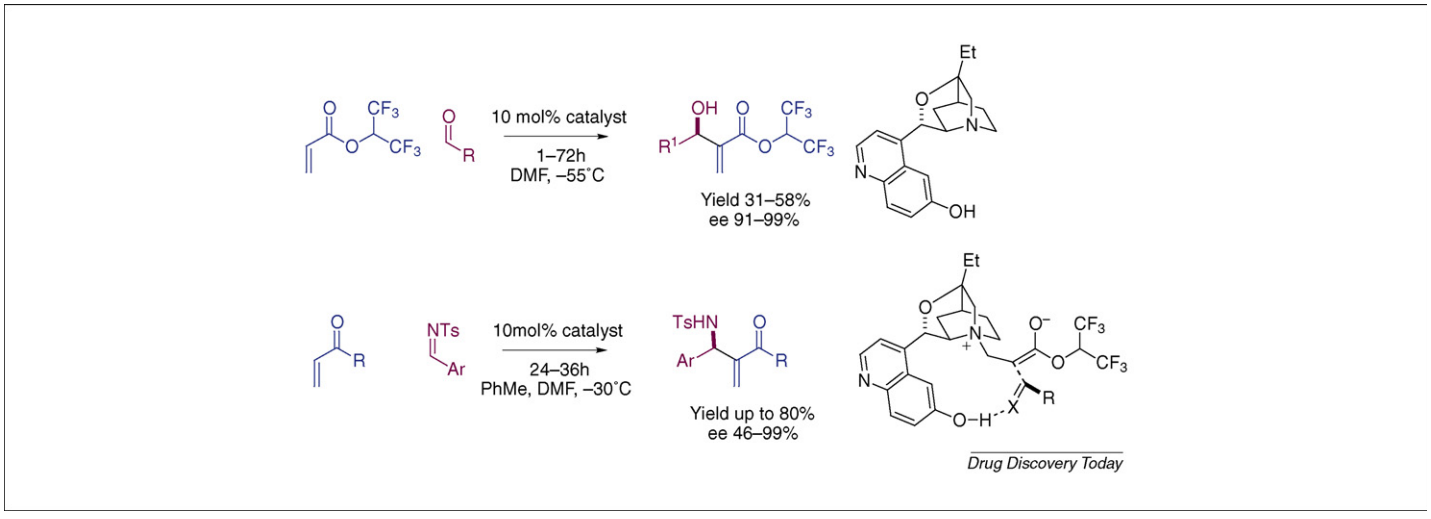

FIGURE 25

Cinchona alkaloid-catalysed Baylis–Hillman reaction.

