

Organocatalysed asymmetric Mannich reactions

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The asymmetric Mannich reaction ranks among the most potent enantioselective and diastereoselective C–C-bond forming reactions. In recent years, organocatalysed versions of asymmetric Mannich processes have been increasingly reported and used in a rapidly growing number of applications. This *tutorial review* provides an overview of the recent history of the asymmetric organocatalysed Mannich reaction, including scope and limitations, and application of different catalyst systems.

1 Introduction

Approximately one decade ago, asymmetric organocatalysis was reinvented as a viable approach for producing enantio-merically pure compounds. While for a long time only isolated cases existed, by the end of the last century numerous successful examples of asymmetric organocatalytic reactions had been developed.¹ In this tutorial review we aim to address organocatalytic versions of the well-known Mannich reaction in particular.² A key element in Mannich reactions is an iminium intermediate **2**, which is susceptible to nucleophilic attack by a variety of nucleophiles such as enolised ketones (**1**) or equivalents thereof, resulting in carbon–carbon bond formation adjacent to the nitrogen atom (Scheme 1).

The products, so-called Mannich bases (**3**), are 1,3-amino ketones, which are versatile intermediates in organic synthesis and have especially proven their value in the synthesis of

alkaloids. This type of conversion by now has also been firmly established as a viable approach to prepare the same products in enantio- and diastereomerically pure form *via* organocatalysis.^{3,4} Several organocatalytic approaches will be reviewed, which can be divided in catalysis by (i) chiral amines (*via* enamine formation), (ii) chiral Brønsted bases, and (iii) chiral Brønsted acids.

2 Catalysis by enamine-forming chiral amines

Chiral amines have the possibility to react with so-called Mannich donors such as ketones or aldehydes. The resulting chiral enamines can attack a Mannich acceptor, usually a prochiral aldimine, thereby introducing one or two chiral centers in the Mannich product. The catalytic cycle is completed by regeneration of the amine catalyst through hydrolysis. The products are β -aminoaldehydes or β -amino-ketones, which are optionally substituted at the α -position.

2.1 Syn-selective approaches

2.1.1 PMP-substituted Mannich acceptors. In the year 2000, List hypothesised that proline might catalyse, besides the aldol

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Jorge Verkade

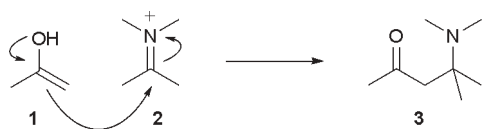
Jorge Verkade (left) was born in Eindhoven, The Netherlands, in 1980. He studied chemistry at the Radboud University Nijmegen, where he obtained his MSc degree in 2005. After a short stay at DSM Research (Geleen, The Netherlands), he joined the group of Professor Rutjes as a PhD student. His research focusses on finding new applications of the organocatalysed asymmetric Mannich reaction.



Floris Rutjes

(The Scripps Research Institute, La Jolla, USA), working on the total synthesis of brevetoxin B, he was appointed assistant professor at the University of Amsterdam in 1995. Four years later, he became full professor in synthetic organic chemistry at the Radboud University Nijmegen. In 2002, he was awarded the Gold Medal of the Royal Netherlands Chemical Society (KNCV) and in 2003 the AstraZeneca award for research in organic chemistry. His research interests include the use of bio- and metal-catalysts in organic synthesis, the development of novel synthetic methodology and the application of microreactors for organic reactions.

Floris Rutjes (right) was born in Heiloo, the Netherlands, in 1966. He studied chemistry at the University of Amsterdam, where he also received his PhD with Professor Nico Speckamp in 1993. After a post-doctoral stay in the group of Professor K. C. Nicolaou

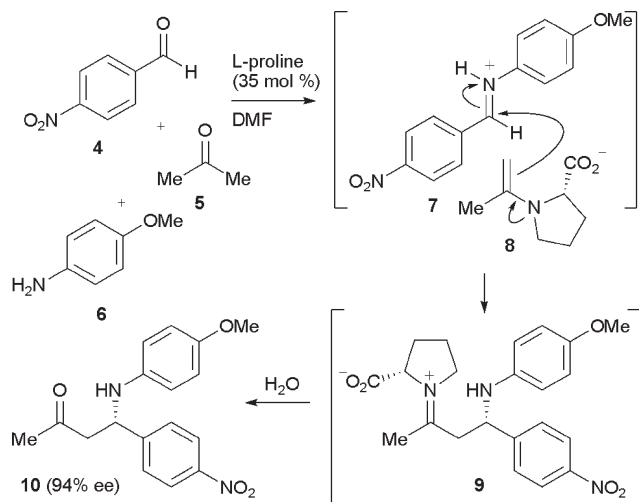


Scheme 1 Essentials of the Mannich reaction.

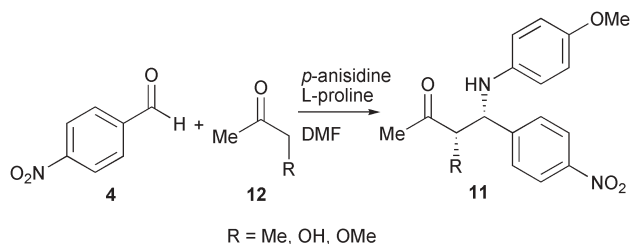
reaction, analogous Mannich reactions in an asymmetric fashion.⁵ It was reported that a one-pot three-component reaction involving a ketone, aldehyde and a primary amine provided the desired Mannich product in enantiopure form. As an example, reaction of L-proline, *p*-nitrobenzaldehyde (**4**), acetone (**5**) and *p*-anisidine (**6**) in DMF led to the desired Mannich adduct **10** in 50% yield with an ee of 94% (Scheme 2). This proceeds *via* the chiral proline-derived enamine **8**, which reacts with the *in situ* formed iminium intermediate **7** in an enantioselective manner. The initially formed iminium adduct **9** hydrolyses in the process and the released proline can enter the next catalytic cycle. The corresponding aldol product (reaction of acetone with the aldehyde **4**) was also formed, but in a considerably lower yield (<20%).

After this discovery, an evaluation of the scope and optimal reaction conditions was initiated. Various proline resembling compounds were examined as potential catalysts.⁶ Several ketones such as butanone, methoxyacetone and hydroxyacetone also furnished the desired products **11** in high yields (92–96%) and excellent ee's (>99%) (Scheme 3). Importantly, in all instances a high *syn*-selectivity (95% de) was observed. While in the case of methoxy and hydroxy substituents single regioisomers were formed, a methyl substituent (butanone) provided a 2.5 : 1 regioisomeric mixture of products.⁶

Structurally diverse aldehydes were also tested in the asymmetric Mannich reaction. α -Unbranched aldehydes appeared to be efficient substrates providing yields up to 90% combined with good to excellent ee values. Evaluation of the primary amine scope showed the necessity of a *p*-methoxy substituent on the aromatic ring. Remarkably, replacement of *p*-anisidine with *p*-chloroaniline caused a marked decrease in enantioselectivity (84% ee), and introduction of *o*-hydroxy- or *o*-methoxyaniline led to almost complete disappearance of



Scheme 2 The first proline-catalysed asymmetric Mannich reaction.



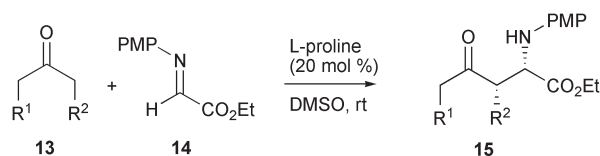
Scheme 3 Variation of the ketone component.

enantioselectivity (<10% ee). A distinct advantage of the use of *p*-anisidine is that the Mannich reaction leads to *p*-methoxyphenyl (PMP)-protected amines, which can be oxidatively converted into the corresponding free amines (*vide infra*). While optimising the reaction conditions, it also appeared that the proline loading could be reduced to 10 mol% in order to obtain the product in good yield (>90%) in a reasonable reaction time (<5 h).

Shortly after List, the Barbas group published similar results on proline-catalysed asymmetric Mannich reactions.⁷ They independently discovered the previously mentioned one-pot three-component proline-catalysed asymmetric Mannich reaction. However, their focus quickly turned to conditions involving preformed imines. For example, in 2002 a highly enantioselective proline-catalysed reaction of ketones **13** with *N*-PMP ethyl iminoglyoxylate (**14**) was reported, which gave the corresponding γ -keto- α -amino acid derivatives **15** in high yields (Scheme 4). Exploration of the scope involving several ketones showed that all reactions proceeded smoothly, typically affording the desired products in good yields (70–80%) and high stereoselectivity (dr >95 : 5 (*syn* : *anti*), ee up to >99%). When asymmetric methyl ketones were used, reaction with the imine always occurred with the most substituted enamine intermediate. Mannich reactions of ketones with PMP-protected imino glyoxylate **14** proceeded well in a wide variety of organic solvents including dimethyl sulfoxide (DMSO).

