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(*S*)- and (*R*)-5-Pyrrolidin-2-yl-1H-tetrazoles: Enantiomeric Organocatalysts of Broad Utility in Organic Synthesis

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Abstract: This mini-review concerns the broad application of (*S*)- and (*R*)-5-pyrrolidin-2-yl-1H-tetrazoles as organocatalysts. A summary of methods for their synthesis is followed by a discussion of the general reaction mechanism and subsequent analysis of each reaction type for which they have proved to be efficient catalytic species. Where relevant, a comparison is made with other organocatalysts in similar asymmetric reaction processes.

Keywords: Asymmetric · Organocatalysis · Proline · Synthesis · Tetrazole

1. Introduction

The field of organocatalysis has seen an exponential increase in interest since the year 2000, when several seminal publications appeared in the literature.[1–3] In these, the inherent advantages of organocatalytic methods were already clearly illustrated: operational simplicity, high efficiency and the absence of metals in a synthetic step. As a result of this and the tremendous amount of work carried out since that time,[4] the power and use of chiral enamine intermediates has been demonstrated beyond doubt and organic chemists now have a suite of organocatalysts able to facilitate a broad range of chemical transformations.

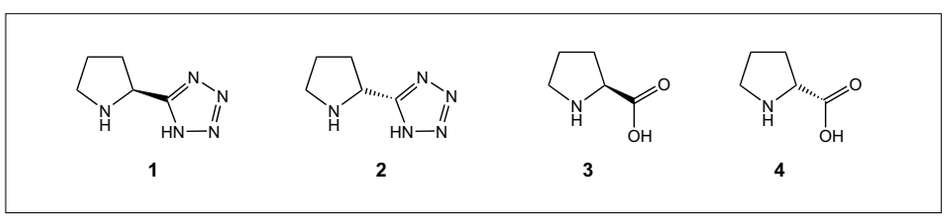

Fig. 1. (*S*)- and (*R*)-5-Pyrrolidin-2-yl-1H-tetrazoles, L- and D-prolines

It is, however, an ambitious task to do proper justice to all the pioneers in the vast field of asymmetric organocatalysis and is outside the scope of this short review article. Rather, the focus will be given to the pyrrolidinyl tetrazoles (**1** and **2**, Fig. 1), derived directly from L- and D-proline (**3** and **4**, Fig. 1) respectively, and developed as organocatalysts concurrently by ourselves, Yamamoto and Arvidsson.[5–7]

Although L-proline (**3**) was first used to catalyse an intramolecular aldol reaction in the early 1970s,[8] it has only been through the extensive recent work by List, Barbas III and others[2–4,9–12] that attention has been properly focussed on this naturally occurring privileged pyrrolidine scaffold. However, on occasion, problems can be encountered: for example, reactions may be sluggish or the enantioselectivity unacceptably low, and the solubility of proline in many conventional organic solvents can be a problem. Normally, for example, proline-mediated reactions need to be carried out in very polar solvents such as N,N-dimethylformamide and dimethylsulfoxide and it would be preferable if these could be avoided in certain situations.

In order to overcome some of the above problems, the pyrrolidinyl tetrazole **1** was synthesised since the tetrazole moiety was expected to have a similar pK_a to the carboxylic acid in proline and yet be more soluble in conventional solvents. Its potential as an organic catalyst could then be readily profiled and compared with other proline-based systems.

Below, a summary of methods for the enantioselective synthesis of this catalyst will be followed by a discussion of the general reaction mechanism and subsequent analysis of each reaction type for which it has proved to be an efficient catalyst. Where relevant, a comparison will be made with other catalysts in similar reaction processes.

2. Synthesis of (*S*)- and (*R*)-5-Pyrrolidin-2-yl-1H-tetrazole

Since both the (*S*)- and (*R*)-enantiomers, **1** and **2**, may be equally readily obtained from L- and D-proline respectively (**3** and **4**), the user is provided with a choice of which product to make in any given asym-

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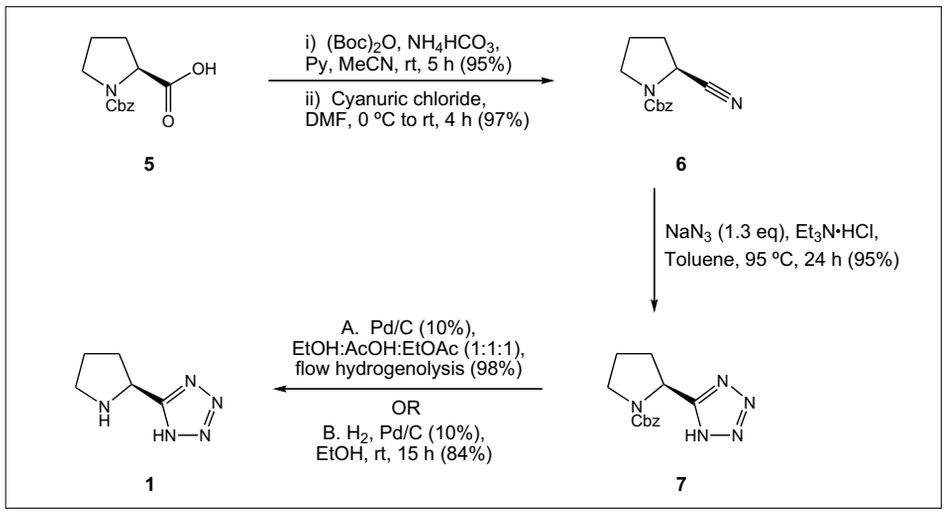
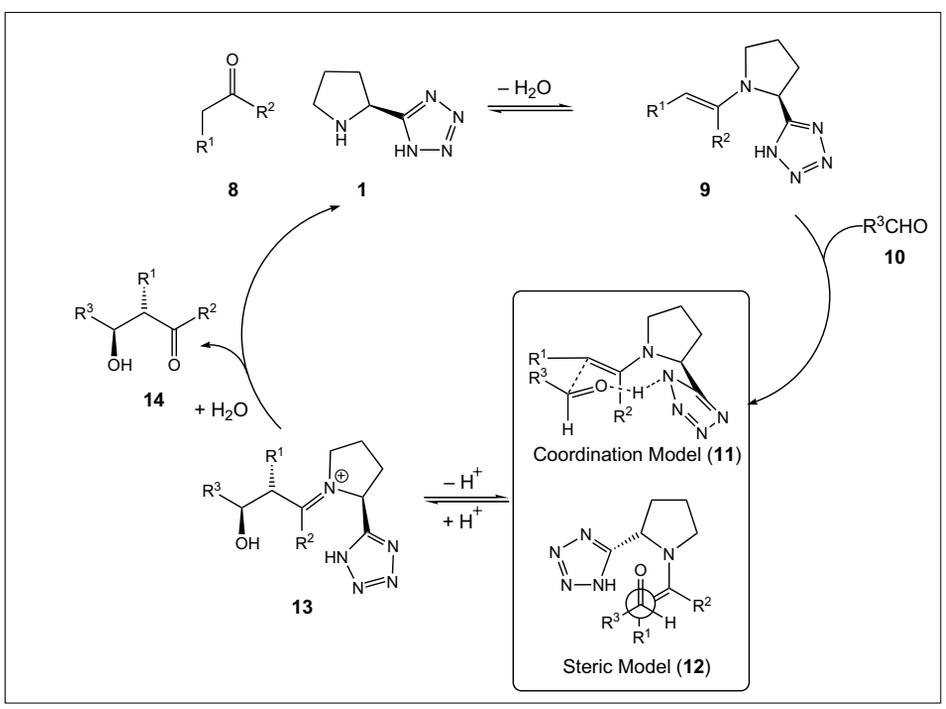
metric reaction process. However, existing methods for its safe preparation have, in the past, suffered from a number of problems.[13–15] Firstly, ammonium azide can be generated in the key, tetrazole-forming step if the reaction is mediated by ammonium chloride and sodium azide. This shock-sensitive compound can sublime onto the sides of the reaction vessel and, due to its explosive nature, is considered to be an unacceptable risk. Furthermore, when the carboxybenzyl protecting group is used, reaction times on scale in the solvent of choice for the hydrogenolysis (acetic acid/water 9:1), are extended (three days), the solvent is not especially volatile and the reaction work-up is laborious.[15] In light of these problems, a safer, more reliable procedure for the synthesis of both the (*S*)- and (*R*)-tetrazole catalysts **1** and **2** has now been developed in our group (Scheme 1), incorporating modified literature chemistry[15,16] and state-of-the-art flow hydrogenation technology for the final deprotection step (Conditions A).[17]

Firstly, Cbz-protected L-proline (**5**) was converted to its prolineamide derivative in a straightforward fashion and then dehydrated with cyanuric chloride, providing nitrile **6**. Concerning the 1,3-dipolar cycloadditon reaction, a variation of existing methods was used,[16] which avoids the generation of shock-sensitive ammonium azide. Thus, treatment of nitrile **6** with triethylamine hydrochloride and sodium azide in toluene at a one-molar concentration resulted in clean formation of the desired enantiopure cyclised tetrazole product **7**.[18]

The final step remaining in the catalyst preparation required removal of the carboxybenzyl protecting group. However, due to the problems detailed previously with the hydrogenolysis,[15] an alternative method was sought employing a flow hydrogenation process: a 0.05 M solution of protected pyrrolidinyl tetrazole **7** in an ethanol/ethyl acetate/acetic acid mixture (1:1:1) was passed through the H-Cube™ flow hydrogenator.[19] Pleasingly, in just 3.5 h, three grams of protected tetrazole **7** could be successfully hydrogenated, thus demonstrating the utility of this new flow technology and improving the deprotection conditions (Conditions A, Scheme 1). In addition, no purification was needed as evaporation of the solvent afforded pure product **1** in 98% yield. However, as the H-cube™ apparatus is not yet standard equipment in every laboratory, a more general hydrogenolysis protocol using regular laboratory equipment has also been developed (Conditions B),[20] and a straightforward trituration of the crude product gives rise to analytically pure tetrazole **1**. It is worthy of note that the chemistry of all four steps in this synthesis is both robust and scalable (reactions have been carried out on 50 g scale) and requires minimal purification, providing ready access to this important organocatalytic species.