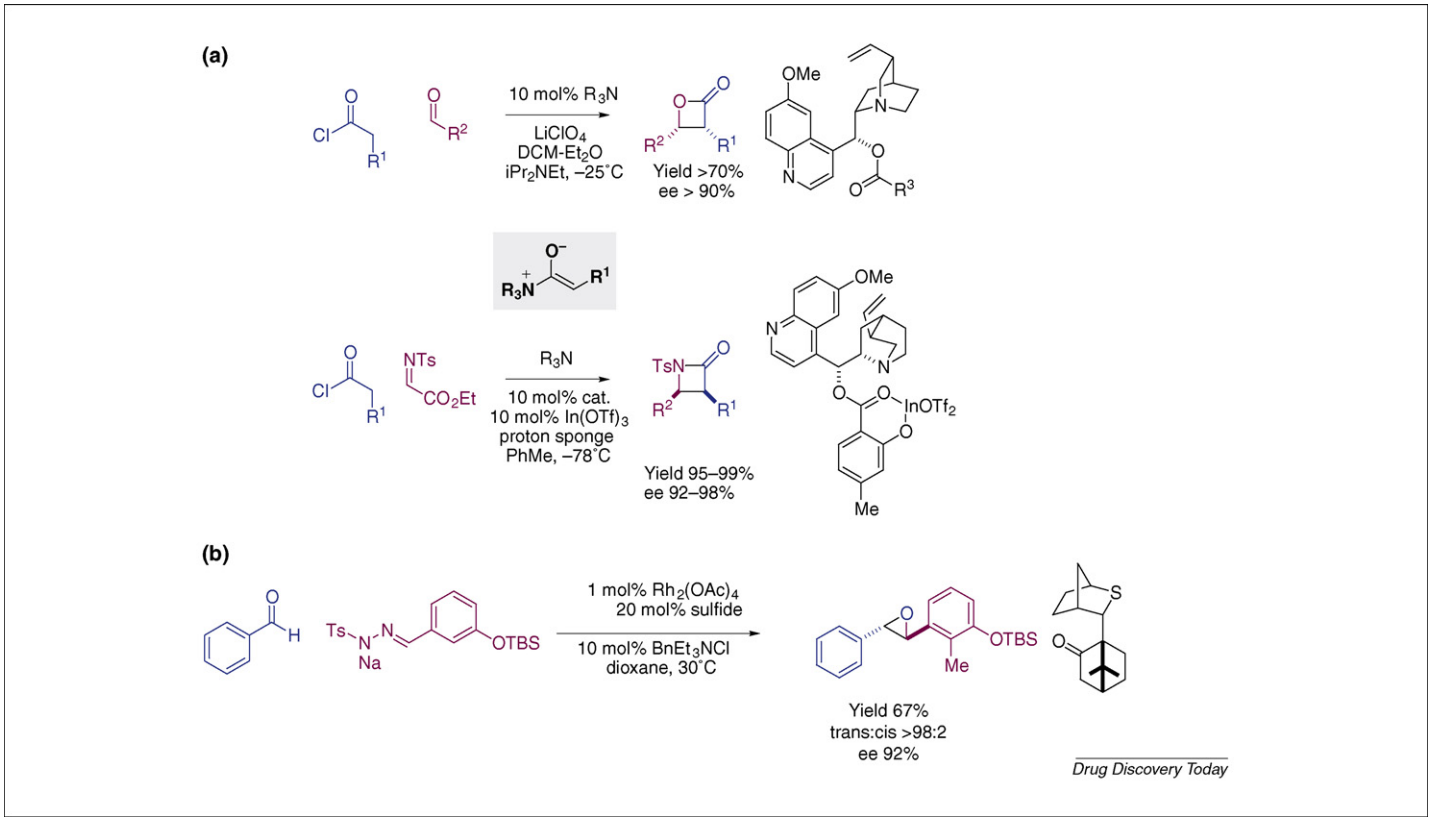

FIGURE 26

Asymmetric reactions through catalytically generated ammonium enolates (a); (b) Asymmetric epoxidation via sulfur ylides.

Cinchona alkaloids can also be used as nucleophilic catalysts in other processes through different mechanisms. The Baylis–Hillman reaction is probably the best known of these processes, and some cinchona alkaloid derivatives catalyse this traditionally problematic transformation with high levels of enantioselectivity (Figure 25) [78]. Although many tertiary amines catalyse the Baylis–Hillman reaction, few amines impart high levels of enantioselectivity. The cinchona derivatives can catalyse the reaction with both aldehydes and tosylimines with moderate to excellent enantiomeric excesses [79,80]. Unfortu-