Mechanistically, the stereochemical outcome of all of these reactions can be explained by invoking a transition state as depicted in Fig. 1. The stereochemical repulsion between the PMP-group and the proline moiety, in combination with protonation of the imine by the acid-functionality of proline, accounts for a *si*-face attack of the (*E*)-aldimine (from *p*-anisidine and acceptor aldehyde) by the *si*-face of the (*E*)-enamine formed by the ketone and proline.⁶ This model explains the stereochemical outcome of many similar reactions that have appeared in literature.

In order to extend the scope of the proline-catalysed asymmetric Mannich reaction, Barbas and co-workers investigated the application of unmodified aldehydes (rather than



Scheme 4 Reactions with imino glyoxylates.

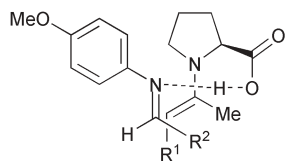
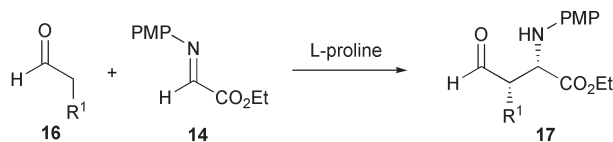


Fig. 1 Mechanistic rationale for the stereoselectivity.

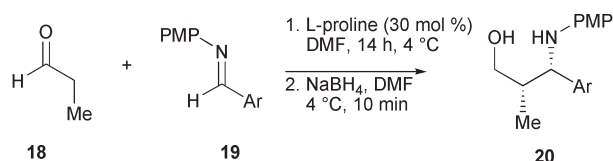
ketones) as the donor.⁸ In 2002, they discovered that the reaction of isovaleraldehyde (**16**, $R^1 = iPr$) with imino ethyl glyoxylate **14** in DMSO afforded the Mannich adducts **17** ($R^1 = iPr$) in high yield (80%) with good stereoselectivity (dr >10 : 1 (*syn* : *anti*), 87% ee). To broaden the scope of this transformation, a number of aliphatic aldehydes **16** were reacted with **14** under the same conditions (Scheme 5).

While the obtained ee was always higher than 90%, it was shown that better diastereoselectivities were obtained in case of larger substituents on the aldehyde donor ($R^1 = Me < Et < iPr < nPent$). It was also observed that the obtained diastereomeric ratios resulting from aldehydes with smaller α -substituents (e.g. $R^1 = Et, nPr$) were significantly higher if determined directly after aqueous work-up than after additional column chromatography. This indicates that epimerisation takes place during the purification on silica gel. The undesired epimerisation could be successfully suppressed by slow addition of propionaldehyde (**18**) to a solution of aromatic *N*-PMP protected aldimines **19** in DMF in the presence of L-proline, followed by *in situ* reduction of the aldehyde function. This yielded the intended 1,3-amino alcohols **20** in reasonable yields, excellent enantioselectivities (90–99% ee) and modest to good diastereoselectivities (dr up to >10 : 1 (*syn* : *anti*)) (Scheme 6). The diastereoselectivity was virtually complete (>19 : 1 (*syn* : *anti*)) when heptanal was used as the donor.

As a next step, the groups of Barbas, Córdova and Hayashi simultaneously reported the viability of a one-pot three-component asymmetric Mannich reaction between two different aldehydes (cross-Mannich reaction).^{8,9,10} Temperature appeared to be a crucial factor in this one-pot three-component cross-Mannich reaction. Typical reaction temperatures of -20 to -10 °C were necessary in order to suppress side reactions such as the homo-aldol reaction.^{8,10} The reaction was also highly solvent dependent, proceeding poorly in



Scheme 5 Unmodified aldehydes as Mannich donors.



Scheme 6 Formation of 1,3-amino alcohols.

acetonitrile, dichloromethane, THF and toluene, but giving high yields and selectivities in DMF and NMP instead.¹⁰

Under these conditions, addition of an aliphatic donor aldehyde **16** to a mixture of *p*-anisidine, an acceptor aldehyde **21** and L-proline, followed by subsequent *in situ* reduction, afforded β -amino alcohols **22** in good yields (up to 88%) with excellent enantioselectivities (up to >99% ee) and good diastereoselectivities (dr 10 : 1 up to >19 : 1 (*syn* : *anti*)) (Scheme 7). The reduction step was in most cases inevitable to suppress epimerisation of the β -amino aldehydes during work-up.

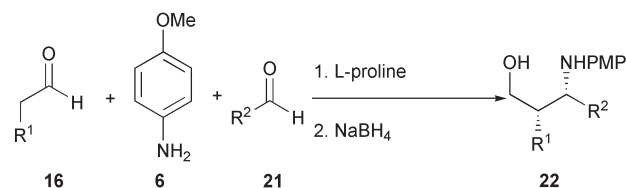
The scope of this reaction was elaborately investigated by the aforementioned groups. Various aliphatic aldehydes were used as Mannich donors **16** and generally good results were obtained. However it was observed that employment of acetaldehyde and 2-substituted acetaldehydes did not result in the expected products.

The acceptor aldehyde **21** scope was also explored. Benzaldehyde, substituted benzaldehydes and heteroaromatic aldehydes appeared suitable Mannich acceptors, whereas the use of aliphatic aldehydes not in all cases led to high selectivities and yields. In the absence of a second aldehyde, proline modestly selectively catalysed the direct asymmetric Mannich reaction of one aliphatic aldehyde being both the donor and acceptor component.^{8,10}

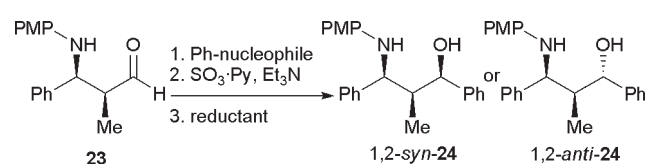
α -Glyoxylate esters were also successfully employed as acceptor aldehydes in the proline-catalysed one-pot three-component reaction with aliphatic donor aldehydes and *p*-anisidine. The resulting β -formyl- α -amino acid derivatives were isolated as such (without reduction) in good yields and excellent diastereo- and enantioselectivities.⁹

Hayashi *et al.* then developed a new strategy to stereoselectively synthesise *syn*- or *anti*- β -amino secondary alcohols (Scheme 8).¹¹ Instead of reducing the Mannich product **23** with $NaBH_4$, it was directly reacted with a Ph-nucleophile (Ph_2CuLi or Ph_3ZnLi) to generate a secondary alcohol. Because this step proceeded only poorly selective, the resulting alcohol was oxidised to the ketone and by adding $LiAlH(OtBu)_3$ or catecholborane subsequently reduced to *syn*- or *anti*-**24**, respectively.

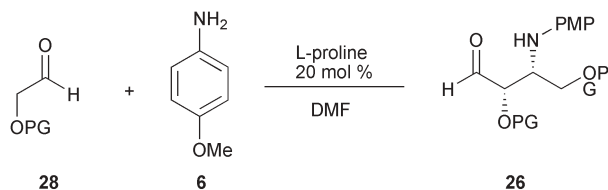
In 2005, the first direct catalytic enantioselective Mannich reaction that provides β -amino- α -oxyaldehydes **25** and



Scheme 7 Cross-Mannich reactions.



Scheme 8 Synthesis of *syn*- or *anti*- β -amino secondary alcohols.



Scheme 9 Formation of 3-aminotetroses.

3-amino tetroses **26** was reported by Córdova and co-workers. 3-Aminotetroses **26** were obtained through a proline-catalysed homo-Mannich reaction of protected glycolaldehydes **28** (Scheme 9).¹² The enantioselectivity of this reaction was high (up to >99% ee), but the diastereoselectivity disappointing with a dr ranging from 1 : 1 to 4 : 1 (*syn* : *anti*).

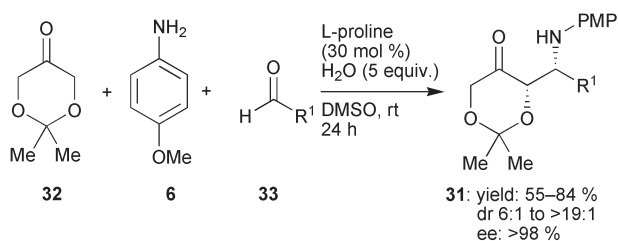
The analogous proline-catalysed addition of protected glycolaldehydes **29** to aromatic imines **30** afforded β-amino-α-oxaldehydes **25** in good yields (up to 95%) and high enantioselectivity (up to 99% ee). The diastereoselectivity was generally moderate (Scheme 10).

