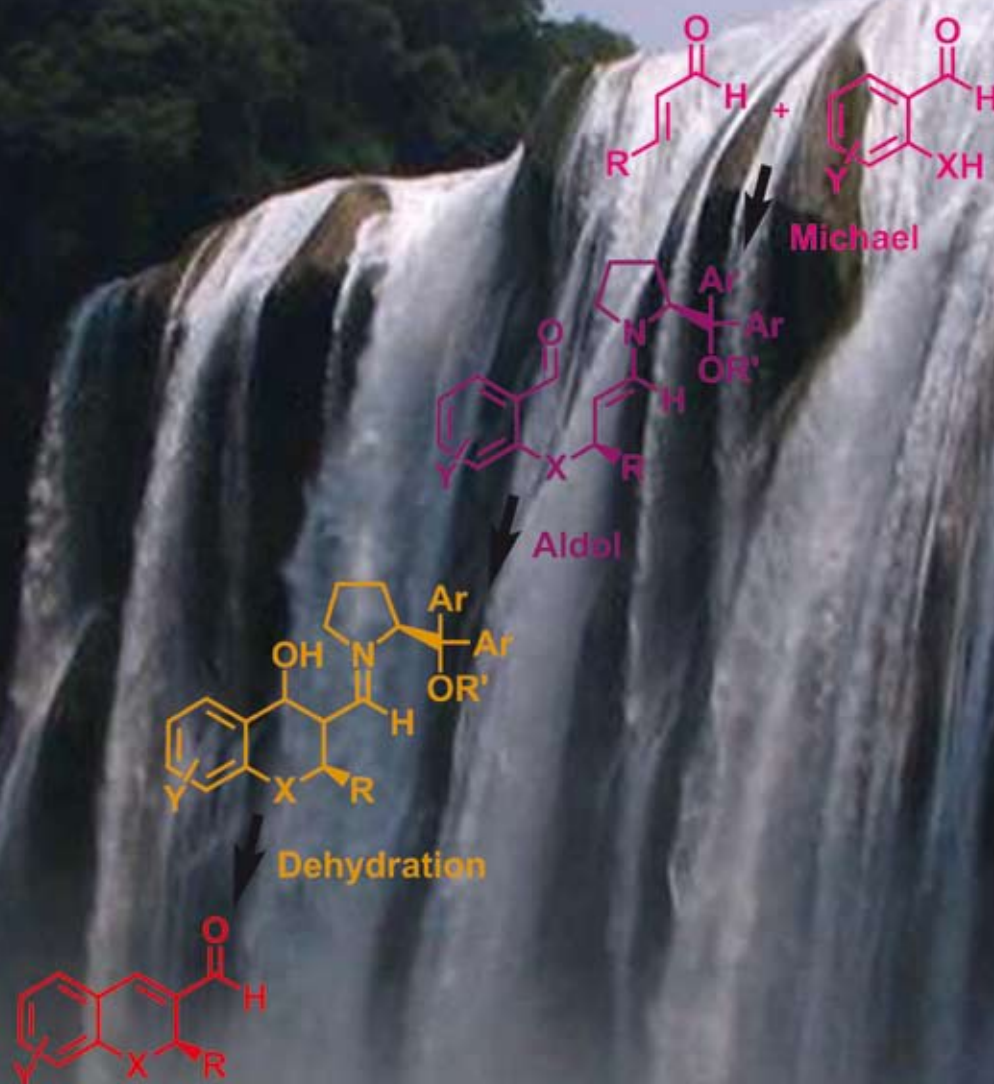


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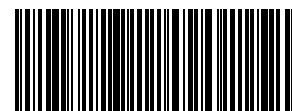
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**EMERGING AREA**  
 X. Yu and W. Wang  
 Organocatalysis: asymmetric  
 cascade reactions catalysed by chiral  
 secondary amines

**Chemical Science**

In this issue...



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# Organocatalysis: asymmetric cascade reactions catalysed by chiral secondary amines

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The utilisation of chiral secondary amines as promoters for asymmetric cascade reactions has been subject of intensive research in asymmetric organocatalysis in the past few years. Key developments in this area are highlighted in this review. As shown, these powerful synthetic methodologies serve as efficient approaches to the construction of complex chiral molecular architectures from simple achiral materials in one-pot transformations under mild conditions with high stereocontrol.

## Introduction

The seminal studies in the (*S*)-proline-catalysed enamine-related Hajos–Wiechert reaction<sup>1</sup> and MacMillan's chiral imidazolidinone iminium chemistry<sup>2</sup> set the stage for the current rekindled interest in organic catalysis. Catalysis by amines stimulated the formation of a new branch of catalysis, nowadays termed "organocatalysis".<sup>3</sup> Generally, chiral secondary amines **1–6** are used for promoting formation of electron-rich enamines from enolisable aldehydes or ketones, which then react with various electrophiles to afford products (Scheme 1, eqn 1).<sup>4</sup> In contrast, MacMillan's chiral imidazolidinones **7**<sup>5</sup> and diarylprolinol ethers **8**<sup>6</sup> are most often used to activate  $\alpha,\beta$ -unsaturated aldehydes by forming electron-deficient iminium ions,<sup>4b,5–7</sup> which render the  $\beta$ -carbons more electrophilic than their carbonyl precursors for nucleophilic attack (eqn 2). Since amine organocatalysis involves the intermediacy of enamine and iminium species, it can serve as an attractive platform in the design of new catalytic cascade processes, in which several bond-forming steps take place in a single operation.

In the past few years, significant progress has been made in the development of organocatalysed asymmetric cascade reactions using chiral secondary amines, as evidenced by a number of publications that have appeared.<sup>4a,c,7,8</sup> These stunning synthetic technologies serve as powerful tools for the efficient construction of complex molecular architectures.<sup>9</sup> Moreover, in these cascade processes, only a single reaction solvent, workup procedure, and purification step is required to produce a product that would otherwise require several steps.<sup>10</sup> Therefore, cascade reactions with the significant improvement of synthetic efficiency, the avoidance of toxic agents, and the reduction of waste and hazardous byproducts fall under the banner of "green chemistry." In this review, key developments in this emerging field are summarised, classified into cascade reactions catalysed by: 1) proline and its analogues **1–6**, 2) MacMillan's chiral imidazolidinones **7**, and 3) chiral diarylprolinol ethers **8**.