Scheme 1. Synthesis of (*S*)-5-pyrrolidin-2-yl-1H-tetrazole



Scheme 2. Mechanism of (*S*)-5-pyrrolidin-2-yl-1H-tetrazole-mediated aldol reaction

3. Reaction Mechanism Involving Carbonyl Compounds

The pyrrolidine tetrazole derivative **1** is believed to react through an analogous mechanism and transition state type as proline (**3**). Reaction of the appropriate carbonyl compound *via* an enamine intermediate (**9**, Scheme 2) is the most widely accepted mechanism, where the incoming electrophile is coordinated to the tetrazole ring in the transition state **11**, thus providing the stereoselection found in the product **14**. Alternatively, in the steric model **12**, the tetrazole substituent serves as a bulky group, blocking the back face and providing stereoselective bias through preferential attack onto the top face of the enamine.[21] Both models provide the same stereochemical outcome but the mechanistic pathway has yet to be fully elucidated and there is still a need for further investigations to be carried out in this area. In addition, there are other factors that have an influence on the overall reaction outcome and these are detailed below in the context of each reaction type.

4. The Aldol Reaction

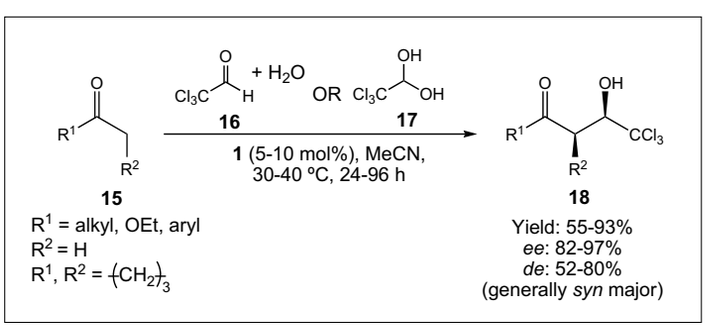
The tetrazole catalyst **1** has now been compared with proline (**3**) in a number of related aldol reaction processes and is gen-

erally comparable or superior under the reaction conditions.[6,7,15,22]

In the first report to be published concerning the asymmetric aldol reaction with pyrrolidinyl tetrazole **1** as catalyst, Yamamoto and co-workers[6] addressed the inherent problem of reacting electron-poor aldehydes, such as chloral (**16**, Scheme 3), with ketones: because these reactive aldehydes have a high affinity for water, they give the corresponding hydrates, which were previously considered unsuitable for asymmetric synthesis. However, using the tetrazole catalyst **1**, Yamamoto showed that reaction of chloral and added water with cyclopentanone proceeded very well. Remarkably, the addition of water was highly significant, since without added water, the reaction was extremely sluggish (<1% conversion after 60 h) and, as the proportion of water was increased (from 100 mol% to 200 and 500 mol%), whilst enantioselection increased (from 84% to 92% and 94% *ee*, respectively), diastereoselection decreased (from 80% to 67% and 52% *de*, respectively, *syn* major). A range of ketones was then examined in their reaction with either chloral itself (**16**) or chloral monohydrate (**17**) and generally good yields (55–93%) and enantioselectivities (82–97% *ee*), usually with *syn* diastereoselectivity, were found (Scheme 3). Other similar aldehyde acceptors were also tested and gave encouraging results (Fig. 2): for example, the monohydrate and ethanol hemiacetal of trifluoroacetaldehyde both reacted with cyclopentanone to give identical product **19** in ~65% yield, with high enantio- (94% and 92% *ee*, respectively) and diastereoselectivities (>95% *de*, *syn* major), and even aqueous formaldehyde reacted with cyclohexanones to provide excellent enantioselectivity (**20** and **21**), although the turnover number was still modest. Some of the results in this study compared well with the original L-proline-catalysed reactions of List and Barbas III,[1,9,10] but the key difference that was highlighted in this case was the enhanced reactivity of the tetrazole catalyst (**1**), leading to lower catalyst loading (5–10 mol%) and expanded substrate scope regarding the ketone component. It is also interesting to note that with usual substrates, whilst the organocatalysed aldol reaction usually produces the *anti* product as the major diastereoisomer, in this work most of the examples (with chloral (**16**) or its monohydrate (**17**)) gave the *syn* diastereoisomer as the major product.

Shortly after this publication, another followed by Arvidsson and Hartikka, which confirmed the increased reactivity and solvent scope of the tetrazole catalyst **1**,[7] most notably that reactions could now be carried out in dioxane and toluene. In addition, for all cases, in the reaction between *p*-nitrobenzaldehyde (**22**, Scheme 4) and acetone (**23**), yields (**1**: 70–93%, **3**: 36–83%) and enantiomeric excesses (**1**: 61–86%, **3**: 44–73%) were greatly improved with the (*S*)-tetrazole **1** compared with L-proline itself (**3**). In order to explain this result, NMR spectroscopic studies were carried out.[15] It has previously been established that formation of bicyclic oxazolidinones such as **25** (Fig. 3) leads to parasitic consumption of L-proline in the aldol reaction in dimethyl sulfoxide.[23] It is reasonable to expect that the carboxylic acid in L-proline (**3**) and the tetrazolic acid in **1** should have differing reactivity and accordingly, 2,2-dimethylpropionaldehyde (**26**) was reacted together with catalysts **1** and **3** respectively, in the absence of acetone (Scheme 5). Interestingly, NMR studies then showed that whereas proline (**3**) gave almost quantitative conversion to the corresponding bicyclic oxazolidinone **27**, the tetrazole analogue **28** was not observed. From this experiment, it could be concluded that the parasitic loss of L-proline (**3**) was the main reason behind the comparatively increased reactivity of **1** in dimethylsulfoxide, but it must be noted that factors related to catalyst solubility should be taken into account in other solvents (for example, proline (**3**) is much less soluble than tetrazole **1** in dichloromethane).

Further support for both the coordinated transition state (**11**, Scheme 2), as well as the improved reactivity of the (*S*)-tetrazole **1** over L-proline (**3**) arises from a density functional theory (DFT) study, carried out by Domingo and co-workers,[24] where the same reaction (Scheme 5) was executed in the presence of acetone. It was found that the formation of an intermolecular hydrogen bond between the acidic hydrogen of the tetrazole substituent and the carbonyl oxygen of the aldehyde very effectively catalyses the carbon–carbon bond formation by good stabilisation of the negative charge developing at the carbonyl oxygen during nucleophilic attack (**11**, Scheme 2). In addition, a larger charge transfer component was observed in the tetrazolic-acid-cata-



Scheme 3. Aldol reaction with chloral or chloral monohydrate

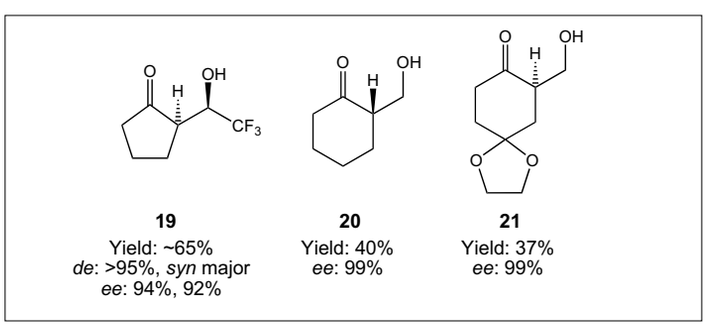
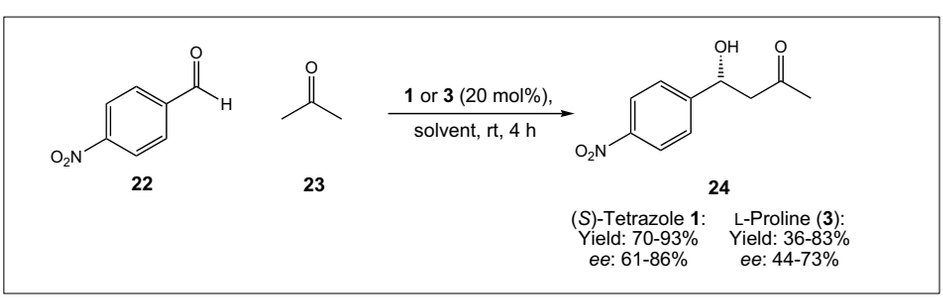