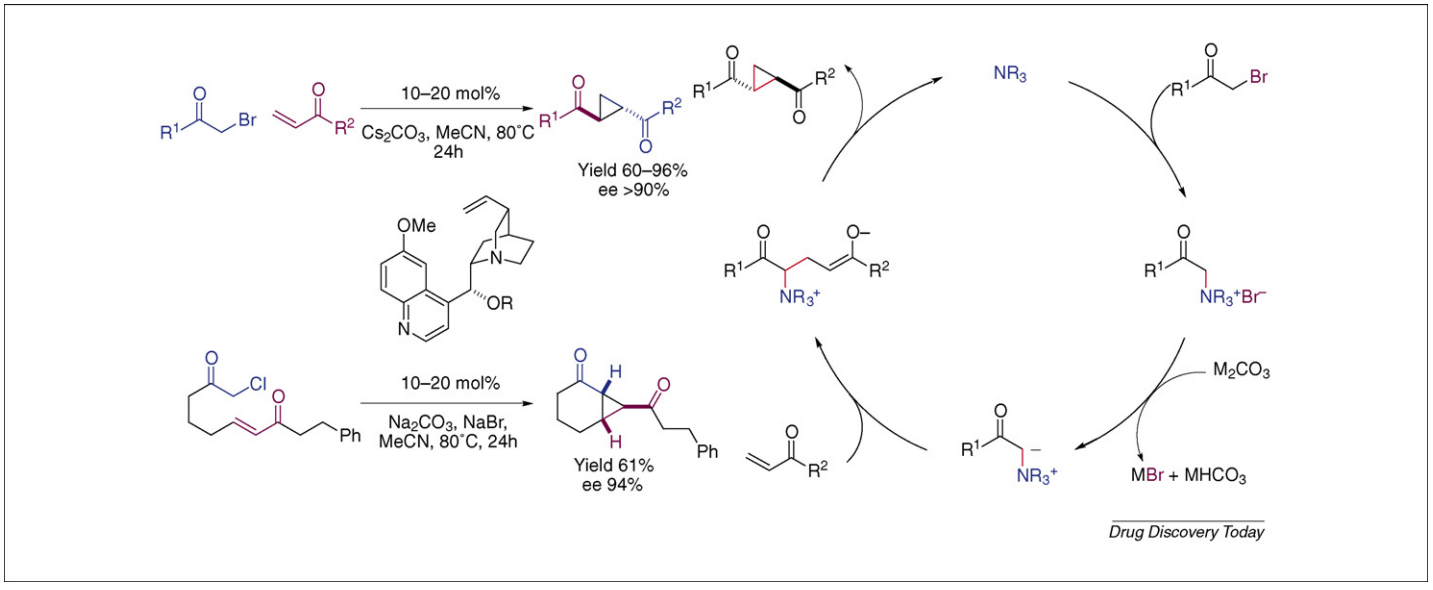

FIGURE 27

Catalytic enantioselective cyclopropanation.

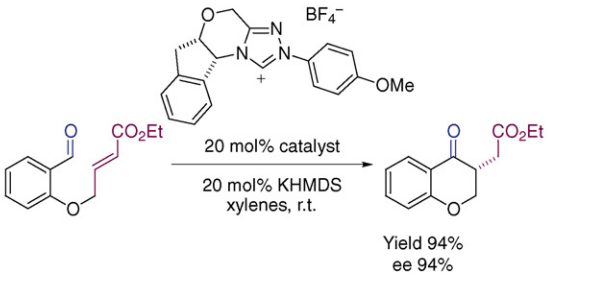

FIGURE 28

Catalytic enantioselective intramolecular Stetter reaction.

nately this method only produces one enantiomer because the corresponding quinine-derived catalyst cannot be formed. However, despite the poor substrate scope, this method is one of the best ways of achieving an asymmetric Baylis–Hillman reaction.

In combination with Lewis acids, cinchona alkaloids can be used to catalyse the formation of β-lactones and lactams from ketenes and aldehydes/imines (Figure 26). Although the reaction proceeds without the Lewis acid co-catalyst, it is far more efficient in its presence. For example, Nelson and co-workers reported that lithium perchlorate assisted the cinchona alkaloid-catalysed addition of ketenes (generated *in situ* from acid chlorides) to aldehydes to form β-lactones in excellent yields, diastereomeric ratios and enantiomeric excesses [81]. Lectka also reported that the indium (III) complex of a salicyl-derived quinine derivative effectively forms the corresponding β-lactam structure from the reaction of ketenes and imines, again with excellent stereoselectivities (Figure 26a) [82].

Aggarwal and co-workers have reported an ylide-mediated epoxidation method that uses a chiral sulfide in combination with a rhodium (II) catalyst to effect the addition of *in situ*-generated diazo compounds to an aldehyde through a Darzen's type mechanism (Figure 26a). This method provides an excellent method for the synthesis of aryl-substituted epoxides, compounds that are key to the synthesis of many medicinally relevant molecules [83].

Cinchona alkaloids can also be used to generate asymmetric ammonium ylides. Gaunt and co-workers have used this to develop a catalytic enantioselective cyclopropanation process that is general over a range of substrates [84]. Mechanistically, the nucleophilic catalyst forms an ammonium salt with an α-bromo carbonyl species. The pK_a-lowering effect of the salt effects deprotonation with a mild base to form the ylide, which, subsequently, undergoes conjugate addition and ring closure to form the cyclopropane as a single diastereomer. The reaction also works in an intramolecular fashion, forming bicylcoalkanes in excellent yields and enantiomeric excesses (Figure 27) [85,86].

The use of nucleophilic carbene catalysts is a rapidly emerging and exciting area for organocatalysis. Although not exclusively described here, we highlight this area with the development of the use of these catalysts for the production of an asymmetric Intramolecular Stetter reaction. Rovis and co-workers report that a chiral carbene catalyst induces excellent enantioselectivity in this transformation over a broad range of cyclic products in good yields and enantiomeric excesses (Figure 28) [87].

Fu and co-workers have reported the use of a chiral monophosphine as an organic catalyst for the [4 + 2]-type annulation of imines with allenes. The *cis*-substituted piperidine products are formed in excellent yields, diastereomeric ratios and enantiomeric excesses, which provides an efficient method for the synthesis of this key heterocyclic motif (Figure 29) [88].