## Proline and its derivatives

Historically, the amino acid (*S*)-proline **1** has been a phenomenal molecule in organocatalysis. It is considered the simplest enzyme<sup>11</sup> and has been demonstrated to catalyse a wide range of asymmetric organic transformations.<sup>4c,12</sup> As a matter of fact, (*S*)-proline was applied in an asymmetric intramolecular aldol–cyclisation cascade reaction (namely the Robinson annulation), over 30 years ago

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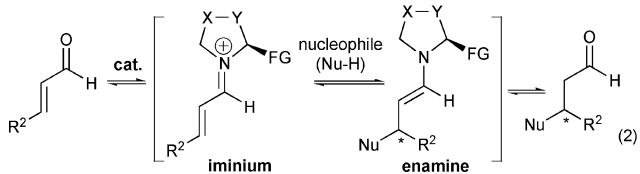
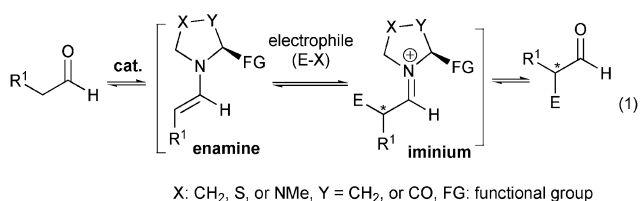
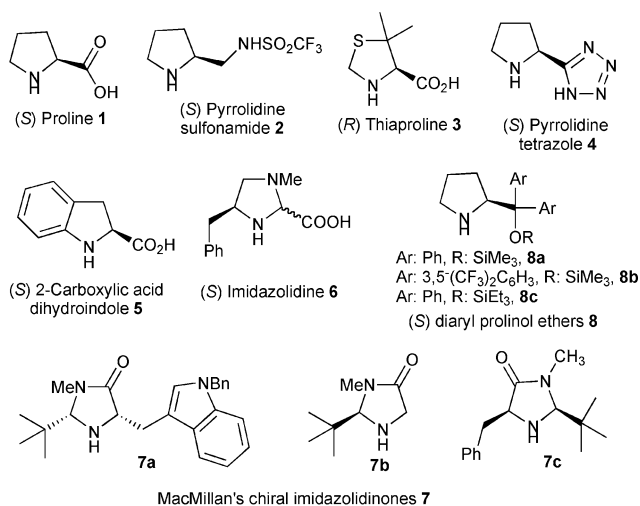
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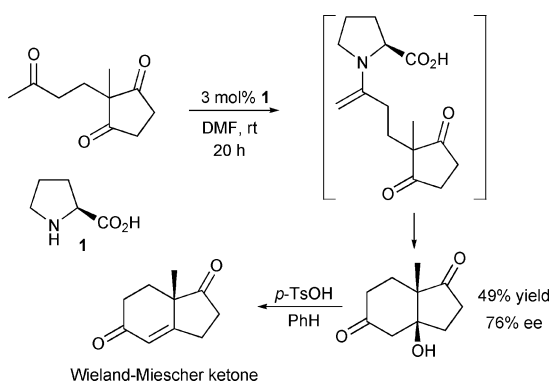
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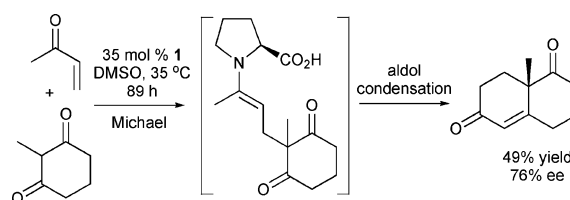
**Scheme 1** Structures of chiral amines discussed in this article for catalysing cascade reactions involved in enamine and iminium chemistry.

(Scheme 2).<sup>1,13</sup> The efficient method afforded the synthetically useful Wieland–Miescher ketones, key building blocks in steroid and natural product syntheses.



**Scheme 2** Intramolecular aldol-cyclisation reaction catalysed by (*S*)-proline 1.

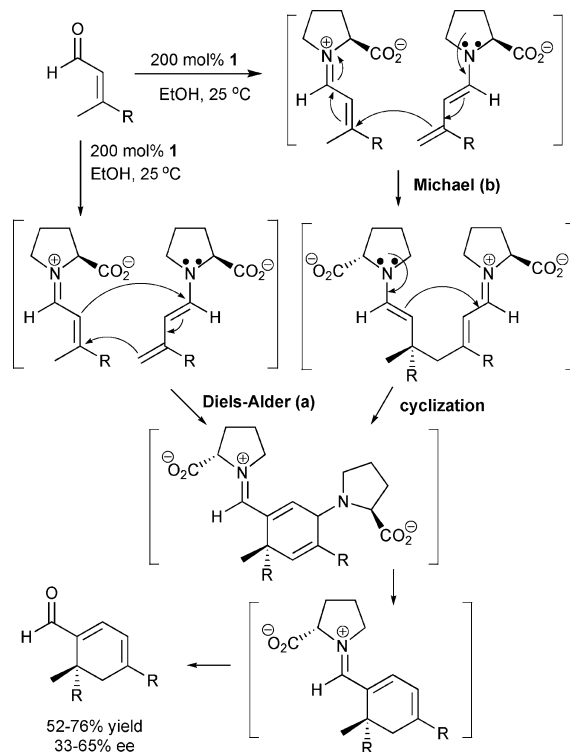
In 2000, Barbas and co-workers extended the strategy to the intermolecular version of the Robinson annulation process (Scheme 3).<sup>14</sup> The approach is more efficient than the intramolecular one because of the use of the readily available enones and 1,3-cyclohexadiketones as starting materials. Moreover, the cascade reaction proceeds in a Michael–aldol-condensation sequence,



**Scheme 3** Intermolecular Robinson annulation reaction catalysed by (*S*)-proline 1.

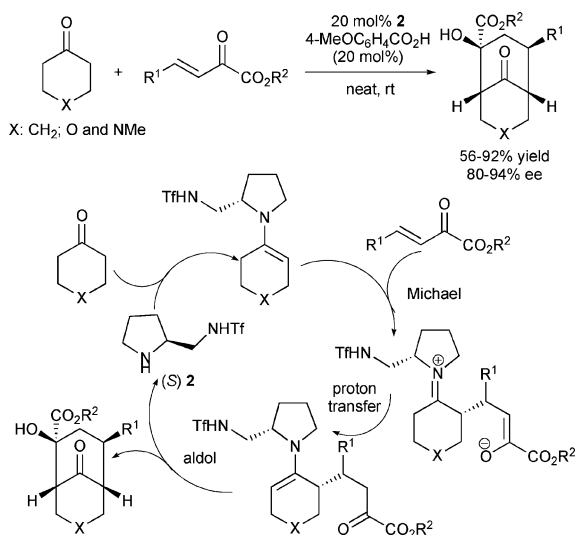
which is different from the intramolecular annulation reaction with an aldol-cyclisation process.

Watanabe and co-workers<sup>15a</sup> reported an (*S*)-proline-catalysed dimerisation of enals to give cyclohexadiene carbaldehydes based on their early work (Scheme 4).<sup>15b</sup> After the survey of a variety of new catalysts, (*S*)-proline was still the best activator. It is noted that 200 mol% (*S*)-proline was used, and moderate enantioselectivity was obtained. Although the reaction mechanism was not clear, it was believed that a Diels–Alder (path a) or a cascade Michael cyclisation process (path b) might be involved.<sup>15a</sup> Using similar tactics, Barbas,<sup>16a</sup> and Hong<sup>16b</sup> have recently independently developed (*S*)-proline-promoted cyclisation reactions as well.