Córdova and co-workers also investigated the influence of water on the Mannich reaction. As an example, a one-step synthesis of carbohydrate derivatives **31** *via* amino acid-mediated Mannich reactions with protected dihydroxyacetone derivative **32** as the nucleophile was successfully developed (Scheme 11). It was shown that the rate and selectivity were increased as compared to the water-free reaction. Still, the stereochemical outcome of this one-pot reaction was in complete accordance with that of previously reported proline-catalysed Mannich reactions. Hence, this methodology provides a direct enantioselective entry for the catalytic synthesis of aminosugars. A small excess of water potentially facilitates proton transfer in the transition state, which both lowers the LUMO of the incoming electrophile and directs the enantioselectivity of the newly formed stereocentres. The higher Brønsted acidity of the amino acid in the presence of water and polar aprotic organic solvents plausibly accounts for the observed higher stereoselectivity.

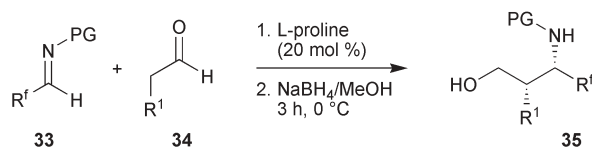
Fustero *et al.* developed a direct and convenient strategy for the synthesis of chiral, non-racemic acyclic fluorinated α-alkyl-β-amino acid derivatives **35** involving a Mannich condensation



Scheme 10 Formation of β-amino-α-oxaldehydes.



Scheme 11 One step synthesis of carbohydrates.



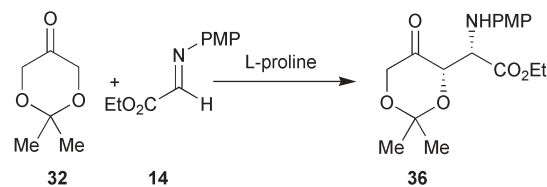
Scheme 12 Synthesis of fluorinated α-alkyl-β-amino acid derivatives.

of fluorinated aldimines **33** with aliphatic aldehydes **34** in the presence of L- or D-proline, followed by reduction of the resulting aldehyde with NaBH₄ (Scheme 12).¹³ Although the yields were moderate (31–41%), the selectivity was outstanding in all cases (dr >19 : 1 (*syn* : *anti*), ee 99%; R^f = CF₃, C₂F₅, ClCF₂ and PhCF₂). Therefore, this strategy can be used for the selective synthesis of *syn*-γ-fluorinated, α-alkyl-β-amino esters and allows the introduction of diversity into both the β-fluoroalkyl and α-alkyl groups of these compounds.

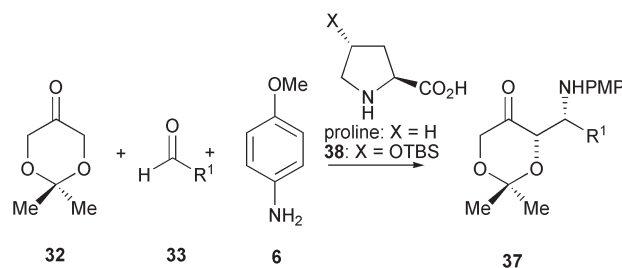
Westermann *et al.* reported the use of protected dihydroxyacetone **32** and imine **14** in Mannich reactions (Scheme 13).¹⁴ In polar solvents (formamide or 2,2,2-trifluoroethanol (TFE)) and in the presence of L-proline as the catalyst, the desired product **36** was obtained (yields up to 78%, dr up to 91 : 9 (*syn* : *anti*), ee up to 99%).

The reaction was accelerated with the use of microwaves. After 10 min irradiation at 300 W, product **36** was obtained in 72% yield with high diastereo- and enantioselectivities (dr 90 : 10 (*syn* : *anti*), ee 95%). A decrease in irradiating power led to a lower yield, although the selectivities remained the same.

The group of Enders also reported a direct organocatalytic synthesis of carbohydrates starting from the acetonide of dihydroxyacetone (**32**). Various protected carbohydrates and aminosugars could be assembled in one step by an almost completely diastereo- and enantioselective proline-catalysed reaction with the *in situ* formed imine of *p*-anisidine (**6**) and an acceptor aldehyde **33** (Scheme 14).¹⁵ Suitable reaction temperatures ranged from 2 °C to ambient temperature. At lower temperatures a decrease in diastereo- and enantioselectivity was observed. The use of catalyst **38** generally led to an enhancement of the reaction rate, due to its superior solubility properties.



Scheme 13 Protected dihydroxyacetone as Mannich donor.



Scheme 14 Protected dihydroxyacetone as Mannich donor.

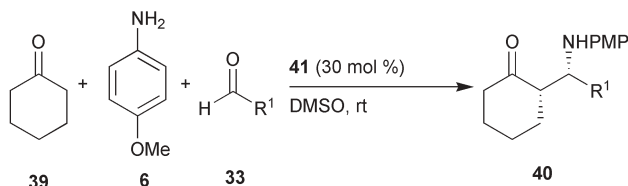
So far, only proline was used in the asymmetric three-component Mannich reaction. Córdova and co-workers reported the use of alternative linear chiral amines and amino acids to catalyse the direct Mannich reaction with high enantioselectivities (Scheme 15).¹⁶ By stirring **39**, *p*-anisidine (**6**), *p*-nitrobenzaldehyde (**4**), serine (**41a**) and DMSO for 48 h, the corresponding Mannich product **40** was formed in a 60% yield, 6 : 1 dr (*syn* : *anti*) and 94% ee. In comparison, the same reaction using proline as catalyst gave **40** in a 50% yield with a dr of 2 : 1 and 84% ee.

Several acyclic chiral amines and amino acids were screened for the direct one-pot three-component Mannich reaction. All amino acids catalysed the reaction with excellent chemoselectivity and the simple aliphatic acyclic amino acids mediated the asymmetric assembly of **40** with high enantioselectivities. After a reaction time of 14 h, **40** was isolated in a 42% yield and 98% ee. Increasing the reaction time to 48 h increased the yield to 68%, however, the ee was decreased to 86%. Thus loss of enantioselectivity occurred at prolonged reaction times. In order to increase the nucleophilicity of the amine and the yield of the Mannich product, one equivalent of dicyclohexyl amine was added to the reaction mixture. This also reduced the ee decrease of **40**. The aliphatic amino acids **41a**, **41c**, **41h** and **41i** catalysed the asymmetric formation of **40** with 2 : 1 to 6 : 1 dr and 91–94% ee. The addition of a small amount of water slightly improved the yield of **40**.

The use of amino derivatives such as **41j** improved the solubility as well as the catalytic efficiency of the organocatalysts in the asymmetric formation of **40** (yield 89%, dr 6 : 1, ee 94%, 12 h).

Córdova and co-workers demonstrated that there is a large number of novel, simple organocatalysts that can be derived from acyclic natural and nonproteogenic amino acids, which could potentially be used and tuned as catalysts for the direct Mannich reaction.

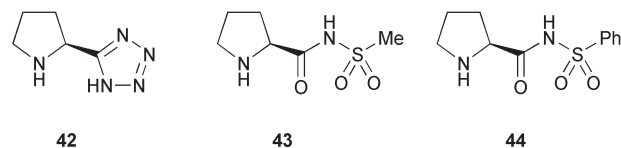
Despite the fact that proline has been often shown to catalyse reactions in high enantio- and diastereoselectivity, a few drawbacks to the use of proline exist. Firstly, the proline-catalysed reaction is generally conducted in solvents such as DMF, dioxane, DMSO and NMP, due to the relatively high solubility of proline in these polar solvents. Secondly, high levels of catalyst loading (10–30%) are usually required. Recently, Ley and co-workers identified three relatively small organic catalysts **42**, **43** and **44**, which proved to work as efficiently in more apolar solvents such as CH₂Cl₂¹⁷ at significantly lower catalyst loadings (Scheme 16).



41a: serine
41b: alanine
41c: valine
41d: 2-amino-pentanoic acid

41e: 2-amino-butanoic acid
41f: 2-amino-³-phenyl-propionic acid
41g: aspartic acid
41h: leucine
41i: isoleucine
41j:

Scheme 15 Screening of various catalysts.



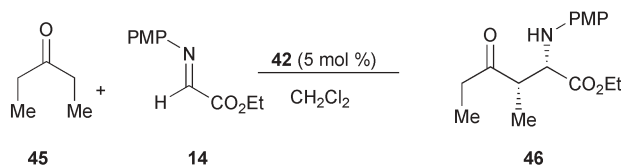
Scheme 16 Apolar organic catalysts.

