Part I
Amino Acid-Derived Catalysts
1 Proline-Related Secondary Amine Catalysts and Applications

Hiyoshizo Kotsuki and Niiha Sasakura

1.1 Introduction

Since the reappearance of l-proline (1) at the forefront of organocatalysis, tremendous efforts have been made to devise new catalysts based on a proline core structure. In this field, the chirality of a pyrrolidine fragment plays a critical role, and the principal concept that underlies the development of new catalysts can be simply explained as the attachment of acidic sites in place of a carboxylic acid group to the side chain. Accordingly, several catalysts with various acidic functionalities have been developed [1]. In general, proline-based organocatalysts can be classified into six major categories: (A) prolinamides, (B) prolinamines, (C) proline tetrazoles, (D) prolinamine sulfonamides, (E) prolinamine thioureas, and (F) diarylprolinols (Figure 1.1). Representative $pK_a$ values of these catalysts are listed in Figure 1.2 [2]. A subtle change in the side-chain assembly may change the $pK_a$ value in the range 8–20, which would have a significant effect on the strength of hydrogen bonding, and thus the catalytic activity and selectivity may be affected.

In this chapter we will deal with organocatalytic asymmetric transformations using these catalysts, mainly focusing on the significant and major achievements in this area published from 2000 to 2011. However, due to space constraints, this chapter will not cover the great utility of diarylprolinol catalysts (category F); for convenience, only references are given [3].

1.2 Prolinamide and Related Catalysts

Owing to the ready availability of prolinamide derivatives through the condensation of proline with amines, prolinamide-based compounds constitute a large family of organocatalysts [4]. Figure 1.3 lists representative examples of these catalysts.
These catalysts are very useful in a wide range of asymmetric syntheses. Asymmetric aldol reactions have been investigated by several research groups; selected examples are compiled in Scheme 1.1.

In this context, prolinamide 2 [5–8] and its aryl-substituted homologs such as 3–5 have been developed [9–14]. Analogous to these examples, binaphthyl diamine-derived compounds such as 6 and 7 have been introduced for use in aqueous systems and as recoverable catalysts [15–18]. For example, Benaglia and coworkers reported that the prolinamide catalyst 7 with a lipophilic side chain showed efficient catalytic activity in water [16b]. Chiral spiro diamine-derived catalysts have also been designed, albeit in moderate enantioselectivity [19]. Owing to the increased acidity of an NH group of thioamide relative to a normal amide, proline-thioamide catalysts such as 8 have been shown to be more effective [20–23].
Figure 1.3 Representative examples of prolinamide organocatalysts.

Scheme 1.1
A successful approach in this field is the design of multifunctionalized catalysts such as 9 and 10 through the incorporation of chiral aminoalcohol and related species onto the side chain [24–35]. The high catalytic activity and enantioselectivity of catalyst 9 can be explained by considering the favorable assembly of donor and acceptor molecules via double hydrogen-bonding stabilization, as depicted in the transition state model 15 [24h]. In these examples, to gain satisfactory results, it is important to match the chirality between the proline core and the attachment.

Several other related systems containing a prolinamide or proline-thioamide core have also been reported [36–42].

In some cases, a chiral diamine assembly can serve as an effective scaffold for the design of multiply functionalized catalysts like 11 and 12 [43–49]. Proline hydrazides [50], dipeptides [51–57], or other small peptides [58–63] bearing a prolinamide core have been shown to be useful in asymmetric aldol reactions.

Catalyst 13 was introduced for use in aqueous systems in the presence of surfactant Brønsted acids as co-catalysts [64], and several other catalysts such as 14 containing a heteroaromatic system have also been reported [65–67].

There has been important progress in the use of proline sulfonamides ($pK_a = 8–11$) [2] as efficient organocatalysts, and Yang and Carter provided an excellent review [68]. Therefore, only a few important aspects are addressed here. Figure 1.4 lists representative examples of these catalysts.