Fig. 2. Alternative aldol reaction products



Scheme 4. Direct comparison between (*S*)-tetrazole **1** and L-proline (**3**) in the aldol reaction

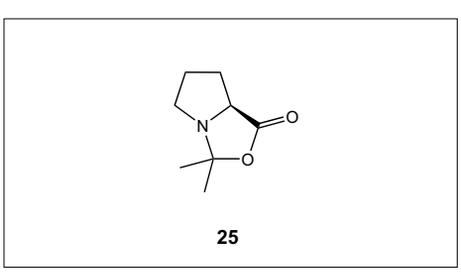
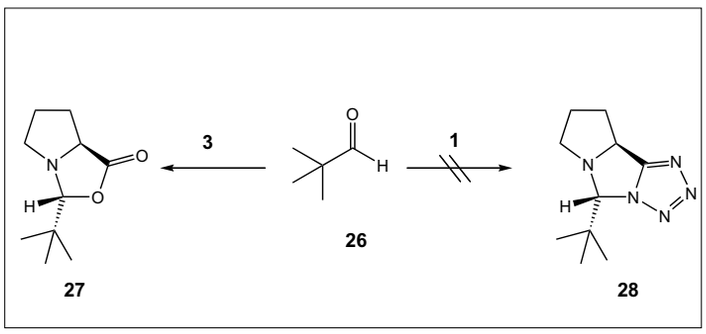
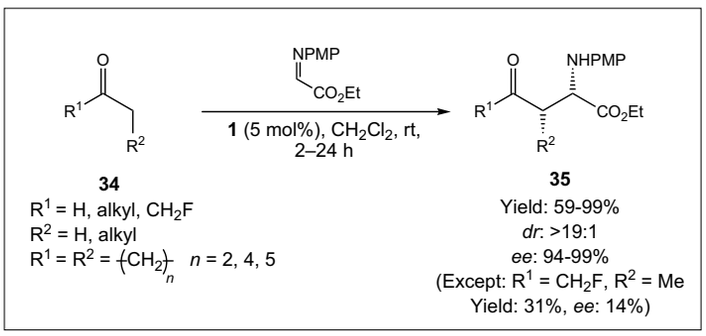


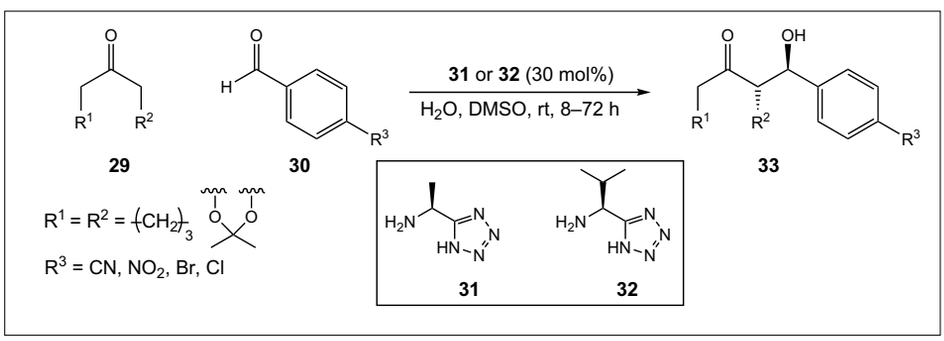
Fig. 3. Bicyclic oxazolidinone formed in the aldol reaction



Scheme 5. Parasitic consumption of L-proline catalyst



Scheme 7. Mannich reaction in dichloromethane



Scheme 6. Aldol reaction mediated by L-alanine and L-valine tetrazolic acids

lysed transition state compared to that associated with the proline-catalysed process, resulting in better solvation of the former transition state and leading to greater catalytic efficiency of the tetrazole catalyst **1**.

Recently, Córdova *et al.* have also adapted the strategy of converting other amino acids to their tetrazolic acid counterparts[25] and the results found were generally analogous to the proline case. For example, using the aldol reaction (Scheme 6), it was found that both the reactivity and solubilities of the L-alanine and L-valine tetrazole derivatives **31** and **32** were generally increased compared with the parent amino acid and, although yields and *ee*s were usually comparable, reaction times were often reduced.

5. The Mannich Reaction

The first paper to appear in the literature on the use of the tetrazole **1** as a new organocatalyst describes its application in the Mannich reaction (Scheme 7).[5] Worthy of note in this work is the observation that, during optimisation studies using cyclohexanone as the ketone substrate, reaction with (*S*)-tetrazole **1** proceeded well in dichloromethane (65% yield, >19:1 *dr*, >99% *ee*), where there was no reaction if L-proline (**3**) was employed as the catalyst, and that if the reaction time was increased from two to sixteen hours, the reaction worked well, even with a tetrazole catalyst loading of just 1 mol% in this particular solvent (70% yield, >19:1 *dr*, >99% *ee*). However, for operational simplicity on the reaction scale, 5 mol% catalyst was typically used, providing yields (generally >60%) and enantioselectivities (generally >94% *ee*) of products that were similar to their proline-catalysed counterparts in dimethylsulfoxide,[26] but with the advantage of being in a conventional reaction solvent (dichloromethane) and thus greatly facilitating reaction work-up.[5,27]

More recently, Barbas III and co-workers have reported a further use of the tetrazole catalyst **1** in an asymmetric Mannich reaction, leading to the expedient synthesis of chiral 1,2- and 1,4-diamine precursors (**39** and **40**, Scheme 8).[28] Of the catalysts tested (**1** and **3**, Fig. 1 and **41**, Fig. 4), pyrrolidinyl tetrazole **1** in dimethylsulfoxide was found to combine the most convenient length of experiment, yield and *syn*:*anti* ratio of products and was thus the catalyst of choice in this reaction process. Reaction regioselectivity was remarkably well controlled by the amine protecting group and provided access to chiral 1,2-azido amines (**39**) from azido ketones and 1,4-diamines (**40**) from phthalimido ketones.

Indeed, the reaction of azido ketones with imines in the presence of **1** afforded the 1,2-azido amine intermediates **39** with excellent yields (60–96%), good diastereomeric ratios (*syn*:*anti* = 70:30 to 91:9) and enantioselectivities up to 99%. The scope of this azido-ketone Mannich reaction also appears to be very broad, coupling a wide range of azidoketones and imines, providing the corresponding products which could be interesting substrates for subsequent 'Click' chemistry-based diversification.[29] On the other hand, the corresponding phthalimido derivatives gave 1,4-diamines **40** in good to excellent yields (41–95%) and *ee*s (57–97%), and the process overall pro-

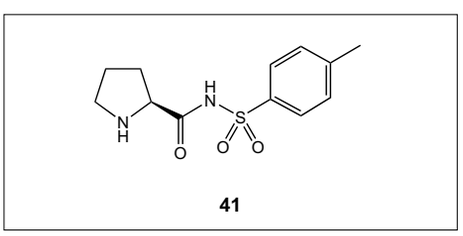
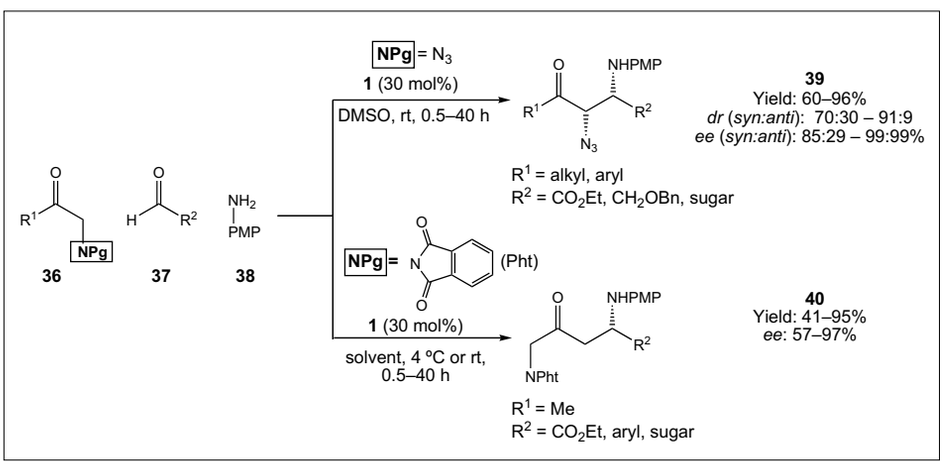
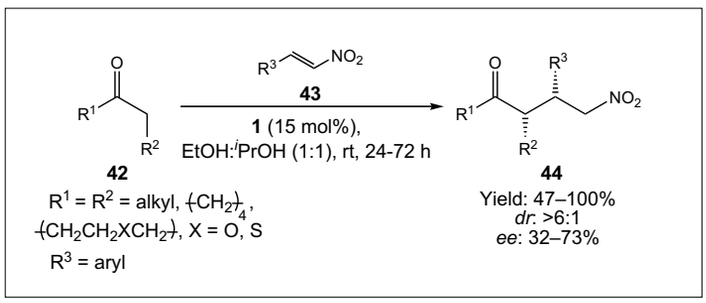


