TUTORIAL REVIEW

CSR
www.rsc.org/csr

Current progress in the asymmetric aldol addition reaction

Claudio Palomo,* Mikel Oiarbide and Jesús M. García†
Departamento de Química Orgánica I, Facultad de Química, Universidad del País Vasco, Apdo. 1072, 20080-San Sebastián, Spain. E-mail: qoppanic@sc.ehu.es

Received 15th July 2003
First published as an Advance Article on the web 20th January 2004

Control of stereochemistry during aldol addition reactions has attracted considerable interest over the years as the aldol reaction is one of the most fundamental tools for the construction of new carbon–carbon bonds. Several strategies have been implemented whereby eventually any single possible stereoisomeric aldol product can be accessed by choosing the appropriate procedure. With earlier methods, stoichiometric quantities of chiral reagents were required for efficient asymmetric induction, with the auxiliary most often attached covalently to the substrate carbonyl. Lewis acid catalyzed addition reactions of silyl enolates to aldehydes (Mukaiyama reaction) later opened the way for catalytic asymmetric induction. In the last few years, both chiral metal complexes and small chiral organic molecules have been found to catalyse the direct aldol addition of unmodified ketones to aldehydes with relatively high chemical and stereochemical efficiency. These techniques along with the more recent developments in the area are discussed in this *tutorial review.*

1 Introduction

The aldol addition reaction is recognized as one of the most fundamental tools for the construction of new carbon–carbon bonds in both the biochemical and purely chemical domains. The reaction components typically include a carbonyl pro-nucleophile, that is an enolizable aldehyde, ketone or carboxylic acid derivative and a carbonyl electrophile, usually an aldehyde and rarely a ketone, Fig. 1. Concomitant with the carbon–carbon bond forming process is the formation of one or two adjacent new stereocenter(s) making control of both the absolute and the relative configuration of the aldol products crucial. Both chiral and achiral groups attached to either substrate components, metal center in the enolate intermediate **I**, or the catalyst/promoter can play a role in controlling stereochemistry during the aldol reaction. In this respect, while virtually all the biochemical aldol reactions use unmodified donor and acceptor carbonyls and take place under catalytic (enzymatic) control, the chemical domain of the aldol addition has traditionally relied on prior transformation of the carbonyl pro-nucleophiles into their corresponding enolate **I** or enolate equivalent **II** in a separate step.[1] The latter "directed" aldol reaction approach has been thoroughly investigated in recent years. By contrast, the "direct" aldol approach prevalent in biochemical methods is still incipient in the chemical practice, however due to both its advantages in terms of atom economy and the strong influence of the principle in other

† Address: Departamento de Química Aplicada, Universidad Pública de Navarra, Campus de arrosadía 31006-Pamplona, Spain.

Claudio Palomo was born in Barcelona (Spain) in 1951. He studied chemistry at the Instituto Químico de Sarriá, in Barcelona, where he received his Chemical Engineering Degree in 1975. After spending two years in a pharmaceutical company (Gema S.A.) in Barcelona, he obtained his Licenciatura in chemistry in 1979 at the University of Barcelona and his PhD in 1983 at the University of the Basque Country. In 1989 he was promoted to full Professor in Organic Chemistry and two years later he joined, as visiting professor, the research group of Professor H. Rapoport at the University of California at Berkeley. His current interests are in the area of asymmetric catalysis.

Mikel Oiarbide studied chemistry at the University of the Basque Country in San Sebastian where he obtained his degree (Licenciatura) in 1986 and his PhD in 1991 under the guidance of Professors Palomo and Aizpurua on additions of tributyltin hydride to nitroalkenes. After a two-year post-doctoral stay with Professor H. Rapoport at the University of California at Berkeley, he joined the Department of Organic Chemistry at San Sebastian as a Lecturer. Since 1994 he has been an associate Professor (Titular) of the University of the Basque Country. In 2003 he was promoted to full Professor.

Jesús M. García was born in San Sebastian (Spain) in 1963. He studied chemistry at the University of the Basque Country, where he obtained his Licenciatura in 1986 and his PhD in 1991 with Professors Palomo and Aizpurua on β-lactam chemistry. After a one year post-doctoral stay with Professor Victor Snieckus at the University of Waterloo (Ontario, Canada) he joined the Department of Organic Chemistry at San Sebastian. Since 1994 he has been an associate Professor (Titular) in the Department of Chemistry, Public University of Navarra in Pamplona.

Claudio Palomo

Mikel Oiarbide

Jesús M. García

DOI: 10.1039/b202901d

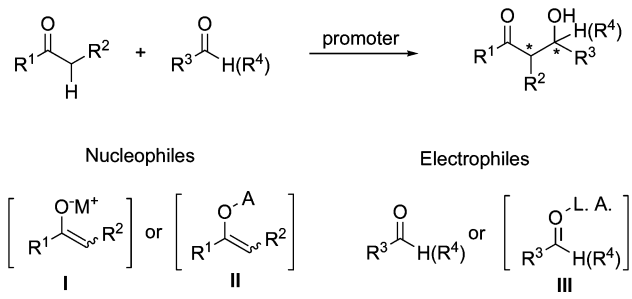


Fig. 1 The general aldol addition reaction and the nucleophiles and electrophiles involved.

reaction types, it has become a hot subject in many leading research groups.

Several review articles have comprehensively covered the work on "directed" methodologies involving either a stoichiometric chiral source[1–3] or a catalytic quantity of a chiral promoter, principally the Mukaiyama aldol reaction.[4–6] Despite there being considerable less work published on "direct" asymmetric aldol reactions, at least one review paper has already appeared which collects the main contributions in the area.[7] A concept article has also appeared which delineates some aspects of the more recent developments.[8] Rather than being a comprehensive account, this short review succinctly describes the basis and the degree of development of the three main following strategies using selected literature references for illustration: (a) chiral auxiliary-based aldol addition reactions, (b) Mukaiyama-type catalytic aldol reactions, and (c) direct catalytic aldol addition reactions. This account is thus presented to provide the non-specialist reader with an instructive overall "state-of-the-art" view of this important organic transformation.

2 Directed aldol addition reactions

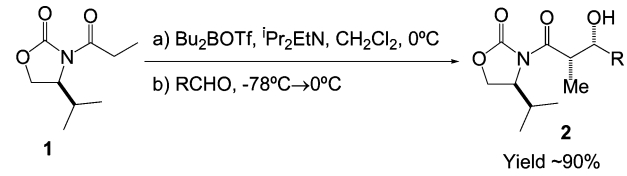
Directed aldol reactions can be classified as either diastereoselective or enantioselective reactions. Diastereoselective aldol additions of substrates bearing a stereogenic center have been extensively studied and successfully employed in the total synthesis of many natural products as can be seen in the recent example illustrated in Scheme 1.[9] This type of internal chirality transfer is not discussed here however the reader is referred to two authoritative compilations on the subject.[2,10]

Asymmetric induction based on the covalent incorporation of a chiral auxiliary within an otherwise achiral substrate donor may be regarded as a second sub-class of diastereoselective aldol additions. The requirement of stoichiometric quantities of chiral inductor and the additional steps needed for its attachment/detachment to/from the substrates/products can be major disadvantages for this approach. Nevertheless, the high reliability of these methods with their often broad substrate tolerances and other practical advantages (*e.g.* product isolation/purification) often outweigh the above limitations. Complementing these diastereoselective processes are the enantioselective aldol reactions involving stoichiometric amounts of chiral ligands.[11] The development of enantioselective directed aldol reactions promoted by catalytic quantities of a chiral species is more advanced. The Lewis acid-catalyzed enantioselective reaction of preformed enol trialkylsilanes with aldehydes, namely the Mukaiyama reaction, and the Lewis base-catalyzed enantioselective reaction of preformed enol trichlorosilanes represent the most important breakthroughs to date in the area.

2.1 Chiral auxiliary based methods

Chiral auxiliary-based aldol bond construction remains the strategy of choice for accessing single isomers of β-hydroxy carbonyl derivatives. To accomplish this goal, a chiral auxiliary is attached to an achiral substrate to induce chirality transfer during aldolization and is subsequently removed from the aldol product. Since the fundamental concepts in this area were well established long ago, only the most recent advances concerning some remaining issues will be discussed in the following section. Two categories have been firmly established with regard to the nature of the enolizable carboxylic acid substrate, namely the propionate and the acetate aldol reactions. For the latter, absolute stereochemistry is the only concern while for the former both absolute and relative stereochemistry must be addressed.