To show a representative example, the reaction of cyclohexanone with *N*-PMP-protected glyoxylate ester **14**, provided the corresponding product by using only 1 mol% of catalyst **42** in various organic solvents (CH₂Cl₂, MeCN, THF) without affecting the yield and enantioselectivity of the reaction. More generally, the reaction of ketone **45** with **14** proceeded with at least the same efficiency as the corresponding proline-catalysed reaction (Scheme 17). The applicability of these new catalysts in apolar solvents looks very promising in case of ketone donors, but whether they are also useful with aldehyde donors remains to be investigated. Extension to one-pot three-component reactions has also not been reported thus far.

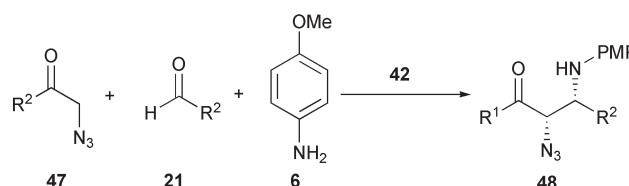
Recently, a new application of catalyst **42** was developed by Barbas and co-workers. It appeared effective in catalysing the reaction between masked 2-aminoketones and *N*-PMP-protected imines.¹⁸ The use of masked 2-aminoketones was considered interesting due to the instability of their unmasked congeners. After optimising the conditions, a series of azidoketones **47** was reacted with *p*-anisidine (**6**) and an aldehyde **21** in the presence of catalyst **42** (Scheme 18). The azidoketones reacted regioselectively affording the α -azido- β -aminoketones **48** in high yields (80–96%), enantio- and diastereoselectivities (ee 80–99%, dr up to 91 : 9 (*syn* : *anti*)).

Remarkably, when phthalimidoacetone (*N*-phthaloyl-protected aminoacetone) **49** was employed, reversed regioselectivity was observed. Reaction with *N*-PMP protected imines provided Mannich products **50** with good yields and reasonable selectivities (Scheme 19).

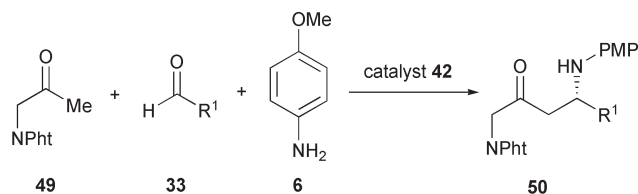
In 2004, Wang *et al.* disclosed another alternative for proline-catalysis.¹⁹ They discovered that pyrrolidine-sulfonamide catalyst **51** was able to induce stereoselectivity in the reaction of cyclohexanone **39** and *N*-PMP-protected glyoxylate ethyl ester **14**. The Mannich-adduct **52** was obtained in very high *syn*-selectivity and excellent enantioselectivity (Scheme 20).



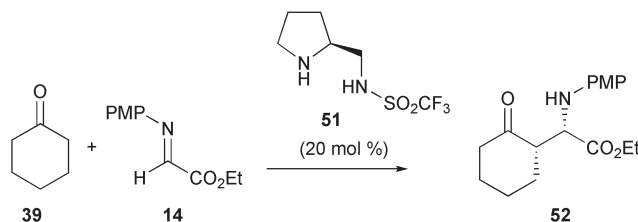
Scheme 17 Organocatalysed Mannich reaction in dichloromethane.



Scheme 18 Synthesis of α -azido- β -aminoketones.



Scheme 19 Reactions of phthalimidoacetone.

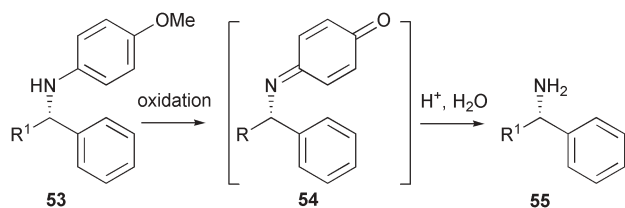


Scheme 20 Pyrrolidine-sulfonamide catalysed Mannich reaction.

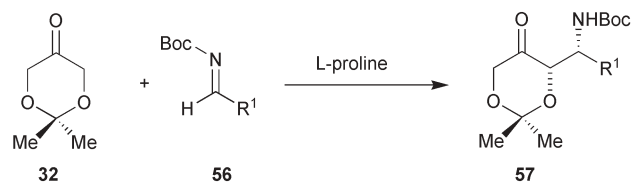
A solvent screening revealed high activities in both protic and aprotic solvents. Yields varying from 76% in MeNO₂ up to 90% in DMSO were observed whereas the solvent did not significantly influence the stereochemical outcome of the reaction. Compound **52** was in all cases obtained with >97% ee and a dr of >95 : 5 (*syn* : *anti*). This catalyst has a broad scope, affords products with excellent selectivity and is applicable in various solvents, thus it might in selected cases be an attractive alternative to proline. However, from an economical point of view proline is favoured, since both enantiomers are commercially available at low cost.

The solubility problem in proline-catalysis also prompted Hayashi and co-workers to develop a more soluble catalyst. They identified *trans*-4-*tert*-butyldimethylsiloxy-L-proline **38** as a more active variant of proline (Scheme 14).²⁰ For instance, the one-pot three-component reactions of ketones, *p*-anisidine and electron-rich aldehydes which was extremely slow in DMF with proline as the catalyst, proceeded in moderate yields (48–63%) and excellent enantioselectivity (90–98% ee) with catalyst **38** instead.

In the preceding reactions, the *para*-methoxyphenyl (PMP) group was used as the imino protecting group. For quite some time, ceric ammonium nitrate (CAN) has been advocated as the method of choice for the oxidative removal of the PMP group.²¹ This proceeds *via* oxidation of the anisidine moiety into the corresponding iminoquinone **54**, followed by aqueous hydrolysis of the imine to liberate the amine (Scheme 21). Mainly due to the moderate reproducibility and laborious nature of the CAN-mediated deprotection, more efficient alternative methods have been developed in recent years to



Scheme 21 PMP deprotection.



Scheme 22 Boc-protected Mannich acceptors.

oxidise the phenolic ring. These methods include the use of electrochemistry,²² cheap oxidants such as trichloroisocyanuric acid or periodic acid,²³ and environmentally benign laccase enzymes,²⁴ all giving rise to the corresponding free amines in generally good yields.

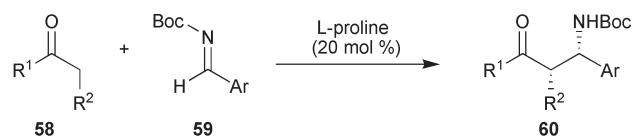
2.1.2 Boc-substituted Mannich acceptors. Enders *et al.* reported the first example of *tert*-butoxycarbonyl (Boc) as the imine protecting group in proline-catalysed Mannich reactions (Scheme 22).²⁵ The resulting products were formed in good yields and selectivities (*e.g.* R¹ = Ph, 85%, de > 99%, ee = 96%).

Soon thereafter, Córdova and List almost simultaneously reported extensive studies on the use of *N*-Boc imines as Mannich acceptors. The Córdova group reported that proline, but also (*R,S*)-4-hydroxyproline were able to stereoselectively catalyse the reaction between aryl-substituted *N*-Boc imines and aliphatic aldehydes in high yields (73–85%) and selectivities (dr >19 : 1, ee up to >99%).²⁶

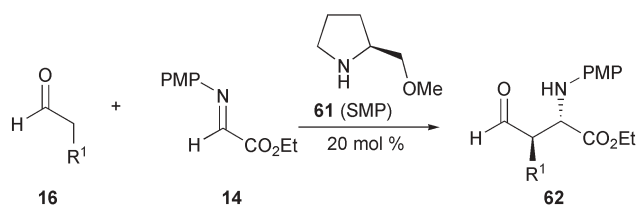
List also reported the synthesis of *N*-Boc protected amino aldehydes **60** employing proline as the catalyst (Scheme 23), but additionally found that acetone could be used as Mannich donor (73% yield, ee >98%).²⁷ It was realised by both groups that this method is limited due to the requirement of preformation of the imines and the incompatibility with aliphatic imines. Both limitations do not apply to *N*-PMP protected imines.