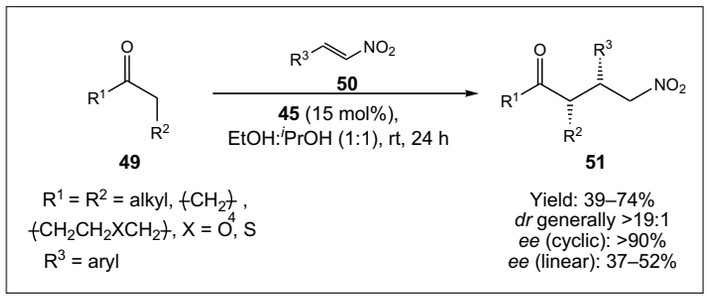
Fig. 4. (*S*)-Sulfonamide catalyst also used in the Mannich reaction



Scheme 8. Protecting group dependent regioselectivity in the Mannich reaction



Scheme 9. 1,4-Addition of ketones to nitro-olefins



Scheme 10. 1,4-Addition to nitro-olefins mediated by homo-proline tetrazole

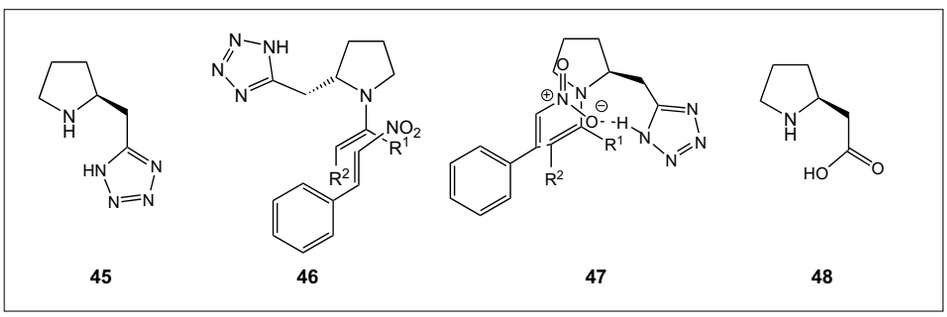


Fig. 5. Potential transition states (**46** and **47**) in the homo-proline tetrazole (**45**) mediated 1,4-addition of ketones to nitro-olefins

vides a simple and expedient access to this significant class of molecules.

6. Conjugate Additions

6.1. *1,4-Addition of Carbonyl Compounds to Nitro-olefins*

The enantioselective addition of carbonyl compounds to nitro-olefins was the second tetrazole-mediated reaction process to be investigated by our group.[27,30] At the time, there were just two publications concerning the L-proline-catalysed variant and there was a clear need to either enhance enantioselectivities or reduce reaction times.[12,31] Pyrrolidinyl tetrazole **1** was successful (Scheme 9) and dramatically improved upon the early results existing in the literature. However, although ketone loading was now significantly reduced, the enantioselection at this stage was still only moderate (73% *ee* at best) and it was thought that it could be increased by the use of homo-proline tetrazole derivative (**45**, Fig. 5)[32] as a catalyst. Depending on the model used, either steric bulk of the tetrazole moiety would be increased (**46**) due to rotation of the methylene link (thus more effectively blocking the back face of the pyrrolidine ring), or coordination generated in the hydrogen-bonded transition state would be improved (**47**). The results showed this hypothesis to be true (Scheme 10) and the yields (generally >60%) and enantioselectivities (cyclic: >90% *ee*, linear: 37–52% *ee*) demonstrated were now generally good to excellent.[33] It is also interesting to note that homo-proline itself (**48**, Fig. 5) displayed very little activity when the reaction was carried out in dimethylsulfoxide and none whatsoever in the mixed isopropanol/ethanol solvent system. Nevertheless, it has since been shown by Terakado *et al*. to give both good yields (51–95%) and enantioselectivities (42–96% *ee*) when *tert*-butanol is used as the solvent and extended reaction times (up to eight days) are employed.[34]

6.2. *1,4-Addition to Enones*

The related process, asymmetric conjugate addition of carbon nucleophiles to electron-poor alkenes (*e.g*. enones), is an important transformation in modern synthetic chemistry,[35] and both malonates and nitroalkanes are a particularly useful source of stabilised carbanions for this purpose. Also, in terms of derivatisation, dimethyl- and diethylmalonate can undergo a facile post-reaction Krapcho decarboxylation,[36] providing access to chiral mono-ester products, while the nitro group is a versatile functionality that can be readily modified, giving access to a broad range of derivatives.[37]

For the asymmetric addition of nitroalkane nucleophiles to enones, reports had previously been published and in the 1990s, for example, a proline rubidium salt was shown to catalyse the reaction with both cyclic and acyclic enones, although enantioselection was only moderate.[38] Subsequently, Hanessian and Pham improved the enantioselectivity for cyclic systems only (62–93% *ee*) using L-proline (**3**) as the catalyst,[39] while the Jørgensen group exploited their imidazoline catalyst (**52**, Fig. 6) for acyclic systems.[40] However, although enantioselectivity was improved (34–86% *ee*), toxic nitroalkane substrates were used in vast excess and long reaction times were generally required. Therefore, in 2005, the prospect of using the (*S*)-tetrazole **1** for the asymmetric conjugate addition of nitroalkanes to α,β-unsaturated enones was investigated. It was indeed shown to be a more general catalyst both for cyclic and acyclic α,β-unsaturated enones,[41] providing good to excellent yield (40–96%) and enantioselectivity (42–98% *ee*) (Scheme 11). Concurrently, using another tetrazolic acid catalyst (**53**, Fig. 6), Jørgensen and co-workers[42] showed that good results (82–97% yield, generally >80% *ee*) were found for a broad range of aromatic substrates and in a more recent publication by Hanessian *et al.*, using a cyclopropane proline analogue (**54**, Fig. 6), still further improvements have been made to this reaction.[43]

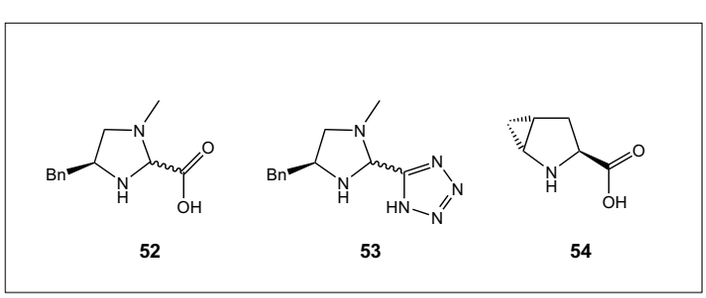
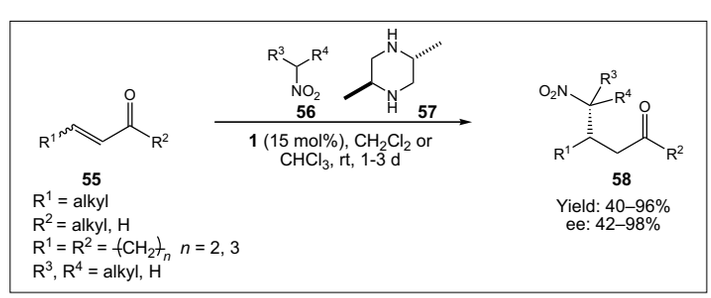
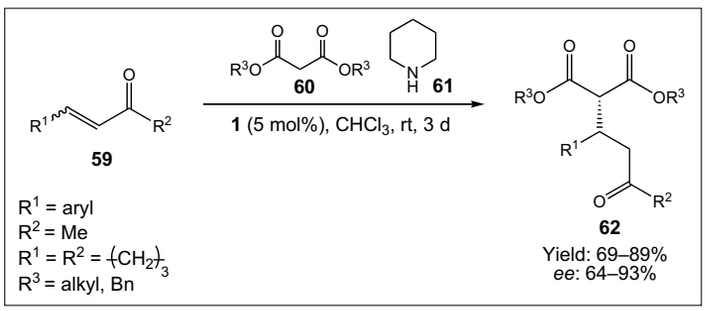