2.1.1 Propionate aldol addition reactions. At present, the boron-mediated aldol reaction of **1** with aldehydes to give the *syn*-aldol product **2** constitutes one of the best aldol bond construction processes (Scheme 2).[12] Conceptually, this development consists of

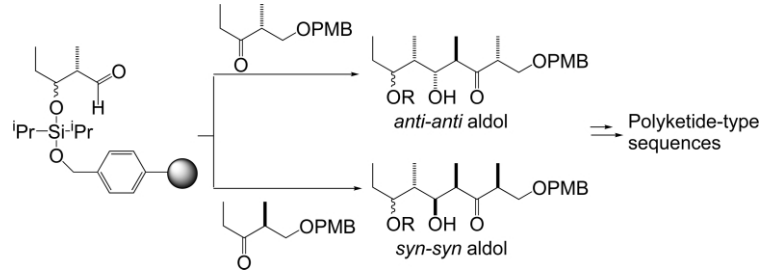


Scheme 2 Boron-mediated aldol reactions of *N*-acyl 2-oxazolidinones and aldehydes to give *syn*-aldol products.

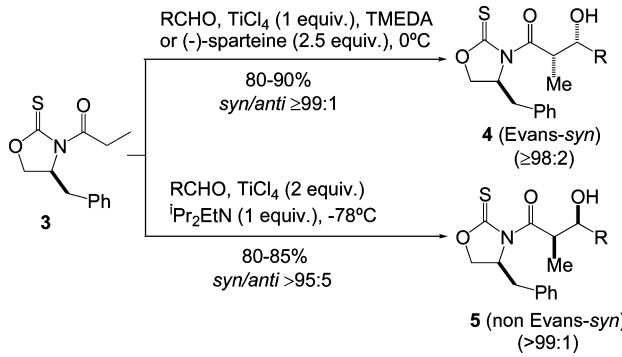
the irreversible and quantitative generation of the *Z*-enolate that reacts with the aldehyde, presumably through a well ordered six-membered chair-shaped "Zimmerman–Traxler" model, to afford essentially only one diastereomeric aldol product out of four possible isomers.

The re-usable chiral auxiliary can be efficiently recovered from the aldol adducts and the method offers a convenient access to each *syn*-isomer by simply choosing the appropriate commercially available chiral source. A significant practical and conceptual advance with these types of auxiliaries has been the development of divergent access to both the "Evans" **4** and "non-Evans" **5** *syn*-aldol products from the same source of chiral information, Scheme 3.[13] Thus, the stereochemical outcome of these reactions can be reversed simply by adjusting the amount of $TiCl_4$ and the amount and nature of amine base.

Apparently the Evans-*syn*-aldol **4** results from a Zimmerman–Traxler type transition state with the titanium metal coordinated to both the enolate oxygen and the aldehyde oxygen. By using two equivalents of $TiCl_4$ it is believed that the highly ordered transition state resulting from a third coordination of titanium with the thiocarbonyl group operates to give the non-Evans-*syn*-aldol **5** (Fig.



Scheme 1 Asymmetric aldol reactions between chiral aldehydes and chiral ketones on solid support as a route to compounds with polyketide-type structure.



Scheme 3 Stereodivergent route to both *syn*-aldols from the same chiral reagent.

2). In this latter case, abstraction of chloride ion by the second equivalent of titanium tetrachloride to form either a trigonal bipyramidal titanium species or a chloro-bridged octahedral

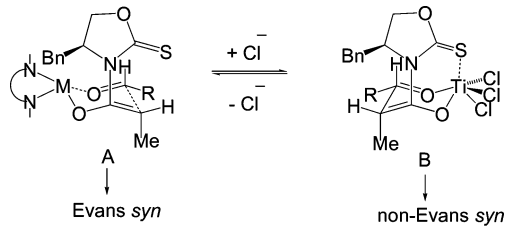
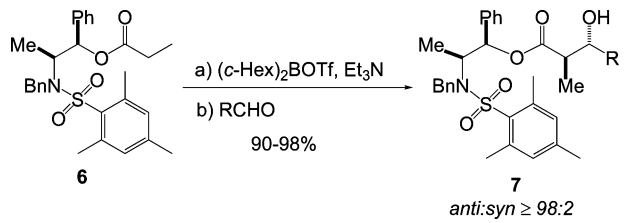


Fig. 2 Transition state models accounting for the formation of the two possible *syn*-aldols.

dimeric species is possible. Either of these could participate in the three point chelated model described. Interestingly, when 2 equivalents of TMEDA or (−)-sparteine are used, the Evans-*syn*-aldol is the major product formed regardless of the quantity of titanium tetrachloride employed. In this latter case, coordination of the second equivalent of diamine to the metal center would prevent coordination of the thiocarbonyl to the metal thus disrupting pathway B.

Despite these advances, the long standing problem associated with the aldol addition reaction in general and with the chiral auxiliary mediated methodologies in particular has been the production of *anti*-aldol products.[14] One problem arises from the fact that *E*-configurated enolates needed for closed transition states to give *anti*-products are not favored. One potential class of reagents favoring *E*-enolate formation, Scheme 4, has been presented recently starting from the commercially available (−)-norephedrine.[15] Under optimized conditions, the boron *E*-enolate of **6** is obtained exclusively which subsequently reacts with a broad range of aldehyde substrates including aliphatic, aromatic, α,β-unsaturated, and functionalised aldehydes affording aldols **7** in up to 99:1 *anti*:*syn* selectivity ratio and dr(*anti*) ≥95:5. The purified aldol products can be converted to the corresponding alcohols



Scheme 4 Norephedrine-derived propionate ester approach to *E*-enolate generation *en route* to *anti*-aldols.

(LiAlH$_4$, THF, 0 °C, 1 h) and/or carboxylic acids (LiOH, THF–H$_2$O, 3 days) without loss of stereochemical integrity.

2.1.2 Acetate aldol addition reactions. "Acetate" aldol reactions deserve special attention. Although Mukaiyama-type aldol reactions of acetate equivalents are well developed (see below), most of the chiral auxiliaries that perform well in diastereoselective propionate aldol additions often perform poorly in the corresponding additions of acetate-derived enolates.[16] One way of compensating for the absence of substituents at Cα of the enolate, which can provide one of the main stereocontrol elements of the C–C bond forming process, is to use chiral auxiliaries featuring high conformational rigidity and/or very crowded stereoelectronic environments. Two highly effective chiral auxiliaries for acetic acid are the Braun's (*R*)-1,2,2-triphenylethylene glycol[17] and 2,6-bis(2-isopropylphenyl)-3,5-dimethylphenol of Yamamoto,[18] Fig. 3. These reagents perform quite well in lithium-mediated acetate aldol reactions to provide good chemical yields and diastereoselectivities with a broad range of aldehyde substrates.

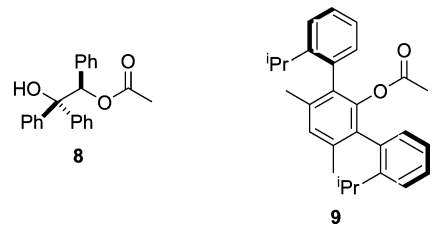
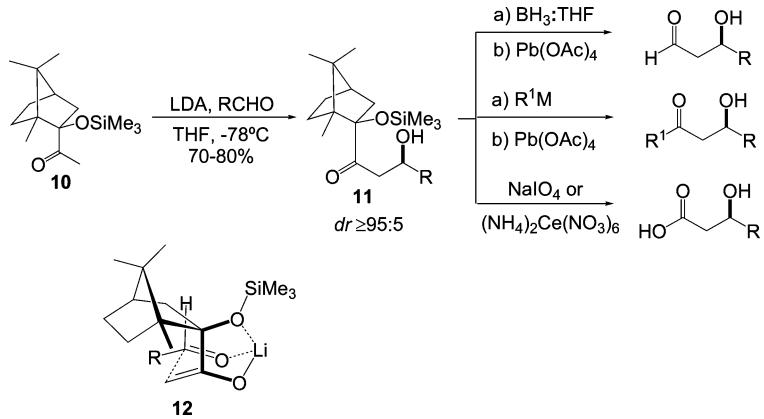


Fig. 3 Bulky chiral acetate esters for highly diastereoselective acetate aldol addition reactions.