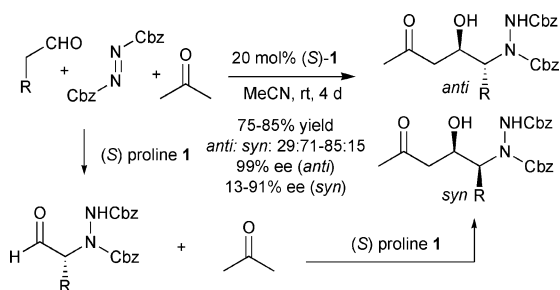
**Scheme 4** Asymmetric Diels–Alder and cascade Michael–cyclisation processes catalysed by (*S*)-proline 1.

Recently, Tang and co-workers described an enantioselective formal cyclisation reaction involving a Michael–aldol sequence catalysed by (*S*)-pyrrolidine trifluoromethanesulfonamide 2 (Scheme 5).<sup>17</sup> Reaction of cyclic ketones with enone esters in the presence of 20 mol% 2 with no solvent at rt furnished bicyclic adducts in moderate to good yields and with good to high ee values.



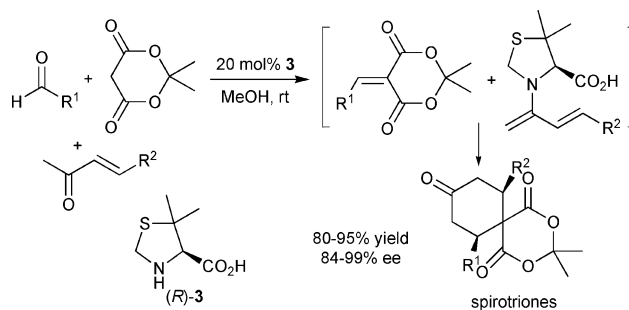
**Scheme 5** Asymmetric formal [3 + 3] cyclisation reaction catalysed by (*S*)-pyrrolidine sulfonamide **2**.

Multicomponent cascade reactions are very attractive in organic synthesis because of atom-economy. Combining the capacity of (*S*)-proline-promoted asymmetric aldol and  $\alpha$ -amination reactions, Barbas and co-workers developed a three-component process for one-pot preparation of functionalised enantioenriched  $\beta$ -amino alcohols from aldehydes, acetone and azodicarboxylates (Scheme 6).<sup>18a</sup> The cascade reaction involved a sequential  $\alpha$ -amination–aldol process. Because of the greater tendency for the formation of an enamine of an aldehyde with (*S*)-proline,  $\alpha$ -amination occurred first with the aldehyde. They also developed an (*S*)-proline-catalysed three-component trimerisation of simple aldehydes through a self-condensation process to afford carbohydrates and polyketides.<sup>18b</sup>



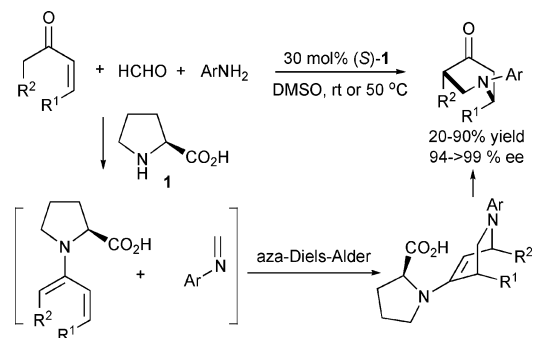
**Scheme 6** Asymmetric amination–aldol reaction catalysed by (*S*)-proline **1**.

The same group also developed a novel three-component Knoevenagel–Diels–Alder reaction catalysed by thiaproline **3** with good to high enantioselectivity, the spirotriones being formed with exclusive *cis*-stereoconfiguration (Scheme 7).<sup>19</sup> However, when (*S*)-proline was employed for the cascade process, both *cis*- and *trans*-diastereomers were obtained. The  $\alpha,\beta$ -unsaturated ester produced from the Knoevenagel reaction of an aldehyde with a cyclic malonate serves as a dienophile for the subsequent Diels–Alder reaction, with the *in situ*-formed diene resulting from (*R*)-thiaproline **3** facilitating enolisation of the enone.



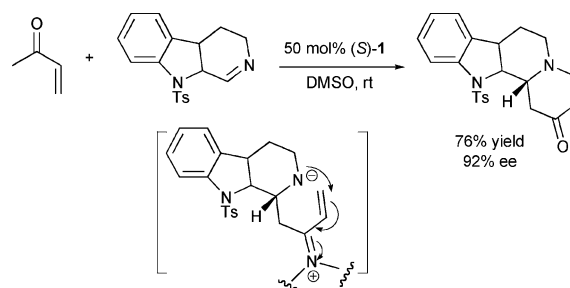
**Scheme 7** Knoevenagel–Diels–Alder reaction catalysed by (*R*)-thiaproline **3**.

Córdova and co-workers reported an (*S*)-proline-catalysed three-component formal aza-Diels–Alder reaction (a Mannich–aza-Michael sequence) to afford highly enantioenriched adducts (Scheme 8).<sup>20</sup> In the cascade process, (*S*)-proline catalysed the formation of a diene from an enone, which then reacted with an imine generated from formaldehyde and an aniline to produce the product and releasing the catalyst.



**Scheme 8** Formal aza-Diels–Alder reaction catalysed by (*S*)-proline **1**.

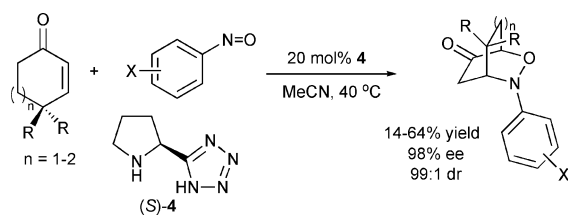
In a related study, in 2003, Ohsawa and co-workers described an (*S*)-proline-catalysed cascade Mannich–aza-Michael process for the assembly of indole alkaloids (Scheme 9).<sup>21</sup> Mechanistically, the reaction pathway is similar to that of the formal aza-Diels–Alder reaction proposed by Córdova.<sup>20</sup> This efficient method enabled the synthesis of the natural product *ent*-dihydrocorynantheol. A similar strategy was also recently reported by Hsung and colleagues.<sup>22</sup>



**Scheme 9** Mannich–aza-Michael reaction catalysed by (*S*)-proline **1**.

Yamamoto and co-workers combined an organocatalytic  $\alpha$ -aminoxylation and a Michael addition reaction to generate a nitroso-Diels–Alder type reaction (Scheme 10).<sup>23</sup> They found