2.2 Anti-selective approaches

Up till now only methods for the preparation of *syn*-Mannich adducts have been described, all based on proline catalysis. In 2002, Barbas *et al.* reported an (*S*)-2-methoxymethylpyrrolidine (SMP) (**61**)-catalysed asymmetric Mannich-type reaction of unmodified aldehydes **16** with PMP-protected imino ethyl glyoxylate **14**, which proceeded in a highly *anti*-selective manner (Scheme 24).²⁸ They screened various catalysts in the reaction of isovaleraldehyde (**16**, R¹ = *i*Pr) and found that commercially available SMP gave optimal results affording the desired β-formyl-functionalised leucine derivative **62** (R¹ = *i*Pr) in 48% yield and reasonable ee (69%, dr >1 : 10 (*syn* : *anti*)). The ee could be improved to 82% by switching the solvent from dioxane to DMSO. Reaction of other aldehydes (*e.g.* R¹ = Et, *n*Bu, *i*Pr, *n*Pent) also afforded products **62** in modest to



Scheme 23 Boc-protected Mannich acceptors.



Scheme 24 *anti*-Selective Mannich reactions.

good ee's (74–92%) and with a diastereomeric ratio that increased with the bulkiness of the aldehyde donor. Similar to the proline-catalysed reactions, it was observed that the diastereomeric ratio of the product resulting from aldehydes with smaller α -substituents (e.g. $R^1 = \text{Et}, i\text{Pr}$) was significantly higher if determined directly after aqueous work-up than after additional column chromatography, indicating that epimerisation easily takes place.

Unfortunately, the scope of this reaction seemed rather limited. For example, it was not possible to obtain the *anti*-adduct from an SMP-catalysed reaction of propionaldehyde and the imine formed from *p*-nitrobenzaldehyde and *p*-anisidine. In this case, low diastereo- and enantioselectivity was observed.²⁹ Jørgensen and co-workers demonstrated that silylated α,α -diarylprolinol **63** (Fig. 2) catalyses the same reaction (depicted in Scheme 25) with significantly improved selectivity.³⁰ Diastereomeric ratios up to 92 : 8 and ee values in the range of 94–98% were observed.

The group of Maruoka developed new chiral aminosulfonamide catalysts to enhance the formation of the *anti*-Mannich product of aldehydes and α -imino esters (Scheme 25).³¹ The first designed catalyst **65a** (5 mol%) was tested in the Mannich reaction of isovaleraldehyde **16** ($R^1 = i\text{Pr}$) and α -imino esters **64** ($R^2 = \text{Et}$) in dioxane giving aldehyde **66** in 60% yield, but

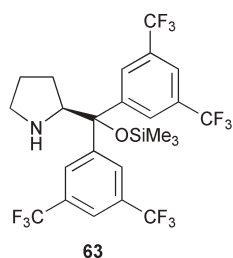
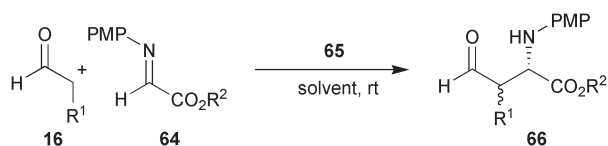
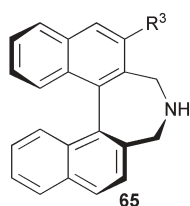


Fig. 2 Silylated α,α -diarylprolinol.



$R^1 = \text{Me}, \text{Bu}, i\text{Pr}, t\text{Bu}, \text{Bn}$
 $R^2 = \text{Et}, \text{allyl}, t\text{Bu}$
 $R^3 = \text{CO}_2\text{H}$ (**65a**), NHSO_2CF_3 (**65b**)



Scheme 25 Chiral aminosulfonamide-catalysed reactions.

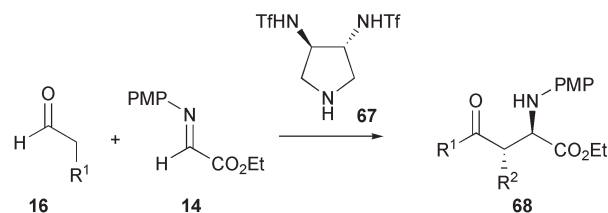
without diastereoselectivity. Modification of the catalyst **65** resulted in excellent reactivity and stereoselectivity (yield 93%, dr >1 : 20 (*syn* : *anti*), 99% ee). Reactions between other aldehydes **16** and the α -imino esters **64** were carried out in dioxane at room temperature. In the case of primary alkyl aldehydes ($R^1 = \text{Me}, \text{Bu}, \text{Bn}$), 1 mol% of **65b** was sufficient to synthesise products **66** with excellent selectivities (yield >92%, dr >11 : 1, ee >99%).

In 2006, the same group reported the synthesis of a novel pyrrolidine-based catalyst **67**, giving better results (yield 88–93%, dr >11 : 1 (*anti* : *syn*), ee 90–95% with sterically hindered aldehydes ($R^1 = i\text{Pr}, t\text{Bu}$) as nucleophiles (Scheme 26). Less reactive ketones could also be used as nucleophiles, leading to the corresponding *anti*- β -amino ketones in good yields and selectivities (yield 95–99%, dr >20 : 1 (*anti* : *syn*), ee >93%).³¹

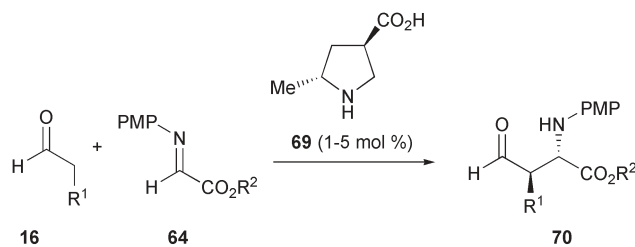
Barbas and co-workers also contributed to the search for *anti*-selective organocatalysts. They designed a novel pyrrolidine-derived catalyst with substituents on the 3- and 5-positions (**69**), showing excellent *anti*-selectivity in the reaction of aldehydes with *N*-PMP protected glyoxylate esters (Scheme 27).³²

Remarkably, the Mannich reaction with ketones and **69** as the catalyst was not very effective, but it was shown that the demethylated congener **72** efficiently catalysed the latter reaction. Both cyclic and linear ketones could be successfully applied, affording the corresponding β -aminoketones in good yields and excellent selectivities (Scheme 28).

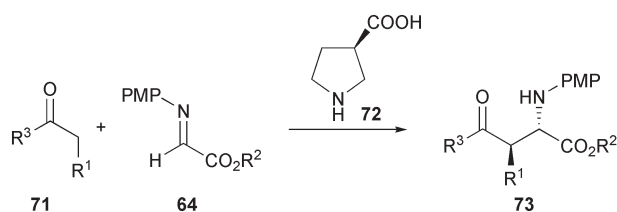
Interestingly, with α -hydroxyketones as donors, no diastereoselectivity was observed. In the case where linear α -amino



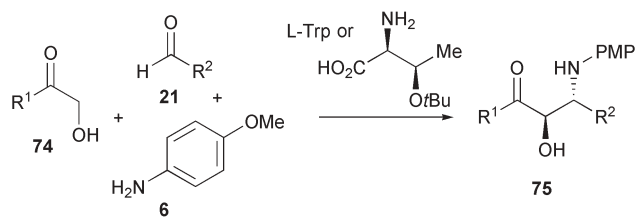
Scheme 26 Novel pyrrolidine-based catalyst.



Scheme 27 Substituted pyrrolidine catalyst.



Scheme 28 3-Substituted pyrrolidine catalyst.



Scheme 29 L-Trp and *O*-*t*Bu-L-Thr catalysed *anti*-selectivity.

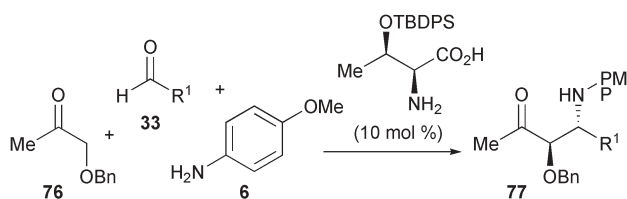
acids (L-Trp and *O*-*t*Bu-L-Thr) were applied as catalysts, α -hydroxy- β -aminoketones were formed in moderate to high selectivities (dr up to 19 : 1 (*anti* : *syn*), ee up to 98%) (Scheme 29).³³

Córdova and co-workers also reported highly enantioselective *anti*-catalysts for the asymmetric Mannich reactions. Readily prepared Me₃Si-protected diphenyl- and bis(2-naphthyl)prolinol appeared very effective in catalysing the reaction of aldehydes with *N*-PMP-protected iminoethyl glyoxylate, giving rise to β -aminoaldehydes in good yields and selectivities.³⁴ Additionally it was found that β -amino acids and in particular β -homovaline could be effectively used as a catalyst in the reaction of ketones and α -iminoethyl glyoxylate, giving *anti*- β -aminoketones.³⁵

