The Application of L-Proline as an Enzyme Mimic and Further New Asymmetric Syntheses Using Small Organic Molecules as Chiral Catalysts

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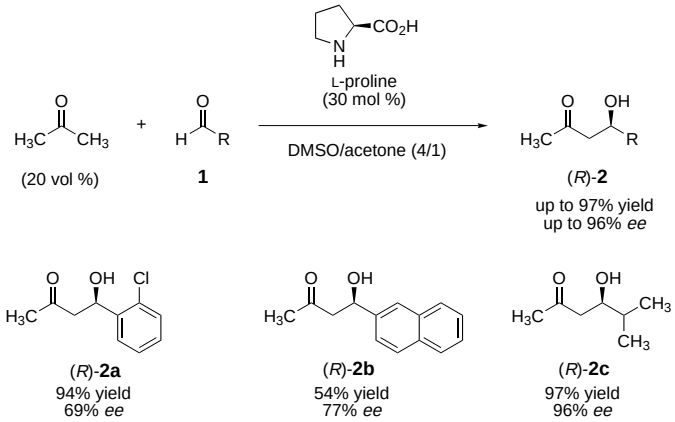
Can a simple organic molecule act like an enzyme? If this were possible, it would represent a remarkable synthetic alternative to many established asymmetric transformations. In particular, such processes would allow the cost effective manufacture of chiral building blocks on an industrial scale. Furthermore, the application of enantiomerically pure, "small" organic molecules represents a promising alternative catalytic concept in addition to other frequently used syntheses based on metal-containing catalysts.[1, 2] However, these organic catalysts should not only function like an enzyme, but should also—with respect to technical application—show the following characteristics: a) easy availability, b) both enantiomers are available with comparable price, c) low price of the organic molecule (if possible directly accessible without derivatization from the "chiral pool"), d) low molecular weight, e) easy separation from the product, and f) easy recovery after work-up without racemization.

The capability of a simple organic molecule from the "chiral pool" to act like an enzyme has now been shown by List, Lerner, and Barbas III[3] for one of the most important organic asymmetric transformations, namely the catalytic aldol reaction.[4] In addition, all the above-mentioned requirements have been fulfilled. The access to the chiral aldol products was realized by means of a simple nonmodified catalytic molecule from the "chiral pool": L-proline. In the described experiments the conversion of acetone with an aldehyde resulted in the formation of the desired aldol products in satisfactory to very good yields and with enantioselectivities of up to 96% *ee* (Scheme 1).[3]



Scheme 1. The direct asymmetric aldol reaction catalyzed by L-proline.

It is noteworthy that, in a similar manner to enzymatic conversions with aldolases of type I or II, a "direct" asymmetric aldol reaction is possible when using L-proline as a catalyst. Accordingly the use of enol derivatives of the ketone component is not necessary, that is, ketones (acting as donors) can be used without previous modification.[5] So far, most of the asymmetric catalytic aldol reactions with synthetic catalysts require the utilization of enol derivatives.[4] The first direct catalytic asymmetric aldol reaction in the presence of a chiral catalyst has recently been reported by Shibasaki et al.[6a] In particular, heterobimetallic complexes have been found to be suitable catalysts.[6] These catalysts can be regarded as enzyme mimics of the metal-containing aldolases of type II (with a zinc cofactor) and they gave excellent yields and enantioselectivities.

In contrast L-proline, which has been used by List et al.,[3] acts as an enzyme mimic of the metal-free aldolase of type I. Similarly to this enzyme, L-proline catalyzes the direct aldol reaction according to an enamine mechanism. Thus, for the first time a mimic of the aldolase of type I was found. The close relation between the reaction mechanism of the aldolase of type I[4b] and the postulated mechanism of the L-proline-catalyzed direct aldol reaction[3] is shown in a graphical comparison in Scheme 2. In both cases the formation of the enamines **IIa** and **IIb**, respectively, represents the initial step. These reactions are carried out starting from the corresponding ketone and the amino functionality of the enzyme or L-proline. The conversion of the enamine intermediates **IIa** and **IIb**, respectively, with an aldehyde, and the subsequent release of the catalyst furnishes the aldol product.

