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Introduction: Organocatalysis – From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis

''Chemists – the transformers of matter''. This quotation, taken from the autobiography ''The Periodic Table'' by Primo Levi, illustrates one of the major goals of chemistry – to provide, in a controlled and economic fashion, valuable products from readily available starting materials. In organic chemistry ''value'' is directly related to purity; in most instances this implies that an enantiomerically pure product is wanted. In recent years the number of methods available for high-yielding and enantioselective transformation of organic compounds has increased tremendously. Most of the newly introduced reactions are catalytic in nature. Clearly, catalytic transformation provides the best ''atom economy'', because the stoichiometric introduction and removal of (chiral) auxiliaries can be avoided, or at least minimized [1, 2].

Until recently, the catalysts employed for enantioselective synthesis of organic compounds such as pharmaceutical products, agrochemicals, fine chemicals, or synthetic intermediates, fell into two general categories – transition metal complexes and enzymes. In 2001 the Nobel Prize in Chemistry was awarded to William R. Knowles and Ryoji Noyori ''for their work on chirally catalyzed hydrogenation reactions'', and to K. Barry Sharpless ''for his work on chirally catalyzed oxidation reactions''. Could there be a better illustration of the importance of asymmetric catalysis? For all three laureates the development of chiral transition metal catalysts was the key to success. It has been a long-standing belief that only man-made transition metal catalysts can be tailored to produce either of two product enantiomers whereas enzymes cannot. This dogma has been challenged in recent years by tremendous advances in the field of biocatalysis, for example the discovery of preparatively useful enzymes from novel organisms, and the optimization of enzyme performance by selective mutation or by evolutionary methods [3, 4]. The recently issued Wiley–VCH book ''Asymmetric Catalysis on Industrial Scale'' (edited by H. U. Blaser and E. Schmidt) [5] vividly illustrates the highly competitive head-to-head race between transition metal catalysis and enzymatic catalysis in contemporary industrial production of enantiomerically pure fine chemicals. At the same time, the complementary character of both types of catalyst becomes obvious.

Between the extremes of transition metal catalysis and enzymatic transformations, a third approach to the catalytic production of enantiomerically pure organic compounds has emerged – *organocatalysis*. *Organocatalysts* are purely ''organic''

