Introduction

Without any doubt, the asymmetric aldol reaction constitutes one of the most important topics in modern catalytic synthesis.[1] Furthermore, the fundamental mechanistic principles observed for the aldol reaction have had a strong influence on the work which led to the establishment of asymmetric routes of many other reaction types. Since the discovery of the catalytic asymmetric aldol reaction with enolsilanes by Mukaiyama et al.,[2] steady improvements have been made.[3, 4] For this conventional type of aldol reaction a series of chiral tin and boron catalysts (usually around 20 mol % catalyst),[3, 4] which act as Lewis acids activating the aldol acceptor, have been shown to be quite efficient, even though until recently some synthetic limitations still remained.[5] During the last few years, however, several new concepts have been developed, all based on innovative principles, which have not only led to a more efficient aldol reaction but which also promise to become fundamental in catalytic asymmetric synthesis in general. This recent progress includes work on a) the classic aldol reaction using silyl enolates in the presence of new transition metal based catalysts, b) the first aldol reactions which allow the use of other O-silylated ketones as starting materials, and c) the first aldol reactions in the presence of chiral nonmetallic Lewis acids or Lewis bases as catalysts.

Discussion

A. The classic aldol reaction using silyl enolates in the presence of new transition metal based catalysts: An important development of the asymmetric aldol reaction entirely based on the principles of conventional Mukaiyama-type catalysis was realized with chiral titanium(IV) complexes. Work in this area was reported independently by the groups of Mikami,[6] Keck,[7] and Carreira,[8] who successfully applied different types of BINOL-based titanium(IV) complexes as highly efficient catalysts (Scheme 1; BINOL = 2,2'-dihydroxy-1,1'-biphenyl). Mikami’s work is impressive in its scope, covering a broad range of functionalized aldehydes and thioester-derived ketene silyl acetals like 1a. Even in the presence of only 5 mol % catalyst 2a, which was prepared from Ti(O-iPr)2Cl2 and (R)-BINOL in the presence of molecular sieves, ee values up to 96 % have been obtained.[6a] Moreover, the Mikami system also served as an efficient catalyst for a diastereoselective and enantioselective aldol reaction using silyl enolates.
reaction of ketone enol silyl ethers with glyoxylates (sylnanti ratio 99:1; ee (syn) up to >99%).

A similar titanium(v) system 2b (10–20 mol%) was reported by Keck et al., who used Ti(O–iPr)₄ instead of Ti(O–iPr)Cl as the titanium source. With a broad variety of aldehydes high enantioselectivities between 89% and >98% ee could be achieved by using the thiocarbonate derivatives 1a.⁵

Although the exact structures of the TiIV–BINOL catalysts 2a and 2b have not yet been clarified in detail, observed nonlinear effects cannot be accomodated on the basis of a monomeric structure alone.⁶ The development of a new BINOL-based ligand (with an imine functionality incorporated) by Carreira et al.⁶ led to a further extension of the titanium-catalyzed method allowing the use of O-silyl O-alkyl ketene acetals 1b. In the presence of only 2–5 mol% of the corresponding catalyst 3, the reaction proceeded with excellent enantioselectivities between 94% and 97% ee.⁷

For the catalytic aldol reaction using enolsilanes, impressive new members of the catalyst family combined with an innovative catalytic concept have been presented by Evans et al.⁸ The well-designed CuII complexes Cu-4 or related pybox derivatives can act as effective enantioselective catalysts by activating α-alkoxy aldehydes and α-keto esters, respectively, through bidentate coordination. The resulting aldol adducts were obtained with up to 99% ee and 100% yield even in the presence of only 0.5 mol% catalyst (for a representative example, see Scheme 2).⁹-¹₀ In addition, the reaction is very general with respect to the enolsilane derivatives. The five-membered catalyst–substrate chelate 1 (Scheme 2) is a strict requirement for stereoselectivity, and the geometry around copper has been shown to be square planar in case of Cu-4 (and square pyramidal in case of the related pybox derivatives) on the basis of the experimental results and ESR spectroscopic experiments.¹¹-¹² This organizational feature with two substrate oxo groups coordinated to the center ion (here Cu) was not known for any of the catalysts previously reported.

