New Catalytic Concepts for the Asymmetric Aldol Reaction

Harald Gröger, Erasmus M. Vogl, and Masakatsu Shibasaki*

Abstract: Mukaiyama's classic catalytic asymmetric aldol reaction with enolsilanes has been improved upon over the years; now new approaches to the reaction have been developed. Those reviewed here are the use of new transition metal based catalysts for the aldol reaction using silyl enolates, the use of other *O*-silylated nucleophiles, tin-modified or even unmodified ketones as substrates, and the use of chiral nonmetallic Lewis acids or Lewis bases as catalysts.

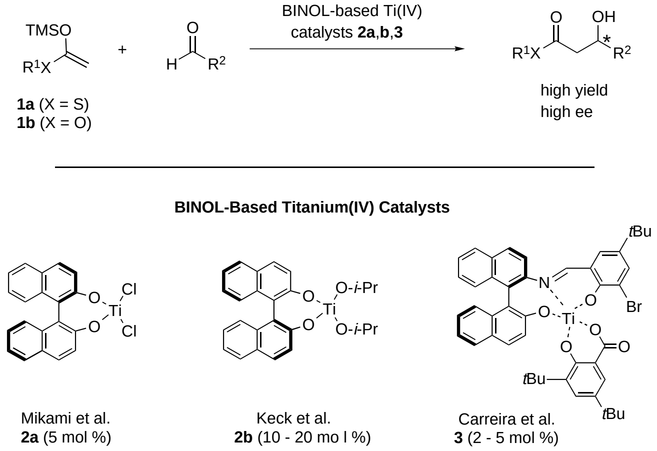
Keywords: aldol reactions · asymmetric catalysis · asymmetric synthesis · C–C coupling · enols

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 nucleophiles as well as *tin-modified* or even *unmodified* 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 $Ti(O-iPr)_2Cl_2$ 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



Scheme 1.

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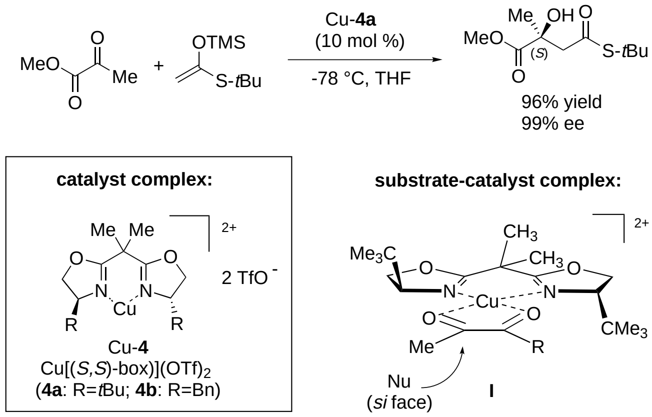
reaction of ketone enol silyl ethers with glyoxylates (*syn*/*anti* ratio 99:1; *ee* (*syn*) up to >99%).[6b]

A similar titanium(IV) system **2b** (10–20 mol%) was reported by Keck et al., who used $Ti(O-iPr)_4$ instead of $Ti(O-iPr)_2Cl_2$ as the titanium source. With a broad variety of aldehydes high enantioselectivities between 89% and >98% *ee* could be achieved by using the thioester derivatives **1a**.[7] Although the exact structures of the Ti^{IV}–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.[6c, 9] The development of a new BINOL-based ligand (with an imine functionality incorporated) by Carreira et al.[8] 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*.[8a]

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.[10] The well-designed Cu^{II} complexes Cu-**4** or related pybox derivatives can act as effective enantioselective catalysts by activating α-alkyloxy 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).[10a] In addition, the reaction is very general with respect to the enolsilane derivatives. The five-membered catalyst–substrate chelate **I** (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.[10a,b] 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.



Scheme 2.

Abstract in Japanese:

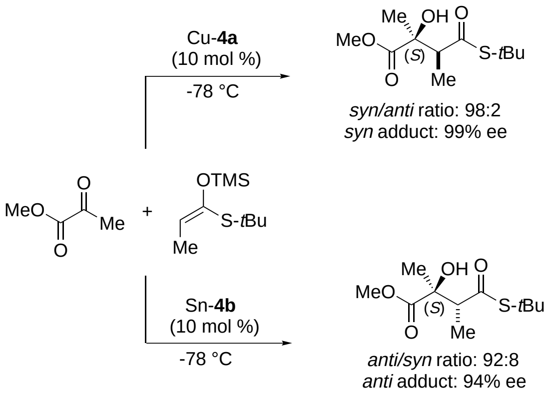
触媒的不斉アルドール反応は最も重要な有機合成反応の一つである。エノールシリルエーテルを活用する向山等による触媒的不斉アルドール反応の開発を契機として様々に着実な進歩が達成されている。特にここ三年間は素晴しい展開がなされており、本稿では三つの方法論に分けて最近の進歩を概観する。