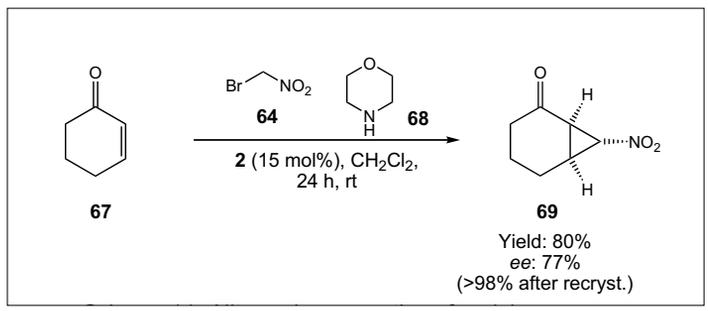
Fig. 6. 1,4-Addition catalysts



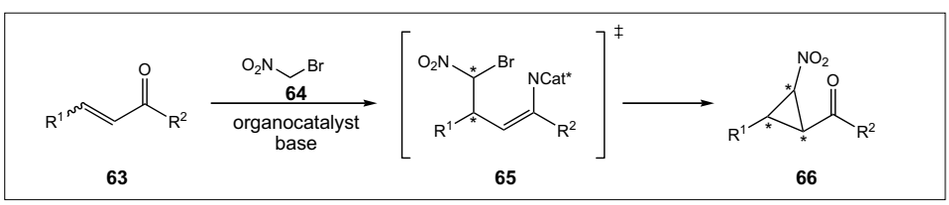
Scheme 11. 1,4-Addition of nitroalkanes to enones



Scheme 12. 1,4-Addition of malonates to enones



Scheme 14. Nitrocyclopropanation of cyclohexenone



Scheme 13. Principle behind the nitrocyclopropanation reaction

Subsequently, in connection with an on-going synthesis project in our group, a scalable method was required for asymmetric addition of malonates to cyclohexenone. Therefore, the opportunity was taken to test the (*S*)-tetrazole **1** as a catalyst for this type of reaction and compare it with the existing organocatalytic methods.[44] Following optimisation of the conditions, good results were indeed found for a range of substrates (Scheme 12), furnishing the products in generally high yields (69–89%) with good to high enantioselectivities (64–93% *ee*).[45] Also, in contrast to existing methods, an external organic base was used and additionally, employment of a vast excess of enone, common to other procedures, was no longer necessary. Consequently, the process was practical to operate and readily scaled.

6.3. *Nitrocyclopropanation*

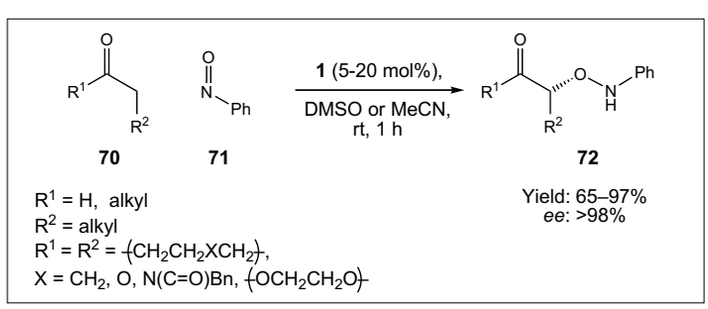
Given that the conjugate addition reactions proceeded well, an extension of these concepts suggested that an unsaturated carbonyl compound should react with bromonitromethane (**64**) in the presence of the tetrazole catalyst (Scheme 13): through conjugate addition and subsequent displacement of the bromide, an enantioselective nitrocyclopropanation would ensue, generating three new stereogenic centres in a single operation. Interestingly, in the literature at that time, there was only one example of a one-step enantioselective nitrocyclopropanation reaction,[46] which is surprising due to the potential utility of these compounds in synthesis.[37]

Following considerable investigation, the reaction was successful and optimisation was carried out using cyclohexenone (**67**) as the substrate (Scheme 14):[47] the reaction was scalable and a single recrystallisation took the initial 77% *ee* up to >98%. Unfortunately however, with other substrates such as the corresponding five- and seven-membered ring congeners, while yields of product were high (73% and 93%, respectively), enantioselectivities were not as good (40% and 35% *ee*, respectively). However, more recent work on both cyclic and acyclic systems in our group is more promising, leading to nitrocyclopropanation products with *ee*s in excess of 70%[48] and the potential for this to become a reaction process of general utility.

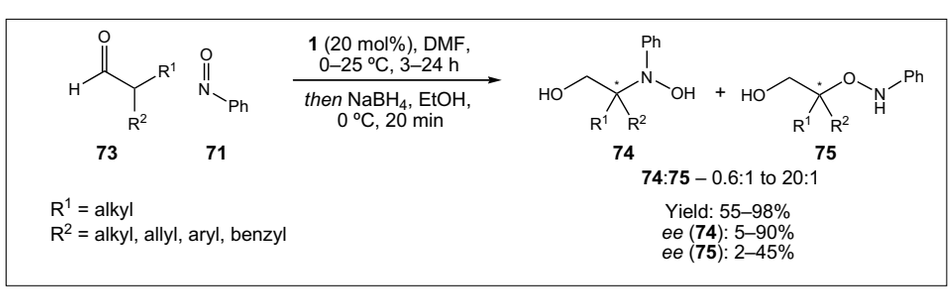
7. α-Oxyamination and α-Oxidation

The Yamamoto group was the first to publish work on the use of pyrrolidinyl tetrazole catalyst **1** for the α-oxyamination of aldehydes and ketones[14,49] (Scheme 15). Reaction of the substrate with nitrosobenzene (**71**) in the presence of just 5–20 mol% catalyst for one hour provided both high enantioselection (>98% *ee*) and reaction yields (65–97%). Of course, in these reactions it is possible to obtain two products (from attack at either oxygen or nitrogen atoms) and in a later investigation by Kim and Park,[50] the authors used biased substrates so as to influence the reaction outcome: in this case, α-branched aldehydes (**73**, Scheme 16), rather than the linear examples of Yamamoto, were used. It was thought that, due to steric repulsion between the α-alkyl group of the enamine and the phenyl group of nitrosobenzene (**76**, Fig. 7), the attack might be directed to the nitrogen (**77**) and furnish α,α'-disubstituted amino aldehydes and alcohols. Overall, mixtures of products were generally formed but interestingly, the *ee* of the nitrogen attack product (**74**, Scheme 16, 5–90% *ee*) was always substantially higher than that of the oxygen attack product (**75**, 2–45% *ee*).

Together with a large group of other organocatalytic species, the tetrazole derivative **1** has now also been examined in the direct α-oxidation of ketones and aldehydes with alternative oxidant species



Scheme 15. α-Oxyamination of ketones and aldehydes



Scheme 16. α-Hydroxyamination vs α-oxyamination of aldehydes

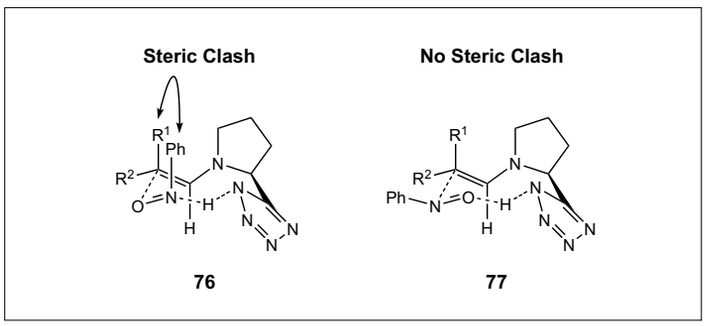
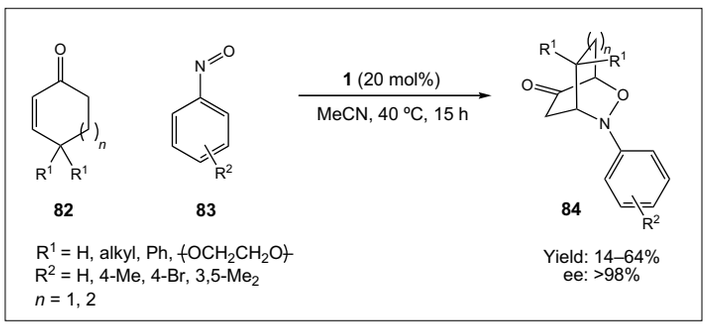
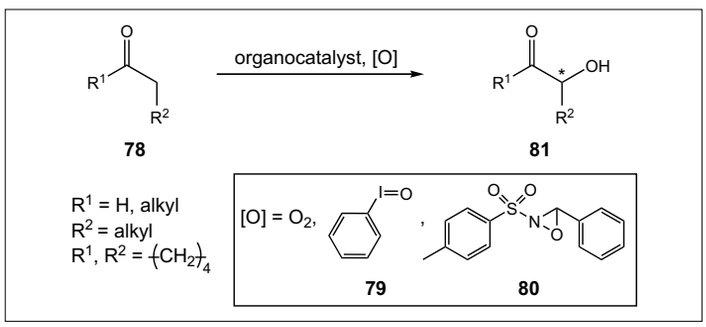


Fig. 7. Postulated transition states in the α-oxyamination *vs* α-hydroxyamination procedure



Scheme 18. Tandem α-oxyamination/Michael reaction



Scheme 17. Direct α-oxidation of aldehydes and ketones

(Scheme 17). Using either molecular oxygen,[51] iodosobenzene (**79**) or N-sulfonyloxaziridine **80**,[52] it does indeed function as a useful catalyst. However, in the case of molecular oxygen, L-alanine was found to be the best organocatalyst out of the range examined (93% yield, 56% *ee* compared with tetrazole **1**: 97% yield, <5% *ee*) and using iodosobenzene (**79**), only traces of product were formed when **1** was employed as the catalyst (compared with L-proline: 32% yield, 65% *ee*). In the case of the N-sulfonyloxaziridine **80**, however, although the tetrazole **1** provided good yields (up to 92%), the enantioselectivities were unacceptably low (around 20% *ee*) and again, it was not the catalyst of choice.