A conceptually different, but in practice equivalent, strategy for carrying out highly efficient asymmetric acetate aldol additions has recently been reported[19] using α-silyloxy methyl ketone **10**, Scheme 5. In such an approach, acetylene is used as the elementary source of carbon (acetyl) and (1*R*)-(+)-camphor as the recyclable source of chiral information, both of which are bulk materials. The method is highly selective for a broad range of aldehydes and allows access to the corresponding aldehyde, ketone, or carboxylic acid aldols as a function of the sequence employed for the cleavage of the α-ketol moiety in **11**. The method is simple and minimal production of waste material accompanies the entire process.



Scheme 5 Highly diastereoselective acetate aldols involving lithium enolates from camphor-derived α-silyloxy methyl ketone.

A transition state model **12** has been proposed which nicely accounts for the stereochemical outcome of the reaction. In this model, three-point chelation operates to provide a chair conformation transition state with the aldehyde R group occupying a pseudo-equatorial position.

Further progress in the area makes use of the boron-mediated double aldol reaction of acetate ester **13**.[20] Under the conditions specified in Scheme 6, treatment of **13** provides bis-aldol products in over 95% yield with a 90:8:2 ratio of diastereomers **17**, **18** and **19**, respectively. The fourth possible isomer is not detected.

Stereochemical correlation between the mono-aldols **15** and **16** and the di-aldol products produced suggests that this double aldol reaction proceeds in a stepwise manner. When the reaction is maintained at −78 °C, mono-aldol **15** is the major product (**15**:**16** = 88:12), with diastereoselectivity being controlled by the auxiliary. When the reaction mixture is allowed to stir at room temperature, the second aldolization takes place and the authors propose the doubly borylated enolate **14** as an intermediate in the reaction based on mechanistic and spectroscopic studies.

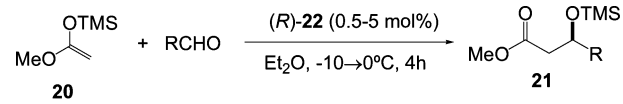
Covalently linked chiral auxiliaries clearly provide high diastereoselectivities in a reliable fashion with broad substrate acceptance and versatile possibilities for stereo-induction. Methods based on the use of catalytic amounts of the chiral source are preferable however, especially for large scale preparative work. Major developments associated with these methods are disclosed in the following sections.

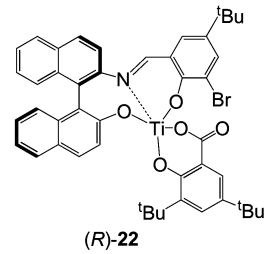
2.2 Mukaiyama-type catalytic aldol addition reactions

In the early eighties work by Mukaiyama and co-workers[21] demonstrated that *in situ* generated Sn(II) enolates add asymmetrically to aldehydes in the presence of stoichiometric quantities of certain chiral diamine ligands as the only chiral inductors. Later on the same group developed the enantioselective aldol addition reaction of silyl enol ethers derived from esters or thioesters to aldehydes catalyzed by sub-stoichiometric quantities of a chiral Lewis acid.[22] In spite of the spectacular advances within the methodology of chiral Lewis acid-catalyzed enantioselective aldol addition reactions between enol silanes derived from either ketone, esters or thioesters and aldehydes,[4–6] some aspects remain only partially addressed if at all. For instance, while the majority of the catalytic systems so far developed produce *syn*-aldols, catalytic systems leading to *anti*-aldols are very much less developed. Similarly, chiral catalysts based on fluoride ion sources remain essentially unexplored.[23] Another active research direction in this area seeks water-compatible catalytic systems. Also, problems associated with Mukaiyama-type reactions involving ketones as electrophiles or aldehydes as nucleophilic components remain essentially unresolved.

Along with the latest developments in Lewis acid-catalyzed Mukaiyama reactions, it has been discovered very recently that the reaction between enol trichlorosilanes and aldehydes can be efficiently catalyzed by Lewis bases. This has opened a new platform for development and now both Lewis acid-promoted and Lewis base-promoted strategies are available for exploring Mukaiyama type reactions.

2.2.1 Lewis acid mediated reactions. A substantial number of Lewis acids containing early and late transition metals and chiral ligands bearing nitrogen, oxygen and phosphorus donors have been developed to carry out Mukaiyama reactions enantioselectively.[4–6] One important aspect of this reaction is that catalyst activity usually depends on how fast intra- or intermolecular silyl transfer to the aldolate oxygen occurs with simultaneous liberation of the active catalyst. Under low catalyst turnover conditions, requirements for both high catalyst loadings and attenuation of the reaction enantioselectivity as a consequence of the "silicon-catalyzed" achiral aldol pathway can be predicted. In this respect, ligands bearing functional groups that may act as a silyl group shuttle have shown to be effective for improving catalyst turnover and activity. One prominent catalyst that meets these design elements is the titanium Schiff base catalyst **22**.[24] This catalyst is characterized by high activity and tolerance to a wide range of nucleophiles and electrophiles. Under optimized conditions, the simple methyl acetate-derived enol silane **20** adds to aldehydes in the presence of as little as 0.5 mol% of **22** at 0 °C to give adducts **21** in high yields and up to 98% ee (Scheme 7).



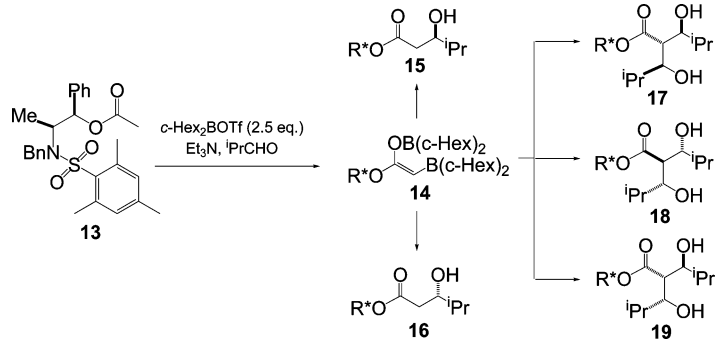


aldehyde	Yield, %	ee, %
$Ph(CH_2)_3$-C≡C-CHO	84	96
$TBSOCH_2C$≡C-CHO	91	96
PhC≡C-CHO	96	94
CH_3CH=CHCHO	82	98
$CH_3(CH_2)_2CHO$	76	95
PhCH=CHCHO	99	98
$PhCH_2CH_2CHO$	98	94
$C_6H_{11}CHO$	81	95

Scheme 7 Mukaiyama aldol reactions of trimethylsilyl ketene acetals and aldehydes catalyzed by (*R*)-**22**.

A significant advance in the Mukaiyama reaction has been the ability to produce *anti*-aldols. The majority of catalysts for the Mukaiyama reaction lead to preferential formation of *syn*-aldols irrespective of the configuration of the enolsilane involved and very few have proven to be suitable for producing the corresponding *anti*-aldols. The ability to produce *syn*-adducts has been attributed to steric repulsion between the alkyl group of the aldehyde (R^1) and the α-alkyl group of the silyl enolate (R^2) in acyclic transition state models, Fig. 4. Based on these open transition models it could be predicted that if bulky Lewis acids are used the interaction between the R^2 group and the Lewis acid may be dominant thus favoring production of *anti*-adducts.

The zirconium catalyst **24** demonstrates this principle (Scheme 8).[25] The reaction of acetal ketene **23** with aldehydes promoted by



Scheme 6 Double aldol addition reaction of borylated enolates.

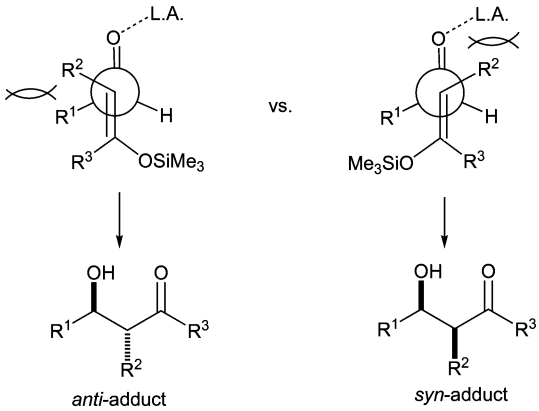
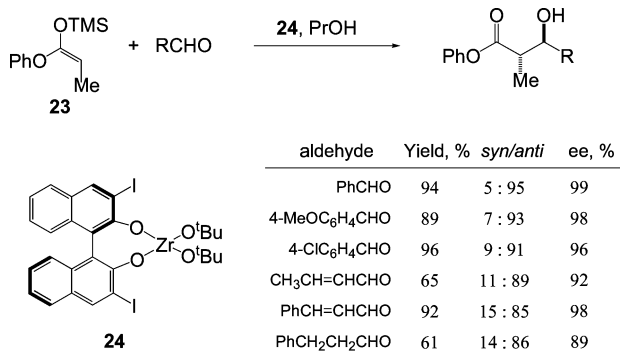


Fig. 4 Assigned transition states for *syn*- and *anti*-selectivity in the Lewis acid-promoted Mukaiyama aldol reaction.



aldehyde	Yield, %	*syn/anti*	ee, %
PhCHO	94	5 : 95	99
4-MeOC$_6$H$_4$CHO	89	7 : 93	98
4-ClC$_6$H$_4$CHO	96	9 : 91	96
CH$_3$CH=CHCHO	65	11 : 89	92
PhCH=CHCHO	92	15 : 85	98
PhCH$_2$CH$_2$CHO	61	14 : 86	89

Scheme 8 Mukaiyama aldol reactions leading to *anti*-aldols using a Zr catalyst.

this catalyst affords preferentially *anti*-aldol adducts independent of the silyl enolate geometry.