まずパートAでは、一般的なエノールシリルエーテル経由の触媒的不斉アルドール反応の発展を議論する。ここで強調されている点は、三上等、Keck等、Carreira等、Evans等、小林等、さらには柴崎等の不斉触媒の開発とその展開である。

パートBでは、エノールシリルエーテル以外の求核剤、すなわちトリブチルチンエノラートやケトンの直接的利用などが中心に議論される。

最後のパートCでは、Denmark等による不斉ルイス塩基の活用やChen等による不斉トリアリルカルベニウムイオンの活用による触媒的不斉アルドール反応の開発が議論される。

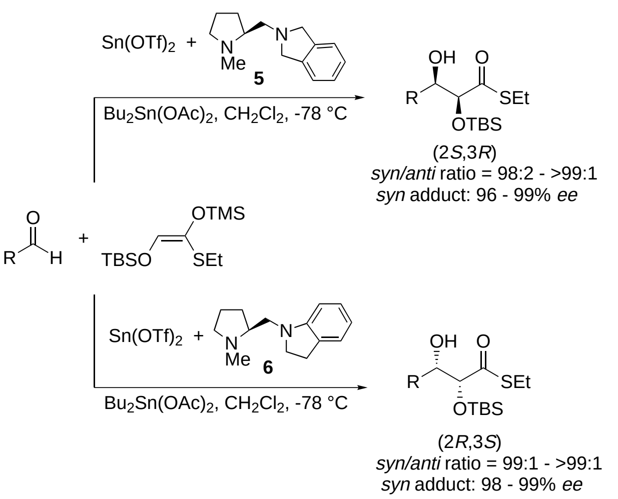
An extension of this method to a diastereo- *and* enantioselective synthetic task was introduced by Evans et al. starting from substituted enolsilanes.[10a,c] It was possible to achieve high *syn* selectivity (*syn*/*anti* ratio up to 98:2) in combination with excellent enantioselectivities (*syn* up to 99% *ee*, Scheme 3). It is noteworthy that (*Z*)- and (*E*)-enolsilane isomers react in a stereoconvergent manner. Interestingly, replacing Cu^{II} by Sn^{II} as center ion in **4** and the related pybox complexes favored the formation of the *anti* adducts in remarkable *ee*s (*anti*/*syn* ratio up to 99:1; *anti* up to 99% *ee*),[10d] thereby constituting one of the first examples of a highly enantioselective, Lewis acid catalyzed *anti*-aldol reaction (Scheme 3).[11] Thus, very efficient diastereo- *and* enantioselective approaches to *syn* as well as *anti* aldol adducts are accessible by Evans' catalytic bichelating concept.



Scheme 3.

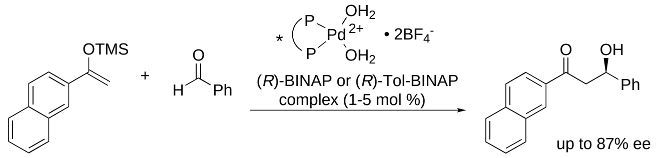
Obtaining *both* enantiomers of the *syn* adduct by using the same initial source of chirality may sound impossible. However, this was recently achieved by Kobayashi et al. by means of Sn^{II} complexes with diamine ligands (**5** and **6**) based on the L-proline framework as chiral Lewis acids in stoichiometric amounts.[12] 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.[13] In the presence of isolable air- and moisture-stable Pd^{II}–BINAP-derived complexes as catalysts [BINAP = (1,1′-dinaphthalene)-2,2′-diylbis(diphenylphosphine)], the addition of silyl enol ethers to aldehydes proceeds *via* a *chiral* Pd^{II} *enolate* to



Scheme 4.

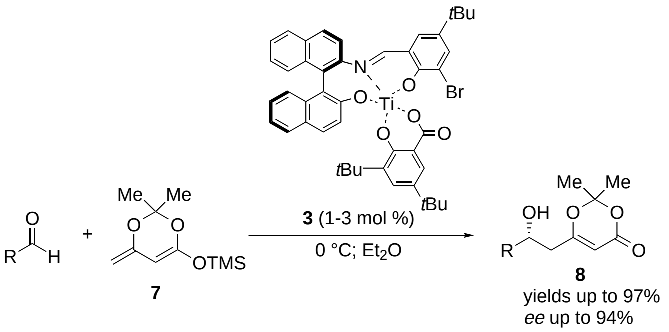
give the products in good chemical yield and with enantioselectivity up to 87% *ee* (Scheme 5). This is the first example of a catalytic asymmetric aldol reaction occurring via a Pd^{II} metal enolate. In addition, an interesting feature of this aldol addition is the sensitive role of defined amounts of water in accelerating the reaction.