Various N-arylsulfonyl-substituted prolinamides such as 16 have been used in asymmetric aldol reactions [69–78]. Carter and coworkers actively sought new efficient catalysts of this type, and found that 17 could serve as an efficient catalyst for asymmetric aldol reactions, even in the absence of any organic solvent, with excellent diastereo- and enantioselectivity (Scheme 1.2) [79].

**Figure 1.4** Representative examples of proline sulfonamide organocatalysts.
1.2 Prolinamide and Related Catalysts

Recently, Ellman and coworkers have shown that chiral sulfinate 18 can catalyze asymmetric aldol reactions of acetone, whereas proline (1) itself gave poor results [80]. Nakamura and coworkers also explored this field, and found that 19 can promote the asymmetric cross-aldol reaction of acetone with activated ketones, to generate a quaternary carbon stereogenic center bearing an OH function [81].

With regard to aldol chemistry, Mannich or domino-Mannich–Michael reactions can also be promoted by N-arylsulfonyl-substituted prolinamide catalysts such as 17 with high levels of enantioselectivity [82, 83].

Importantly, prolinamide catalysts work well in Michael addition reactions using nitroolefins as acceptors [58, 64, 84–95]. For example, Nájera and coworkers used bifunctional catalyst 20 by virtue of the synergistic effect of double hydrogen-bonding activation, as depicted in the transition state model 21 (Scheme 1.3) [90]. For the same purpose, prolinamides containing a heteroaromatic system like 14 have also been reported [96].

Analogously to these examples, proline-derived peptide catalysts can also efficiently promote Michael addition reactions [97–99]. Prolinamide or prolyl sulfonyamide catalysts are also effective for intramolecular Michael addition reactions [100–102]. Recently, Yang and Carter reported a short-cut strategy to construct an all-carbon substituted quaternary carbon stereogenic center on a cyclohexeneone framework via Robinson-type annulation using the 17-type catalyst (Scheme 1.4) [103].
While some examples of prolinamide-catalyzed enantioselective Biginelli condensation [104, 105] and other types of C–C bond formation [106, 107] are known, their synthetic utility is unclear. Finally, for convenience, with regard to asymmetric heteroatom functionalization and transfer hydrogenation using prolinamides as catalysts, only references are given [108–114].

1.3 Prolinamine and Related Catalysts

Among several organocatalysts derived from L-proline (1) as a chiral source, pyrrolidine–tertiary amine conjugates constitute a powerful and useful family in asymmetric synthesis [115]. In 1994, Kawara and Taguchi reported pioneering work on the use of such catalysts in asymmetric Michael addition reactions [116]. Since then, several related catalysts have been developed. Figure 1.5 lists representative examples.

In 2001, after screening several chiral diamines and protonic acid additives, Yamamoto and coworkers reported that a TfOH salt of 22 could efficiently promote asymmetric aldol reactions [117]. Thereafter, similar studies using chiral diamines such as 22–24 with Brønsted or Lewis acid additives have also been reported [118–122]. In 2006, the Mase/Takabe/Barbas groups discovered that prolinamine catalyst 25 with a lipophilic side chain showed efficient catalytic activity in water (Scheme 1.5) [123]. Thus, cyclohexanone reacts smoothly with various aldehydes in water to afford the desired aldol products in high yields with excellent diastereo-
and enantioselectivity. Recently, the recyclability of analogous catalysts has been reported by others [124].

Scheme 1.5

Prolinamine catalyst 26 has been introduced for the same purpose [125]. With regard to asymmetric aldol reactions, it has been shown that prolinamine catalysts such as 22 can also work well for intramolecular aldol [126–128], Henry (nitroaldol) [129], Mannich [130, 131], and domino-Michael–aldol reactions [132] as valuable asymmetric transformations.

Similar to aldol chemistry, prolinamine-catalyzed asymmetric Michael addition reactions have attracted considerable attention from synthetic chemists, and successful examples have been developed (Scheme 1.6).