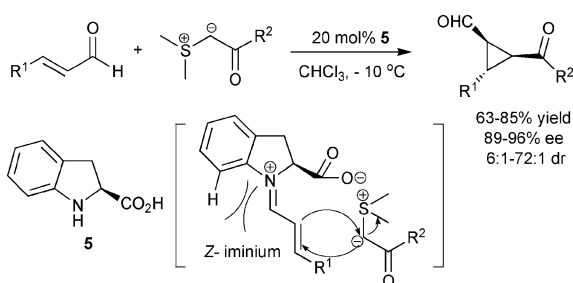




**Scheme 10** Formal aza-Diels–Alder reaction catalysed by (*S*)-pyrrolidine tetrazole **4**.

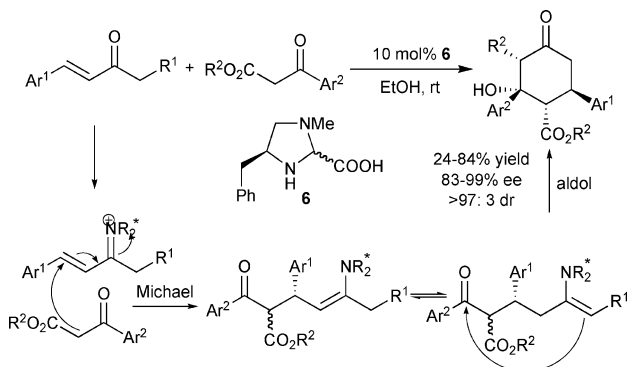
pyrrolidine tetrazole **4** was a better catalyst than proline in terms of catalyst activity and enantio- and diastereoselectivity.

Inspired by Corey's work in the use of the stabilised ylides for cyclopropanation of  $\alpha,\beta$ -unsaturated aldehydes,<sup>24</sup> MacMillan and co-workers recently disclosed a cascade Michael–substitution-type reaction catalysed by the proline analogue 2-carboxylic acid dihydroindole **5** for the preparation of 3-membered ring systems (Scheme 11).<sup>25</sup> After screening a range of organocatalysts, compound **5** was found to be an effective catalyst for the cyclopropanation process. Critically, its ability to preferentially generate a (*Z*)-iminium species (as a result of steric hindrance of the phenyl ring) contributed to its high catalytic activity and enantioselectivity. This (*Z*)-iminium salt readily participated in cyclopropanation with the charged sulfur ylide, directed by an additional electrostatic interaction.



**Scheme 11** Cyclopropanation catalysed by (*S*)-2-carboxylic acid dihydroindole **5**.

In conjunction with their early studies of using imidazolidine **6** for Michael addition of stabilised carbanions, Jørgensen and co-workers developed a cascade Michael–aldol process (Scheme 12).<sup>26</sup> A ketoester served as a nucleophile for the initial conjugate addition to the enone activated by amine **6**, followed by intramolecular

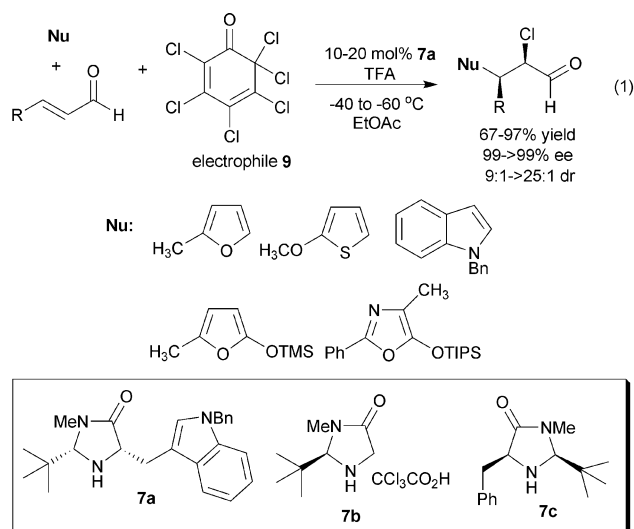


**Scheme 12** Michael–intramolecular aldol reaction catalysed by chiral imidazolidine **6**.

aldol reaction to furnish 6-membered cyclohexanones with good to high enantioselectivity and excellent diastereoselectivity. Notably, in the cascade process, four new stereogenic centres were efficiently created.

## MacMillan's chiral imidazolidinones

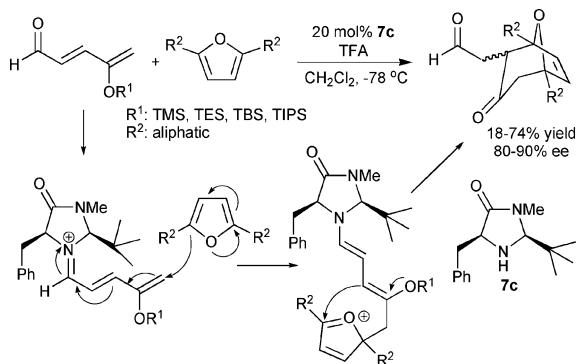
MacMillan's chiral imidazolidinones have proved to be effective activators for  $\alpha,\beta$ -unsaturated aldehydes through formation of an iminium ion.<sup>5</sup> It was realised that the nucleophilic attack involved in the formation of the iminium ion results in an electron-rich enamine, which may be intercepted by an electrophile. Based on this hypothesis, MacMillan *et al.* developed a new cascade Friedel–Crafts–halogenation reaction (Scheme 13).<sup>27a</sup> A variety of chiral imidazolidinones were screened for the cascade process; **7a** was found to be the best promoter for the Friedel–Crafts–chlorination reaction, in which the quinone **9** served as the chlorination reagent.



**Scheme 13** Friedel–Crafts–halogenation and hydrogenation–halogenation reactions catalysed by chiral imidazolidines **7**.

Under the optimised reaction conditions, an excellent level of enantioselectivity (99% or higher), a good dr (9 : 1 to >25 : 1) and good yields were achieved for a variety of electron-rich aromatics and enals (eqn 1). They also successfully extended the strategy for cascade hydrogenation–chlorination and fluorination reactions (eqns 2 and 3).<sup>27a</sup> The chemistry was established based upon their recent discoveries of the use of Hantzsch esters for asymmetric hydrogenation of  $\alpha,\beta$ -unsaturated systems in conjunction with electrophilic halogenation.<sup>27b</sup> More significantly, they found that two amine catalysts could be employed in a one-pot system to promote the sequential iminium/enamine chemistry without interfering with each other. At the same time, List and co-workers described a related cascade process involving a hydrogenation–Michael addition sequence (eqn 4).<sup>27c</sup>

In 2003, Harmata and co-workers described a formal [3 + 4] cycloaddition reaction catalysed by a chiral imidazolidinone **7c** (Scheme 14).<sup>28</sup> Under the optimised reaction conditions, treatment of several 4-trialkylsilyloxypentadienals and a diene in the presence of **7c** and trifluoroacetic acid resulted in the formation of [4 + 3] cycloaddition products with ee values ranging from 80 to 90%.