However, a difference between both catalytic cycles can be seen in the reaction sequence for the formation of the

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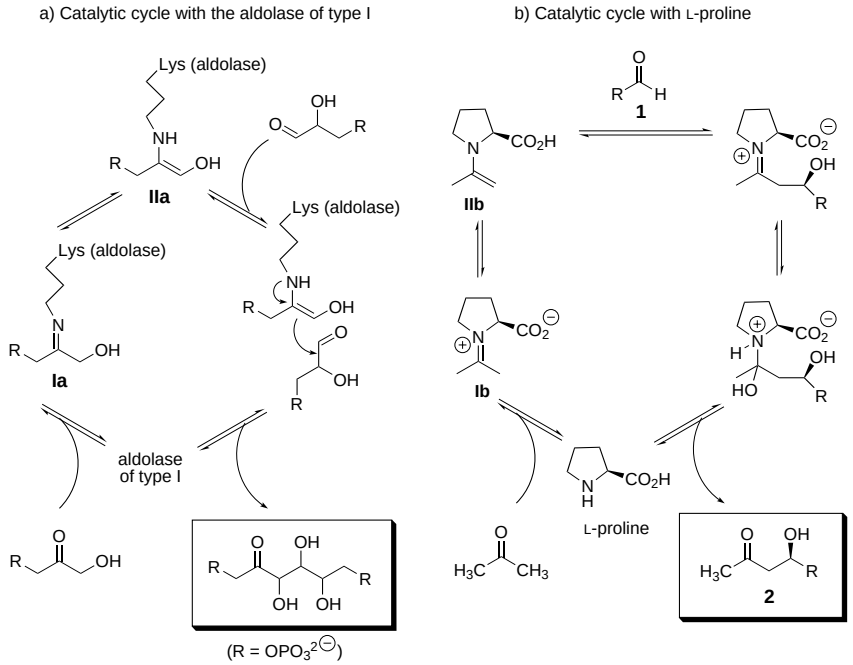


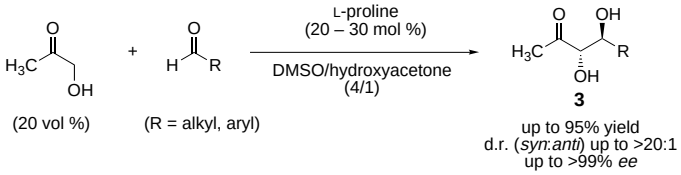
Scheme 2. The catalytic cycles of the direct aldol reaction with aldolase of type I (a) or L-proline (b).

enamines which are key intermediates of these aldol reactions. In the case of the aldolase of type I a primary amino function of the enzyme is used for the formation of a neutral imine (**Ia**), while the enamine synthesis proceeds through a positive iminium system (**Ib**) when starting from L-proline (Scheme 2). In this connection, investigations by List et al. on the dependence of the catalytic potential from the type of amino acid are of particular interest. In these studies it has been shown that for the catalytic activity the pyrrolidine cycle (in L-proline) is required as well as the carboxylic acid group.[3]

Promising prospects for synthetic applications in the future were opened up by List et al.'s experimental studies into the substrate range (Scheme 1). The reaction proceeds well when using aromatic aldehydes as the starting material, with enantioselectivities of 60–77% *ee* and yields of up to 94%. The direct L-proline-catalyzed aldol reaction proceeds very efficiently when using isobutyraldehyde as a substrate. For this reaction the product **2c** has been obtained in a very good yield of 97% and with an excellent enantioselectivity of 96% *ee*.

The concept of the proline-catalyzed aldol reaction has recently been extended by List et al. towards the synthesis of aldol products with two stereogenic centers.[7] The desired *anti*-diols have been obtained in a regio-, diastereo- and enantioselective step starting from achiral compounds. Impressive diastero- and enantioselectivities were observed, with a diastereomeric ratio up to >20:1 and *ee* values of up to >99% (Scheme 3). In addition, the reaction leads to a high regioselectivity, >20:1.

From an industrial point of view, the following characteristics of these aldol reactions developed by List et al. are noteworthy and could make this process into a synthetic alternative for existing asymmetric methods: the *direct* aldol reaction possesses a high synthetic value, since the use of modified starting materials is not necessary, and the ketones can be used directly instead of enol derivatives. Furthermore, the price of L-proline—which is available on technical scale in both enantiomeric forms—is only about 40 $ kg^{-1}. This represents a highly economically attractive access to a chiral catalyst—in particular compared with other types of chiral catalysts.[8] In addition, the possibility of easily separating the proline catalyst from the product and recovering it by aqueous work-up (due to its water solubility) is also of economical interest. At present, the increase of the enantioselectivity and the improvement of the substrate range indicate the challenge of the future. Such improvements could enable the realization of a technical applicability of the direct asymmetric aldol reaction using L-proline. Another disadvantage is the large excess of the ketone component. Furthermore, for an efficient catalytic process, a decrease of the required catalytic amount of 20–30 mol% would be desirable.