An interesting feature of this catalytic system is that the addition of protic additives (alcohols) and small amounts of water are critical for catalyst turnover and formation respectively. As Fig. 5

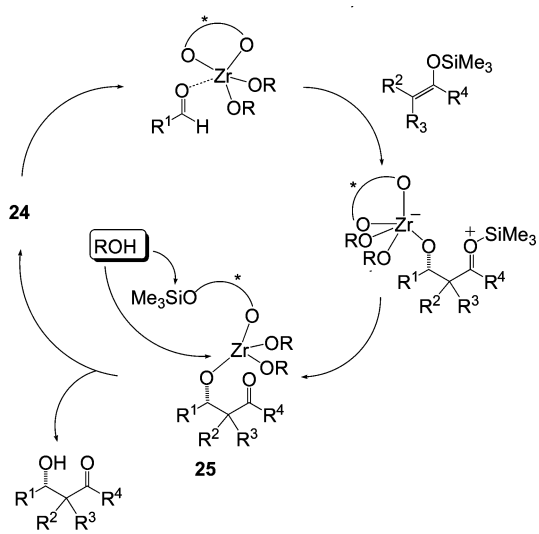
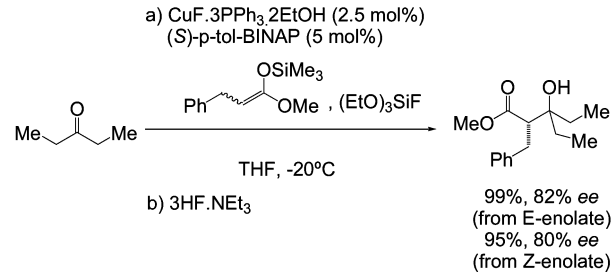


Fig. 5 Catalytic cycle for the Mukaiyama reaction promoted by catalyst **24**.

illustrates, the alcohol reacts with intermediate **25** wherein the Si–O bond or the Zr–O bond is cleaved. In the case of cleavage of the Si–O bond, the resulting anionic oxygen attacks Zr and the aldol product is obtained and the catalyst regenerated. Also, when the Zr–O bond is cleaved, another alcohol molecule cleaves the Si–O bond. This mechanism is supported by the fact that aldol adducts are obtained with free hydroxyl groups and trimethylsilyl ethers of alcohols are observed by GC-MS analysis.

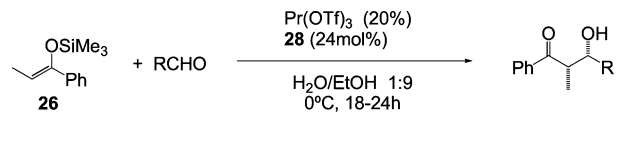
Although many excellent asymmetric catalysts have been developed for the Mukaiyama reaction using aldehydes as acceptors, only very few methodologies have been reported for the catalytic aldol reaction of ketones, with pyruvates being one remarkable exception.[26] The difficulty is partly due to the attenuated reactivity of ketones and the intrinsic reversibility of aldol additions of ketones. In addition, stereocontrol here is challenging because of the less steric dissimilarity of the two entities flanking the carbonyl group compared with aldehydes. A new catalyst system that can be applied to reactions between simple ketones and trimethylsilyl enolates and can, in principle, be extended to catalytic enantioselective reactions has appeared,[27] Scheme 9. The method uses trimethylsilylacetal ketenes as donors

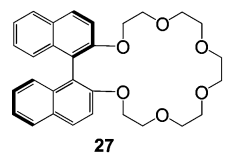


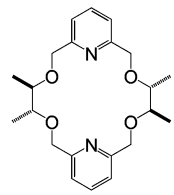
Scheme 9 Asymmetric Mukaiyama aldol reaction with simple ketones as acceptors.

in the presence of a catalytic amount of a copper fluoride salt and triphenylphosphine and a stoichiometric quantity of silyl fluoride salt.

Enantioselective Mukaiyama aldol reactions in aqueous media, although incipient, constitute another important advance in the area.[28] Two main difficulties need to be addressed for such reactions to work efficiently. Firstly, many cations (*i.e.* Lewis acids) hydrolyse very easily in water and, secondly, chiral ligand-coordinated metal complexes tend to be unstable in water. One attractive solution to address these issues is based upon the concept of multicoordination. Both transition metals and rare earth metals upon coordination to newly designed chiral ligands have provided effective Lewis acid catalysts for aldol reactions in aqueous media.[29] Thus, of the transition metal cations examined, *i.e.* Fe^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+}, the combination of Pb^{2+} with ligand **27** provides the best results (for the reaction of **26** with benzaldehyde, 62% yield, *syn:anti* 90:10 and ee 55%). On the other hand, rare earth triflates in combination with bis-pyridino-10-crown-6 ligand **28** promote the reaction between the enolsilane **26** and several aldehydes enantioselectively, Scheme 10. Aromatic aldehydes are best suited for these reactions and the ionic diameter of the metal cation greatly influences both diastereo- and enantioselectivity.



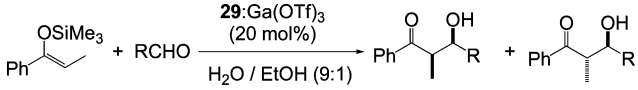

27

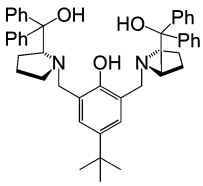

28

aldehyde	*syn/anti*	*ee*, %	yield, %
PhCHO	91:9	78	85
4-MePhCHO	92:8	75	91
4-ClPhCHO	90:10	83	87
2-thiofuranyl-CHO	91:9	72	100
2-pyridyl-CHO	85:15	85	99
(E)-PhCH=CHCHO	78:22	76	77
(E)-CH$_3$CH=CHCHO	81:19	69	70
PhCH$_2$CH$_2$CHO	67:33	47	53

Scheme 10 Mukaiyama *syn*-aldol reactions in wet alcoholic media.

For the above systems, when the amount of water in the mixture is increased, yields and selectivities tend to decrease remarkably. Mukaiyama aldol reactions that are tolerant of higher water/organic solvent ratios have been described recently, including complexes obtained from gallium(III) and chiral semi-crown ligands, particularly Trost's ligand **29**, *vide infra*, which provides uniformly good results (Scheme 11).[30]





29

aldehyde	Yield, %	*syn/anti*	ee, % (*syn*)
PhCHO	85	85 : 15	85
4-MeC_6H_4CHO	89	90 : 10	88
4-$MeOC_6H_4CHO$	80	88 : 12	84
4-ClC_6H_4CHO	77	82 : 18	78
PhCH=CHCHO	90	90 : 10	86
1-naphthyl-CHO	87	80 : 20	82
4-$NO_2C_6H_4CHO$	82	77 : 23	62
$CH_3(CH_2)_4CHO$	82	89 : 11	30

Scheme 11 Catalytic Mukaiyama aldol reactions in aqueous media.

Although most organic materials have limited solubility in water, these findings show that protic, less volatile solvents or mixtures of protic solvents and water are suitable for aldol reactions, and have opened the way for exciting new research in the area.