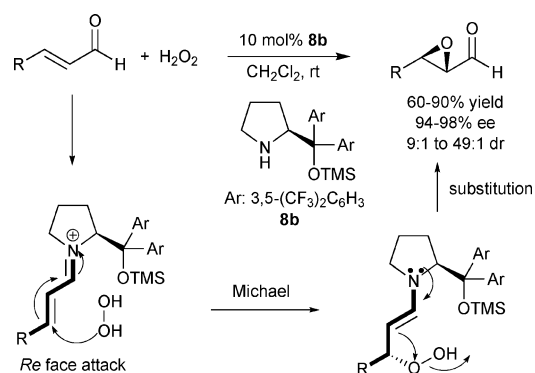
**Scheme 14** Formal [4 + 3] cycloaddition reaction catalysed by chiral imidazolidinones **7c**.

## Chiral diarylprolinol silyl ethers

Chiral diarylprolinol ethers, particularly silyl ethers, have recently emerged as general catalysts for catalysing a wide range of organic reactions through enamine/iminium chemistry.<sup>6</sup> In addition to catalysing single-step transformations, remarkably they have proved to be the most successful organic catalysts for cascade processes.<sup>7,8b</sup>

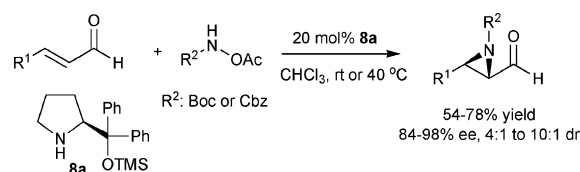
Jørgensen and co-workers described the first iminium-catalysed epoxidation reaction of  $\alpha,\beta$ -unsaturated aldehydes (Scheme 15).<sup>29</sup> The process, catalysed by diarylprolinol silyl ether **8b**, gave products with an excellent level of enantioselectivity and in good yields when  $\text{H}_2\text{O}_2$  was used as the oxidant. The epoxidation process was believed to involve an oxa-Michael–substitution cascade. The bulky silyl ether side chain of the catalyst only allowed *Re* face attack, resulting in high stereocontrol. It is noteworthy that MacMillan,<sup>30a</sup> Córdova,<sup>30b</sup> Lattanzi<sup>30c</sup> and Zhao<sup>30d</sup> have also independently reported similar epoxidation methods for enals and enones.

Logically, the organocatalytic epoxidation strategy can be applied to the aziridination of enals. As recently demonstrated by



**Scheme 15** Epoxidation catalysed by chiral diarylprolinol silyl ether **8b**.

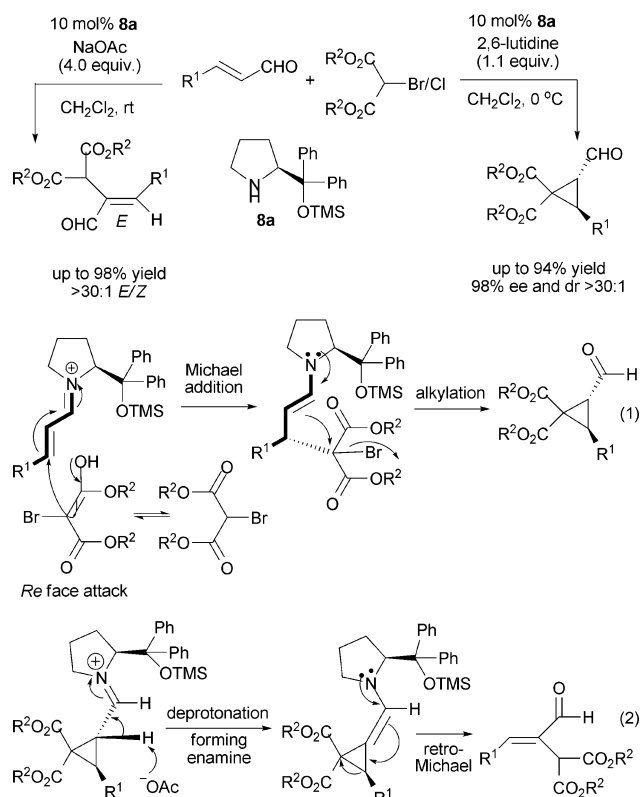
Córdova and co-workers, acylated hydroxylcarbamates can engage in an aza-Michael–nucleophilic substitution cascade, catalysed by pyrrolinol silyl ether **8a** (Scheme 16).<sup>31</sup> Generally good to high enantio- and diastereoselectivities were observed in this aziridination.



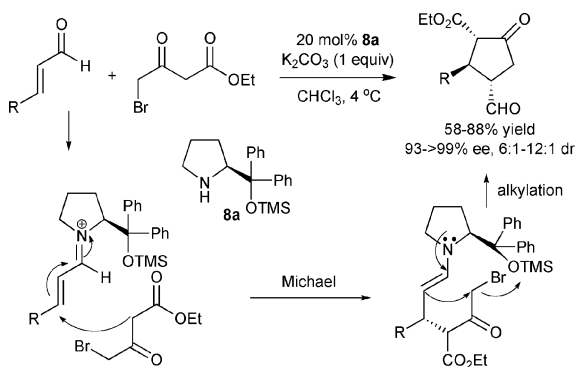
**Scheme 16** Aziridination catalysed by chiral diarylprolinol silyl ether **8a**.

In contrast to the use of sulfur ylides, the employment of readily available alkyl halides for a catalytic Michael–alkylation reaction with  $\alpha,\beta$ -unsaturated aldehydes to produce cyclopropanes is a more attractive option, but an extremely challenging one because of the high tendency for *N*-alkylation of the secondary amino group of the catalyst by alkyl halides, leading to poisoning of the catalyst. Wang,<sup>32a</sup> Córdova<sup>32b</sup> and Ley<sup>32c</sup> have independently developed new amine-catalysed Michael–alkylation cascades to generate highly functionalised chiral cyclopropanes in a one-pot transformation. By the careful design of the substrates and optimisation of the reaction conditions, a bromo/chloro malonate (as a nucleophile and electrophile) reacted with an  $\alpha,\beta$ -unsaturated aldehyde in the presence of chiral diphenylprolinol TMS ether **8a** (as a promoter) and 2,6-lutidine (as an acid scavenger) to enable the Michael–alkylation cascade to proceed efficiently (Scheme 17, eqn 1).<sup>32a</sup> The tandem reactions afforded trisubstituted chiral cyclopropanes with high levels of enantio- (90–98% ee) and diastereoselectivities ( $\geq 30 : 1$  dr) and in high yields without intoxicating the catalyst. Moreover, the nature of the bases and their amount used was critical for the formation of the products. It was found that when 4 equiv. of NaOAc was used, (*E*)- $\alpha$ -malonate-substituted  $\alpha,\beta$ -unsaturated aldehydes were produced with high stereoselectivity.<sup>32a</sup> A mechanistic investigation revealed that the  $\alpha,\beta$ -unsaturated aldehydes were generated from the subsequent ring-opening of cyclopropanes *via* a retro-Michael reaction (eqn 2).

