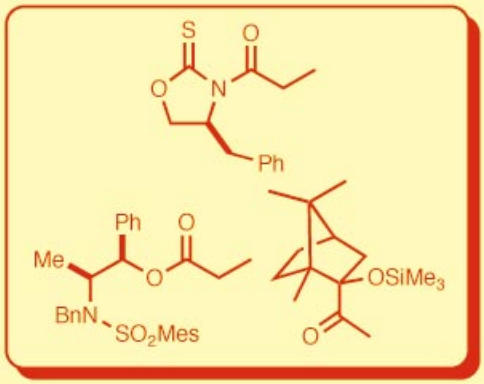
Large scale?

Coupled processes?

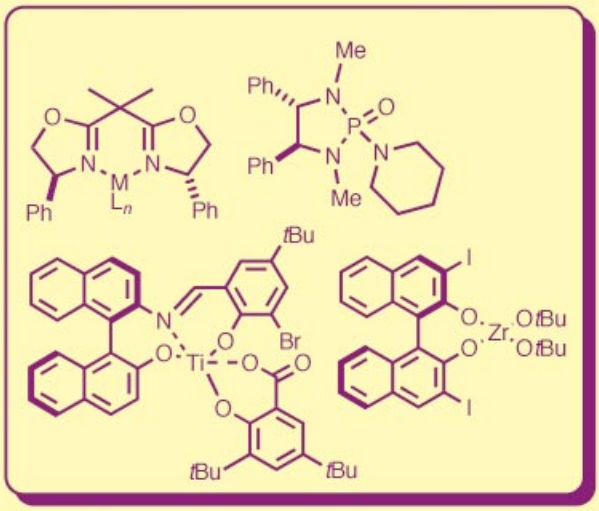
syn/anti?

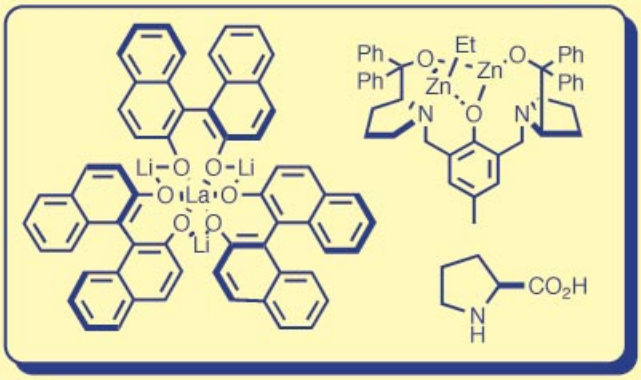
Environmentally friendly?



Stoichiometric
Diastereoselective
Acetate aldols
Preformed enolates

Catalytic
Acetate aldols
Enantioselective
Preformed enolates





Unmodified ketones
Enantioselective
Atom economy
Catalytic

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The Aldol Addition Reaction: An Old Transformation at Constant Rebirth

Claudio Palomo,*[a] Mikel Oiarbide,[a] and Jesús M. García[b]

Dedicated to Professor Marcial Moreno-Mañas on the occasion of his 60th birthday

Abstract: The main recent conceptual advances in asymmetric aldol reactions are presented. Methods ranging from stoichiometric chiral auxiliary-mediated to direct, catalytic reactions are covered, including the Mukaiyama aldol reactions which use stoichiometric base and silylating reagents, but catalytic (substoichiometric) amounts of the chiral inductor. The salient features of each new development are noted, paying special attention to practical concerns and to the potential implementation for large scale production. After examination of pros and cons of each strategy, gaps and limitations that deserve further investigation are highlighted.

Keywords: aldol reaction · catalysts · chiral auxiliaries · practical processes

Introduction

The aldol addition reaction, that is the addition of an enolizable carbonyl compound to an aldehyde (or ketone) leading to an aldol product, is a classical transformation in organic synthesis.[1] As a result of this reaction, a new C–C bond is formed and up to two new adjacent stereocenters can be generated simultaneously (Figure 1). Because of the presence of the aldol structural motif—and other structures derived therefrom—in many molecules of interest, the aldol addition reaction has been one of the most widely used synthetic operations for the construction of stereochemically complex natural and nonnatural products.[2] The most elemental, simple, direct base or acid promoted aldol reactions[3] involve intermediate species such as the nucleophiles **I** and **II**

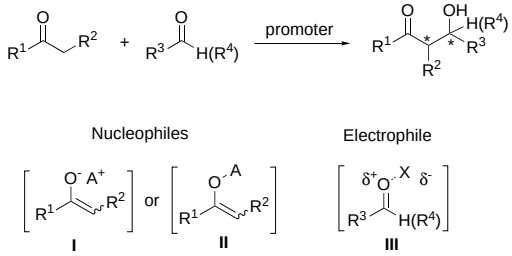

Figure 1. The general aldol reaction, and the nucleophilic and electrophilic species involved.

and the electrophile either aldehyde or acid-activated aldehyde **III**, and usually suffer from reversibility, dehydration side reaction, and lack of chemo-, regio-, and stereoselectivity.