Scheme 5.

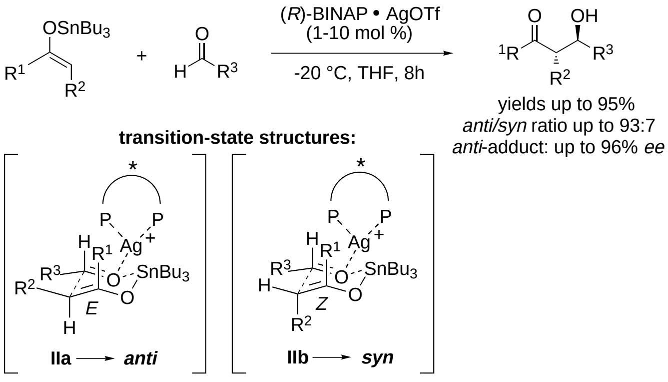
B. Aldol-type reactions using alternative nucleophiles: A proof that the asymmetric Mukaiyama reaction is not limited to *O*-silyl enol ethers of ketones, esters, and thioesters but also proceeds efficiently if *O*-silyl dienolates are utilized was given by Carreira et al. (Scheme 6).[8b, 14] By employing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

The aldol adducts **8** are interesting precursors for *δ*-hydroxy-*β*-keto esters and *β*,*δ*-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 *α*,*β*-unsaturated aldehydes to yield the products **8** with *ee*s 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.



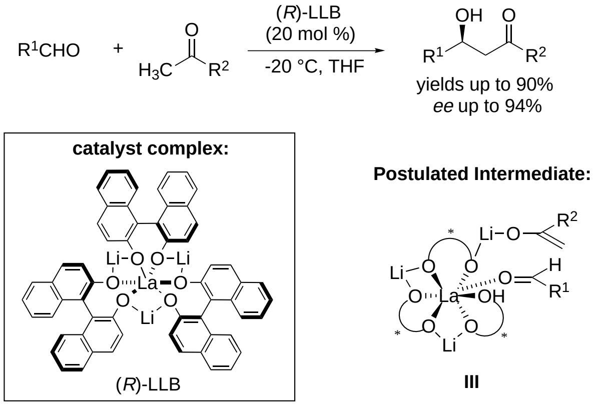
Scheme 6.

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*/*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 **IIa** and **IIb**.[16]



Scheme 7.

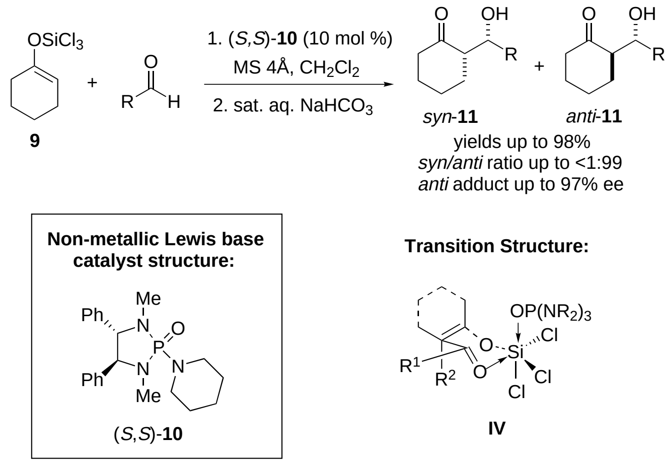
For the first time even unmodified ketones have been successfully subjected to a *direct* asymmetric aldol reaction by Shibasaki et al.[17] The direct aldol reaction, which is known from studies on enzymes, has been realized using the multifunctional Shibasaki catalyst LLB containing both Lewis acidity 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



Scheme 8.

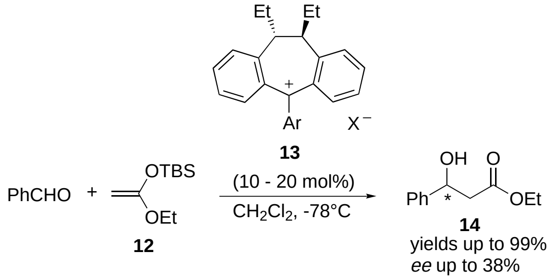
groups (shown in intermediate **III**) appeared to be responsible for the reaction proceeding without the need for any other activation of the starting materials, especially the ketone component.

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 reaction sequences.[5a, 18] 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 $-80\,^{\circ}C$. 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*s up to 97% in nearly quantitative yields. It should be emphasized that in the absence of 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.



Scheme 9.

As a novel *nonmetallic* Lewis acid catalyst, the chiral triarylcarbenium ion **13** was used by Chen et al. in a Mukaiyama-type reaction leading to enantiomerically 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.



Scheme 10.

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.

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