This raises a valid general point regarding the area of organocatalysis: optimisation is generally very catalyst-specific. The reaction conditions which prove optimum for one catalytic species are often not the best for another,[53] and therefore, with some optimisation studies concerning just solvent and temperature, the yields and enantioselectivities provided by tetrazole catalyst **1** could be improved.

8. Tandem Reactions

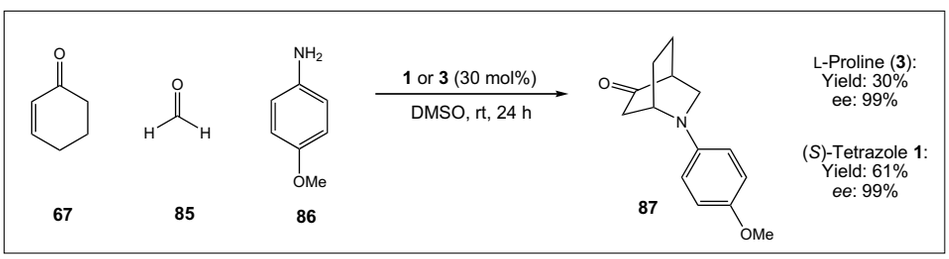
The first example of a tandem reaction carried out under the influence of pyrrolidinyl tetrazole **1** was published by Yamamoto *et al.* in 2004.[54] A highly enantioselective approach (>98% *ee*) for the synthesis of nitroso Diels-Alder adducts (**84**, Scheme 18) was realised *via* a tandem α-oxyamination/Michael reaction sequence and the results disclosed considerably improved the regio- and stereoselectivity of this process.[54,55] The same reaction catalysed by L-proline (**3**) was also examined but although the products provided 98–99% *ee*, yields were less than 40%,[54] proving the tetrazole **1** once again to be the better catalyst. Similarly, in initial investigations into formation of aza-Diels-Alder adducts (Scheme 19), Córdova and co-workers showed that the pyrrolidinyl tetrazole derivative **1** provided a better result (61% yield, 99% *ee*) than L-proline itself (**3**) (30% yield, 99% *ee*) at room temperature,[56] in reaction with the cyclohexenone substrate. However, probably due to its subsequent lower activity in the reaction of the cycloheptanone congener (20% yield and 96% *ee* compared with L-proline (**3**): 75% yield, 98% *ee*), it was not used in the remainder of the study.

Later, in 2005, we described a new organocatalytic route to chiral dihydro-1,2-oxazines (Scheme 20).[57,58] An α-oxyamination reaction with nitrosobenzene (**71**), followed by nucleophilic attack on a vinyl phosphonium salt subsequently forms a dihydro-1,2-oxazine **92** through an intramolecular Wittig process. This reaction sequence affords the chiral products from achiral aldehydes and ketones and proceeds in moderate to excellent yields (33–82%) and excellent enantioselectivities (>99% *ee*) over the two steps (Scheme 21). Substituted vinyl phosphonium salts could be employed, providing highly substituted products and matched/mismatched effects were investigated using citronellal as the chiral aldehyde: although yields were similar, diastereoselectivity did differ with a diastereomeric excess of only 83% in the mismatched compared with 99% in the matched case.[57] Cleavage of the N–O bond was also accomplished in high yields (83–100%), using zinc in methanolic hydrogen chloride, thus also demonstrating the potential of the reaction to provide *cis*-allylic amino alcohols (**94**), which have further potential as chiral building blocks in organic synthesis.

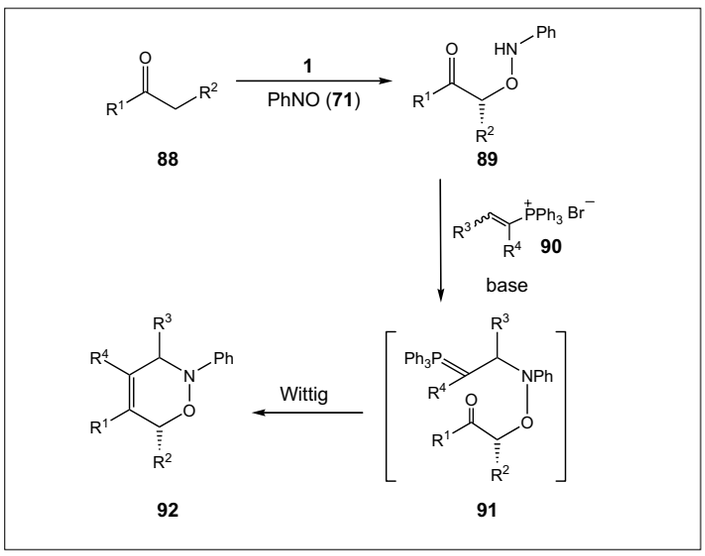
In an extension to this work, chiral 3,6-dihydropyridazines (**98**, Scheme 22) have now been synthesised from aldehydes[59] and ketones[60] and work is ongoing towards demonstrating the general utility of this method in total synthesis.

9. Application in Total Synthesis

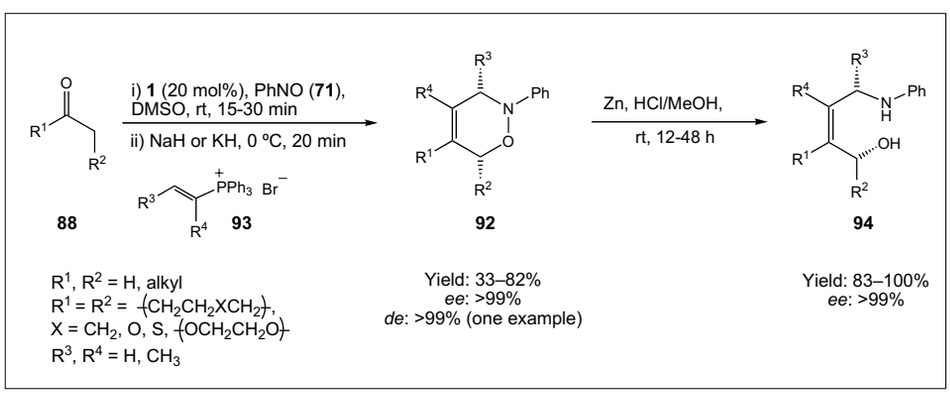
Application of any organocatalyst in multi-step synthesis is still in its infancy,[9,61] yet likely to be of major importance in the future. To our knowledge, there are



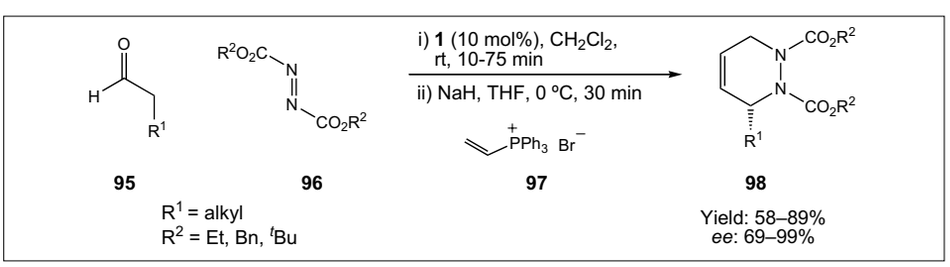
Scheme 19. Aza-Diels-Alder reaction



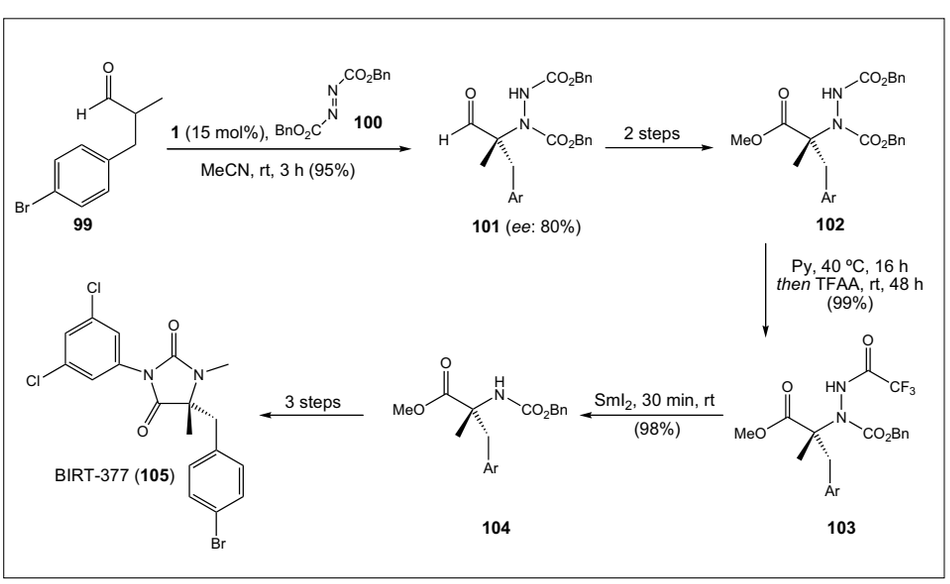
Scheme 20. Mechanism of dihydro-1,2-oxazine formation