To make the reaction practical, and therefore selective, "directed" stepwise aldol methodologies that use preformed species **I** or **II** have been developed.[4] In this way impressive achievements in asymmetric aldol methodology have been reached, which basically rely on the use of chiral auxiliaries, ligands and catalysts as the main stereochemical controllers.[5] These modern methods involve increasing sophistication, which might be rather interesting for academia, but at the same time less attractive for industrial implementation. To fulfill the new demands of the market, operationally simple and general, economical, non-polluting procedures are required, which must be capable of accessing each individual stereoisomer in high efficiency. Driven precisely by these demands, new concepts have recently emerged in the field, in both "directed" and "direct" versions, and further refinements for the near future can be predicted. The aim of this concept article is to critically summarize these advances, pointing out the gaps that challenge future investigations with special focus on practical concerns.

Discussion

Directed aldol reactions under stoichiometric conditions: Aldol addition reactions under the assistance of stoichiometric amounts of a chiral inductor are inherently less atom efficient than catalytic methods. Under certain circumstances, however, this handicap can be counterbalanced by the

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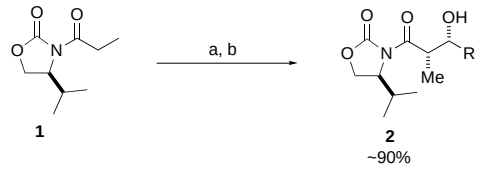
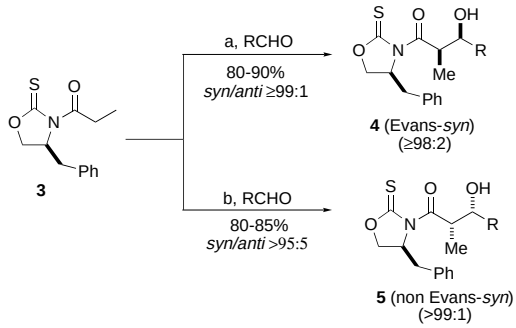
benefits that may apply to the stoichiometric methods. In this sense, covalently bound chiral auxiliaries have become popularly used not only in academia but also in large scale work.[6] Auxiliaries usually are more straightforward to prepare from commercial sources than catalysts, and often facilitate the adduct isolation – separation – purification processes, which can be of fundamental practical importance. From a conceptual point of view, auxiliaries can allow for a more efficient fine tuning of the regio- and stereochemistry than in catalytic systems. Yet, since the catalyst-substrate link is based on noncovalent interactions, catalytic methods are more susceptible to the structural shape of each individual substrate, resulting in a greater variability. Prototype chiral auxiliaries useful in aldol and other reactions are the α-amino acid derived oxazolidin-2-ones developed by Evans almost 20 years ago, Scheme 1.



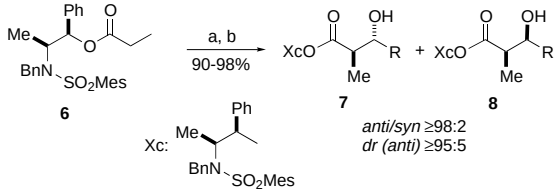
Scheme 1. Boron-mediated aldol reactions of a *N*-acyl 2-oxazolidinone and aldehydes to give *syn*-aldol products:[7] a) Bu_2BOTf, iPr_2EtN, CH_2Cl_2, 0 °C; b) RCHO, −78 → 0 °C.

Conceptually, this development consists of the irreversible and quantitative generation of a *Z*-enolate from **1** that presumably reacts through a well ordered, closed transition state, with aldehydes to yield *syn*-aldol products **2** in a highly predictable manner. The chiral auxiliary can be efficiently recovered from the aldol adducts for reuse, and the method offers a convenient access to each *syn* isomer by the proper choice of the commercial source of chiral information.[7] A significant practical and conceptual advance in this type of auxiliaries has recently been documented by Crimmins, based on a mechanistic model. This approach provides both the "Evans" **4** and "non-Evans" **5** *syn*-aldol product (Scheme 2) from the same source of chiral information as a result of a stereodivergent control of the reaction stereochemistry by adjusting the amount of $TiCl_4$, and the amount and nature of the amine base. Of practical importance, the reactions work efficiently at temperatures as high as 0 °C and with just one equivalent of the aldehyde substrate.[8]



Scheme 2. Stereodivergent route to both *syn*-aldols from the same substrate reagent:[8] a) $TiCl_4$ (1 equiv), TMEDA or (−)-sparteine (2.5 equiv), 0 °C; b) $TiCl_4$ (2 equiv), iPr_2EtN (1 equiv), −78 °C.