Scheme 3. Diastereo- und enantioselective aldol reactions.

Nevertheless, the aldol reaction with L-proline as an enzyme mimic is a successful example for the concept of using simple organic molecules as chiral catalysts. However, this concept is not limited to selected enzymatic reactions, but opens up a general perspective for the asymmetric design of a multitude of catalytic reactions.[2, 9–14] This has also been demonstrated by publications in recent months about developments in the field of "asymmetric syntheses with chiral organic molecules as catalysts". In the following paragraphs this will be exemplified by selected excellent contributions (Scheme 4 and Scheme 5).

To start with a further application of L-proline as a catalyst in asymmetric synthesis, List developed an efficient three-component Mannich reaction for the preparation of β-amino ketones.[9] In the presence of L-proline as a catalyst the Mannich product **4** has been obtained in 50% yield and with 94% *ee* (Equation (1) in Scheme 4). This method can be applied to a series of different aldehydes, whereby *ee* values of up to 96% are obtained. It is noteworthy that—similiarly to the proline-catalyzed aldol reaction—the Mannich reaction can also be extended to an enantio- and diastereoselective process. So, the *vic*-amino alcohol **5** is formed with a

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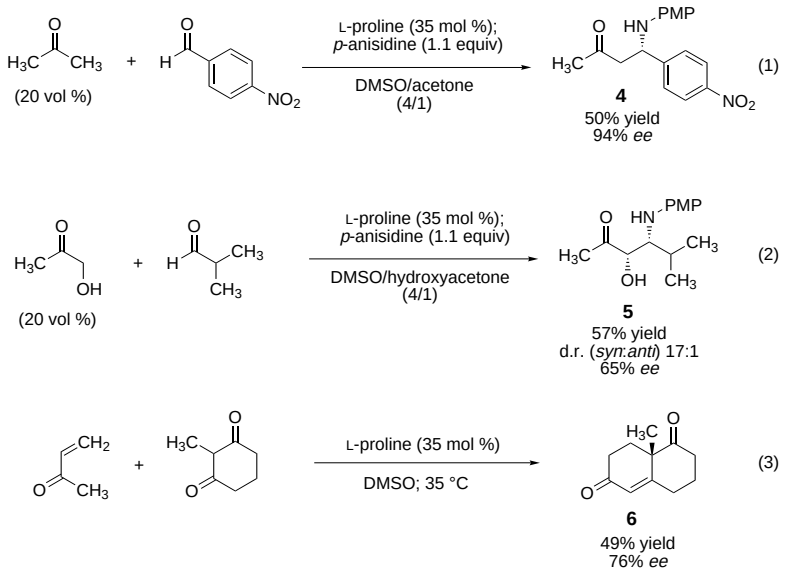
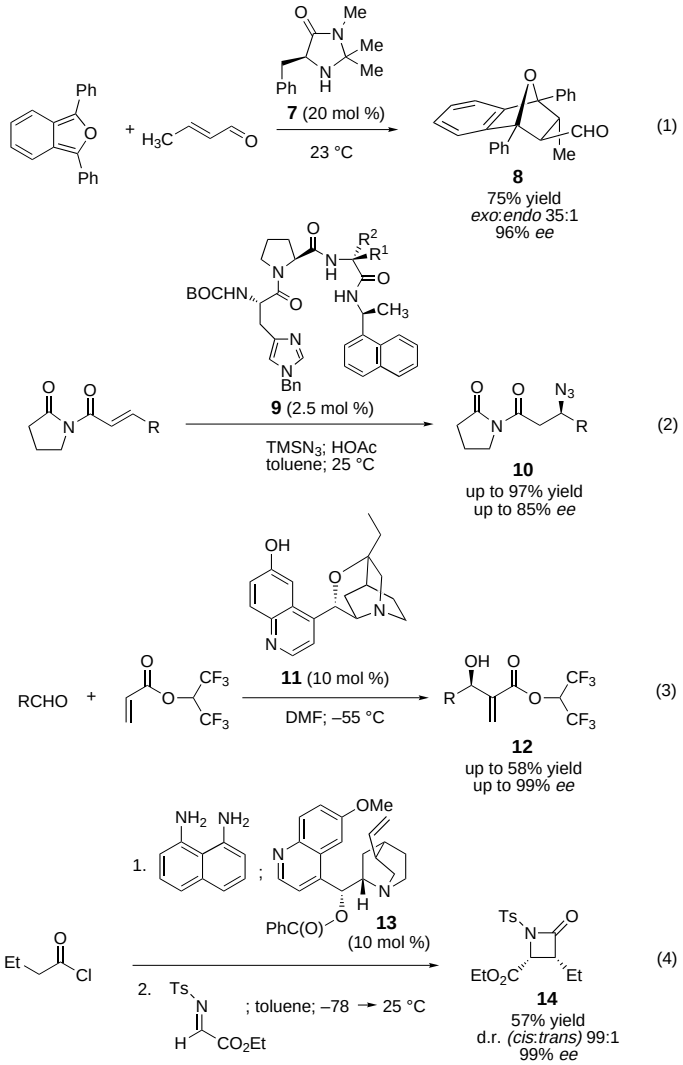