Scheme 21. Organocatalytic route to chiral 1,2-oxazines



Scheme 22. Synthesis of chiral 3,6-dihydropyridazines



Scheme 23. Synthesis of BIRT-377 (**105**)

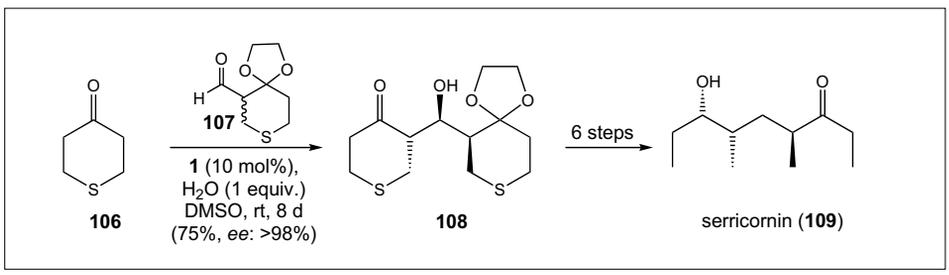
just two publications that demonstrate the use of pyrrolidinyl tetrazole **1** as a catalyst in total synthesis programmes, by Chowdari and Barbas III[62] and Ward *et al.*,[63] respectively. In the former, a catalytic, enantioselective total synthesis of cell adhesion inhibitor BIRT-377 (**105**, Scheme 23) was described. The quarternary stereocentre was constructed through a direct proline-tetrazole-catalysed asymmetric α-amination (**99** → **101**) and in the course of the studies, a one-pot selective benzyloxycarbonyl deprotection/trifluoroacetylation method was developed (**102** → **103**). This provided the key intermediate **103**, which then underwent a smooth samarium-diiodide-mediated nitrogen–nitrogen bond cleavage, furnishing unnatural amino acid derivative **104**, which gave BIRT-377 (**105**) in just three more steps and overall 51% yield from aldehyde **101**.

In the more recent work,[63] the synthesis of serricornin (**109**, Scheme 24), a sex pheromone produced by the female cigarette beetle, is described in just seven steps from readily available mono-protected dicarbonyl **107**. Ward *et al.* had originally been developing stereoselective aldol reactions of **106** and **107** as the foundation for a thiopyran-based synthetic route to polypropionates, using traditional metal bases in the transformation.[64] In an extension of this method, they recently reported that L-proline (**3**) catalyses the enantioselective direct aldol reaction of **106** with (±)-**107**:[65] because the organocatalysed isomerisation of the aldehyde is faster than the aldol process, dynamic kinetic resolution occurs to give adduct **108** (56% yield, >98% *ee*). However, the yield was rather low, probably due to parasitic consumption of catalyst **3** and, on a scale larger than one gram, the reaction work-up was complicated by the need to remove large amounts of unreacted **106** by either sublimation or chromatography: all attempts to reduce the amount used in the reaction gave product **108** in lower yield and/or enantioselectivity.

Therefore, the authors focussed on the use of the more soluble tetrazole analogue **1** and pleasingly, with only two equivalents of **106**, they found that a 75% yield and >98% *ee* could be obtained when the reaction was run at high concentration.[63] This thus represented a greatly improved synthesis of key intermediate **108**, allowing for the provision of enough material to complete the synthesis.

10. Conclusions

The whole area of asymmetric organocatalysis has now blossomed into a very fruitful component of modern organic synthesis and the application of organocatalysts, par-



Scheme 24. Synthesis of serricornin (**109**)

ticularly in tandem reaction sequences, is poised to have a very significant impact on the way synthesis will be conducted in the future. In this context, it is clear then that pyrrolidinyl tetrazole **1**, already proven to be of great utility in bringing about useful chemical transformations, is a valuable addition to the suite of effective organocatalysts now available.

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[1] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874.

[2] B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336; T. Bui, C. F. Barbas III, *Tetrahedron Lett*. **2000**, *41*, 6951.

[3] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386.

[4] For a comprehensive book concerning this area, see: 'Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis', Eds. A. Berkessel, H. Groger, Weinheim: Wiley-VCH, **2005**; For a selection of leading reviews in the area, see: B. List, *Synlett* **2001**, 1675; B. List, *Tetrahedron* **2002**, *58*, 5573; E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481; W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res*. **2004**, *37*, 580; P. I. Dalko, L. Moisan, *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; J. M. Janey, *Angew. Chem., Int. Ed.* **2005**, *44*, 4292; Y. Hayashi, *J. Synth. Org. Chem. Jpn.* **2005**, *63,* 464; J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719; M. Limbach, C*hem. Biodiv.* **2006**, *3*, 119; B. List, *Chem. Commun.* **2006**, *819*; G. Guillena, D. J. Ramon, *Tetrahedron: Asymmetry* **2006**, *17*, 1465; M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, *45*, 4305. See also special issues on organocatalysis: *Acc. Chem. Res*. **2004**, *37*, issue 8; *Adv. Synth. Catal.* **2004**, *346*, issues 9-10.

[5] A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558.

[6] H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem., Int. Ed.* **2004**, *43*, 1983.

[7] A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831.

[8] U. Eder, G. Sauer, R. Wiechert, German Patent DE 2014757 **1971**; Z. G. Hajos, D. R. Parrish, German Patent DE 2102623 **1971**; U. Eder, G. Sauer, R. Wiechert, *Angew. Chem., Int. Ed. Engl*. **1971**, *10*, 496; Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615.

[9] B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573.

[10] K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260.

[11] W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199; A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, *620*; N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254; Y. Sekiguchi, A. Sasaoka, A. Shimomoto, S. Fujioka, H. Kotsuki, *Synlett* **2003**, 1655.

[12] D. Enders, A. Seki, *Synlett* **2002**, 26.

[13] J. M. McManus, R. M. Herbst, *J. Org. Chem.* **1959**, *24*, 1643; Z. Grzonka, B. Liberek, *Roczniki Chemii* **1971**, *45*, 967; Z. Grzonka, B. Liberek, *Tetrahedron* **1971**, *27*, 1783; Z. Grzonka, E. Gwizdala, T. Kofluk, *Pol. J. Chem.* **1978**, *52*, 1411; R. G. Almquist, W.-R. Chao, C. Jennings-White, *J. Med. Chem*. **1985**, *28*, 1067.

[14] N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5374.

[15] A. Hartikka, P. I. Arvidsson, *Eur. J. Org. Chem.* **2005**, 4287.

[16] K. Koguro, T. Oga, S. Mitsui, R. Orita, *Synthesis* **1998**, 910; A. W. Bridge, R. H. Jones, H. Kabir, A. A. Kee, D. J. Lythgoe, M. Nakach, C. Pemberton, J. A. Wrightman, *Org. Proc. Res. Dev*. **2001**, *5*, 9.

[17] V. Franckevičius, K. Rahbek Knudsen, M. Ladlow, D. A. Longbottom, S. V. Ley, *Synlett* **2006**, 889.

[18] For an alternative cyclisation method to form the tetrazole ring system, see: G. Sedelmeier, International Patent WO 2005/014602 A1 **2005**; G. Sedelmeier, V. Aurregi, International Patent WO 2007/009716 **2007**.

[19] For further information, please refer to the product details on the company website: *http://thalesnano.com*. Address: Thales Nanotechnology, 1031 Budapest, Zahony ucta 7 (Graphisoft Park), Hungary. Fax: +36 1 6666190; Tel.: +36 1 6666100.

[20] V. Aureggi, V. Franckevičius, M. O. Kitching, S. V. Ley, D. A. Longbottom, A. J. Oelke, G. Sedelmeier, *Org. Synth.* **2007**, submitted.

[21] The aldol reaction is shown in Scheme 2 but other enamine-mediated reaction processes are thought to proceed *via* analogous transition states.

[22] R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 3541; J. T. Suri, D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 1383; J. T. Suri, S. Mitsumori, K. Albertshofer, F. Tanaka, C. F. Barbas III, *J. Org. Chem.* **2006**, *71*, 3822; C. Grondal, D. Enders, *Tetrahedron* **2006**, *62*, 329; S. Samanta, C.-G. Zhao, *Tetrahedron Lett.* **2006**, *47*, 3383.