There are many processes to be developed, based on nucleophilic catalysis, and the concept of generating asymmetric anions through contact ion pairs is a methodology with wide-ranging possibilities. Furthermore, other reactive species such as chiral ammonium enolates and ammonium ylides have great potential for the development of new chemistry.

H-bonding catalysis

The final area covered in this review is the use of H-bonding catalysts in enantioselective synthesis. Although H-bonding catalysts have been known for some time, until recently the applica-

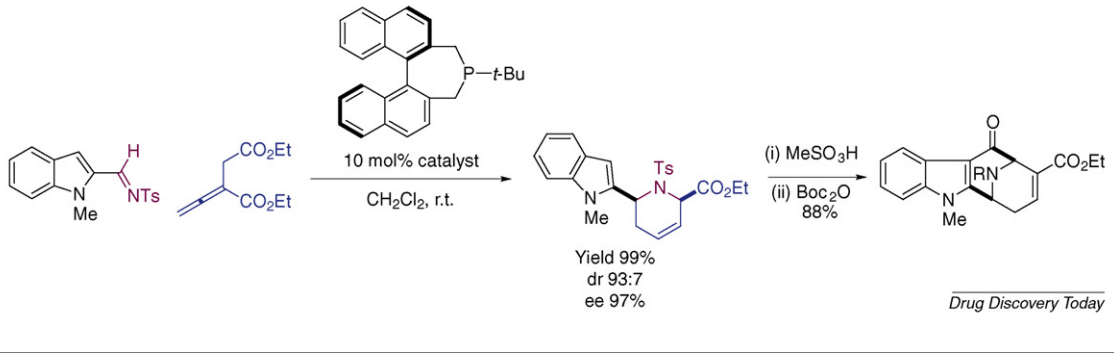

FIGURE 29

Phosphine-catalysed [4 + 2]-type annulation and imines.