Scheme 4. Further asymmetric reactions with L-proline as a catalyst. PMP = *p*-methoxyphenyl.



Scheme 5. Current contributions in asymmetric synthesis with small organic molecules as catalysts. BOC = *tert*-butoxycarbonyl, Bn = benzyl, TMS = trimethylsilyl, Ac = acetyl, Ts = *p*-toluenesulfonyl.

diastereomeric ratio of 17:1 and an enantioselectivity of 65 % *ee* (Equation (2) in Scheme 4).

In addition, Bui and Barbas III reported an optimized protocol for the Hajos-Eder-Sauer-Wiechert reaction, which was found in the 1970s. This reaction furnishes the chiral Wieland–Miescher ketone **6**. It has now been shown, that this synthesis (which comprises three reactions) can be carried out as a one-pot synthesis (49 % yield, 76 % *ee*, Equation (3) in Scheme 4).[10] Proline functions as an efficient catalyst for all three reaction steps (Michael addition, cyclization, and dehydratization).

From a mechanistic point of view, an approach that is comparable to the L-proline-catalyzed asymmetric reactions has recently been described by MacMillan et al. for the asymmetric catalytic Diels–Alder reaction.[11] As a catalyst the chiral amino acid derivative **7** was used. The catalytic cycle is again based on the formation of an enamine as a key step; the enamine is formed from an amino functionality (of **7**) and the C=O bond of the α,β-unsaturated carbonyl compound. This "organo-catalytic" Diels–Alder reaction proceeds with a high diastereoselectivity (*exo*:*endo* ratio of up to 35:1) and with up to 96 % *ee* (Equation (1) in Scheme 5).

An asymmetric version of a Michael addition can be also realized with simple chiral organic molecules as catalysts. This has been demonstrated by Miller et al. for the addition of an azide to α,β-unsaturated carbonyl compounds.[12] In the presence of the tripeptide **9** as the catalyst (2.5 mol %) the products **10** have been formed in excellent yields and with up to 85 % *ee* (Equation (2) in Scheme 5). In addition, this reaction represents an attractive access to β-amino acids.

Recently, Hatakeyama et al. succeeded in developing the first highly efficient asymmetric catalytic Baylis–Hillman reaction.[13] It is remarkable that this was also achieved by using the concept of small organic molecule catalysis. In the presence of 10 mol % of catalyst **11** the products **12** have been obtained with enantioselectivities of 90 % *ee*, in many cases even of up to 99 % *ee*. Interestingly, in the case of this reaction with the alkaloid derivative **11**, a chiral (tertiary) amine structure has once again been found to be an efficient catalyst (Equation (3) in Scheme 5).

A further application of nucleophilic amines as chiral catalysts has been reported by Lectka et al. in the first highly enantioselective synthesis of β-lactam ring systems with one or two stereogenic centers.[14] In the first step a ketene is formed from the corresponding acid chloride. Subsequently, the ketene reacts with an imine in a diastereo- and enantioselective reaction under formation of the β-lactam. For example, the preparation of the pharmaceutically interesting product **14** has been realized with a diastereomeric ratio of 99:1 and an *ee* value of 99 % (Equation (4) in Scheme 5).

In conclusion, the recent contributions by List et al., as well as MacMillan, Miller, Barbas III, Hatakeyama, and Lectka with their respective co-workers, towards the application of simple small molecules as efficient chiral catalysts in asymmetric synthesis appear to be very interesting for chemists

from academia as well as from industry. Without doubt it is also surprising to observe that a simple amino acid molecule—as described by List et al.—can, in principle, act like an enzymatic system, thus representing an efficient enzyme mimic.