[23] D. Seebach, M. Boes, R. Naef, W. Bernd Schweizer, *J. Am. Chem. Soc*. **1983**, *105*, 5390; B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5839.

[24] M. Arnó, R. J. Zaragozá, L. R. Domingo, *Tetrahedron: Asymmetry* **2005**, *16*, 2764.

[25] A. Córdova, W. B. Zou, P. Dziedzic, I. Ibrahem, E. Reyes, Y. M. Xu, *Chem. Eur. J.* **2006**, *12*, 5383.

[26] A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842.

[27] A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84.

[28] N. S. Chowdari, M. Ahmad, K. Albertshofer, F. Tanaka, C. F. Barbas III, *Org. Lett*. **2006**, *8*, 2839.

[29] Z. P. Demko, K. B. Sharpless, *Angew. Chem., Int. Ed*. **2002**, *41*, 2113.

[30] A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808.

[31] B. List, P. Pojarliev, H. J. Martin, *Org. Lett*. **2001**, *3*, 2423.

[32] C. E. T. Mitchell, A. J. A. Cobb, S. V. Ley, *Synlett* **2005**, 611.

[33] For related publications using alternative catalytic species, see: O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147; J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Synthesis* **2004**, 1509; T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558; D. Enders, S. Chow, *Eur. J. Org. Chem*. **2006**, 4578; N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc*. **2006**, *128*, 4966; S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451; Y. Xu, W. Zou, H. Sundén, I. Ibrahem, A. Córdova, *Adv. Synth. Catal*. **2006**, *348*, 418; Y. Xu, A. Córdova, *Chem. Commun*. **2006**, 460; D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Adv. Synth. Catal*. **2006**, *348*, 826; M. K. Zhu, L. F. Cun, A. Q. Mi, Y. Z. Jiang, L. Z. Gong, *Tetrahedron: Asymmetry* **2006**, *17*, 491.

[34] D. Terakado, M. Takano, T. Oriyama, *Chem. Lett.* **2005**, *34*, 962.

[35] M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033; N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171.

[36] A. P. Krapcho, *Synthesis* **1982**, 805; A. P. Krapcho, *Synthesis* **1982**, 893.
[37] R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933.
[38] M. Yamaguchi, T. Shiraishi, Y. Igarashi, M. Hirama, *Tetrahedron Lett.* **1994**, *35*, 8233; M. Yamaguchi, Y. Igarashi, R. S. Reddy, T. Shiraishi, M. Hirama, *Tetrahedron* **1997**, *53*, 11223.
[39] S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975.
[40] N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem*. **2002**, *67*, 8331.
[41] C. E. T. Mitchell, S. E. Brenner, S. V. Ley, *Chem. Commun.* **2005**, 5346; C. E. T. Mitchell, S. E. Brenner, J. García-Fortanet, S. V. Ley, *Org. Biomol. Chem.* **2006**, *4*, 2039.
[42] A. Prieto, N. Halland, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 3897.
[43] S. Hanessian, Z. Shao, J. S. Warrier, *Org. Lett*. **2006**, *8*, 4787.
[44] A. Kawara, T. Taguchi, *Tetrahedron Lett*. **1994**, *35*, 8805; M. Yamaguchi, T. Shiraishi, M. Hirama, *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176; M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem*. **1996**, *61*, 3520; N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2003**, *42*, 661; T. Ooi, D. Ohara, K. Fukumoto, K. Maruoka, *Org. Lett*. **2005**, *7*, 3195.
[45] K. Rahbek Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun.* **2006**, 66.
[46] S. Arai, K. Nakayama, T. Ishida, T. Shioiri, *Tetrahedron Lett.* **1999**, *40*, 4215; the following publication was published as reference [47] was in proof: S. H. McCooey, T. McCabe, S. J. Connon, *J. Org. Chem.* **2006**, *71*, 7494.
[47] H. M. Hansen, D. A. Longbottom, S. V. Ley, *Chem. Commun*. **2006**, 4838.
[48] V. Wascholowski, Unpublished results **2007**.
[49] For prior work in this area, using L-proline (**3**) as the catalyst, see: S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; G. Zhong, *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293; Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem., Int. Ed.* **2004**, *43*, 1112; Y. Hayashi, J. Yamaguchi, T. Sumiya, K. Hibino, M. Shoji, *J. Org. Chem*. **2004**, *69*, 5966; A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem., Int. Ed.* **2004**, *43*, 1109.
[50] S. G. Kim, T. H. Park, *Tetrahedron Lett.* **2006**, *47*, 9067.
[51] H. Sundén, M. Engqvist, J. Casas, I. Ibrahem, A. Córdova, *Angew. Chem., Int. Ed.* **2004**, *43*, 6532.
[52] M. Engqvist, J. Casas, H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 2053.
[53] For a selection of publications where the pyrrolidinyl tetrazole (**1**) was examined but not found to be the catalyst of choice under the given reaction conditions, see: I. Ibrahem, J. Casas, A. Córdova, *Angew. Chem., Int. Ed.* **2004**, *43*, 6528; D. D. Steiner, N. Mase, C. F. Barbas III, *Angew. Chem., Int. Ed*. **2005**, *44*, 3706; H. Sundén, N. Dahlin, I. Ibrahem, H. Adolfsson, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 3385; R. Dodda, C.-G. Zhao, *Org. Lett.* **2006**, *8*, 4911; S. Samanta, C. G. Zhao, *J. Am. Chem. Soc.* **2006**, *128*, 7442; I. Ibrahem, W. Zou, J. Casas, H. Sundén, A. Córdova, *Tetrahedron* **2006**, *62*, 357.
[54] Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962.
[55] M. Momiyama, Y. Yamamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 1190.
[56] H. Sundén, I. Ibrahem, L. Eriksson, A. Córdova, *Angew. Chem., Int. Ed.* **2005**, *44*, 4877.
[57] S. Kumarn, D. M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Lett.* **2005**, *7*, 4189.
[58] S. Kumarn, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2006**, 3211.
[59] A. J. Oelke, S. Kumarn, D. A. Longbottom, S. V. Ley, *Synlett* **2006**, 2548.
[60] A. J. Oelke, unpublished results **2007**.
[61] For examples of the use of organocatalysis in the synthesis of natural products or medicinally active compounds, see: D. Enders, A. Lenzen, M. Müller, *Synthesis* **2004**, 1486; H. F. Du, D. B. Zhao, K. L. Ding, *Chem. Eur. J*. **2004**, *10*, 5964; S. G. Kim, J. Kim, H. Jung, *Tetrahedron Lett.* **2005**, *46*, 2437; Y. Hayashi, T. Urushima, M. Shin, M. Shoji, *Tetrahedron* **2005**, *61*, 11393; S. Zhang, W. Duan, W. Wang, *Adv. Synth. Catal.* **2006**, *348*, 1228; S.-G. Kim, T.-H. Park, B. J. Kim, *Tetrahedron Lett.* **2006**, *47*, 6369; G. Luppi, M. Monari, R. J. Corrêa, F. D. Violante, A. C. Pinto, B. Kaptein, Q. B. Broxterman, S. J. Garden, C. Tomasini, *Tetrahedron* **2006**, *62*, 12017; S. P. Kotkar, A. Sudalai, *Tetrahedron: Asymmetry* **2006**, *17*, 1738; S. Brandau, A. Landa, J. Franzén, M. Marigo, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2006**, *45*, 4305; S. P. Kotkar, A. Sudalai, *Tetrahedron Lett.* **2006**, *47*, 6813; S. Umbreen, M. Brockhaus, H. Ehrenberg, B. Schmidt, *Eur. J. Org. Chem.* **2006**, 4585; T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett.* **2006**, *8*, 1533; J. Yamaguchi, M. Toyoshima, M. Shoji, H. Kakeya, H. Osada, Y. Hayashi, *Angew. Chem., Int. Ed.* **2006**, *45*, 789; D. Enders, M. Vrettou, *Synthesis* **2006**, 2155.
[62] N. S. Chowdari, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 867.
[63] D. E. Ward, V. Jheengut, G. E. Beye, *J. Org. Chem.* **2006**, *71*, 8989.
[64] D. E. Ward, C. C. Man, C. Guo, *Tetrahedron Lett.* **1997**, *38*, 2201; D. E. Ward, C. Guo, P. K. Sasmal, C. C. Man, M. Sales, *Org. Lett.* **2000**, *2*, 1325; D. E. Ward, M. Sales, C. C. Man, J. H. Shen, P. K. Sasmal, C. Guo, *J. Org. Chem*. **2002**, *67*, 1618; D. E. Ward, H. M. Gillis, O. T. Akinnusi, M. A. Rasheed, K. Saravanan, P. K. Sasmal, *Org. Lett.* **2006**, *8*, 2631.
[65] D. E. Ward, V. Jheengut, O. T. Akinnusi, *Org. Lett.* **2005**, *7*, 1181.