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger

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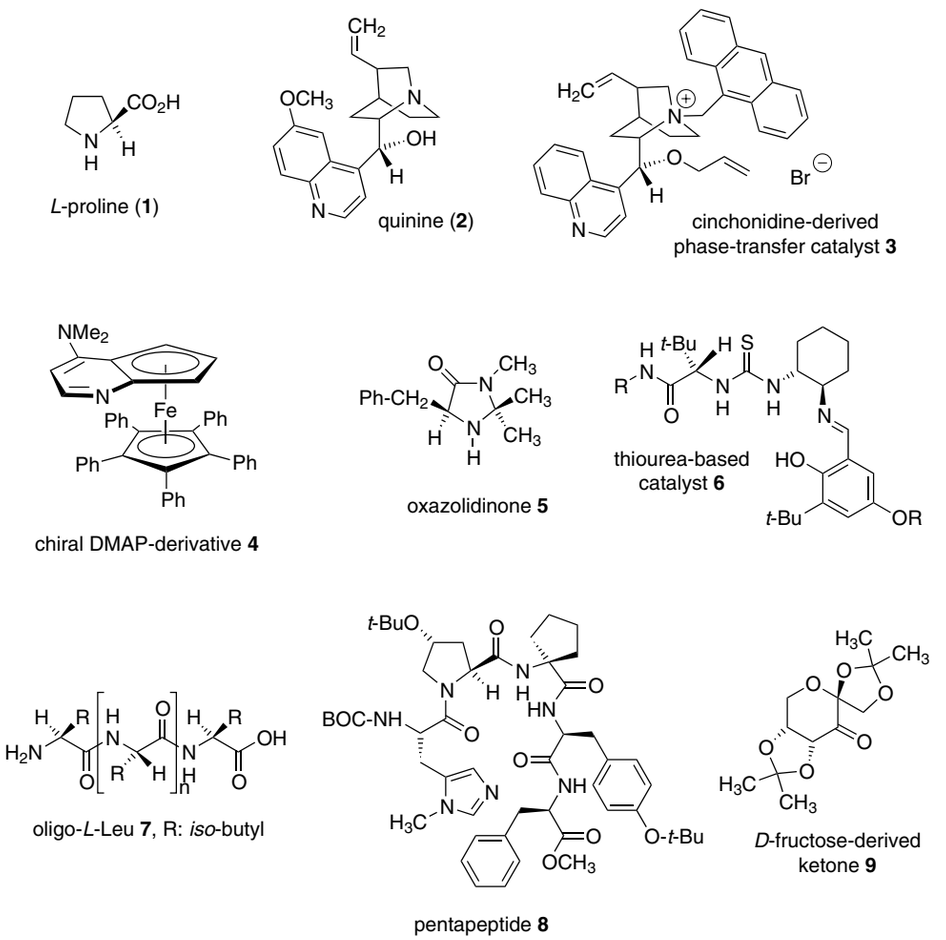
molecules, i.e. composed of (mainly) carbon, hydrogen, nitrogen, sulfur and phosphorus. As opposed to organic ligands in transition metal complexes, the catalytic activity of organocatalysts resides in the low-molecular-weight organic molecule itself, and no transition metals (or other metals) are required. Organocatalysts have several advantages. They are usually robust, inexpensive and readily available, and non-toxic. Because of their inertness toward moisture and oxygen, demanding reaction conditions, for example inert atmosphere, low temperatures, absolute solvents, etc., are, in many instances, not required. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination, e.g. pharmaceutical products. A selection of typical organocatalysts is shown in Scheme 1.1. Proline (**1**), a chiral-pool compound which catalyzes aldol and related reactions by iminium ion or enamine pathways, is a prototypical example (List et al.). The same is true for cinchona alkaloids such as quinine (**2**), which has been abundantly used as a chiral base (Wynberg et al.) or as a chiral nucleophilic catalyst (Bolm et al.) and which has served as the basis for many highly enantioselective phase-transfer catalysts. The latter are exemplified by **3** (Corey, Lygo et al.) which enables, e.g., the alkylation of glycine imines with very high enantioselectivity. The planar chiral DMAP derivative **4** introduced by Fu et al. is extremely selective in several nucleophilic catalyses. Although it is a ferrocene it is regarded an organocatalyst because its ''active site'' is the pyridine nitrogen atom.

Amino acid-derived organocatalysts such as the oxazolidinone **5** introduced by MacMillan et al. or the chiral thiourea **6** introduced by Jacobsen et al. have enabled excellent enantioselectivity in, e.g., Diels–Alder reactions of α,β-unsaturated aldehydes (oxazolidinone **5**) or the hydrocyanation of imines (thiourea **6**). Peptides, such as oligo-L-leucine (**7**) have found use in the asymmetric epoxidation of enones, the so-called Juliá–Colonna reaction (recently studied by Roberts, Berkessel et al.). Peptides are ideal objects for combinatorial optimization/selection, and the pentapeptide **8** has been identified by Miller et al. as an artificial kinase that enables highly enantioselective phosphorylation. The chiral ketone **9** introduced by Shi et al. is derived from D-fructose and catalyzes the asymmetric epoxidation of a wide range of olefins with persulfate as the oxygen source. This small (and by no means complete) selection of current organocatalysts is intended to illustrate the wide range of reactions that can be catalyzed and the ready accessibility of the organocatalysts applied. With the exception of the planar chiral DMAP derivative **4**, all the organocatalysts shown in Scheme 1.1 are either chiral-pool compounds themselves (**1**, **2**), or they are derived from these readily available sources of chirality by means of a few synthetic steps (**3**, **5**–**9**).