Despite these advances, two long standing problems associated with the aldol addition reaction in general, and the chiral auxiliary mediated methodologies in particular, are the production of *anti* aldol products and the "acetate" aldol reaction, respectively. Most of the auxiliaries developed to date preferentially give *syn*-aldol products. In some instances, the use of an extra amount of a Lewis acid can serve to switch the stereochemical outcome of the reaction to afford mainly *anti* isomers.[9] Nevertheless, a waste of costly reagents can be predicted for large scale preparations and these methods are, therefore, hardly of any atom economy. Here, the main problem arises from the fact that *E*-configured enolates, needed in the closed transition state to give the *anti* products, are not favored. Thus, one important future direction of organic chemistry is the development of practical and inexpensive reagents which induce preferential formation of *E*-enolates. One potential class of such reagents has been presented recently by Abiko and Masamune starting from the commercially available (−)-norephedrine (Scheme 3).[10] 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 functionalyzed aldehydes, to afford aldols **7**/**8** in up to 99:1 *anti*:*syn* selectivity ratio. Yet, auxiliary detachment (three days of reaction) may be a problem, while the stereodivergent access to both *anti* aldols from the same source of chirality remains unexplored.



Scheme 3. Norephedrine-derived propionate ester designed for *E*-enolate generation en route to *anti*-aldols.[10] a) $(c\text{Hex})_2BOTf$, Et_3N; b) RCHO.

As mentioned above, "acetate" aldol reactions deserve special attention. While Mukaiyama-type aldol reactions of acetate equivalents are well developed (see below), as a matter of fact, most of the chiral auxiliaries perform poorly in "acetate" aldol reactions.[11] To compensate the absence of substituents at Cα of the enolate as one of the main stereocontrol elements of the C–C bond forming process, chiral auxiliaries featuring high conformational rigidity and/or very crowded stereoelectronic environments can be designed. This, however, may be detrimental to the reactivity of the enolate, and a balance in between stereodiscriminating ability and reactivity should be approached sharply. The chiral acetate esters **9** and **10**, derived from the Braun's (*R*)-1,2,2-triphenylethylene glycol,[12] and 2,6-bis(2-isopropylphenyl)-3,5-dimethylphenol of Yamamoto[13] (Figure 2) meet these criteria, and their lithium enolates do react with aldehydes in good enough chemical yields and very high diastereoselectivities.

A conceptually different, but in practice equivalent, strategy for carrying out highly efficient asymmetric aldol

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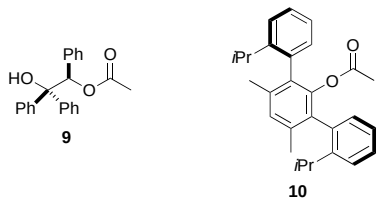
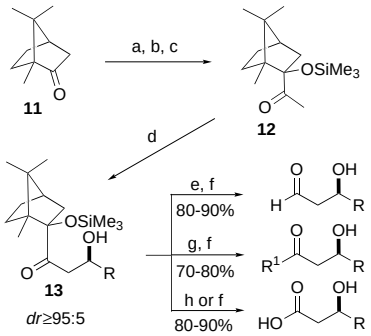


Figure 2. Sterically crowded chiral acetate esters that display high diastereoselectivity in lithium-mediated aldol reactions.[12, 13]

reactions is the use of chiral α-hydroxy alkyl ketones, which also are readily affordable from natural sources in few steps.[14] Although excellent levels of diastereoselectivity can be attained,[15] the destruction/immolation of the chiral information source during the α-ketol cleavage step to give the desired aldols hampers their use for large scale. In this context, Palomo and co-workers have recently designed the first chiral α-hydroxy methyl ketone that works under non-destructive conditions, which is very attractive for "acetate" aldols. In such an approach, acetylene is used as the elementary source of carbon (acetyl) and (1*R*)-(+)-camphor (**11**) as the recyclable source of chiral information,[16] both of which are bulk material. The method is highly selective for a broad range of aldehydes, and allows the access to the corresponding either aldehyde, ketone, or carboxylic acid aldols as a function of the sequence employed for the cleavage of the α-ketol moiety in **13** (Scheme 4). The method is quite simple, and a minimal production of waste material accompanies the entire process.



Scheme 4. Chiral acetate equivalent affordable from acetylene and (1*R*)-(+)-camphor and its lithium-mediated aldol reactions:[16] a) HC≡CLi, 90%; b) H_2O/Hg^{2+}; c) *N*-trimethylsilyl oxazolidinone, TfOH cat., 85% (two steps); d) LDA, THF, −78 °C, RCHO; e) $BH_3 \cdot THF$; f) CAN; g) R^1M; h) $NaIO_4$.