Recently, Córdova and co-workers applied a similar strategy to a cascade Michael–alkylation reaction, which created cyclopentanones with high enantioselectivity and moderate to high diastereoselectivity (Scheme 18).<sup>33</sup>



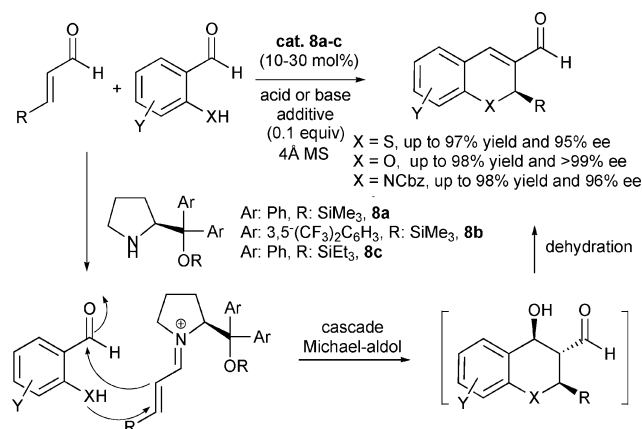
**Scheme 17** Michael-alkylation reaction catalysed by chiral diarylprolinol silyl ether **8a**.



**Scheme 18** Michael-alkylation reaction catalysed by chiral diarylprolinol silyl ether **8a**.

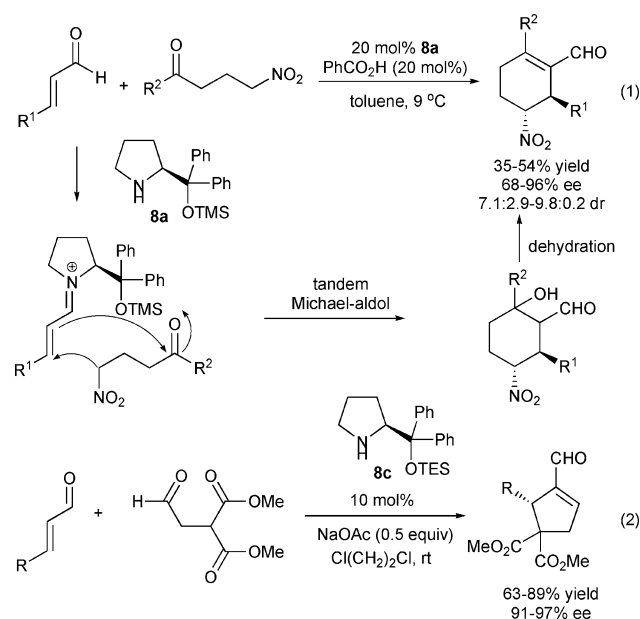
Wang<sup>34</sup> and Córdova<sup>35</sup> have developed enantioselective cascade hetero-Michael-aldol-dehydration processes, where S, O and N served as nucleophiles for the initial conjugate addition reaction (Scheme 19). These cascade processes provided an efficient approach to the preparation of biologically significant benzo(thio)pyrans and hydroquinolines. By rational design of substrates and careful manipulation of reaction conditions, these cascade processes, catalysed by chiral diarylprolinol silyl ethers **8**, proceeded with high levels of enantioselectivity and in high yields. It was found that, in addition to the organocatalysts, the additives (acids and bases) were also important factors governing enantioselectivity, and reaction rate and yields.

The cascade Michael-aldol condensation processes also were extended to the use of carbons as nucleophiles for the initial



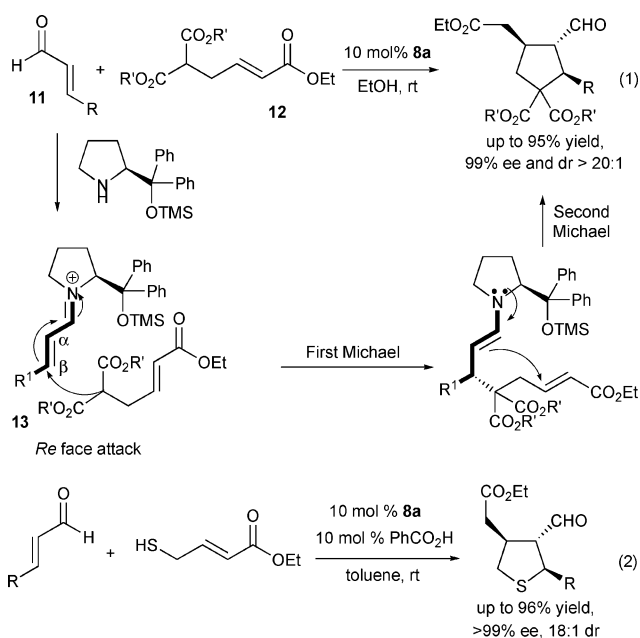
**Scheme 19** Hetero-Michael-aldol dehydration reactions catalysed by chiral diarylprolinol silyl ethers **8**.

Michael reaction.<sup>36</sup> As demonstrated by Enders and Wang respectively, readily enolisable carbon-centred nitroalkanes (Scheme 20, eqn 1)<sup>36a</sup> and malonates (eqn 2)<sup>36b</sup> were used as nucleophiles for the cascade Michael-aldol condensation reactions with the formation of two new contiguous C-C bonds.



**Scheme 20** Michael-aldol dehydration reactions catalysed by chiral diarylprolinol silyl ethers **8**.

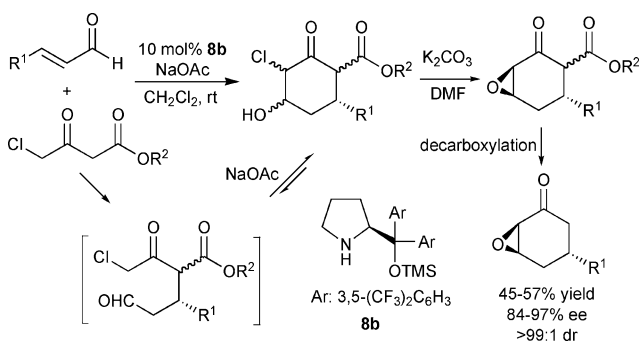
It has been envisioned that the change of the aldehyde group to an  $\alpha,\beta$ -unsaturated ester as an electrophile in a nucleophilic/electrophilic substance, would allow for a second conjugate addition reaction, producing a new cascade Michael-Michael process (Scheme 21). To this end, Wang and co-workers have recently developed catalytic double Michael cascades.<sup>37</sup> It is critical to recognise that the reactivity of the  $\alpha,\beta$ -unsaturated system in **12** participating in the second conjugate addition reaction must be high enough to allow the intramolecular Michael reaction, but lower than that of the  $\alpha,\beta$ -unsaturated iminium **13**, derived from an  $\alpha,\beta$ -unsaturated aldehyde **11** (Scheme 21, eqn 1).<sup>37a</sup> Generally, an  $\alpha,\beta$ -unsaturated ester **12** undergoes conjugate addition at a lower