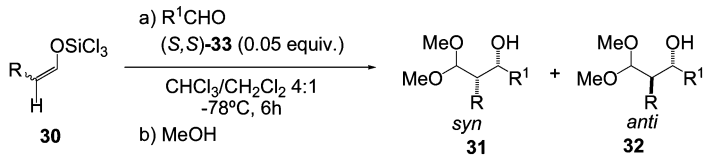
2.2.2 Lewis base mediated reactions. All of the Lewis acid-catalyzed Mukaiyama reactions, except for those promoted by chiral carbenium ions,[31] imply the participation of a metal-based catalyst which activates the electrophilic component of the reaction. A conceptually different approach is based on the activation of the nucleophilic component such as has been achieved by using trichlorosilyl enolates as nucleophiles and chiral phosphoramides as Lewis base catalytic promoters.[32] Replacement of a chlorine by coordination of the phosphoramide oxygen to the silicon appears to lead to a cationic silicon enolate intermediate species that subsequently binds to the electrophilic carbonyl to effect aldolization. For this latter step, two independent pathways are proposed: a boat-like transition structure with low facial selectivity which would lead to the *syn*-isomer and a chair-like transition structure involving a second molecule of phosphoramide, which would lead to the *anti*-product. The relative importance of both reaction pathways depends on the size and concentration of the catalyst as well as the architecture of the substrate. This method is particularly suitable for alkyl(aryl) methyl ketones, substrates that have proven to be very difficult in the context of typical Mukaiyama procedures.

The development of this approach has resulted in the first method for carrying out catalytic enantioselective cross-aldol reactions of aldehydes,[33] a problem that has found no general solution until now. Under optimized conditions, geometrically defined trichlorosilyl enolates of aldehydes **30** undergo high yielding addition to aldehydes in the presence of phosphoramide **33**. The *syn*-adducts **31** are the predominant species obtained from (*Z*)-enolates, while (*E*)-configured enolates give rise to the *anti*-isomers **32** (Scheme 12). Although enantioselectivities are good, they are highly variable and strongly dependent upon both the enolate and aldehyde structures.

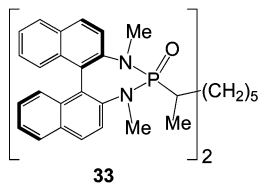
The problem of stereoselective addition of silyl enolates to ketones has recently been addressed within the context of chiral Lewis base-promoted Mukaiyama-type reaction. To overcome the unfavorable kinetics and thermodynamics of this reaction, a successful combination of the highly reactive trichlorosilyl enolate of methyl acetate **35** and catalytic amounts of an *N*-oxide has been employed.[34] The asymmetric version of the approach uses chiral bis-*N*-oxide catalysts such as **34**, Scheme 13, to provide aldol products **36** with excellent yields, and ee values ranging from high for aromatic ketones to moderate for aliphatic and olefinic ketones.

3 Direct catalytic aldol addition reactions

Activation of the donor carbonyl component *via* metal enolate or silyl enol ether formation usually requires a previous and irreversible synthetic operation that may be one-pot (metal enolates) or may require a separate reaction with subsequent isolation of the activated intermediate (silyl enolates). In either case, stoichiometric quantities of reagents are required. From several aspects, direct methods that allow the cross aldol reaction of otherwise unmodified carbonyl donors present much interest, especially if a sub-stoichiometric amount of the promoter (catalyst) is sufficient. Indeed, biochemical aldol reactions such as those catalyzed by aldolases and catalytic antibodies perfectly meet the atom economy principle by using unmodified carbonyl donors. The use of aldolases and catalytic antibodies, however, is little implanted in practical synthesis presumably because they still



30 **31** **32**

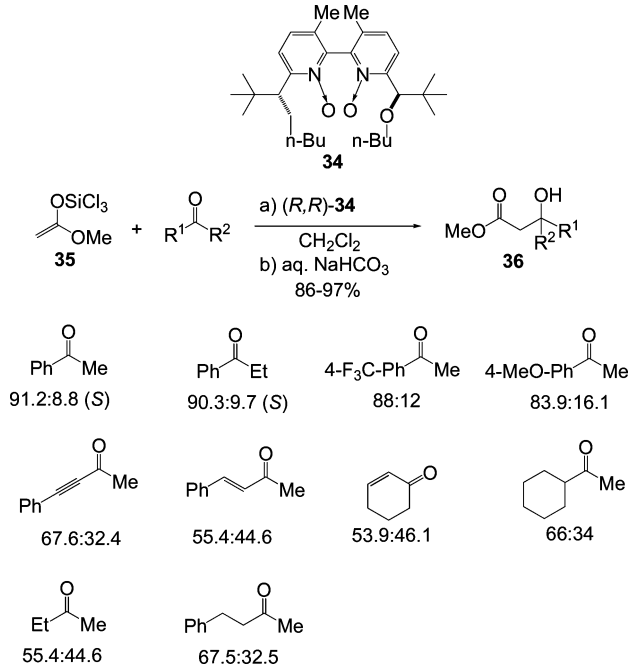


33

enolate	R	R^1	Yield, %	*syn/anti*	ee, %
(*Z*)	n-Pent	Ph	92	99 : 1	90
(*E*)	n-Pent	Ph	91	3 : 97	82
(*Z*)	Me	Ph	95	98 : 2	81
(*E*)	Me	Ph	97	1 : 99	59
(*Z*)	Me	2-naphthyl		99 : 1	86
(*E*)	Me	2-naphthyl		2 : 98	53
(*Z*)	Me	PhCH=CH	86	99 : 1	42
(*E*)	Me	PhCH=CH	88	1 : 99	26
(*Z*)	Me	PhC≡C	98	98 : 2	7
(*E*)	Me	PhC≡C	99	2 : 98	76
(*Z*)	Me	$PhCH_2CH_2$	47	95 : 5	8
(*E*)	Me	$PhCH_2CH_2$	79	1 : 99	66

Reactions run on 1.0 mmol scale

Scheme 12 Lewis base promoted Mukaiyama-type aldol reaction.



Scheme 13 Chiral Lewis base-promoted Mukaiyama-type reactions of ketones.

present a narrow substrate scope. The development of purely chemical methods for the direct, catalytic aldol addition reaction had been awaiting small molecules capable of simultaneously activating the donor and the acceptor carbonyls. Such small molecules now are known and can be grouped into artificial metal complexes and purely organic molecules (organocatalysts) – either natural or designed.

3.1 Metal complexes as catalysts

Inspired by the mode of action of type II aldolases, the first examples of metal complex-induced direct asymmetric aldol addition reactions were reported by Shibasaki using catalyst **37**. The catalyst design is based around the general principle of two-center catalysis (see Fig. 6).[35] Two sites of opposite character can be identified in the metal complex: a basic site and an acidic site, each capable of independently activate in close proximity both the donor ketone (substrate 2) and the acceptor aldehyde (substrate 1), respectively. The chiral backbone of the catalyst can induce a preferential orientation of both substrates thus resulting in the production of an unequal stereoisomeric distribution of aldol products.

Since that report, a few metal-complexes have been documented to be capable of promoting direct asymmetric aldol reactions under

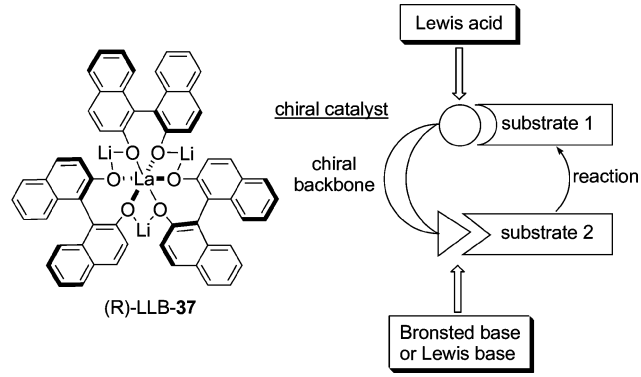


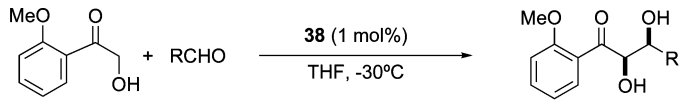
Fig. 6 First metal complex able to catalyze direct aldol addition reactions and the Shibasaki's general principle for two-center catalysis.

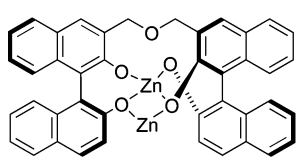
catalytic conditions.[7] Most of these catalysts are effective with loadings in the 1–20 mol% range. Some catalysts performance can be greatly affected by additives which are used to optimize catalyst turnover and reaction ee or to minimize formation of side-products such as dehydration products. Examples are the use of molecular sieves and the use of water or a KHMDS/water mixture. To date, the substrate scope for these catalytic systems is relatively narrow. Methyl ketones (acetone, acetophenone) are the best suited carbonyl donors, but they have to be used in large excess in most cases. Also, the efficiency with respect to the substrate aldehyde employed decreases in the order highly-α-branched > less-α-branched > unbranched ≈ aromatic.