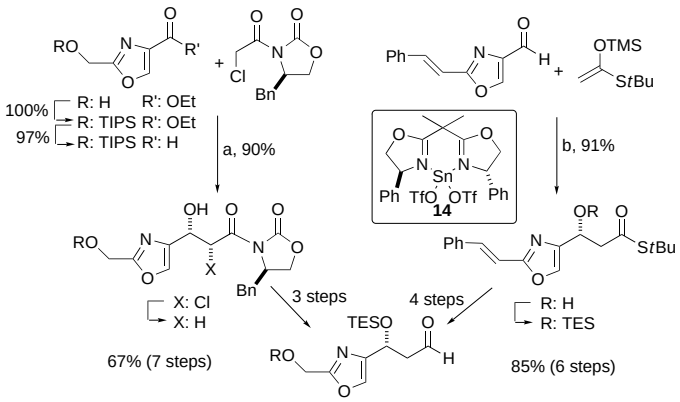
Here, as in most of the methods for generating lithium enolates, LDA or a related lithium amide base have to be used, which implies a consumption of an alkyllithium and a secondary amine. It would be more atom efficient if the lithium enolates were available using only alkyllithium reagents as the base. Chiral auxiliaries and conditions for this development still are unprecedented. To further progress in the development of efficient lithium enolate systems for aldol addition and other reactions, it would be of great help to better understand the complex structures that lithium enolates adopt in solution[17] and to identify the actual active species in each type of reaction.

The benefits derived from the use of chiral auxiliary-mediated strategies are slighty narrowed as there is the need for extra operational steps, such as the attachment/detachment of the covalently bound auxiliary from the adduct. Two different alternatives which can overcome such a requirement are the use of chiral lithium amide bases and the use of metal enolates bearing chiral ligands, both of which make use of stoichiometric amounts of the chiral components. Although boron and, to a lesser extent, tin(II), tin(IV), and titanium(IV) enolates are the standard in the field,[14] enantioselective aldol reactions can also be carried out by the assistance of chiral lithium amide bases. Here, while the chiral amide ligand is easily recoverable by acid/base aqueous work-up extractions, low levels of enantioselectivity are generally attained, and still more refinement is needed.[18] On the other hand, metal enolates of ketones and esters[14, 19] bearing chiral ligands also provide the "free" aldol product without the need of any auxiliary detachment. The separation of the ligand by-product from the target aldol and the restoration of the original metal/ligand reagent from the ligand by-product can, however, be a cumbersome task on large scale. Certainly, methods that are based upon the use of substoichiometric amounts of the asymmetric inductor are more preferable: A small amount of a chiral material can provide large quantities of single enantiomer product in an inherently "atom-economic" manner, whilst generating minimal waste.[20] Major concepts associated to these methods are disclosed in subsequent sections.

Directed catalytic aldol reactions with preformed enolates: With the discovery of the Lewis acid promoted addition reaction of an enolsilane to an aldehyde to yield an aldol, namely the Mukaiyama aldol reaction,[21] new oportunities for development emerged. This reaction has rapidly moved from the use of a stoichiometric amount of the (chiral) Lewis acid promoter to the more recent substoichiometric/catalytic versions.[22] Since stoichiometric generation of a trialkylsilyl enol ether or acetal (thio)ketene in a separate and distinct chemical operation is a prerequisite, the Mukaiyama reaction is only catalytic in metal promoter, but stoichiometric with respect to silicon. In this regard, a number of Lewis acids which consist of a metal, including early and late transition elements, and chiral ligands bearing nitrogen, oxygen, and phosphorous donors have been documented.[22, 23, 24] Nonetheless, the Lewis acid-catalyzed aldol reactions still are considerably sensitive to subtle variations in the preparative details of catalyst generation, the solution-state structure of the catalytically active species, and minor variations in reaction conditions. In many cases, for example in tin(II) triflate–chiral diamine complexes[25] and acyloxyborane and oxazaborolidine[26] mediated Mukaiyama reactions, Lewis base solvents such as propionitrile or nitromethane elicit optimum catalyst efficiency, while both relatively high catalyst loadings ($\geq$20 mol%) and the slow addition of the nucleophile to the reacting mixture are generally required for success. Similar trends can also be observed in most of the reactions promoted by chiral titanium complexes bearing BINOL ligands.[27] In these cases, the necessity to precisely adhere to the procedures used for reproducibility is remarked

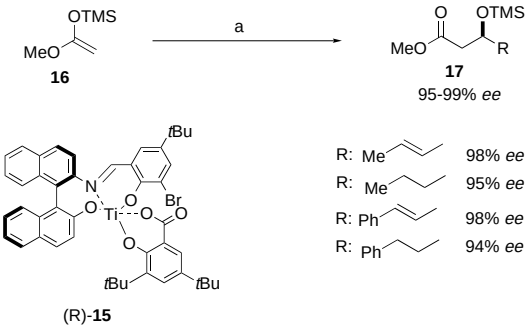
by the authors themselves, as far as both unpredictable solvent effects on chemical yield and enantioselectivity, and unusual concentration effects (lower and higher concentration of the catalyst gives rise to decreased yields and/or *ee*'s) are encountered.[28] Catalyst activity is, therefore, a fundamental concern, specially with respect to large scale preparative work wherein reproducibility is a crucial factor. The search for more active catalytically systems can, in principle, be oriented toward 1) the addition of "external" activators to the preexisting catalyst, or 2) the design of de novo catalytic systems that may also be effective in other chemical transformations. Alternative 1), which may start from catalysts with well established scope, appears to be the most straightforward to study. Here, the concept of asymmetric activation of the catalyst by the aid of additional chiral or achiral activators can be applied to the Mukaiyama reaction with some success.[29] Nonetheless, the activator reagent is in general a ligand that is added to the reaction mixture, and therefore removal of the catalyst/activator residues from the final product can in some instances be difficult on a large scale and introduces additional constraints.