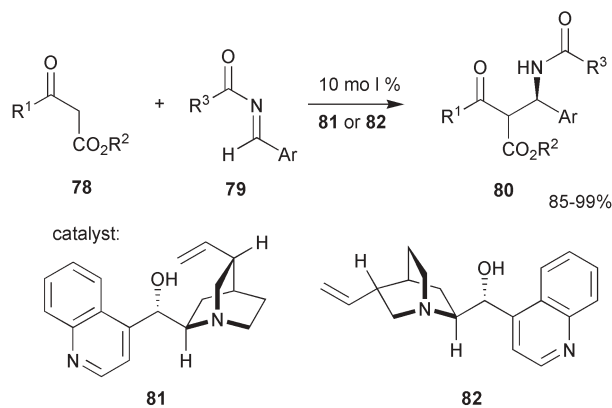
Threonine-derived organocatalysts were reported by the group of Lu as effective catalysts in purely aqueous systems.³⁶ For example, *O*-TBDPS-protected threonine could catalyse the reaction of *O*-benzyl hydroxyacetone (76) with a variety of *in situ* formed *p*-anisidine-derived imines with reasonable selectivities (ee 62–94%, dr 3 : 2 to 20 : 1 (*anti* : *syn*)) (Scheme 30). Aliphatic aldehydes were also investigated, but gave rise to decreased yields and selectivities.

3 Catalysis by Brønsted bases

In the previous examples, the crucial C–C-bond forming step occurred through the reaction of an enamine nucleophile with a protonated imine. The protonation of the imine is essential to render it sufficiently electrophilic to react with the enantiomerically pure nucleophilic enamine. It is, however, also possible to react nucleophiles with neutral imines, although in these cases generally an electron-withdrawing substituent on the imine nitrogen is required to enhance its electrophilicity. The nucleophile is often an active methylene compound, which upon deprotonation with a chiral amine, provides a chiral ion pair of which the anion reacts with the Mannich acceptor in an enantioselective fashion. The presence of a thiourea moiety can enhance the reaction, most likely through cooperative hydrogen bonding with the imine precursor, thereby rendering it more active towards



Scheme 30 *O*-Benzyl hydroxyacetone as donor.



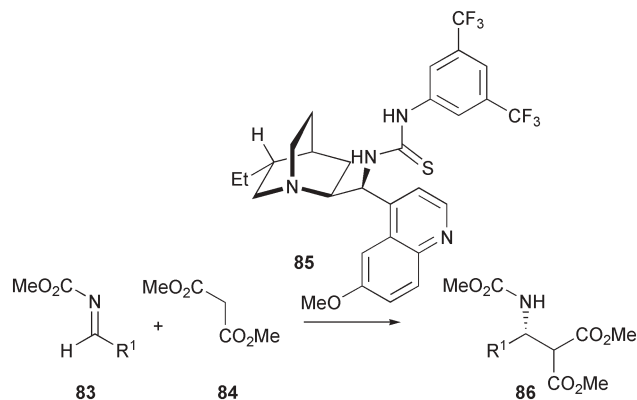
Scheme 31 Cinchona alkaloid catalysis.

nucleophilic attack. In addition, the hydrogen bonding properties of the thiourea moiety can also be invoked to account for increased reactivity of the nucleophile (*vide infra*).

3.1 Use of cinchona alkaloid-derived bases

Schaus and co-workers have developed a diastereo- and enantioselective direct Mannich reaction of β -ketoesters 78 to acyl aryl imines 79 catalysed by the alkaloids cinchonine (81) and cinchonidine (82) (Scheme 31) to synthesise enantioenriched dihydropyrimidones and β -amino alcohols.³⁷ It was observed that employment of 81 or 82 led to opposite selectivities. The stereoselective control was explained through complexation of the chiral alkaloid with the nucleophile. A variety of β -ketoesters and 1,3-diketones 78 were reacted with aryl methyl benzylidene carbamates 79 in the presence of catalyst 81, giving generally high yields and nearly complete selectivities. They expanded the scope of this reaction by including α -substituted β -ketoesters as donors, thereby gaining access to β -amino esters with α -quaternary centers. Additionally, arylpropenyl acylimines appeared suitable as Mannich acceptors.

The same group reported that the hydroquinine-derived thiourea 85 could serve as an effective catalyst as well. The reaction between dimethyl malonate 84 and a variety of methyl carbamate-protected aromatic imines 83 afforded the corresponding Mannich adducts 86 in good selectivities and almost quantitative yields (Scheme 32).³⁸ Computational modelling



Scheme 32 Hydroquinine-derived thiourea catalysis.

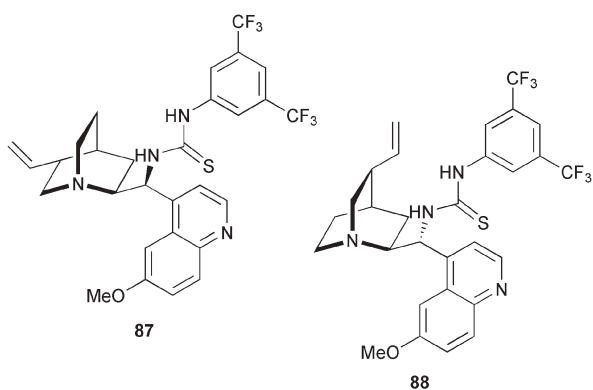


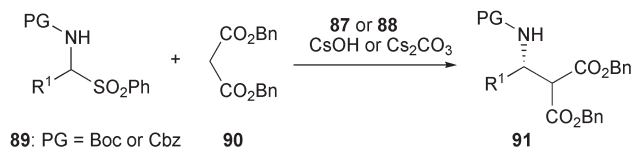
Fig. 3 Cinchona alkaloids with thiourea moiety.

studies established that malonate anion stabilisation *via* a chiral ion pair with the hydroquinine moiety and simultaneous hydrogen bonding of the thiourea part of the molecule with the anion accounted for the excellent selectivity of this reaction.

Well aware of the beneficial effect of cooperative hydrogen-bonding catalysis with readily available cinchona alkaloids, Deng and co-workers investigated the use of cinchona alkaloids bearing a thiourea functionality as catalysts (**87** and **88**) for the addition of dimethyl malonates to *N*-Boc-protected imines (Fig. 3). After optimisation of reaction conditions, the desired products were obtained in excellent yields (up to 99%) and enantioselectivities (ee up to 99%). The imine scope was not limited to aromatic imines, but also aliphatic acceptors could be applied. β -Ketoesters could also be used as donors, providing access to β -ketoamines albeit with only moderate diastereomeric control.³⁹ Dixon *et al.* reported comparable results for reactions with Boc- and Cbz-protected aldimines catalysed by a slightly different catalyst.⁴⁰

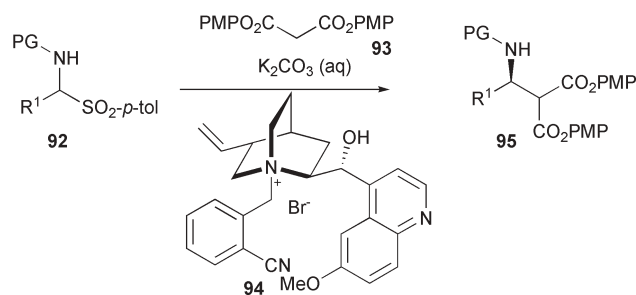
A major drawback of the use of *N*-Boc-protected imines is the low stability of particularly aliphatic imines. This was realised by Deng and co-workers and overcome by the implementation of gradual and *in situ* generation of carbamate-protected imines from stable α -amidosulfones.⁴¹ This also led to higher optical purities when employing catalyst **88** due to the relatively high concentration of the catalyst compared to the imine. As an illustration, with the same amount of catalyst, 95% ee was obtained with *in situ* generation of the imines, whilst preformed imines afforded the desired products in only 74% ee. Additional examples involving the use of aromatic and aliphatic carbamate-protected α -amidosulfones and dibenzylmalonate provided further insight into the scope of this reaction (Scheme 33).

The *in situ* formation of *N*-carbamate protected imines and their use as Mannich acceptors was also reported by Sgarzani and co-workers.⁴² Cinchona alkaloid **94** was designed, which showed excellent enantioselectivity in the reaction of *p*-anisyl



89: PG = Boc or Cbz

Scheme 33 *In situ* generation of *N*-carbamate-protected imines.



Scheme 34 *In situ* generation of *N*-carbamate protected imines.

malonate **93** with various *in situ* generated *N*-Boc- or *N*-Cbz-protected aldimines. Both aliphatic and aromatic α -amido *p*-tolylsulfones were tolerated. The enantiomeric excesses were generally in the 85–99% range (Scheme 34).