In this field, prolinamine catalysts 22 and 24 are particularly useful for promoting asymmetric Michael addition reactions between several donor and acceptor molecules [120b, 133–136]. On a related topic, catalyst 27 and related diamine or triamine catalysts have been developed [137–139]. Interestingly, the Mase/Takabe/Barbas groups reported that diamine catalyst 25 could again serve as an efficient catalyst for asymmetric Michael addition reactions even in brine solution [140]. Similarly, several types of water-active catalysts such as 26 have been developed [141, 142].
Independently, Alexakis and coworkers reported that \textit{2,2'}-bipyrrrolidine catalyst 28 showed excellent catalytic activity in several types of asymmetric Michael addition reactions [143]. It has been postulated that the isopropyl group on one of the \(C_2\)-symmetric pyrrolidine rings should block not only the back face against the approach of Michael acceptors but also shift the equilibrium towards one of the two rotamers. Since then, closely related catalysts have also been reported [144]. Furthermore, different types of catalysts such as 29 have been shown to be useful in asymmetric Michael addition reactions [145–148].

While catalyst 22/23 has been known to be valuable in other \(C-C\) bond-forming strategies, for example, 1,3-dipolar cycloaddition [149], hetero-Diels–Alder reaction [150], Friedel–Crafts-type alkylation [151], double-Michael reaction [152], [2,3]-Wittig rearrangement [153], and Claisen–Schmidt condensation [154], only references are given here.

Finally, while various reactions under the catalysis of 22 or 24, for example, asymmetric epoxidation of \(\alpha,\beta\)-unsaturated aldehydes [155], \(\beta\)-hydroalkoxylation of \(\alpha,\beta\)-unsaturated enones [156], and stereoselective reduction of \(\alpha,\beta\)-unsaturated enones (Scheme 1.7) [157], have also been reported, they have been demonstrated in only a limited number of experiments.

![Scheme 1.7](image)

1.4 Proline Tetrazole and Related Catalysts

Proline tetrazole catalysts (category C in Figure 1.1) are readily accessible from \textit{L}-proline (1) [158]. They are remarkably useful in asymmetric synthesis [159]. As shown in Figure 1.2, the \(pK_a\) of tetrazole is very similar to that of carboxylic acid. Moreover, the advantage of tetrazole catalysts is their robust and lipophilic nature compared to \textit{L}-proline (1) itself, which allows them to escape parasitic bicyclo-oxazolidinone formation [160].

In 2004, Yamamoto and Arvidsson independently reported the catalytic activity of the \textit{L}-proline tetrazole catalyst 30 in asymmetric aldol reactions of ketones with aldehydes [161–163]. At the same time, Ley and coworkers reached similar conclusions by applying this system to asymmetric Mannich and Michael addition reactions (Scheme 1.8) [164]. Since then, the scope of this chemistry has been expanded by several research groups [165–174].
Ley and coworkers have been quite active in this field, and have found that 30 or its homolog could efficiently promote asymmetric Michael addition reactions using various Michael acceptors and donors [164b, 175]. In these cases, the reactions require the use of a basic amine such as trans-4,5-dimethylpiperazine as a co-catalyst to increase the nucleophilicity of donor molecules by deprotonation. Typical examples are shown in Scheme 1.9.

A mechanistic investigation of this chemistry using density functional theory calculations [176] and reactions in ionic liquids as solvents have also been reported [177]. Interestingly, the Michael addition reaction of bromonitromethane to cyclic or acyclic enones constitutes a convenient way of preparing cyclopropane ring compounds in moderate to good enantioselectivity (Scheme 1.10) [178].
Very similar results have also been reported with the use of sulfur ylides as donor molecules [179]. With regard to the asymmetric Biginelli reaction [180] and multicomponent coupling reactions [181] using 30 or its analog as a catalyst, only references are given here.