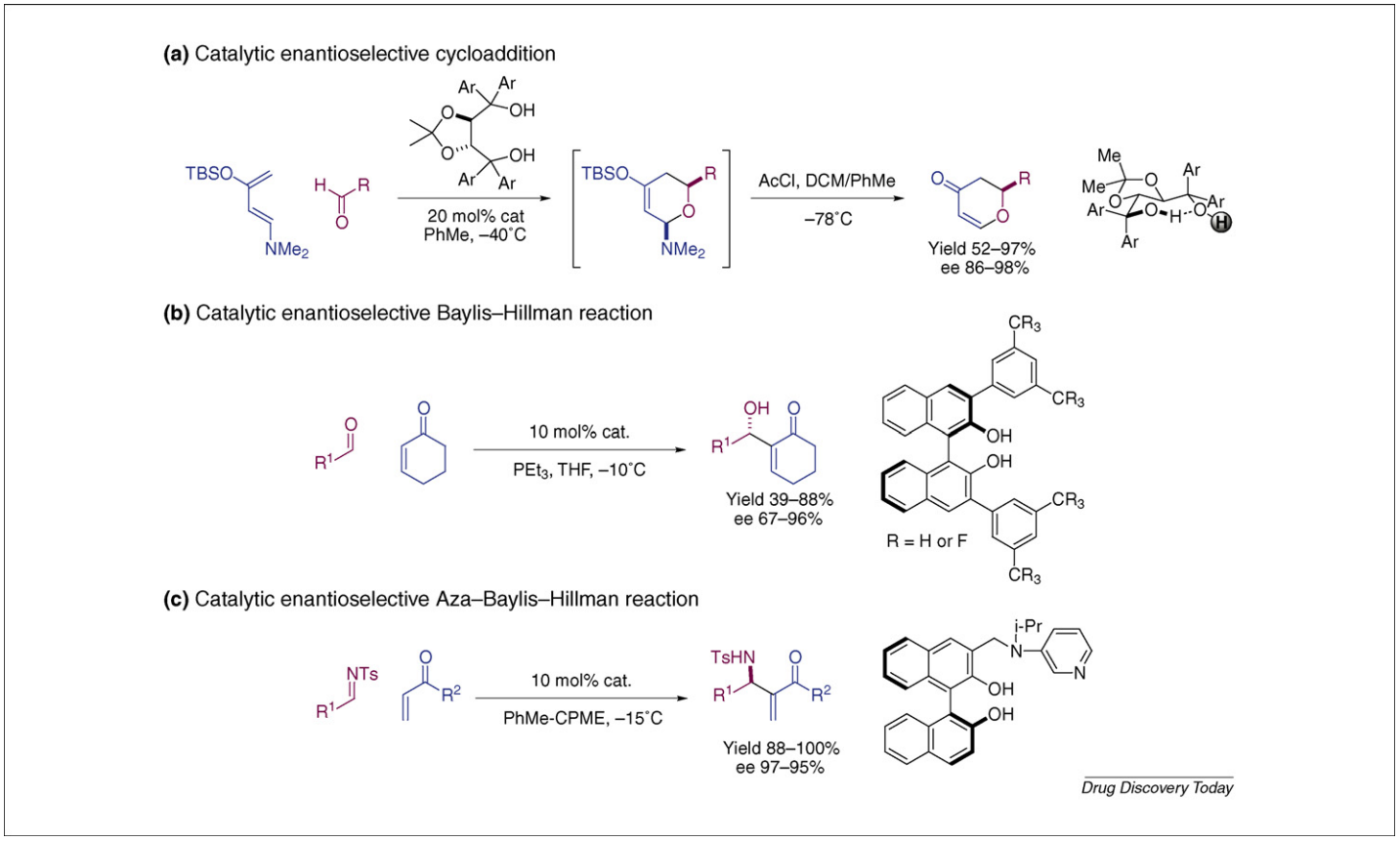

FIGURE 30

Chiral diol-catalysed asymmetric transformations.

tion of chiral acids has received little attention [89–91]. The ability to activate electrophiles with H-bonding bears a direct analogy to Lewis acid activation. Instead of using metals to coordinate the lone pair of a carbonyl, it relies on a hydrogen bond to enhance activation and generate a chiral environment around the electrophilic species. This catalytic strategy has potential as a general paradigm for synthesis.

Chiral diol derivatives can be used as H-bond donors to activate carbonyl compounds for cycloaddition reactions. For example, Taddol activates aldehydes via a single hydrogen bond and catalyses hetero-Diels Alder reactions to form dihydropyranones in excellent yields and enantiomeric excesses (Figure 30a) [92]. The conventional Diels Alder reaction is also catalysed efficiently to produce the carbocyclic derivatives [93]. Binol-derived catalysts also promote reactions such as the Baylis–Hillman reaction in combination with either an aldehyde or imine, which provides a useful solution to the long-standing problem of an enantioselective Baylis–Hillman reaction (Figure 30b,c) [94,95].

Jacobsen's group has developed a range of chiral thioureas that are versatile, effective catalysts. These catalysts are used most commonly to activate imines through hydrogen bonding to the nitrogen atom. A range of latent nucleophiles can be added to these electrophiles in excellent enantiomeric excesses and, in general, with a broad substrate scope. Strecker (Figure 31a) [96], hydrophosphorylation (Figure 31b) [97], nitro-Mannich (Figure 31c) [98] and Mannich (Figure 31d) [99] reactions are all possible, which indicates that these catalysts have versatile properties as general catalysts for asymmetric organic synthesis.

In addition, the cyanosilylation of ketones has also been achieved in high yields and enantiomeric excesses in a similar process to the Strecker reaction, but using a slightly different catalyst (Figure 32a) [100]. Jacobsen's work has inspired others to investigate thiourea catalysis and, subsequently, indole (Figure 32b) [101] and malonate (Figure 32c) [102] additions to nitroalkenes have been reported with good enantiomeric excesses. Interestingly, the bifunctional cinchona alkaloid-thiourea catalyst used for the malonate addition is epimeric at C9 from the naturally occurring alkaloid structure and generates the product in higher enantiomeric excess [102].

In combination with the acylation of an imine derived from tryptamine, a thiourea-catalysed acyl Piclet–Spengler reaction has been developed that forms isoquinolines in good yields and enantiomeric excesses. [103] Although the exact mechanism of the activation is unclear, this process provides the first access to this important class of reactions. Similarly, Mannich-type reactions onto acylated isoquinolines yields the chiral products in high enantiomeric excesses, affording similar compounds to a conventional Piclet–Spengler type process (Figure 33) [104].

A range of binol-derived phosphoric acids also catalyse a range of interesting processes involving imines. Mannich reactions seem to be ideally suited to this class of organocatalysis, and the binol phosphoric acid catalyses both the addition of β-diketone