**Scheme 21** Double Michael reactions catalysed by chiral diarylprolinol silyl ether **8a**.

rate than an  $\alpha,\beta$ -unsaturated aldehyde **11**, and will not interfere with the secondary amine catalyst. Furthermore, a carbon nucleophile should be active enough to only engage in the first Michael addition reaction. To address this, an enolisable malonic ester was utilised. After extensive investigation, it was found that the less hindered, linear and flexible malonate  $\alpha,\beta$ -unsaturated ester **12** could effectively participate in the organocatalytic diastereo- and enantioselective cascade double Michael reaction, whereby two C–C bonds and three contiguous stereogenic centres and a quaternary carbon centre were efficiently created in a one-pot transformation with a high control of relative and absolute stereochemistry (eqn 1). This catalytic strategy also proved to be a highly efficient and facile approach to synthetically useful, highly functionalised chiral trisubstituted tetrahydrothiophenes (eqn 2).<sup>37b</sup>

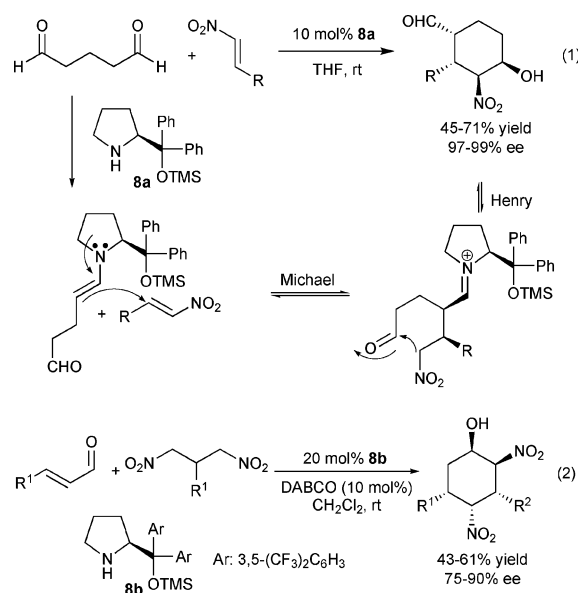
A cascade Michael–Darzens type reaction with enals using  $\gamma$ -chloro- $\beta$ -ketoesters as bifunctional nucleophilic/electrophilic molecules was developed by Jørgensen and colleagues (Scheme 22).<sup>38</sup> In the presence of organocatalyst **8b**, the ketoester attacked the **8b**-enal iminium complex to give a conjugate addition



**Scheme 22** Michael–Darzens-type reaction catalysed by chiral diarylprolinol silyl ether **8b**.

adduct, which underwent an intramolecular aldolisation under basic conditions (NaOAc). Treatment of the cyclic cyclohexanone with  $K_2CO_3$  gave rise to an epoxide. Notably, the final products after saponification and decarboxylation were obtained with high levels of enantio- and diastereoselectivity, although poor stereoselectivity was observed in the aldol cyclisation step. The high stereoselectivity of the final products was due to the reversible aldol reaction, which enabled an energetically favored diastereomer to undergo a subsequent irreversible epoxide formation process.

Very recently, Hayashi<sup>39a</sup> and Jørgensen<sup>39b</sup> have independently developed cascade Michael–Henry reactions, catalysed by diarylprolinol silyl ethers **8a** and **8b** respectively (Scheme 23). In these two approaches, two different strategies were used. Hayashi and colleagues<sup>39a</sup> used **8a** to catalyse the formation of an enamine from a 1,5-dialdehyde for a Michael addition to a nitroalkene, which underwent a subsequent intramolecular Henry reaction to afford a tetrasubstituted chiral hexane with high enantioselectivity for the major isomer among the four diastereoisomers formed (eqn 1). In contrast, Jørgensen and co-workers<sup>39b</sup> used **8b** as an activator (in the presence of DABCO) for an electrophilic enal, which was subjected to a Michael process with a dinitroalkane. The Michael adduct underwent a subsequent intramolecular Henry reaction to give pentasubstituted cyclohexanes with high stereocontrol for the major diastereomer of three isomers obtained (eqn 2).

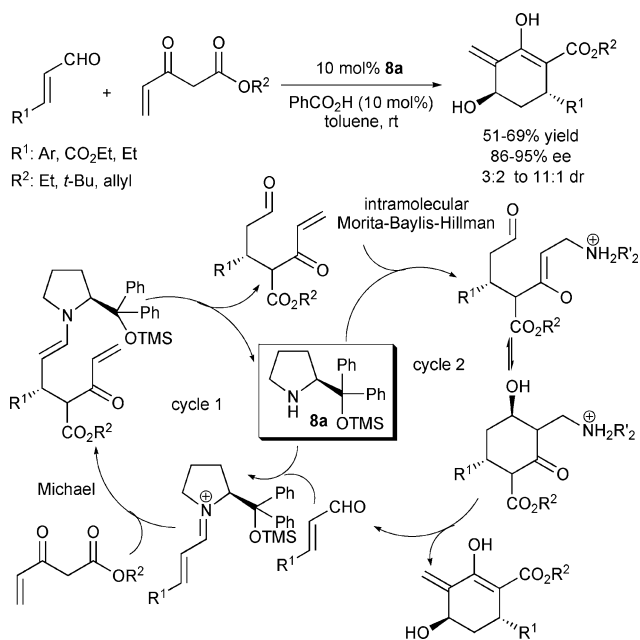


**Scheme 23** Michael–Henry reactions catalysed by chiral diarylprolinol silyl ethers **8a** and **8b**.

A novel cascade Michael–Morita–Baylis–Hillman reaction was recently explored by Jørgensen using prolinol silyl ether **8a** as the catalyst (Scheme 24).<sup>40</sup> The cascade process involved two cycles. In the first cycle, **8a**-initiated conjugate addition of a ketoester to an  $\alpha,\beta$ -unsaturated aldehyde gave rise to a Michael adduct, which served as the starting material for the second cycle, the **8a**-assisted intramolecular Morita–Baylis–Hillman reaction. Generally, good enantio- and diastereoselectivity and between moderate and good yields were obtained with a diverse array of enals and  $\beta$ -ketoesters.