On the other hand, as an example of the above mentioned strategy 2), newly and very active cationic Cu^{II} and Sn^{II} complexes, incorporating chiral bidentate bisoxazoline and pyridine-bisoxazoline ligands, have been recently introduced by Evans (Scheme 5).[30] While the activity of these catalysts is remarkable (typically, a 5 mol% of the catalyst suffices for excellent yields and enantioselectivities), the method exhibit a strong specificity to substrates capable of engaging in five-membered chelates with the catalyst, such as α-heteroatom-substituted aldehydes and, noticeable, pyruvic esters.



Scheme 5. A Sn^{II}-bisoxazoline complex as efficient catalyst for the enantioselective Mukaiyama reaction, and comparison with the chiral auxiliary approach:[30e] a) nBu$_2$OTf, Et$_3$N, CH$_2$Cl$_2$, $-78\,^{\circ}$C; b) 10 mol% **14**, CH$_2$Cl$_2$, $-78\,^{\circ}$C.

Catalyst not only must be chemically and stereochemically efficient, but also general in substrate acceptance. Towards this end, the structural modification of the ligand(s) of a preexisting catalytic system characterized by a wide substrate generality may be the right choice for development. Structural modification of ligands can be carried out on the basis of combinatorial chemistry[31] or, in a more directed way, by applying rational concepts inferred from the knowledge of the reaction mechanism. It is believed that the catalyst activity in Mukaiyama reactions depends on how fast the intra- or intermolecular silyl group transfer to the aldolate oxygen with simultaneous liberation of the active catalyst occurs. Under low catalyst turnover conditions, both the requirement for higher catalyst loadings and an attenuation of the reaction enantioselectivity as a consequence of the "silicon-catalyzed" achiral aldol pathway can be predicted. Taking into account this working hypothesis, ligands bearing functional groups that may act as a silyl group shuttle should be beneficial for the catalyst turnover and, therefore, for the catalyst activity. Guided by this design elements, Carreira has found the most prominent metal complex catalyst for the Mukaiyama type aldol addition, the titanium(IV)-Schiff base catalyst **15** (Scheme 6).[32] This catalyst is characterized by a high activity



Scheme 6. Hihgly active Ti^{IV}-based catalyst for the Mukaiyama reaction.[32] a) RCHO, (*R*)-**15** (0.5–5 mol%), Et$_2$O, $-10 \rightarrow 0\,^{\circ}$C, 4 h.

and tolerance of a wide array of nucleophiles and electrophiles. Under optimized conditions, the simple methyl acetate-derived enol silane **16** adds to aldehydes in the presence of as little as 0.5 mol% of **15** at $0\,^{\circ}$C to give adducts **17** in high yields and up to 99% *ee*. Here, slow addition of substrates to the catalyst solution at low temperature is not necessary, and catalyst loadings of less than 5 mol% are usually required for success.[33] On the other hand, this system works efficiently with commercially available 2-methoxypropene as the latent enolate,[34] thus precluding the procedural requirement for generating the enolate equivalent in a separate operation.

Enhancement of the asymmetric induction by the assistance of simple (achiral) additives is another conceptual approach that can be employed for catalyst optimization.[35] The implementation of this concept to the Mukaiyama reaction is nicely demonstrated in the reaction of acetal ketenes **19** with aldehydes promoted by the zirconium catalyst **18**, where the addition of an alcohol (50 mol% to the catalyst) to yield each aldol **20** in good yields and enantioselectivities is critical (Scheme 7).[36] In addition, the reaction proceeds at $0\,^{\circ}$C and is highly *anti* selective, while the majority of the catalysts for the Mukaiyama reaction lead to preferential formation of the corresponding *syn* aldols irrespective of the configuration of the enolsilane involved.

All the above catalytic Mukaiyama reactions imply the participation of a metal-based catalyst. Usually, an amount within about 1–20 mol% of the metal containing catalyst is employed, and often its recovery is not reported or is difficult.