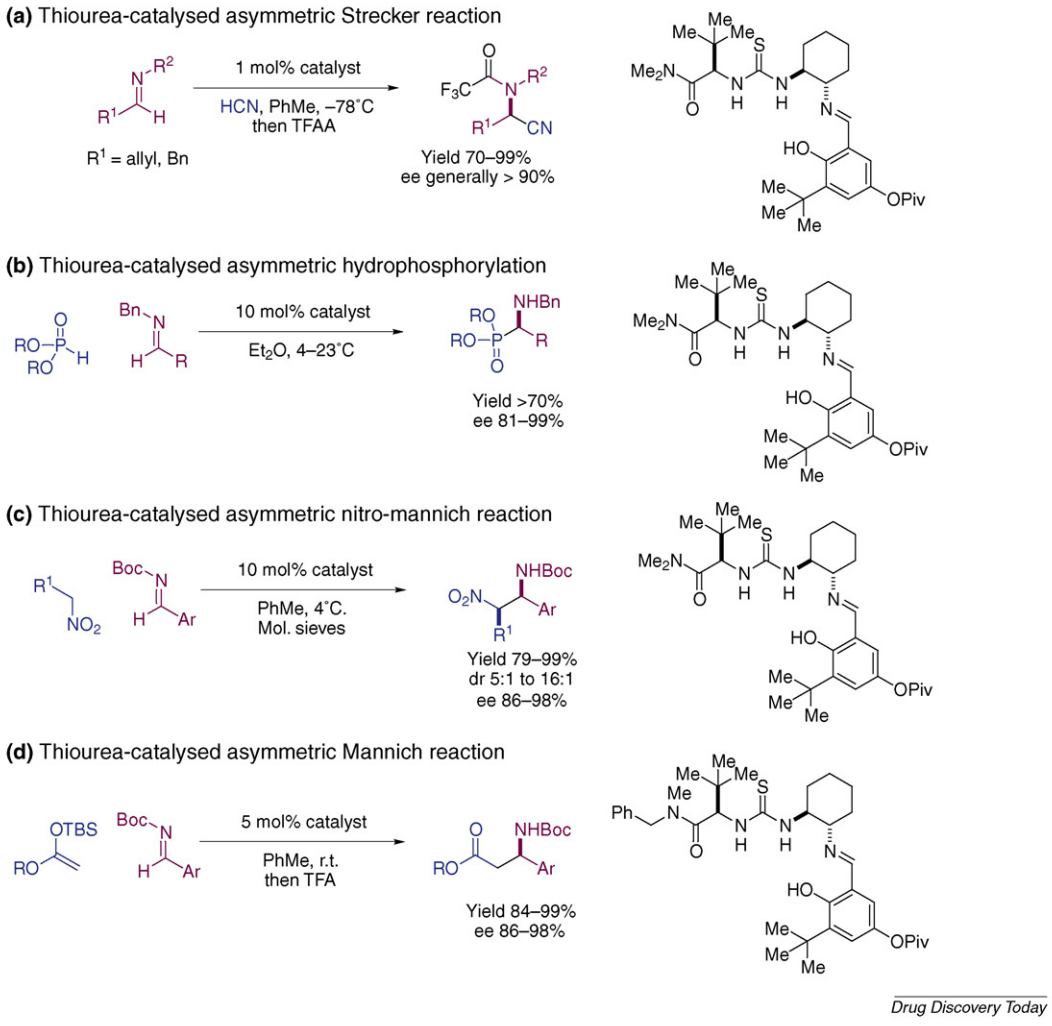

FIGURE 31

Asymmetric reactions catalysed by chiral thioureas.

(Figure 34a) [105] and silyl enol ethers (Figure 34b) [106] to imines in excellent yield and enantiomeric excess.

Electron-rich furan derivatives can be added to imines via a Freidel–Crafts type mechanism to form chiral amines adjacent to the heterocycle (Figure 34c) [107]. The furan can be converted readily to a range of functionalities, emphasizing the usefulness of this process. Diazo compounds also have high nucleophilicity and can be added readily to imines and further functionalized to useful compounds (Figure 34d) [108]. Although, to date, no further heterocyclic addition has been reported, such reactions are likely to find broad use in synthesis. Recently, List and co-workers reported a direct Pictet–Spengler reaction with a range of aldehydes to form isoquinolines in high yields and enantiomeric excess [109]. A geminally substituted tryptamine is needed, but this limitation does not significantly affect the utility of this process (Figure 34e).

Finally, an enantioselective reductive amination has been reported by several research groups. Rueping first reported that a phosphoric acid catalysed the reduction of an imine with a Hantzch ester in good enantiomeric excess [110]. List reported an improvement to this method and highlighted the ability to perform a one-pot process from aldehyde to amine in enantiomeric excesses up to 90% [111]. MacMillan finally reported a one-pot, direct, reductive amination with broad substrate scope that enables the effective reductive amination of a range of methyl ketones and aryl amines (Figure 34f) [112]. It is even possible to obtain good enantiomeric excess with 2-butanone where the silylated phosphoric acid can distinguish between a methyl group and an ethyl group, delivering the product in high enantiomeric excess. This reaction will undoubtedly have a major impact on the pharmaceutical chemistry.