An extension of this method to a diastereo- and enantioselective synthetic task was introduced by Evans et al. starting from substituted enolsilanes.¹³-¹⁴ It was possible to achieve high syn selectivity (syn/anti ratio up to 98:2) in combination with excellent enantioselectivities (syn up to 99% ee, Scheme 3). It is noteworthy that (Z)- and (E)-enolsilane isomers react in a stereoeconvergent manner. Interestingly, replacing CuII by SnII as center ion in 4 and the related pybox complexes favored the formation of the anti adducts in remarkable ees (antisyn ratio up to 99:1; anti up to 99% ee),¹⁴ thereby constituting one of the first examples of a highly enantioselective, Lewis acid catalyzed anti-aldol reaction (Scheme 3).¹⁵ Thus, very efficient diastereo- and enantioselective approaches to syn as well as anti aldol adducts are accessible by Evans’ catalytic bichelating concept.

Obtaining both enantiomers of the syn adduct by using the same initial source of chirality may sound impossible. However, this was recently achieved by Kobayashi et al. by means of SnIII complexes with diamine ligands (5 and 6) based on the l-proline framework as chiral Lewis acids in stoichiometric amounts.¹⁶ Only by modifying the position of the nitrogen around the bicyclic system could both syn enantiomers of the resulting dihydroxythioester derivatives be obtained in high enantioselectivity (syn/anti ratio up to >99:1; syn up to >99% ee; Scheme 4).

A catalytic asymmetric aldol reaction of silyl enolates that is mechanistically different from the above-described Lewis acid mediated processes was found by Shibasaki et al.¹¹ In the presence of isolable air- and moisture-stable PdII-derivatives as catalysts [BINAP = (1,1’-dinaphthylène)-2,2’-d-dibys(diphenylphosphine)], the addition of silyl enol ethers to aldehydes proceeds via a chiral PdII enolate to

Abstract in Japanese:

触媒の不斉アルドール反応は最も重要な有機合成反応の一つである。エノールシル化合物に使われるようなの等による触媒の不斉アルドール反応の開発を契機として種々の進歩が達成されてい る。特にこの二年度間は著しい進歩がなされており、本稿ではこれら の方法論に分けて最近の進歩を概説する。

まずパートAでは、一般的なエノールシルエーテルの由来の触媒の 不斉アルドール反応の発展を概説する。ここで強調されている点 は、三等や、Keck等、Carreira等、Evans等、小林等、さらには 架橋等の不斉触媒の開発とその展望である。

パートBでは、エノールシルエーテル以外の求核剤、すなわち トリフルオルメチレンエーテルやケトンの直接的利用などが中心に講 題される。

最後のパートCでは、[Denmark等による不斉リウム塩基の活 用やChen等による不斉トリフルオルメチレンエーテルの活用による 触媒の不斉アルドール反応の開発が講題される。
give the products in good chemical yield and with enantioselectivity up to 87% ee (Scheme 5). This is the first example of a catalytic asymmetric aldol reaction occurring via a Pd(II) metal enolate. In addition, an interesting feature of this aldol addition is the sensitive role of defined amounts of water in accelerating the reaction.

B. Aldol-type reactions using alternative nucleophiles: A proof that the asymmetric Mukaiyama reaction is not limited to O-silyl enol ethers of ketones, esters, and thioesters but also proceeds efficiently if O-silyl dienolates are utilized was given by Carreira et al. (Scheme 6).\(^{[8b, 14]}\) By employing O-silyl dienolate 7 and 1–3 mol % of the titanium(IV) complex 3, a highly enantioselective direct route to acetooacetate adducts has been made accessible for the first time with high yields and es (up to 94%).

The aldol adducts 8 are interesting precursors for \(\delta\)-hydroxy-\(\beta\)-keto esters and \(\beta,\delta\)-diol esters, which are ubiquitous structural subunits in biologically active natural products.\(^{[8b]}\) Another application of the Carreira catalyst 3 is the aldol reaction of 2-methoxypropene and derivatives thereof, which constitutes a further alternative to the classic enantioselective Mukaiyama aldol addition with silyl enol ethers.\(^{[8c]}\) Most recently it was shown that the same O-silyl dienolates 7 can also react with aromatic, heteroaromatic, or \(\alpha,\beta\)-unsaturated aldehydes to yield the products 8 with es up to 95% in the presence of a new catalyst system consisting of (S)- Tol-BINAP, [Cu(OTf)\(_2\)] and (Bu\(_4\)N)Ph\(_3\)SiF\(_2\).\(^{[15]}\) According to the authors, this system, which contains (S)- Tol-BINAP-CuF\(_2\) as the active catalytic species, is unprecedented as the catalyst complex seems to substitute the silyl group of the O-silyl dienolate 7 before the aldol reaction takes place and does not act as a Lewis acid.