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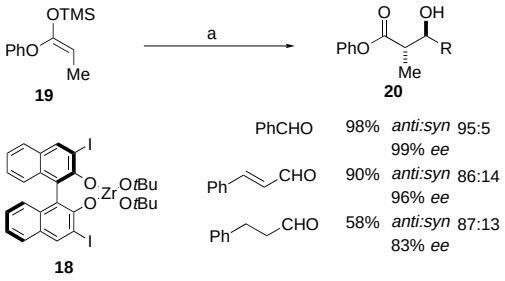
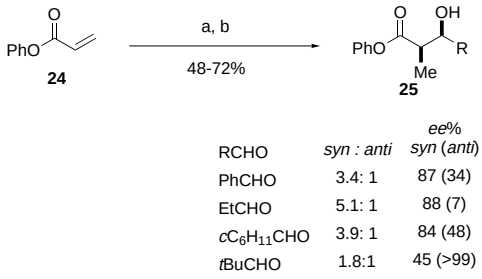


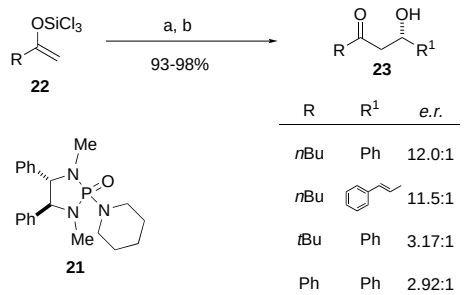
Scheme 7. Zirconium-based catalyst for *anti*-aldol reactions:[36] a) RCHO, **18** (2–10 mol%), *n*PrOH (50 mol%), toluene, 0 °C.



RCHO	*syn* : *anti*	*ee*% *syn* (*anti*)
PhCHO	3.4: 1	87 (34)
EtCHO	5.1: 1	88 (7)
$cC_6H_{11}CHO$	3.9: 1	84 (48)
*t*BuCHO	1.8:1	45 (>99)

Scheme 9. Reductive asymmetric aldol reaction:[38] a) RCHO, Et_2MeSiH, $[(cod)RhCl]_2$ (2.5 mol%), (*R*)-BINAP (6.5 mol%); b) H_3O^+.

For environmental and other practical reasons, reaction systems which do not involve metals are desirable, specially when the presence of even traces of a metal in the product can be prohibitive, as for example in pharmaceutical compounds. The group of Denmark has developed some chiral Lewis bases (phosphoramides) which efficiently promote the reaction of trichlorosilyl enolates **22**, readily available from trimethylsilyl enol ethers, with aldehydes to give **23** in high *ee* values (Scheme 8). Here, the metal-free catalyst, for example **21**, activates the nucleophilic silyl enolate rather than the electrophilic carbonyl. The reactions proceed through a closed transition state, with participation of hexacoordinate silicon species, and the method is particularly suitable for alkyl(aryl) methyl ketones,[37] a case that is not well solved in the context of the typical Mukaiyama procedures. The need for an extra step to convert the initial trimethylsilyl enol ethers into the required trichlorosilyl enol ethers can represent, however, a disadvantage from a practical standpoint.



R	R^1	*e.r.*
*n*Bu	Ph	12.0:1
*n*Bu		11.5:1
*t*Bu	Ph	3.17:1
Ph	Ph	2.92:1

Scheme 8. Chiral Lewis base catalyst designed for aldol reactions with trichlorosilyl enolates:[37] a) R^1CHO, (*S*,*S*)-**21** (5 mol%), CH_2Cl_2, −78 °C; b) $NaHCO_3$(aq).

Besides the problems associated with the search of an "ideal" catalyst for the Mukaiyama type reactions, many technological improvements still remain to be addressed. For example, to integrate the "enolization" and the subsequent "aldolization" steps into a sole operation, by generating the enolsilane in situ, would be of high practical interest. Such a development has been recently achieved by Morken, who has demonstrated that in the presence of excess (*R*)-BINAP (1.3:1 ligand/metal; 2.5 mol% $[(cod)RhCl]_2$) the reaction between phenyl acrylate **24**, aldehydes, and diethylmethylsilane provides a mixture of *syn* and *anti* β-hydroxy esters **25** in good *ee* values for some cases (Scheme 9).[38] Aromatic and aliphatic aldehydes are tolerated, but α,β-unsaturated aldehydes are not good substrates for this reaction. Although further refinement is needed, this three component coupling reaction is operationally rather simple and, most notably, occurs at ambient temperature, which are two requirements for technically feasible catalytic processes.

With regard to developing cost-effective processes, the search of reactions that may proceed in water as solvent may provide some benefits. Incipient results on the Mukaiyama reaction by means of water-tolerant Lewis acids have recently been achieved in protic solvents including water.[39] Although most of the organic materials have limited solubility in water, these findings have shown that protic, less volatile solvents or mixtures of protic solvents and water are suitable for aldol reactions, and have opened the way for exciting research in this area.

Yet, an additional challenge is the development of immobilized catalytic systems,[40] where the recyclability of the catalyst is not longer a problem that otherwise affects the procedural costs and the products purity.

Unmodified ketones at work (direct catalytic aldol reactions): The search for efficient methods which combine unmodified, therefore often commercial, carbonyl substrates as nucleophiles, and chiral, catalytic reagents for chirality transfer is a priority in the field. A partial advance in controlling the aldolization of α,β-unsaturated ketones and esters has been realized by means of (over)stoichiometric amounts of bulky triaryloxy aluminium (ATPH) reagents.[41] The main concept is that selective complexation of ATPH with the unsaturated carbonyl is followed by sterically/conformationally directed γ-deprotonation and aldolization steps. Although the asymmetric variant of this reaction system still remains unrealized, this development represents the first "direct" vinylogous aldol reaction.[42] An attempt to control regiochemistry during aldolization of unsymmetrical ketones for the cross-aldol reaction with aldehydes has been realized with substoichiometric amounts (10 mol%) of $TiCl_4$ at 0 °C.[43] Nevertheless, the asymmetric variant of this strategy,[44] which uses binary combinations of titanium-BINOL complexes and nonracemic α-hydroxy acids, still requires stoichiometric quantities of the chiral ligands.