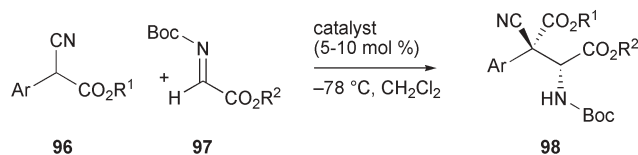
An interesting variation on this motif was reported by the Jørgensen group. They described a highly enantioselective procedure for the reaction of α -aryl-substituted cyanoacetates **96** with *N*-Boc protected iminoglyoxylates **97** in the presence of a chiral tertiary amine catalyst (Scheme 35).⁴³

Various catalysts were screened for the reaction of **96** ($R^1 = nPr$; Ar = Ph) with **97** ($R^2 = Et$), but commercially available (DHQD)₂PYR gave the best diastereo- and enantioselectivity (Fig. 4). The scope of α -aryl-substituted cyanoacetates was investigated and it was found that in all cases similarly high selectivities could be observed, but in the case of a 2-bromo-substituted aryl moiety, the nature of the ester group of **97** seemed to direct the selectivity. An ethyl group completely inverted the diastereoselectivity, whereas the enantioselectivity diminished almost completely.

The substrate tolerance of the catalytic system was further demonstrated by the use of the cyclic β -ketoester **99** (Scheme 36). The reaction smoothly afforded Mannich base **101** in a high yield and essentially as a single isomer in excellent ee.

3.2 Use of other chiral bases

The results achieved with cinchona alkaloid-derived thiourea catalysts prompted Takemoto and co-workers to investigate



Scheme 35 α -Aryl-substituted cyanoacetates as donors.

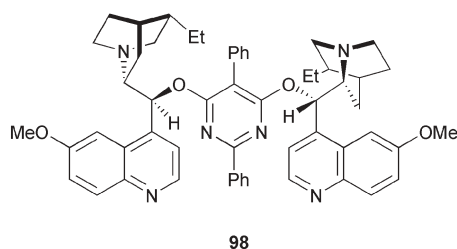
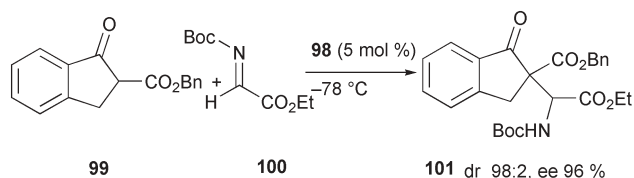


Fig. 4 (DHQD)₂PYR.

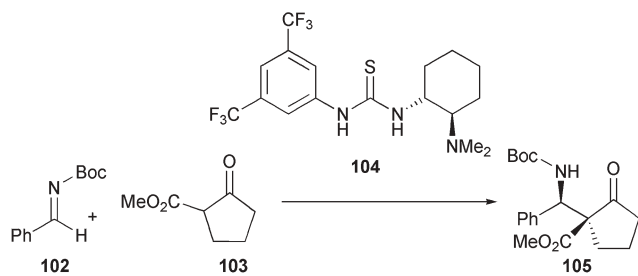


Scheme 36 Cyclic β -ketoester as Mannich donor.

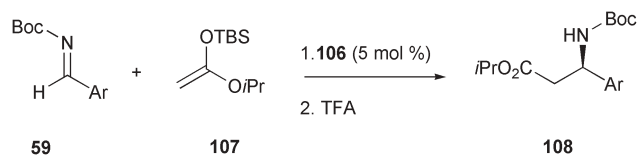
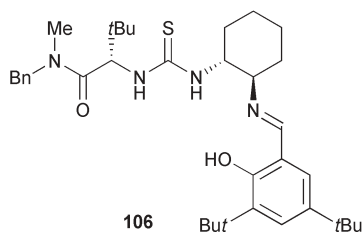
the possibility of the use of the simple thiourea compound **104** in the Mannich reaction.⁴⁴ It effectively catalysed the reaction of diethyl malonate with *N*-Boc-protected aldimines as opposed to other *N*-protected aldimines. Although the thiourea catalyst led to high enantioselectivities for reacting β -ketoesters with aldimines, no diastereoselectivity was observed. This was possibly due to epimerisation of the product. Subsequently, cyclic 1,3-dicarbonyl compounds having a substituent at the 2-position were employed as substrates (Scheme 37). The product **105** was obtained in 89% yield and the selectivities were good (ee 88%, dr 92 : 8). A series of reactions with cyclic substrates was disclosed, but the selectivities were generally fairly modest. The authors suggested that a dual activation of the electrophile and the nucleophile accounted for the observed selectivity, but no definite proof was provided.

It must be noted that thiourea-catalysed reactions were already earlier reported by Wenzel and Jacobsen in 2002. At that time, they realised that the conditions required for the removal of *N*-aryl protecting groups posed a serious drawback to the organocatalysed reactions described above. As a result, they reported an efficient route to *N*-Boc-protected β -amino acids *via* the enantioselective addition of silyl ketene acetals to *N*-Boc aldimines catalysed by thiourea catalyst **106** (Fig. 5).⁴⁵

Addition of silyl ketene acetal **107** to *N*-Boc-protected *ortho*-, *meta*-, *para*- and unsubstituted arylimines **59** proceeded with generally good enantioselectivity (88–93% yield, up to 97% ee) to afford the Mannich bases **108** (Scheme 38). It must however



Scheme 37 Thiourea catalyst.



Scheme 38 Thiourea catalysis with silyl ketene acetals.

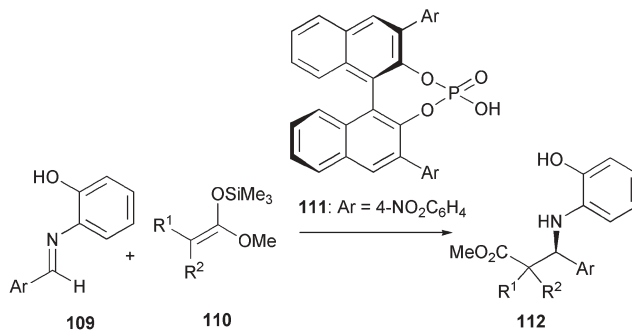
be noted that reactions were conducted at -40 to -30 °C to suppress the non-catalytic (racemic) pathway. Aliphatic *N*-Boc-protected imines were not investigated since no useful method was available for their synthesis.

4 Catalysis by chiral Brønsted acids

A third pathway for enantioselective organocatalysed Mannich reactions proceeds *via* enantiopure Brønsted acids. Instead of reaction with an enantiopure nucleophile (Section 2), in this case the acid protonates the imine, leading to an iminium ion with an enantiopure counterion. This counterion directs the incoming nucleophile and leads to an optically active Mannich product. Most often, the acids involved are readily accessible enantiopure phosphoric acids.

An early example was reported by Akiyama *et al.*⁴⁶ They synthesised a series of chiral phosphate catalysts, of which phosphoric acid **111** proved to give the best results. For example, reaction of the aromatic aldimines **109** with silyl ketene acetal **110** ($R^1 = R^2 = \text{Me}$) catalysed by **111** afforded the Mannich bases **112** in excellent yield (98–100%) and reasonable enantioselectivity (80–89% ee) (Scheme 39). Addition of monosubstituted silyl ketene acetals **110** ($R^1 = \text{H}$, $R^2 = \text{Me}$, Bn) to aromatic aldimines **109** led to highly *syn*-selective reactions (dr 87 : 13 to 95 : 5 (*syn* : *anti*)), while the enantioselectivity was also maintained (81–96% ee). In addition, it was concluded that the hydroxy-substituent on the *ortho*-position of the protecting group was essential to ensure high levels of enantioselectivity.

Expecting to have different electronic and steric properties, the novel Brønsted acid **113**, based on the well-known TADDOL scaffold, was also prepared by the group of Akiyama (Fig. 6).⁴⁷ By varying the Ar functionality and the alkyl groups on the acetal moiety, the catalyst initially showed only modest selectivity (ee 50–75%) for the reaction depicted in Scheme 40. However, when the imine protective group was changed from *o*-hydroxyphenyl to *o*-hydroxy-*p*-methylphenyl,



Scheme 39 Enantioselective phosphoric acid catalysis.

Fig. 5 First thiourea-catalysed asymmetric Mannich reaction.