The historic roots of organocatalysis go back to the use of low-molecular-weight compounds in an attempt both to understand and to mimic the catalytic activity and selectivity of enzymes. As early as 1928 the German chemist Wolfgang Langenbeck published on ''Analogies in the catalytic action of enzymes and definite organic substances'' [6]. The same author coined the term ''Organic Catalysts'' (''Organische Katalysatoren'') [7] and, in 1949, published the second edition (!) of the first book on ''Organic Catalysts and their Relation to the Enzymes'' (''Die

A selection of typical organocatalysts:

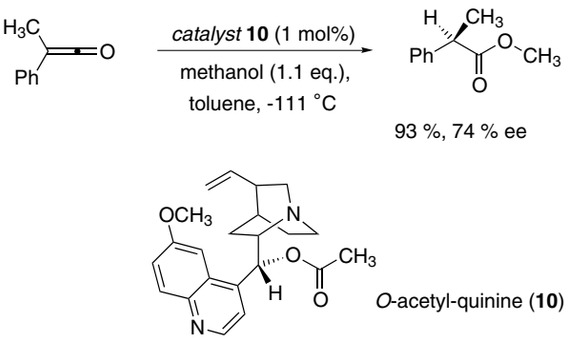


Scheme 1.1

organischen Katalysatoren und ihre Beziehungen zu den Fermenten'') [8]. It is fascinating to see that, for example, the use of amino acids as catalysts for aldol reactions was reported for the first time in 1931 [9]. Refs. [6]–[9] also reveal that the conceptual difference between covalent catalysis (called ''primary valence catalysis'' at that time) and non-covalent catalysis was recognized already and used as a means of categorization of different mechanisms of catalysis. As discussed in Chapter 2, this distinction between ''covalent catalysis'' and ''non-covalent catalysis'' is still viable and was clearly a farsighted and revolutionary concept almost 80 years ago.

The first example of an *asymmetric organocatalytic reaction* was reported by Bredig and Fiske as early as 1912, i.e. ca. 90 years ago [10]. These two German chemists reported that addition of HCN to benzaldehyde is accelerated by the alkaloids quinine (**2**) and quinidine and that the resulting cyanohydrins are optically active and of opposite chirality. Unfortunately, the optical yields achieved in most of these early examples were in the range $\leq 10\%$ and thus insufficient for preparative purposes. Pioneering work by Pracejus et al. in 1960, again using alkaloids as catalysts, afforded quite remarkable 74% ee in the addition of methanol to phenylmethylketene. In this particular reaction 1 mol% *O*-acetylquinine (**10**, Scheme 1.2) served as the catalyst [11].

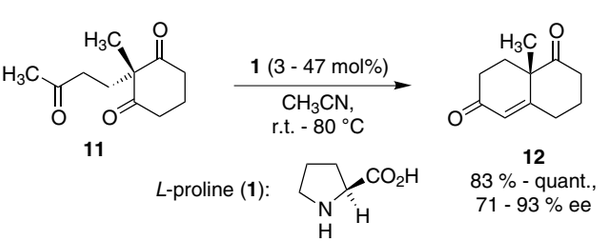
Alkaloid-catalyzed addition of methanol to a prochiral ketene by *Pracejus et al.* (ref. 11):



Scheme 1.2

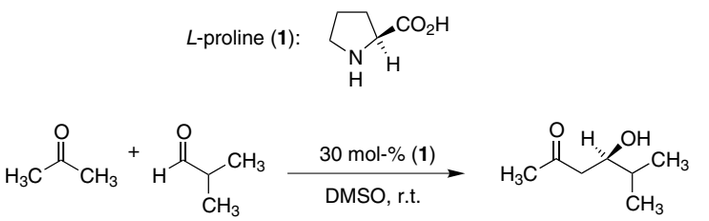
Further breakthroughs in enantioselectivity were achieved in the 1970s and 1980s. For example, 1971 saw the discovery of the Hajos–Parrish–Eder–Sauer–Wiechert reaction, i.e. the proline (**1**)-catalyzed intramolecular asymmetric aldol cyclodehydration of the achiral trione **11** to the unsaturated Wieland–Miescher ketone **12** (Scheme 1.3) [12, 13]. Ketone **12** is an important intermediate in steroid synthesis.