[1] For a comprehensive summary of methods in asymmetric catalysis, see: a) G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann, *Methods Org. Chem. (Houben-Weyl) 1st ed.*, Vol. E21, **1995**; b) E. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis*, *Vol. 1–3*, Springer, Heidelberg, **1999**.

[2] For selected previous contributions about the application of simple organic molecules as chiral catalysts, see: a) asymmetric hydrocyanation using cyclic dipeptides: K. Tanaka, A. Mori, S. Inoue, *J. Org. Chem.* **1990**, *55*, 181; b) asymmetric hydrocyanation using a chiral imine: M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901; c) asymmetric hydrocyanation using chiral bicyclic guanidine derivatives: E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157; d) the Hajos-Eder-Sauer-Wiechert reaction with proline: C. Agami, N. Platzer, H. Sevestre, *Bull. Soc. Chim. Fr.* **1987**, *2*, 358, and references therein; e) asymmetric Michael additions with alkali metal salts of proline: M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520, and references therein.

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

[4] For a review about the asymmetric catalytic aldol reaction, see: a) H. Gröger, E. M. Vogl, M. Shibasaki, *Chem. Eur. J.* **1998**, *4*, 1137; b) T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.

[5] This also means that a further reaction step—either deprotonation or silylation—that would be necessary to prepare the required enolates and enol ethers, respectively, can be avoided.

[6] a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871; b) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168.

[7] W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386.

[8] The use of proline analogues which are waste materials in industrial processes might be also a starting point for further optimization; for selected contributions in this field, see: a) J. Wilken, C. Thorey, H. Gröger, D. Haase, W. Saak, S. Pohl, J. Muzart, J. Martens, *Liebigs Ann.* **1997**, 2133; b) J. Wilken, J. Martens, *Liebigs Ann.* **1997**, 563; c) S. Wassmann, J. Wilken, J. Martens, *Tetrahedron: Asymmetry* **1999**, *10*, 4437.

[9] B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336.

[10] T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951.

[11] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.

[12] T. E. Horstmann, D. J. Guerin, S. J. Miller, *Angew. Chem.* **2000**, *112*, 3781; *Angew. Chem. Int. Ed.* **2000**, *39*, 3635.

[13] Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219.

[14] A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831.

Diamond Surfaces: Just Big Organic Molecules?

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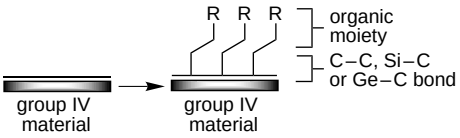
While the organometallic surface chemistry of oxide-free semiconducting group IV materials has been dabbled in since the early 1960s,[1] an incredible explosion of interest and resources directed to this area has taken place in the latter half of the 1990s (Scheme 1).[2] Silicon has received the bulk of the attention because of its applications in micro- and optoelectronic devices, MEMs (microelectromechanical machines), and sensors, to name a few.[3] Derivatization through Si–C bonds appears promising due to the stability of this bond and to tap into the vast repertoire of known organic reactions that will allow for precise tailoring of surface characteristics and functions.[2] Recent work concerning silicon's heavier congener, germanium, appears to demonstrate similar reactivity patterns under ultrahigh vacuum (UHV) conditions to that of silicon, allowing access to Ge–C derivatized surfaces, although much research remains to be done to generalize this.[4]



Scheme 1. Modification of the surfaces of group IV elements.

The surface chemistry of silicon's more "northerly" and expensive neighbor, carbon in form of diamond, is even more poorly understood.[5] The chemistry of the unsaturated carbon allotropes, including C_{60} and carbon nanotubes, have been, and are, the subject of intense investigation.[6] Unfortunately, the inertness at room temperature and expense of studying diamond has inhibited the same level of fundamental research. Because of the unique characteristics of diamond, such as mechanical hardness, wide band gap, and optical transparency, among others, interest in diamond surface chemistry has both academic and potential technological appeal.[7]

One of the more pressing questions concerning diamond reactivity is whether its surface chemistry parallels that of Si(100) and Ge(100), or is it more similar to solution phase, molecular organic compounds? Certainly, molecular silicon and germanium compounds have differing reactivity from structurally similar carbon-based molecules in heterolytic reactions due to the availability of empty *n*d orbitals, which

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