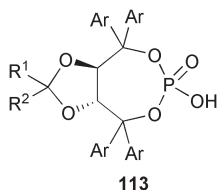


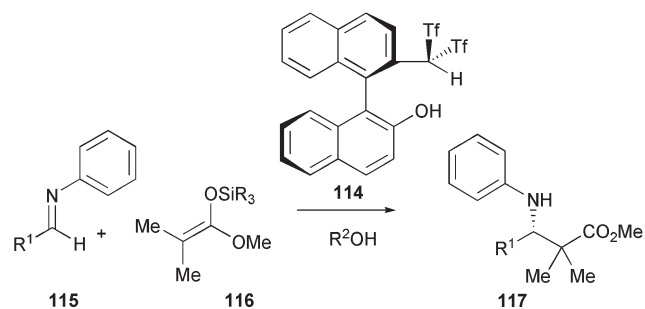
Fig. 6 TADDOL-based catalyst.

a dramatic increase of the enantiomeric excesses to 85–92% was observed without diminishing the yields.

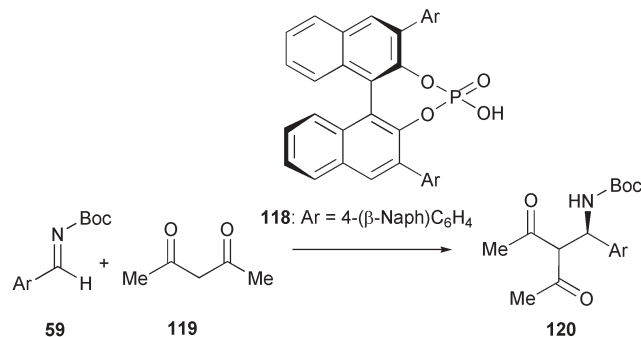
Yamamoto and co-workers reported the introduction of the concept of Brønsted acid-assisted chiral Brønsted acid (BBA) catalysis for the design of **114** as a new asymmetric Mannich catalyst (Scheme 40).⁴⁸ The BBA catalyst bears two acidic protons. Mechanistically, the imine **115** is activated by the hydroxy proton, while the bis(triflyl)methyl proton simultaneously fixes the OH–N bond, thereby stabilising the configuration of the chiral transition state. Attack of the silyl ketene acetals **116** affords products **117**. Unfortunately, enantiomeric excesses initially did not exceed 53%, but the reactivity was improved by adding 2,6-xyleneol as an achiral proton source to trap the silicon species resulting from the reaction. Various *N*-phenyl-protected β -amino esters were obtained with a maximum ee of 77%. It was also shown that the *N*-protective group could be replaced by a diarylmethyl moiety, giving enantiomeric excesses up to 87%.

Uraguchi and Terado used the similar chiral phosphate catalyst **118** to catalyse the enantioselective addition of acetylacetone **119** to the *para*- and *ortho*-substituted *N*-Boc-protected aromatic aldimines **59**, providing the Mannich bases **120** in high yields (93–99%) and high enantioselectivity (90–98% ee) (Scheme 41).⁴⁹

Schoepke and co-workers reported the first enantioselective Brønsted acid-assisted chiral Brønsted acid-catalysed direct Mannich reaction of poorly reactive acetophenone.⁵⁰ They reasoned that activation of the aldimine should occur *via* ion pair formation with the chiral Brønsted acid, while activation of the ketone donor must be mediated by an achiral acid which cannot form an ion pair with the aldimine. Elaborating on this concept, the reaction of acetophenone with the *N*-4-chlorophenyl-protected aldimine **121** was investigated using the chiral BINOL-phosphate **122** in combination with acetic acid, which led to a high selectivity (76% ee) (Scheme 42). The scope was also evaluated to show that aromatic and heteroaromatic aldimines could be applied in the reaction with acetophenone



Scheme 40 Brønsted acid-assisted chiral Brønsted acid catalysis.

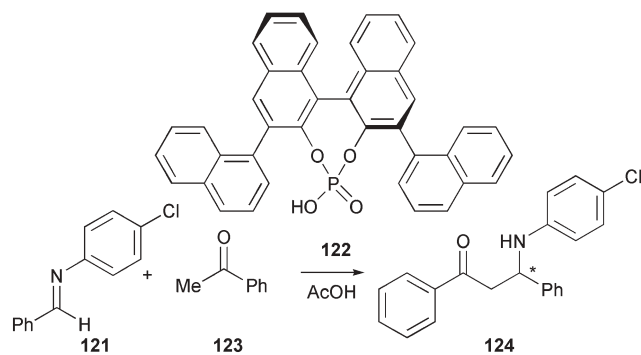


Scheme 41 Chiral phosphate catalysis.

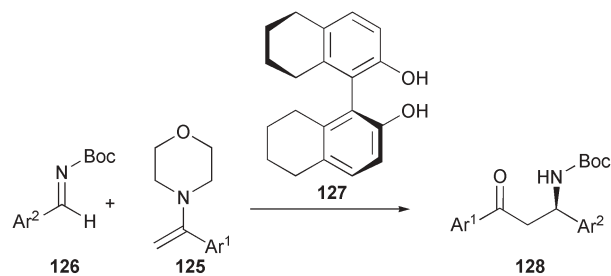
to afford the corresponding β -aminoketones in moderate yields and selectivities.

The use of acetophenone as a donor was also reported by Tillman and Dixon, but they had to preactivate the ketone as its enamine with morpholine.⁵¹ They tested a variety of modified BINOL structures as catalysts in the reaction of enamine **125** with the *N*-Boc protected aldimine **126** and found that the best results were obtained with (*S*)-H₈-BINOL **127**. Only aromatic substrates were reported as acceptable donors and acceptors for this catalyst. Yields were good, but enantiomeric excesses generally moderate (mostly in 60–80% range) (Scheme 43).

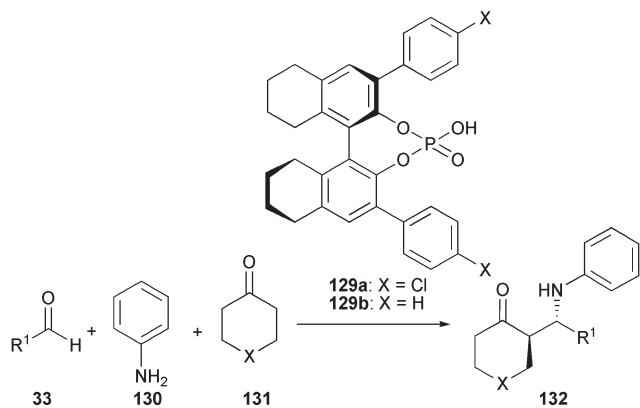
The previous examples showed enantioselective Brønsted-catalysed reactions, leading to compounds with only one chiral center. Gong and co-workers were the first to report *anti*-selective examples of chiral Brønsted acid-catalysed reactions.⁵² Moderate diastereoselectivities (dr in the 80 : 20 to 90 : 10 range) were observed in the reaction of cyclic ketones with aniline and aromatic aldehydes and catalyst **129** (Scheme 44), while enantioselectivities were generally high (90–95% ee).



Scheme 42 Brønsted acid-assisted chiral Brønsted acid-catalysis.



Scheme 43 Preactivated acetophenone as Mannich donor.



Scheme 44 *anti*-Selective Brønsted acid-catalysed reactions.

With 4-Cl or 4-F-substituents, the reaction of acyclic ketones with aromatic aldehydes in the presence of (substituted) aniline also proceeded with high enantioselectivities (up to 86% ee). No diastereoselective examples were reported.

5 Conclusions

This survey of organocatalytic methods for the synthesis of asymmetric Mannich bases leads us to conclude that this is a promising field for which many new applications in the synthesis of biologically active compounds will emerge. It also becomes evident that the use of proline as the catalyst gives easy access to *syn*-products in high yields with high regio-, chemo-, diastereo- and enantioselectivity. Since proline is commercially available in L- and D-form, the products can also be obtained in both enantiomeric forms. Both one-pot three-component reactions and reactions with preformed imines have extensively been studied using unmodified ketones and aldehydes as Mannich-donors. It must be noted that a relatively high catalyst loading generally has to be used (typically 10–30 mol%). This is mainly due to the low solubility of proline in (a)polar organic solvents. Some research groups have therefore developed new, more soluble catalysts to overcome this problem. However, this led to more expensive catalysts of which the scope still needs to be fully investigated. Moreover, since proline catalysis only gives access to *syn*-adducts, *anti*-directing catalysts were also desired. Nowadays, a series of enamine forming amines are available that give rise to the *anti*-products in good selectivity.

Besides catalysis by proline and derivatives, chiral bases have also been successfully employed in combination with electron-poor imines and active methylene compounds. Success in this particular reaction is often facilitated by introducing thiourea moieties, that interact with the system through cooperative hydrogen bonding.

Finally, chiral Brønsted acids (mostly phosphoric acids) have been employed to include the iminium ion in a chiral ion pair, which also results in enantioselective addition onto the iminium species.

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