The *Hajos-Parrish-Eder-Sauer-Wiechert*-reaction (refs. 12,13):

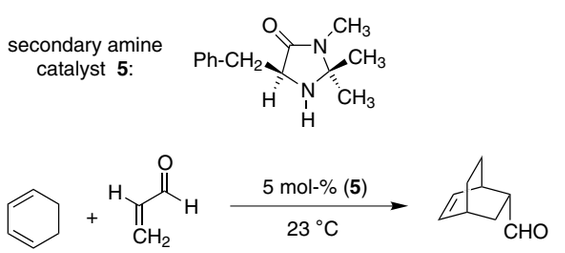


Scheme 1.3

Proline (**1**)-catalyzed intermolecular aldol reaction, *List et al.* (refs. 14,15):



Secondary amine **5**-catalyzed Diels-Alder reaction, *MacMillan et al.* (ref. 15):

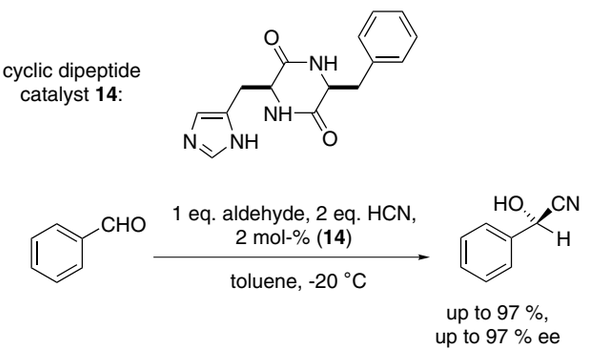


Scheme 1.4

Surprisingly, the catalytic potential of proline (**1**) in asymmetric aldol reactions was not explored further until recently. List et al. reported pioneering studies in 2000 on *inter*molecular aldol reactions [14, 15]. For example, acetone can be added to a variety of aldehydes, affording the corresponding aldols in excellent yields and enantiomeric purity. The example of *iso*-butyraldehyde as acceptor is shown in Scheme 1.4. In this example, the product aldol **13** was obtained in 97% isolated yield and with 96% ee [14, 15]. The remarkable chemo- and enantioselectivity observed by List et al. triggered massive further research activity in proline-catalyzed aldol, Mannich, Michael, and related reactions. In the same year, MacMillan et al. reported that the phenylalanine-derived secondary amine **5** catalyzes the Diels–Alder reaction of α,β-unsaturated aldehydes with enantioselectivity up to 94% (Scheme 1.4) [16]. This initial report by MacMillan et al. was followed by numerous further applications of the catalyst **5** and related secondary amines.

A similarly remarkable event was the discovery of the cyclic peptide **14** shown in Scheme 1.5. In 1981 this cyclic dipeptide – readily available from L-histidine and L-phenylalanine – was reported, by Inoue et al., to catalyze the addition of HCN to

The *cyclo*-*L*-His-*L*-Phe catalyst **14** by *Inoue et al.* (refs. 17,18):

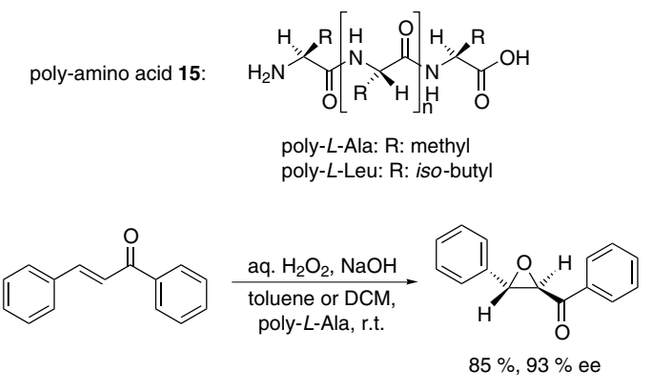


Scheme 1.5

benzaldehyde with up to 90% ee [17, 18] (Scheme 1.5). Again, this observation sparked intensive research in the field of peptide-catalyzed addition of nucleophiles to aldehydes and imines.