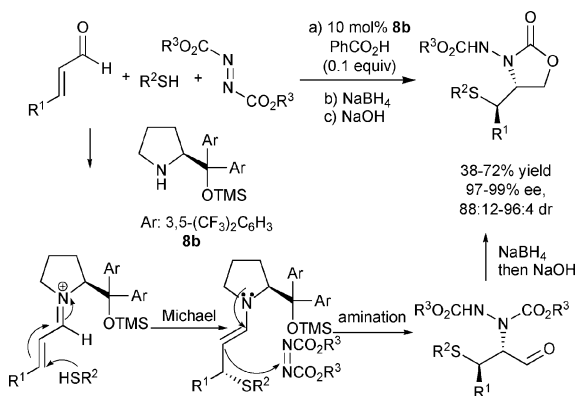
These chiral prolinol silyl ethers were also applied to multi-component cascade reactions. In 2005, Jørgensen and co-workers





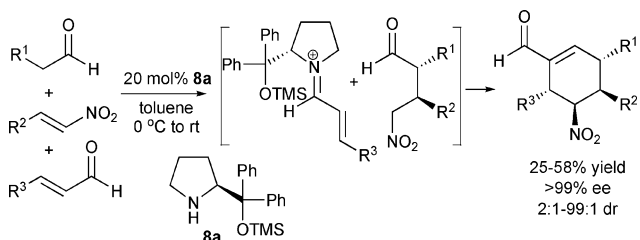
**Scheme 24** Michael–Morita–Baylis–Hillman reaction catalysed by chiral diarylprolinol silyl ether **8a**.

developed an **8b**-catalysed cascade Michael–amination process (Scheme 25).<sup>41</sup> The resulting aldehyde products were reduced to alcohols *in situ*, followed by base-catalysed lactonisation to give oxazolidinones. This cascade reaction afforded the end products with excellent enantioselectivities and good diastereoselectivities.



**Scheme 25** Multicomponent Michael–amination reaction catalysed by chiral diarylprolinol silyl ether **8b**.

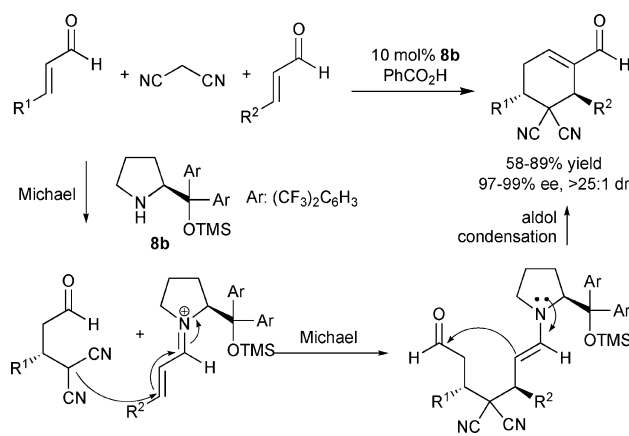
A milestone in organocatalysed cascade reactions resulted from the work by Enders and co-workers (Scheme 26),<sup>42</sup> who



**Scheme 26** Triple cascade Michael–Michael–aldol condensation reaction catalysed by chiral diphenylprolinol silyl ether **8a**.

developed a powerful three-component triple cascade process. The process involves a Michael–Michael–aldol condensation sequence (enamine–imine–enamine), catalysed by diphenylprolinol TMS ether **8a** to form tetrasubstituted cyclohexene carbaldehydes with high chemo-, regio- and stereocontrol from readily available aldehydes, nitroolefins, and enals. Remarkably, three C–C bonds and four new stereogenic centres are efficiently created in a one-pot transformation.

Using a similar approach, Jørgensen and co-workers disclosed a three-component Michael–Michael–aldol condensation process (Scheme 27).<sup>43</sup> Reaction of two different enals and a 1,3-dinitrile in the presence of catalyst **8b** afforded a highly enantioenriched cyclohexene carbaldehyde as a single diastereomer. The catalytic system was also applied to unsymmetric stabilised cyano- and nitroesters with excellent enantioselectivity, but modest yield and variable diastereoselectivity.

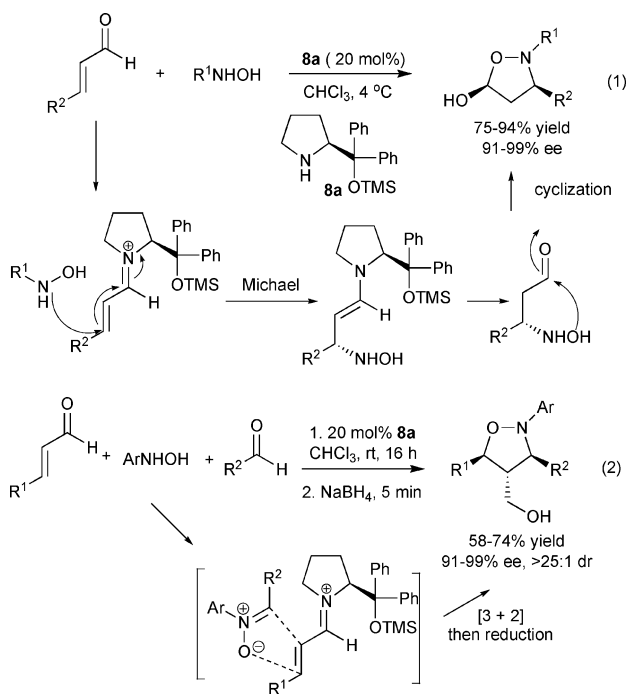


**Scheme 27** Three-component Michael–Michael–aldol condensation reaction catalysed by chiral diarylprolinol silyl ether **8b**.

Based on their previous study of **8a**-catalysed cascade aza-Michael–cyclisation reactions (Scheme 28, eqn 1),<sup>44a</sup> Córdova and co-workers extended a related approach to the synthesis of isoxazolidines, with the formation of three new stereogenic centres in a three-component one-pot transformation (eqn 2).<sup>44b</sup> It was proposed that a [3 + 2] cyclisation was involved in the reaction of **8a**-activated enals with the nitrones formed *in situ* from hydroxylamines and aldehydes.

## Conclusions

The examples described above have nicely demonstrated the power of cascade reactions promoted by chiral secondary amines. These cascade processes have provided new and highly efficient approaches to complex chiral molecular architectures from simple achiral substances. The beauty of organocatalysed cascade processes is further emphasised by the very mild reaction conditions and simple operational procedures. Moreover, it has been recognised that the cascade strategy in the construction of complex molecules is no longer just the territory of nature's enzymes. Undoubtedly, the future direction in this emerging field is to continue expanding the scope of organocatalytic cascade reactions through the identification of new modes of reactivity and the *de novo* design of substrates, and to apply these powerful strategies



**Scheme 28** Aza-Michael-cyclisation reactions catalysed by chiral diarylprolinol silyl ether **8a**.

for the efficient assembly of biologically interesting molecules, including natural products.

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