Recent improvements have also been made in approaches that allow the use of types of nucleophiles other than classic silyl enolates. Yamamoto et al. found that tributyltin enolates are suitable surrogates when a chiral BINAP-containing silver(I) complex was utilized as catalyst (ee up to 95%).\(^{[16]}\) In contrast to previous work involving chiral Lewis acids, the application of this catalyst system in a diastereo- and enantioselective synthesis afforded the anti adduct as major diastereomer in high ee, with (\(E\))-enolates as starting materials (\(anti/\text{syn}\) ratio up to 93:7; \(anti\) up to 96% ee; Scheme 7). Using (\(Z\))-enolates, the syn adducts were obtained with syn/anti ratios of up to \>99:1 (syn up to 95% ee). Thus, the diastereoselectivity depends on the geometry of the enol stannane, as illustrated by the transition-state structures Ia and IIb.\(^{[8b]}\)

For the first time even unmodified ketones have been successfully subjected to a direct asymmetric aldol reaction by Shibasaki et al.\(^{[17]}\) The direct aldol reaction, which is known from studies on enzymes, has been realized using the multifunctional Shibasaki catalyst LLB containing both Lewis acidity and Brønsted basicity similar to the corresponding aldolases. In the presence of (\(R\))-LLB, the desired aldol adducts are directly accessible at up to 94% ee, starting from a variety of aldehydes and unmodified ketones (Scheme 8).

Regarding the mechanism of this conversion, the central lanthanum(III) ion should function as a Lewis acid, thereby activating the aldehyde, whereas the lithium binaphthoxide moiety acts as a Brønsted base. The synergetic effect of both
groups (shown in intermediate III) appeared to be responsible for the reaction proceeding without the need for any other activation of the starting materials, especially the ketone component.

C. Aldol reactions in the presence of chiral nonmetallic Lewis acids or Lewis bases as catalysts: Recently Denmark et al. impressively demonstrated that the presence of catalytic amounts of transition metals is no prerequisite for successful asymmetric aldol reactions.[12, 13] In contrast to previously used chiral Lewis acids such as, for example, oxazaborolidines,[4b] which interact with the aldehyde, this concept utilizes chiral bases which seem to coordinate temporarily to the silicon atom of trichlorosilyl enolates like 9 (Scheme 9). Such enolates constitute strongly activated ketones and react spontaneously with a number of aldehydes at \(-80^\circ \text{C}\). The authors first found that in the aldol reaction of 9 catalytic amounts of hexamethyl phosphoramide (HMPA) led to an acceleration of the rate of reaction. After several chiral phosphoramides had been screened as catalysts, 10 mol% of (S,S)-10 (Scheme 9) was found to furnish products in ee up to 97% in nearly quantitative yields. It should be emphasized that in the absence of the catalyst the E-enolate affords mainly the syn adduct (syn/anti ratio 16:1) while in the presence of (S,S)-10 there is a dramatic reversal in diastereoselectivity and the anti-aldol product is preferentially formed (anti/syn ratio up to \(>99:1\); anti up to 97% ee). Hypothetically, the hexacoordinate siliconate species IV has been suggested to be involved in stereoselection.

As a novel nonmetallic Lewis acid catalyst, the chiral triarylcarnenium ion 13 was used by Chen et al. in a Mukaiyama-type reaction leading to enantioselectively enriched aldol products (Scheme 10).[19] Although nonchiral trityl salt-mediated catalytic aldol reactions were reported earlier by Mukaiyama, the construction of a suitable chiral carbenium ion remained a challenge. The ee now reported for the conversion of benzaldehyde and 12 into aldol adduct 14 in the presence of catalytic amounts of the triaryl carbenium ion 13 (10–20 mol%) depends on various factors like the counterion of 13 or the reaction time and does not exceed 40%. However, chiral carbenium ions like 13 may be modified to increase their enantiodiscriminating potential. Surely, chiral trityl salts will be of interest for other catalytic processes as well.

In conclusion, exciting and promising new catalytic concepts for the asymmetric aldol reaction based on different ideas to achieve high stereoselectivity have been developed quite recently. It remains to be seen which of the concepts discussed above will be of broadest generality and which will prove to be a catalyst for stimulating further research.

Acknowledgments: Postdoctoral fellowships from the Japan Science and Technology Corporation (H.G.) and the Japan Society for the Promotion of Science (E.M.V.) are gratefully acknowledged.

Received: February 9, 1997 [C’995]

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[11] In parallel Yamamoto et al. and Denmark et al. also reported about asymmetric anti-aldol reactions. Their concepts are described below.
[14] Independently of Carreira et al., a comparable enantioselective addition of dienolates to aldehydes has also been reported: M. Sato, S. Sunami, Y. Sugita, C. Kaneko, Heterocycles 1995, 41, 1435–1444.