Some α-substituted methyl ketones, particularly α-hydroxy methyl ketones, work nicely in reactions promoted by these polymetallic catalysts. For example, as little as 1 mol% of catalyst **38** is sufficient to promote the reaction between α-hydroxy acetophenones and aldehydes to give the corresponding *syn*-adducts,[36] Scheme 14. On the other hand, the dinuclear zinc complex **39** works remarkably well in the reaction of α-hydroxy methyl acetophenone with aldehydes to yield the complementary *syn*-aldols, Scheme 15.[37] It is reasonable to assume that the enolate of the α-hydroxyketone serves as a bidentate ligand bridging the two zinc atoms during aldolization as depicted in scheme.

Other unmodified carbonyl compounds tolerated in these reactions include ethyl α-diazoacetate, which reacts with aldehydes in the presence of zirconium catalyst **40**, Scheme 16.[38] However, chemical yields and/or enantioselectivities appear to be only moderate for the majority of aldehydes tested.

Development of catalytic systems for activating esters or methylene ketones (*e.g.* 3-pentanone) is more challenging. The Ti-based catalyst obtained by combining racemic BINOL (2 mol equiv.) and the $Ti_2(^tBuO)_7$/(*R*)-mandelic acid complex is able to promote the cross aldol reaction of 3-pentanone and aldehydes



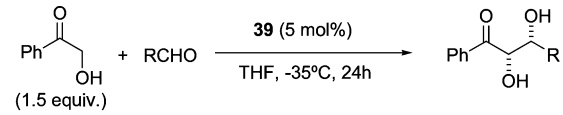


38

aldehyde	yield, %	*syn:anti*	ee,%[a]
$PhCH_2CH_2CHO$	94	89:11	92
$CH_3(CH_2)_4CHO$	88	88:12	95
$(CH_3)_2CHCH_2CHO$	84	84:16	93
$CH_3CO(CH_2)_2CHO$	91	93:7	95
$BnO(CH_2)_2CHO$	81	86:14	95
$BnOCH_2CHO$	84	72:28	96
$(CH_3)_2CHCHO$	83	97:3	98
c-$C_5H_{11}CHO$	95	97:3	98

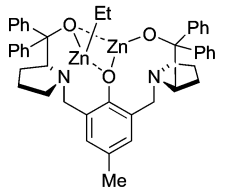
[a] Of the major diastereomer.

Scheme 14 Direct aldol addition reactions of α-hydroxy *o*-methoxyacetophenone giving either *syn*- or *anti*-aldol products.

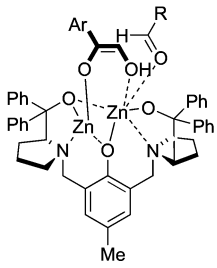


aldehyde	yield, %[a]	d.r.	ee,%
$C_6H_{11}CHO$	83	30:1	92
$(CH_3)_2CHCHO$	89	13:1	93
$(Ph)_2CHCHO$	74	1:0	96
$(CH_3)_2CHCH_2CHO$	65	35:1	94
$Ph(CH_2)_2CHO$	78	9:1	91
$CH_3(CH_2)_6CHO$	89	5:1	86
$CH_2=CH(CH_2)_8CHO$	91	5:1	87

[a]Reactions run on 0.5 mmol scale at 0.3 M in aldehyde in the presence of 100 mg of 4A MS.

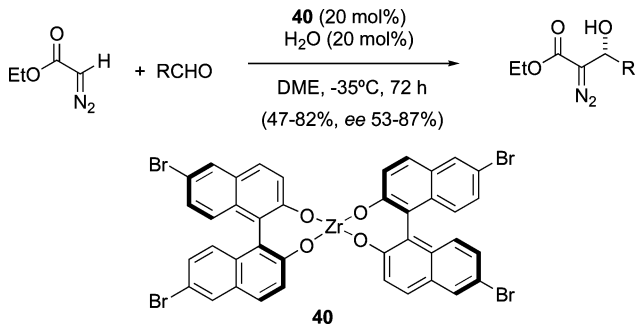


39



Proposed reaction model

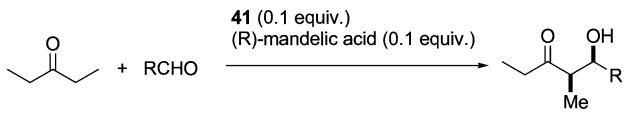
Scheme 15 Direct aldol addition reactions of α-hydroxy acetophenone catalyzed by **39**.



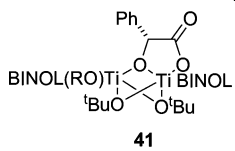
40

Scheme 16 Direct aldol addition reactions of ethyl α-diazoacetate with a Zr catalyst.

providing high diastereoselectivities and ee values, especially when aromatic aldehydes are employed, Scheme 17.[39] Although the



aldehyde	yield, %	*syn:anti*	ee,%
PhCHO	68	85:15	88
^tBuCHO	70	81:19	86
PhC≡CHO	71	75:25	81
$(CH_3)_2CHCHO$	39	71:29	74
CH_3CH_2CHO	75	76:24	76

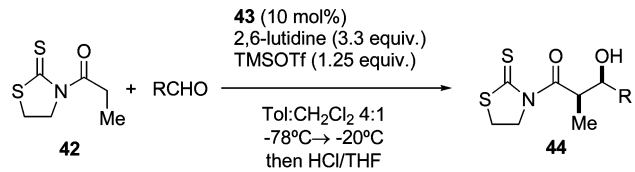


41

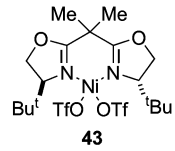
Scheme 17 Direct aldol reactions of 3-butanone with aldehydes.

actual structure of the catalytically active species is not known, structure **41** is proposed. A striking observation noticed by the authors with no satisfactory explanation to date is that by using (S)-mandelic acid instead of the R enantiomer, very much lower enantioselectivities are observed.[40]

On the other hand, the first examples of catalytic, enantioselective direct aldol reactions of simple carboxylic acid derivatives have been recently reported, Scheme 18.[41] Reaction partners are *N*-propionyl thiazolidin-2-thione **42** and the corresponding aldehyde and the *syn*-aldols **44** are obtained with high diastereoselectivity. A combination of a tertiary amine base (2,6-lutidine), trimethylsilyl



42 44



43

aldehyde	yield, %[a]	*syn:anti*	ee,%
PhCHO[b]	81	94:6	97
4-Me-Ph-CHO	80	93:7	95
α-Naphthaldehyde	73	93:7	92
(E)-PhCH=CHCHO	63	88:12	93
CH_3CHO	86[c]	97:3	93
CH_3CH_2CHO	84[c]	97:3	90
$(CH_3)_2CHCHO$	70[c]	98:2	90

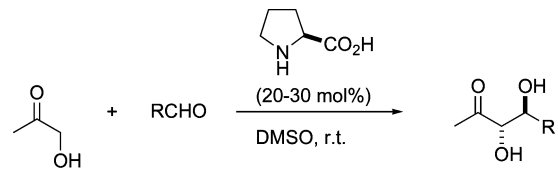
[a] Isolated yield of a single diastereomer after column chromatography. [b] 5 mol% catalyst was used. [c]Isolated as a mixture of diastereomers.

Scheme 18 Catalytic, enantioselective direct aldol addition reactions of simple carboxylic acid derivatives.

triflate and a catalytic amount of the Ni(II)-bis-oxazoline complex **43** promotes the reaction giving very high ee's irrespective of the nature of the aldehyde employed. Since a base and a silylating reagent are required for the reaction success, a Mukaiyama type reaction might be conceived. However, based on experimental evidence, the authors conclude that a Mukaiyama aldol mechanism does not follow and, instead, they proposed an alternative catalytic cycle where decomplexation of the aldol-catalyst edduct, and therefore catalyst turnover, is facilitated by silylation of the aldol by TMSOTf.

3.2 Organocatalysis

Aldol addition reactions of unmodified ketones or aldehydes promoted by purely organic molecules without assistance of any metal are another important modern achievement in the area. Since the pioneering finding by List, Barbas III and co-workers that 30 mol% of the simple amino acid L-proline could promote the aldol addition reaction of acetone to an array of aldehydes in up to > 99% ee,[42] the concept of small organic molecules as catalysts has received great attention. Apart from acetone, hydroxyacetone also behaves nicely in reactions with aldehydes in the presence of L-proline to afford the corresponding *syn*-diols in high enantioselectivities and variable yields, Scheme 19.[43,44]



aldehyde	yield, %[a]	d.r.	ee,%
$cC_6H_{11}CHO$	60	>20:1	>99
$(CH_3)_2CHCHO$	62	>20:1	>99
Ph(Me)CHCHO	51	>20:1	>95
2-Cl-PhCHO	95	1.5:1	67
$(CH_3)_3CCH_2CHO$	38	1.7:1	>97

[a]Isolated yield after column chromatography.