Summary

Enantioselective organocatalysis has had a major impact on chemical synthesis over the past five years and has brought

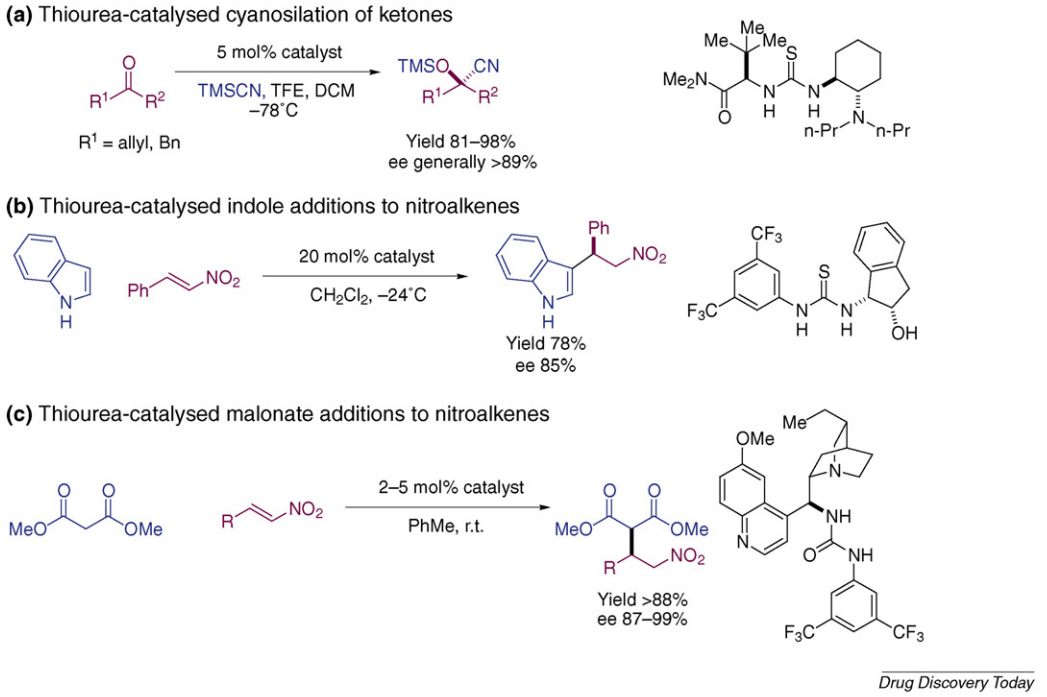

FIGURE 32

Thiourea-catalysed asymmetric reactions.

about an increase in the development of new asymmetric catalytic methodology that is being applied in many areas of chemistry. Undoubtedly, the design and discovery of many new processes and strategies in the coming years will extend its rise in popularity. However, it is important that lessons are learnt from the advent of metal catalysis, and that the study of reaction mechanism (especially through kinetics) accompanies the expansion in the repertoire of available reactions. This will enable better design of catalysts and a better understanding of reactions.

In summary, enantioselective organocatalysis has a major role alongside metal-catalysed processes of chemical synthesis because, together, these complementary disciplines will revolutionize the way that synthesis is carried out in the future, and will enable us to move closer to being able to make any molecule in an efficient, rapid and stereoselective manner.

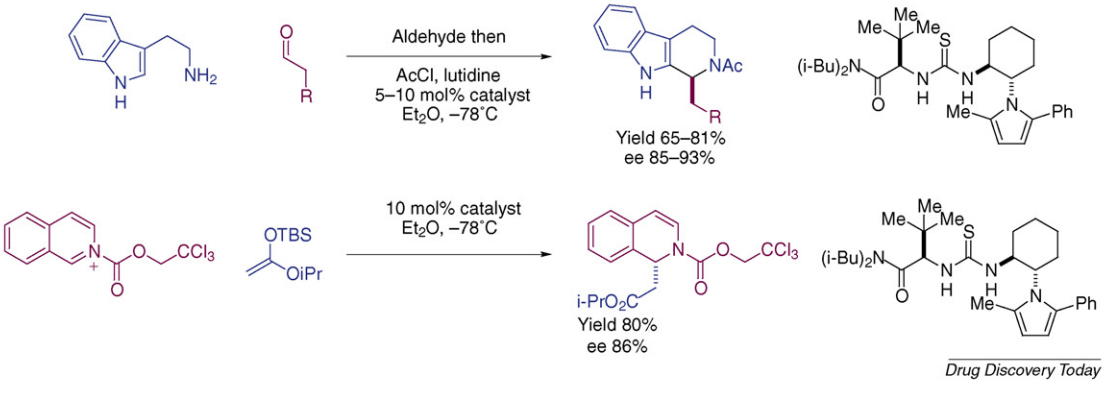

FIGURE 33

Thiourea-catalysed asymmetric reactions of acylated imines.