Two different approaches can be taken toward the realization of direct asymmetric catalytic aldol reactions: those that use biochemical catalysts such as aldolases and catalytic antibodies, and those that use chiral chemical catalysts such as

chiral Lewis acids and bases or nonmetallic small organic molecules. Enzymes are generally chemo-, regio-, diastereo-, and enantioselective, and during their use protecting group chemistry can be kept to a minimum. In addition, most of the enzymes operate at ambient temperature under very mild conditions and enable to combine several enzymes in one-pot, multistep operations in an environmentally advantageous option. Nevertheless, in certain cases the reaction is limited to a narrow range of substrates. The achievements in this field are summarized in the literature.[45] On the other hand, the finding or invention of simple catalysts that hold broad substrate acceptance is a key challenge in the field, and would help aldol reactions to be more amenable to scale-up. Undoubtedly, a promising approach to this goal is the design of low molecular weight catalysts that mimic enzymes (Figure 3). The first catalyst which meets this criterium just appeared four years ago as a result of the seminal investigation of Shibasaki's group on asymmetric catalysis.[46]

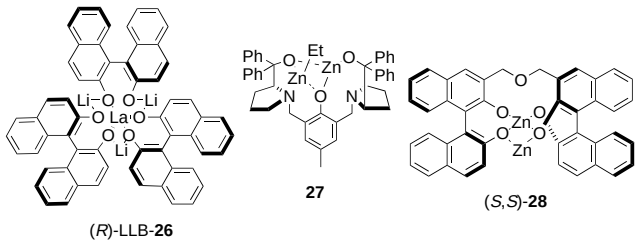
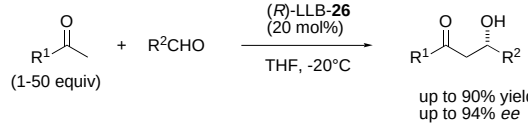


Figure 3. Chemically designed bimetallic complexes for the asymmetric direct aldol reaction with unmodified ketones.

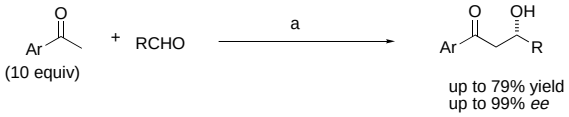
The concept[47] is based on the use of bifunctional catalysts such as the heterobimetallic $LaLi_3$tris(binaphthoxide) (LLB) **26**, which bear both a Lewis acidic site and a Brønsted basic site, and is capable of simultaneously activating the nucleophilic ketone and the electrophilic aldehyde. Reactions of methyl ketones with aldehydes under the presence of a 20 mol% of LLB in THF at $-30/-20\,^{\circ}C$ give, after 3–10 days of reaction, the aldol adducts in good yield and high *ee* (Scheme 10). The reaction with ketones incorporating α'-hydrogens also works well provided that a large excess of the



Scheme 10. Direct aldol reactions of methyl ketones promoted by a La/Li heterobimetallic complex.[47] a) (*R*)-LLB-**26** (20 mol%), THF, $-20\,^{\circ}C$.

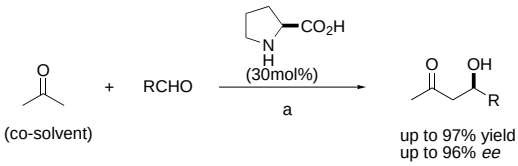
ketone (up to 50 mol%) is used. Most notably, the incorporation of KOH, generated from $KN(SiMe_3)_2$ and H_2O, to the catalyst lead to a more active heteropolymetallic species, which is able to promote aldol reactions at considerably lower catalyst loadings (8 mol%) and more reasonable reaction times (5 h).[47b] Thus, one important advantage of using chemically designed catalysts is that their structure can easily be modified to improve their efficiency.

Catalysts, on the other hand, are often expensive and thus one of the first steps during reaction optimization is, certainly, to reduce catalyst loadings. For example, the semicrown Zn^{II} complex **27**,[48] which has been designed by Trost on the basis of the recognition ability of crown compounds and the behavior of aldolase II-type enzymes, works very efficiently in the direct aldol reaction of ketones with aliphatic α-branched aldehydes with loadings as little as 5 mol% (Scheme 11).



Scheme 11. Direct aldol reactions of aryl methyl ketones promoted by a semicrown-Zn^{II} complex:[48] a) **27** (5 mol%), $Ph_3P{=}S$ (15 mol%), THF, $5\,^{\circ}C$, 2 d.