Finally, we should emphasize the synthetic utility of the 30-catalyzed α-oxidation of carbonyl compounds via an “O-nitroso aldol reaction” [182]. This method is very attractive as a metal-free oxidation system. For example, Yamamoto and coworkers found that aminooxylations of ketones or aldehydes proceed with almost perfect enantioselectivities (97–99% ee) in the presence of 30 as a catalyst (Scheme 1.11) [183]. Mechanistically, nitroso compounds possess two electrophilic centers, that is, nitrogen and oxygen atoms, but the exclusive formation of O-alkylation products indicates that a hydrogen-bonding transition state like 31 seems to be satisfactorily stabilized with the more basic nitrogen atom. As an extension of this strategy, asymmetric domino-Michael–aldol reactions have also been developed by these authors, and these provide a convenient way to prepare 3-oxa-2-aza-bicycloketone derivatives in high enantioselectivity [184].

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R}'
\end{align*}
\]

\[
\begin{align*}
\text{cat 30} (5 \text{ mol%}) & \quad \text{DMSO} \\
\text{rt, 1 h} & \quad \text{yield up to 97%} \\
\text{ee up to >99%}
\end{align*}
\]

Scheme 1.11

Since then, extensive efforts have been made to apply this method to other multiple functionalizations [185–189] or to discover other possible oxidizing agents such as N-sulfonyloxaziridines [190]. As a related chemistry, asymmetric amination at the α-position of a carbonyl compound has also been reported with the use of azodicarboxylate esters as electrophiles [187c, 191–194]. Ley and coworkers have developed an ingenious strategy for obtaining chiral dihydropyridazine derivatives by the combination of asymmetric α-amination and Wittig olefination in a one-pot operation (Scheme 1.12) [187c, 192a].

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R}'
\end{align*}
\]

\[
\begin{align*}
1. \text{cat 30} (20 \text{ mol%}) & \quad \text{CH}_2\text{Cl}_2, \text{rt} \\
2. \text{NaH or KH} (2.5 \text{ equiv}) & \quad 0 \degree \text{C}, \text{THF}-(\text{DMSO}) \\
& \quad \text{yield up to 89%} \\
& \quad \text{ee up to 99%}
\end{align*}
\]

Scheme 1.12
As a different family of heteroaromatic-substituted organocatalysts, imidazole- and triazole-based compounds have been known to be quite effective for asymmetric aldol and Michael addition reactions. Figure 1.6 lists representative examples of these catalysts.

The utility of ionic liquid conjugate catalysts such as 32 and 33 can be ascribed to their recyclability [195–199]. On the other hand, triazole-based catalysts such as 34 and 35 are readily accessible via Huisgen 1,3-dipolar cycloadditions, so-called “click reactions,” from azidomethyl-pyrrolidine and acetylenic precursors, and hence make it possible to design new immobilized catalysts [200–207].

Interestingly, it has been shown that the 33-catalyzed asymmetric $S_{N1}$-type $\alpha$-alkylation of aldehydes or ketones proceeds well in excellent diastereoselectivity and good enantioselectivity (Scheme 1.13) [208].

Prolinamine sulfonamide catalysts (category D in Figure 1.1) can be envisaged as a reversal of prolinamides (A), and constitute a fascinating group of organocatalysts. The catalytic activity of these compounds can be ascribed simply to the sufficient acidity ($pK_a = 10$) of a sulfonamide key structure (Figure 1.2). Figure 1.7 lists representative examples of these catalysts.

For example, in 2004, Wang and coworkers reported a series of asymmetric transformations, for example, $\alpha$-aminoxylation, Mannich reactions, and $\alpha$-sulfonylation, under the catalysis of pyrrolidine trifluoromethanesulfonamide 36; the product yields and diastereo- and enantioselectivities are quite good in most
cases [209–211]. The proposed mechanism is essentially the same as that in the case of tetrazole catalyst 30 (Scheme 1.14); in contrast to the planar nature of a tetrazole in 30, a trifluoromethanesulfonyl group in 36 is non-planar. This difference may change the stability of a hydrogen-bonding network at the transition state.

![Scheme 1.14](image)

Scheme 1.14

After these reports, the same group extended the utility of this catalytic system to asymmetric Michael addition and aldol reactions [212, 213]. Sulfonamide catalysts such as 37–39 have also been developed for the same purpose [214–219]. The behavior of these catalysts, typically exemplified by enantioselective Michael addition reactions of cyclohexanone with nitroolefins, is compiled in Scheme 1.15.