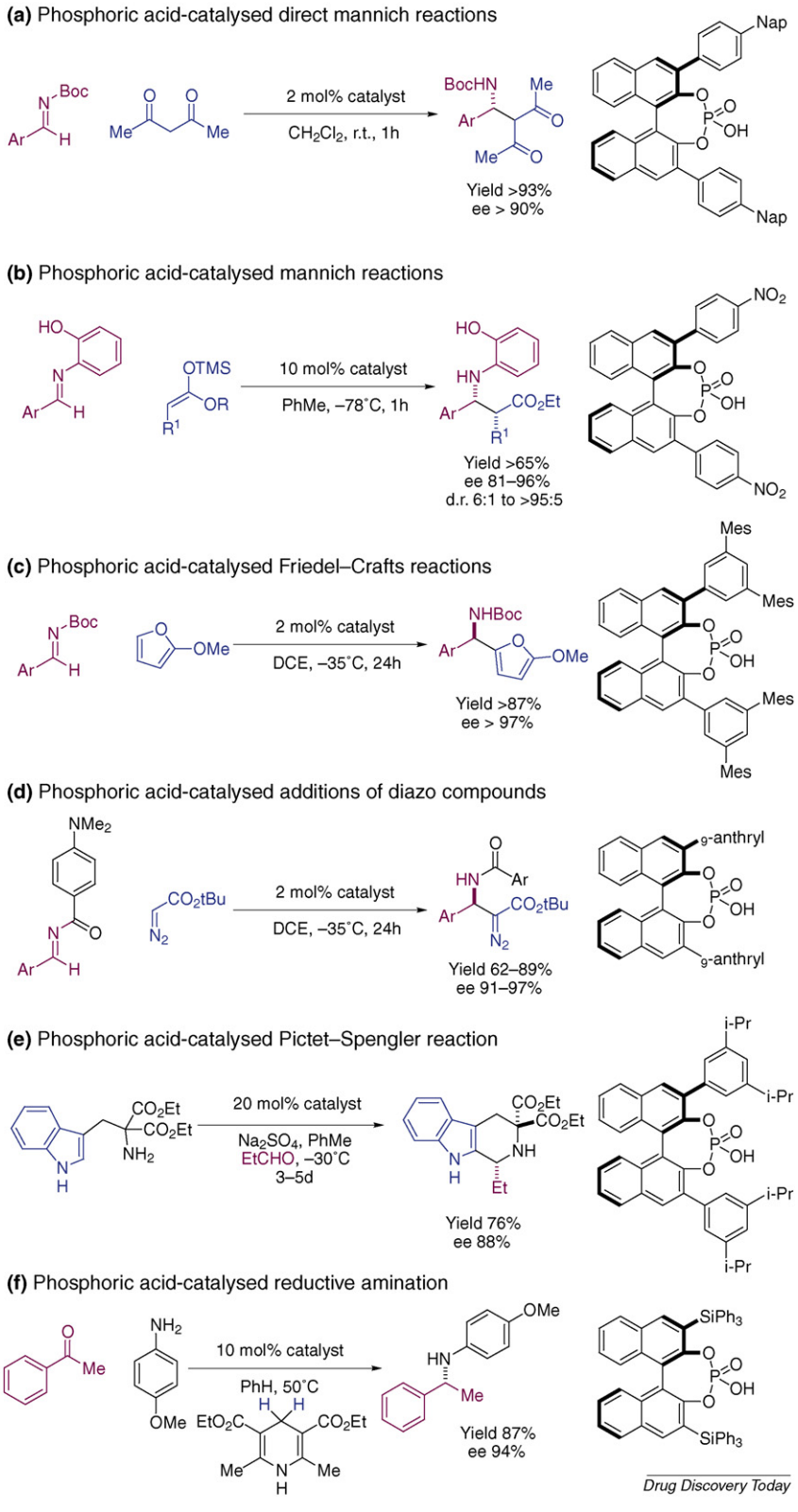

FIGURE 34

Binol-derived phosphoric acids as Brønsted acid catalysts for asymmetric synthesis.

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