Besides the need to develop robust and reliable catalyst systems for a wider range of donors and acceptors, another significant challenge in asymmetric aldol reactions is discovering new catalytic reactions. In this respect, List, Barbas III, and co-workers,[49] have identified proline[50] as an amine-based asymmetric class I aldolase mimic that efficiently catalyzes the direct aldol addition of acetone and a variety of aldehydes. A distinguishing feature of the method is that no metal intervention is required for the reaction to proceed. Thus, under optimized conditions, a 30 mol% of L-proline promotes the reaction between acetone and aromatic aldehydes in a DMSO/acetone 4:1 mixture at room temperature in good to excellent yield and good enantioselectivities. The method is also suitable for aliphatic α-branched aldehydes (isobutyraldehyde; 90% yield, 96% *ee*), but is less effective for α-unbranched aldehydes (Scheme 12).[51]



Scheme 12. L-Proline as a cheap catalyst for the direct aldol reaction of acetone:[49] a) DMSO, RT, 4 h.

The scope of these three distinct methodologies has been subsequently broadened for the use of α-hydroxy ketones **29** as nucleophiles, in almost parallel developments by the groups involved (Table 1). Shibasaki's LLB assisted reaction of α-hydroxy ketones and aldehydes affords preferentially *anti* diols, while the new Zn-BINOL homobimetallic catalyst **28** (Figure 3) yields *syn* products.[52] Meanwhile, the proline triggered reaction of hydroxyacetone with aldehydes gives *anti* aldols in high *ee* values.[49b, 53] In a complementary fashion, the corresponding α-hydroxy methyl ketones upon reaction with aldehydes in the presence of as little as 5 mol% of the Trost Zn^{II}-crown catalyst **27**, give the *syn* diols in high yields and very high *ee* values at $-30\,^{\circ}C$.[54]

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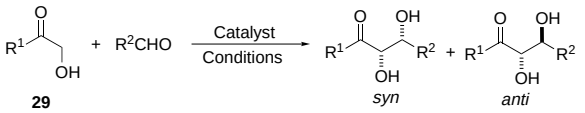
Table 1. Asymmetric direct aldol addition of hydroxyketones and aldehydes promoted catalytically.[49b, 52–54]



29

Catalyst	Conditions			Yield [%]	*syn*/*anti*	*ee* [%]
26[a] 10 mol %	THF	– 50 °C	24 – 40 h	78 – 92	1:5 – 1:2	90 – 95
L-proline 30 mol %	DMSO	RT	24 – 72 h	38 – 95	1: > 20 – 1:1.5	67 – > 99
27 2.5 mol %	THF	– 35 °C	24 h	62 – 98	35:1 – 3:1	81 – 98

[a] In the original paper the enantiomeric form of catalyst **26** [(*S*)-LLB] was used instead. For convenience, data are extrapolated for **26** [(*R*)-LLB] herein.

These somewhat complementary contributions provide among the most promising platforms for the development of truly catalytic aldol addition reactions in a selective and cost-effective way.[55] Obviously, the degree of development is still far from being optimum, since important limitations in substrate specificity and catalyst loading are still present. Another important unresolved issue concerns chemoselectivity when cross aldol reactions between both enolizable aldehyde acceptor and ketone donor are involved. Undoubtedly, new catalytic systems for the direct aldol reaction will be soon unveiled. Taking into account that coupling between an electrophilic (aldehyde) and a nucleophilic (ketone or equivalent) component must take place, the principle of asymmetric two-center catalysis[56] may be useful during design.

Conclusion

Although the aldol addition reaction is known for long time and extensive studies have been devoted over the years, new concepts have appeared very recently that deserves attention. From an overview of the literature, it is clear that often intellectually very interesting contributions are difficult for a practical implementation. Diastereomeric approaches under stoichiometric conditions have reached high standards as a consequence of long studying, and despite the need of extra attachment/detachment steps, still are in force because of their reliability, reproducibility, and generality. Investigations to improve chiral auxiliaries and ligands for stoichiometric usage that better adhere to the industrial requirements should be sustained. The Mukaiyama aldol reaction has represented a big breakthrough in the field, which has shifted much attention from the "stoichiometric" arena. While progress towards the development of catalytic, reproducible Mukaiyama methodologies has been done, still there is the need for a better understanding of the complete set of experimental parameters that govern the reactions, and further studies can be predicted for the near future. Finally, it appears that, because of obvious practical reasons, the not very far future will be dominated by the direct, catalytic asymmetric aldol methodologies. Relatively high degrees of chemo-, regio-, and stereocontrol have been achieved very recently by direct catalytic methods, but still they lack substrate generality. The search of new catalytic systems must be urgently supported by studies directed to the understanding of the actual role that the catalyst/promoter play in the reaction mechanism, something which is little known about. In addition, the development of multicomponent coupling reactions and methods that use ecologically benign reaction media and innovative separation techniques is another issue to be addressed, while some topics, such as the stereocontrolled creation of quaternary centers by means of aldol reactions still remain virtually unexplored.

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