Scheme 19 L-Proline-catalyzed reaction of hydroxyacetone with aldehydes.

The catalytic cycle of the proline-catalyzed aldol addition reaction proceeds *via* an enamine intermediate. Enamine-mediated mechanisms are also prominent in aldol reactions catalyzed by the aldolase I type enzymes and catalytic antibodies, where enamine formation is considered to be the rate limiting step of the process.

With this assumption, the product configuration is consistent with a Zimmerman–Traxler six-membered ring chair-like model for the aldolization step, Fig. 7, a proposal that has been supported by

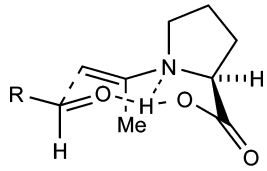
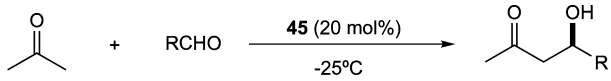
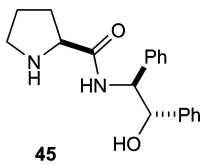


Fig. 7 Transition state model for the L-proline-catalyzed aldol addition reaction of acetone to aldehydes.

kinetic and stereochemical evidence,[45] as well as computational calculations.[46] In this model, clearly only one molecule of proline intervenes, and internal coordination of the nitrogen atom participates in the hydrogen-bonding activation of the aldehyde carbonyl.

Two limitations associated with the proline-catalyzed aldol reaction are the relatively large amount of proline required (20–30 mol%) and the low enantioselectivities obtained when aromatic aldehydes are employed. In a recent report,[47] amino alcohols of the type **45**, Scheme 20, have been shown to alleviate these limitations.





45

aldehyde	yield, %[a]	ee,%
4-NO_2-C_6H_4CHO	66	93
3-NO_2-C_6H_4CHO	63	87
4-Br-C_6H_4CHO	77	90
PhCHO	51	83
cC_6H_{11}CHO	85	97
$(CH_3)_2$CHCHO	43	98
^{t}BuCHO	51	>99
CH_3CH_2CHO	17	87

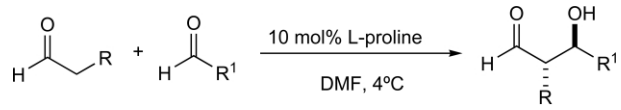
[a]Isolated yields.

Scheme 20 Direct aldol addition reactions of acetone catalyzed by aminoalcohol **45**.

This development also demonstrates that the catalytic activity of proline can potentially be retained or even increased by anchoring to the carboxy terminus groups possessing acidic hydrogens available for coordination to the acceptor aldehyde, opening the way for future new designs.

The use of enolizable aldehydes as carbonyl donors has long been problematic,[48] but the proline-catalyzed aldolization has unexpectedly opened new routes towards this challenging goal. The self-aldol reaction of propanal catalyzed by L-proline in the presence of a third, non-enolizable aldehyde affords pyranoses in moderate yields and stereoselectivities.[49] Proline has also been shown to efficiently catalyse the addition of aldehydes to particularly active electrophiles such as pyruvates,[50] while very high *syn:anti* selectivities as well as ee's have recently been shown for the *enolexo* intramolecular aldolization of 1,7-dialdehydes leading to substituted cyclohexanols.[51]

The cross-aldol reaction of aldehydes is a formidable synthetic challenge on account of the propensity of aldehydes to polymerize and because of the mechanistic requirement for non-equivalent aldehydes to selectively partition into two discrete components, a nucleophilic donor and an electrophilic acceptor. Quite recently, however, such a realization has been achieved[52] using the proline catalyst and slow syringe pump addition of the donor aldehyde to the mixture of L-proline (10 mol%) and the acceptor aldehyde in DMF (Scheme 21).



R	R^1	yield, %[a]	*anti/syn*	ee,%
Me	Et	80	4:1	99
	^{t}Bu	88	3:1	97
	cC_6H_{11}	87	14:1	99
	Ph	81	3:1	99
	^{i}Pr	82	24:1	>99
^{n}Bu	^{i}Pr	80	24:1	98
Bn	^{i}Pr	75	19:1	91

[a]Combined yield of diastereomers.

Scheme 21 The proline-catalyzed cross-aldol addition reaction of aldehydes.

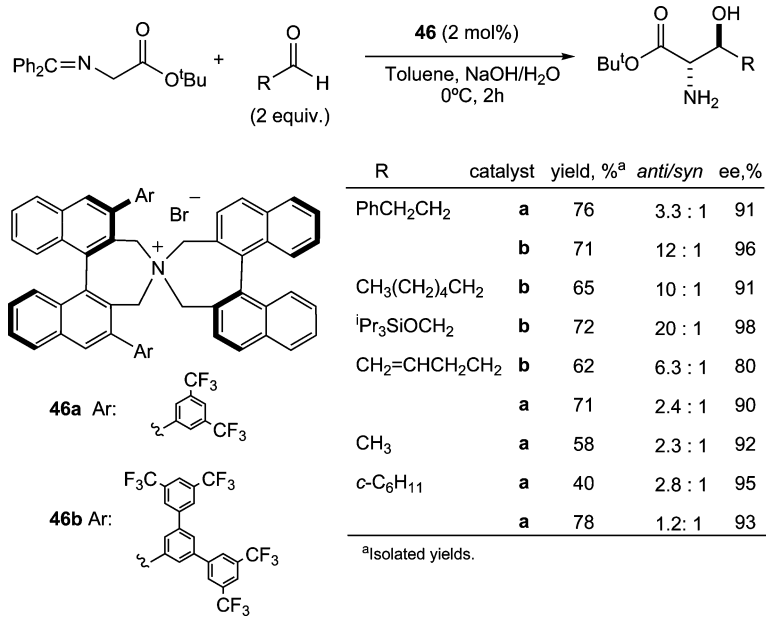
Two additional developments in the field of direct aldol addition reactions catalyzed by chiral organic molecules other than L-proline and its congeners have been documented. One of the strategies is based on the use of a 1:1 mixture of chiral 1,2-diamines and a protonic (carboxylic, sulfonic or phosphonic) acid.[53] It has been shown that these systems are able to promote the reaction of acetone or some other symmetric ketones with a narrow array of aromatic aldehydes or cyclohexyl carbaldehyde. The formation of considerable amounts of dehydrated aldol product in some instances and the low *syn:anti* selectivity attained are some limitations at present. A mechanism is proposed for this reaction that is reminiscent of the proline-mediated aldolization, wherein the protonated amino group mimics the role played by the carboxylic group of proline.

The second alternative, Scheme 22, is based upon the use of some chiral quaternary ammonium salts such as **46** derived from binaphthyls under phase-transfer conditions.[54] As little as 2 mol% of the chiral ammonium salts are capable of forming the aldol addition products derived from glycine Schiff bases and aldehydes in good yields, moderate *anti:syn* selectivity, and very high ee's.

Finally, organocatalysis for direct aldol additions in aqueous systems is still not well developed. Although proline and several chiral diamines do promote the addition reaction of acetone, (di)hydroxyacetone and other ketones to aldehydes in buffered aqueous media, the obtained diastereo- and enantioselectivities are still disappointing.[55,56]

4 Conclusions

The asymmetric aldol addition reaction is clearly one of the best developed organic transformations. This carbon–carbon bond formation process can be efficiently carried out using several distinct strategies making it a very attractive option when planning synthetic routes. Diastereoselective methods based on stoichiometric usage of chiral auxiliaries give highly predictable stereocontrol for most types of aldehyde electrophiles. This generality and reliability is counterbalanced by the need for stoichiometric amounts of the chiral source and because of the necessity for additional steps (*i.e.* auxiliary attachment and detachment). Alternative strategies involving only catalytic quantities of the chiral reagents have been developed and have been applied particularly well to Mukaiyama type reactions where both chiral Lewis acids and bases can be used as promoters. In the Lewis base catalysed reactions, aldehydes can be used as carbonyl donors and protocols for aldol addition reactions to electrophilic ketones with formation of quaternary stereocenters have been developed. Formation of the latent enolate species in a previous, stoichiometric and irreversible step is the major shortcoming of these approaches. The most atom



R	catalyst	yield, %[a]	*anti/syn*	ee,%
$PhCH_2CH_2$	**a**	76	3.3 : 1	91
	b	71	12 : 1	96
$CH_3(CH_2)_4CH_2$	**b**	65	10 : 1	91
$^iPr_3SiOCH_2$	**b**	72	20 : 1	98
$CH_2=CHCH_2CH_2$	**b**	62	6.3 : 1	80
	a	71	2.4 : 1	90
CH_3	**a**	58	2.3 : 1	92
c-C_6H_{11}	**a**	40	2.8 : 1	95
	a	78	1.2: 1	93

[a]Isolated yields.