![Scheme 1.15](image)

Scheme 1.15
With regard to the asymmetric $\alpha$-amination of carbonyl compounds using pyrrolidine sulfonamides as catalysts, only references are given here [220, 221].

1.6 Prolinamine Thiourea and Related Catalysts

Prolinamine thiourea catalysts (category E, Figure 1.1) have been introduced primarily for the purpose of designing new bifunctional catalysts by connecting a pyrrolidine base with a remote hydrogen-bonding thiourea function [222]. Figure 1.8 lists representative examples of these catalysts.

For example, Tang and coworkers found that bifunctional thiourea catalyst 40 could efficiently promote the asymmetric Michael addition reactions of ketones or $\alpha$-branched aldehydes with various Michael acceptors (Scheme 1.16) [223]. In particular, the driving force in the present system can be ascribed to the strong hydrogen bond-forming character of thiourea with nitroolefin acceptors, as depicted in the transition state model 46.
Since then, extensive efforts have been made to devise new powerful catalysts such as 41–43 through the modification of a key element of 40, albeit in most cases with similar or less efficiency [224–231]. Guanidinyl catalysts such as 44 and 45 have been developed to realize the conjugate addition reaction of malonates or nitroalkanes to α,β-unsaturated enones in high enantioselectivity, although the number of experiments has been limited (Scheme 1.17) [232, 233]. A plausible mechanism to account for the (S)-configuration of the major products can be ascribed to the transition state model 47.

Finally, it has been shown that thiourea-type bifunctional catalysts are also useful for asymmetric aldol reactions [234, 235] and α-chlorination of aldehydes [236]. Furthermore, 4-substituted bifunctional analogs have been developed for use in anti-selective Mannich reactions [237].

1.7 Miscellaneous

As described so far, various pyrrolidine-based chiral organocatalysts open the door to a remarkably fruitful world of synthetic chemistry. In general, the synthetic protocol used to design new catalysts relies on the naturally occurring chiral source L-proline (1) as a key component. This should be a reasonable approach to achieving final success by mimicking “nature.” To characterize newly designed organocatalysts, carbonyl group functionalization, typically through Michael addition and aldol reactions, seems to be the easiest and most useful approach. These transformations are initially driven by the condensation of carbonyl compounds with a
chiral pyrrolidine secondary amine to reversibly form iminium-enamine intermediates, but relatively low enantioselectivities were observed in aldol reactions catalyzed by proline ester congeners [238], except in the case of Loh’s catalysts [239]. Hence, several different types of proline-related organocatalysts have been developed. Figure 1.9 lists representative examples of these catalysts.

For example, in 2003, Melchiorre and Jørgensen reported that the enantioselective Michael addition reaction of aldehydes with vinyl ketones proceeded efficiently in the presence of 48 as a catalyst (yield up to 93%, ee up to 85%) [240]. In our research laboratory, we have also been very interested in devising new catalysts with a pyridine ring as a rigid planar base adjacent to a pyrrolidine chiral ring. Along these lines, a series of new catalysts (49), that is, DPYMP [49a] and PPYMP [49b], were prepared from l-prolinol, and we found that they showed excellent catalytic activity in terms of productivity, diastereoselectivity, and enantioselectivity (Scheme 1.18) [241]. The results can be explained by invoking the transition state model 55, in which the pyridinium ring must effectively shield the Si-face of an enamine double bond.

![Diagram of catalysts](image)
For the same purpose, various chiral pyrrolidine catalysts such as 50–54 have also been introduced [242–250]. The versatile nature of pyrrolidine catalysts has been recognized by other transformations: aldol reaction [251], Mannich-type reaction [252, 253], and oxa-Michael reaction [254]. Among these, Maruoka’s work on anti-selective Mannich reactions is noteworthy (Scheme 1.19, compare with Scheme 1.8) [253]. In this case, the remote hydrogen-bonding form 57 derived from catalyst 56 can overcome the steric preference so that the opposite sense of stereochemistry should be observed.

\[
\text{Scheme 1.19}
\]