Also striking was the discovery, by Juliá, Colonna et al. in the early 1980s, of the poly-amino acid (**15**)-catalyzed epoxidation of chalcones by alkaline hydrogen peroxide [19, 20]. In this experimentally most convenient reaction, enantiomeric excesses > 90% are readily achieved (Scheme 1.6).

The *Juliá-Colonna* epoxidation of chalcones (refs. 19, 20):

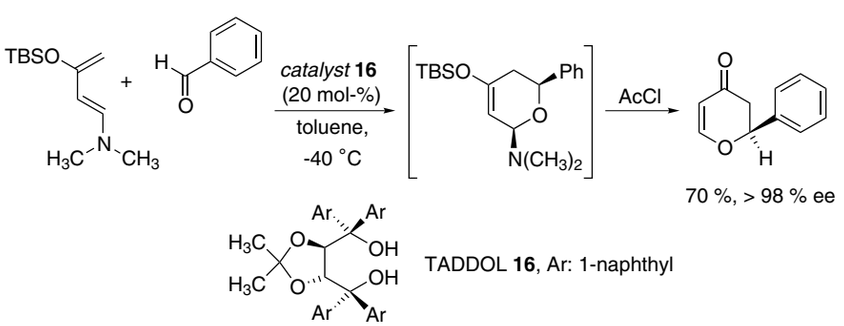


Scheme 1.6

As discussed above, asymmetric organocatalysis is, in principle, an "old" branch of organic chemistry, with its beginnings dating back to the early 20th century (for example the first asymmetric hydrocyanation of an aldehyde in 1912). This

initial phase of organocatalysis was, however, mainly mechanistic/biomimetic in nature, and the relatively low enantiomeric excess achieved prohibited "real" synthetic applications. Isolated examples of highly enantioselective organocatalytic processes were reported in the 1960s to the 1980s, for example the alkaloid-catalyzed addition of alcohols to prochiral ketenes by Pracejus et al. (Scheme 1.2) [11], the Hajos–Parrish–Eder–Sauer–Wiechert reaction (Scheme 1.3) [12, 13], the hydrocyanantion of aldehydes using the Inoue catalyst **14** (Scheme 1.5) [17, 18], or the Juliá–Colonna epoxidation (Scheme 1.6) [19, 20], but the field still remained "sub-critical". Now, triggered by the ground-breaking work of List, MacMillan, and others in the early 2000s, the last ca. five years have seen exponential growth of the field of asymmetric organocatalysis. Iminium and enamine-based organocatalysis now enables cycloadditions, Michael additions, aldol reactions, nucleophilic substitutions, and many other transformations with excellent enantioselectivity; new generations of phase-transfer catalysts give almost perfect enantiomeric excesses at low catalyst loadings; chiral ureas and thioureas are extremely enantioselective catalysts for addition of a variety of nucleophiles to aldehydes and imines; and so forth. Organocatalysis currently seems to be in the state of a "gold rush" and at short intervals new "gold mines" are discovered and reported in the literature. A very recent example is the finding by Rawal et al. that hetero-Diels–Alder reactions – a classical domain of metal-based Lewis acids – can be effected with very high enantioselectivity by hydrogen bonding to chiral diols such as TADDOL (**16**, Scheme 1.7) [21].

The TADDOL (**16**) catalyzed hetero-*Diels-Alder*-reaction
by *Rawal et al.* (ref. 21):



Scheme 1.7

Compared with earlier approaches, both prospecting and exploiting of the fields is greatly aided and accelerated by advanced analytical technology and, in particular, by synergism with theoretical and computational chemistry. Overall, asymmetric organocatalysis has matured in recent few years into a very powerful, practical, and broadly applicable third methodological approach in catalytic asymmetric

synthesis [22]. This book is meant as a "mise au point" dated 2005; it is hoped it will satisfy the expectations of readers looking for up-to-date information on the best organocatalytic methods currently available for a given synthetic problem and those of readers interested in the development of the field.

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