Scheme 22 Phase-transfer organocatalysis for the direct aldol addition reaction.

efficient approach is the direct aldol addition strategy. In recent years both metal complexes bearing chiral ligands and small chiral organic molecules have been unveiled that catalyze the addition of unmodified ketones to aldehydes and, remarkably, the difficult aldehyde cross-aldol reaction has been achieved within this context. Overall, turnover and frequency numbers for the catalytic systems capable of promoting direct aldol reactions are still low and in many cases considerable amounts of catalysts are required for efficiency. In addition, there are still some limitations with regard to the suitability of the substrate donor and acceptor carbonyls. The current momentum acquired by the "direct" approach in this and related areas will undoubtedly continue.

Acknowledgement

This contribution is dedicated to the memory of Professor Henry Rapoport. We thank Dr. Michael Kelso for helpful comments. This work was financially supported by the University of the Basque Country and Ministerio de Ciencia y Tecnología (Spain).

References

1 M. Braun, in *Stereoselective Synthesis, Houben-Weyl*, **Vol. E21/3**, Eds. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Thieme, Stuttgart, 1996, p. 1603.
2 C. J. Cowden and I. Paterson, *Org. React.*, 1997, **51**, 1.
3 R. Mahrwald, *Chem. Rev.*, 1999, **99**, 1095.
4 S. G. Nelson, *Tetrahedron: Asymmetry*, 1998, 357.
5 E. M. Carreira, in *Comprehensive Asymmetric Catalysis*, **Vol. 3**, Eds. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Heildelberg, 1999, pp. 997–1065.
6 D. Machajewski and C.-H. Wong, *Angew. Chem. Int. Ed.*, 2000, **39**, 1352.
7 B. Alcaide and P. Almendros, *Eur. J. Org. Chem.*, 2002, 1595.
8 C. Palomo, M. Oiarbide and J. M. García, *Chem. Eur. J.*, 2002, **8**, 36.
9 I. Paterson and T. Temal-Laïb, *Org. Lett.*, 2002, **4**, 2473.
10 I. Paterson, C. J. Cowden and D. J. Wallace, in *Modern Carbonyl Chemistry*; Ed. J. Otera, Wiley-VCH, Weinheim, 2000, pp. 249–297.
11 J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, 1995.
12 D. A. Evans, *Aldrichimica Acta*, 1982, **15**, 23 and references therein.
13 M. T. Crimmins, B. W. King and E. A. Tabet, *J. Am. Chem. Soc.*, 1997, **119**, 7883.
14 D. A. Evans, C. W. Downey, J. T. Shaw and J. S. Tedrow, *Org. Lett.*, 2002, **4**, 1127and references therein.
15 A. Abiko, J.-F. Liu and S. Masamune, *J. Am. Chem. Soc.*, 1997, **119**, 2586.
16 M. Braun, *Angew. Chem. Int. Ed. Engl.*, 1987, **26**, 24.
17 M. Braun and S. Graf, *Org. Synth.*, 1998, **9**, 497 and references therein.
18 S. Saito, K. Hatanaka, T. Kano and H. Yamamoto, *Angew. Chem. Int. Ed.*, 1998, **37**, 3378.
19 C. Palomo, A. González, J. M. García, C. Landa, M. Oiarbide, S. Rodríguez and A. Linden, *Angew. Chem. Int. Ed.*, 1998, **37**, 180.
20 A. Abiko, T. Inoue, H. Furuno, H. Schwalde, C. Fieres and S. Masamune, *J. Am. Chem. Soc.*, 2001, **123**, 4605 and references therein.
21 N. Iwasawa and T. Mukaiyama, *Chem. Lett.*, 1982, 1441.
22 (*a*) T. Mukaiyama, S. Kobayashi, H. Uchiro and I. Shiina, *Chem. Lett.*, 1990, 129; (*b*) S. Kobayashi and T. Mukaiyama, in *Stereocontrolled Organic Synthesis*, Ed. B. M. Trost, Blackwell, Cambridge, 1994, pp. 37–65.
23 T. Ooi, K. Doda and K. Maruoka, *Org. Lett.*, 2001, **3**, 1273.
24 E. M. Carreira, R. A. Singer and W. S. Lee, *J. Am. Chem. Soc.*, 1994, **116**, 8837.
25 Y. Yamashita, H. Ishitani, H. Shimizu and S. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 3292.
26 D. A. Evans, C. S. Burgey, M. C. Koxlowski and S. W. Tregay, *J. Am. Chem. Soc.*, 1999, **121**, 686.
27 K. Oisaki, Y. Suto, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 5644.
28 U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751.
29 T. Hamada, K. Manabe, S. Ishikawa, S. Nagayama, M. Shiro and S. Kobayashi, *J. Am. Chem. Soc.*, 2003, **125**, 1989 and references therein.
30 H.-J. Li, H.-Y. Tian, Y.-J. Chen, D. Wang and C. J. Li, *Chem. Commun.*, 2002, 2994.
31 C.-T. Chen, S.-D. Chao, K.-C. Yen, C.-H. Chen, I.-C. Chou and S.-W. Hon, *J. Am. Chem. Soc.*, 1997, **119**, 11341.
32 S. E. Denmark and R. A. Stavenger, *Acc. Chem. Res.*, 2000, **33**, 432.
33 S. E. Denmark and S. K. Ghosh, *Angew. Chem. Int. Ed.*, 2001, **40**, 4759.
34 S. E. Denmark and Y. Fan, *J. Am. Chem. Soc.*, 2002, **124**, 4233.
35 M. Shibasaki, M. Kanai and K. Funabashi, *Chem. Commun.*, 2002, 1989and references therein.
36 N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguzhi and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 2169.
37 B. M. Trost, H. Ito and E. R. Shilcoff, *J. Am. Chem. Soc.*, 2001, **123**, 3367.
38 W. Yao and J. Wang, *Org. Lett.*, 2003, **5**, 1527.
39 R. Mahrwald and B. Ziemer, *Tetrahedron Lett.*, 2002, **43**, 4459.
40 R. Mahrwald, *Org. Lett.*, 2000, **2**, 4011.
41 D. A. Evans, C. W. Downey and J. L. Hubbs, *J. Am. Chem. Soc.*, 2003, **125**, 8706and references therein.
42 B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395.
43 W. Notz and B. List, *J. Am. Chem. Soc.*, 2000, **122**, 7386.
44 K. Sakthivel, W. Notz, T. Bui and C. F. Barbas III, *J. Am. Chem. Soc.*, 2001, **123**, 5260.

45 L. Hoang, S. Bahmanyar, K. N. Houk and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 16.
46 S. Bahmanyar, K. N. Houk, H. J. Martin and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 2475.
47 Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang and Y.-D. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 5262.
48 B. Alcaide and P. Almendros, *Angew. Chem. Int. Ed.*, 2003, **42**, 858.
49 N. S. Chowdari, D. B. Ramachary, A. Córdova and C. F. Barbas III, *Tetrahedron Lett.*, 2002, **43**, 9591.
50 A. Bøgevig, N. Kumaragurubaran and K. A. Jørgensen, *Chem. Commun.*, 2002, 620.
51 C. Pidathala, L. Hoang, N. Vignola and B. List, *Angew. Chem. Int. Ed.*, 2003, **42**, 2785.
52 A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 6798.
53 M. Nakadai, S. Saito and H. Yamamoto, *Tetrahedron*, 2002, **58**, 8167.
54 T. Ooi, M. Taniguchi, M. Kameda and K. Maruoka, *Angew. Chem. Int. Ed.*, 2002, **41**, 4542.
55 A. Córdova, W. Notz and C. F. Barbas III, *Chem. Commun.*, 2002, 3024.
56 T. J. Dickerson and K. D. Janda, *J. Am. Chem. Soc.*, 2002, **124**, 3220.