In 2003, Juhl and Jørgensen found that, after screening a series of pyrrolidine catalysts, catalyst 48 is again of great value for the inverse-electron-demand hetero-Diels–Alder reaction: after pyridinium chlorochromate (PCC) oxidation, lactone products could be obtained as a single diastereomer in excellent enantioselectivity (Scheme 1.20) [255]. The proposed transition state model 58 indicates effective shielding of the Si-face of the enamine double bond by the diarylmethyl substituent on the pyrrolidine ring of the catalyst.

\[
\text{Scheme 1.20}
\]

A closely related study has also been reported with the use of a 53-type catalyst [256].
Finally, another set of pyrrolidine-derived organocatalysts is listed in Figure 1.10.

In 2004, Jørgensen and coworkers reported that the asymmetric α-chlorination of aldehydes proceeds well in the presence of C₂-symmetric diphenylpyrrolidine (59) as a catalyst using N-chlorosuccinimide (NCS) as a chlorinating agent [257]. Thereafter, they also explored its applicability to fluorination (48-type catalyst) and bromination (Scheme 1.21) [258].

![Figure 1.10 Miscellaneous examples of pyrrolidine-based organocatalysts.](image)

The synthetic utility of this method is clear: it provides easy manipulation of the products to give various important chiral building blocks such as chlorohydrins, epoxides, aziridines, amino acids, and amino alcohols [257–259], and is readily applicable to natural product synthesis [260].

Recently, considerable efforts have been made to discover new organocatalytic systems for asymmetric epoxidation. In 2003, Aggarwal and coworkers reported that the asymmetric epoxidation of olefins proceeded in good yields and with moderate enantioselectivities using Oxone® (Wako Chemicals, Osaka, Japan) as an oxidant in the presence of a 48-type catalyst (Scheme 1.22) [261]. According to their proposal, the protonated ammonium salt species can act not only as a phase-transfer catalyst to carry the real oxidant species to the organic phase but also as a promoter to activate the chiral oxidant via hydrogen-bonding stabilization, as depicted in 63.
On the other hand, Maruoka and coworkers achieved the asymmetric α-benzoyloxylation of aldehydes using the newly designed catalyst 60 (Scheme 1.23) [262].

![Scheme 1.22](image)

On the other hand, Zhong and coworkers found that the 62-catalyzed system was effective for enantioselective [4+1]-annulation using 2-nitroacrylates and α-iodoaldehydes, to form cis-isoxazoline N-oxide derivatives in high yields and in high diastereo- and enantioselectivity (Scheme 1.25) [266].

![Scheme 1.24](image)

Novel catalysts 61 and 62 have been invented to increase the catalytic activity by incorporation of an electronegative group (fluorine or azido) at the β-position relative to the NH group: an electrostatic interaction (or gauche-effect) between those groups might be favorable for stabilizing reactive intermediates [263–266]. For example, Gilmour and coworkers reported the 61-catalyzed asymmetric epoxidation of α,β-unsaturated aldehydes (Scheme 1.24) [265].

![Scheme 1.23](image)

On the other hand, Zhong and coworkers found that the 62-catalyzed system was effective for enantioselective [4+1]-annulation using 2-nitroacrylates and α-iodoaldehydes, to form cis-isoxazoline N-oxide derivatives in high yields and in high diastereo- and enantioselectivity (Scheme 1.25) [266].
1.8 Conclusions

As described above, a great deal of success has been achieved in a wide variety of asymmetric transformations using a series of proline-related organocatalysts. This organocatalytic asymmetric synthesis offers several advantages over metal-catalyzed systems; for example, the ready availability of both enantiomers, ease of handling without the need for an inert atmosphere or anhydrous conditions, and inexpensive and non-toxic reagents. Unfortunately, however, significant limitations still remain to be overcome in this field, including high catalyst loading, a long reaction period, and harmful organic solvent media. We hope that this exceedingly attractive field in modern organic chemistry can lead to new, much more powerful catalysts as well as highly efficient organocatalyst-based asymmetric transformations.

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