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Direct Asymmetric Aldol-Tishchenko Reaction

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The asymmetric direct aldol reaction of nonpreactivated substrates constitutes one of the most powerful tools in current synthetic chemistry. In the last few years, chiral metal complexes have been found to catalyze the direct aldol addition of unmodified ketones to aldehydes with both high efficiency and selectivity. However, many problems have to be overcome in this still young field of chemistry. The most challenging aspect of this chemistry is the substrate limitation of known catalysts. In this field, the asymmetric aldol-Tishchenko reaction can be regarded as a parallel methodology that expands the scope of possible applications. In the aldol-Tishchenko reaction, two aldehyde molecules undergo addition to form an aldol adduct, which is subsequently reduced by a third aldehyde to yield 1,3-diol monoesters through a [3,3]-bond reorganization. With the use of aldehydes and ketones in the aldol-Tishchenko reaction, diols with three adjacent stereogenic centers can be created in one single operation. Thus, the reaction can be regarded as an extremely atom efficient method for the construction of enantiomerically enriched products that can serve as fundamental building blocks in synthesis. Moreover, the aldol-Tishchenko condensation is nowadays the most efficient methodology available for the direct catalytic asymmetric aldol reaction of methylene ketones. This article provides a synopsis of this field and highlights some of the challenges that still remain.

Introduction

The development of new methods for the synthesis of complex natural and unnatural molecules remains an enduring challenge in current organic chemistry. One of the major efforts in this area has been the controlled construction of molecules bearing sequences of stereocenters.[1] A wide variety of enantioselective chemical transformations are now performed by using only catalytic amounts of chiral promoters, which provides access to optically active compounds in a highly economic fashion. Among traditional methodologies for generating chiral compounds, aldol-type reactions are classical and powerful methods for their synthesis through carbon–carbon bond formation.[2]

The impressive achievements in asymmetric aldol reactions made to date rely on the conversion of the donor substrate into a more reactive species such as silyl enol ethers or ketene silyl acetals (Mukaiyama-type aldol reaction),[3] which use no less then stoichiometric amounts of reagents in separate steps.

Undoubtedly the most elegant and most economically attractive way to introduce chirality into a molecule is through the use of only a catalytic amount of a chiral controller. To date, one of the most exciting applications of this strategy is the *direct* aldol reaction of non-preactivated carbonyl nucleophiles (Scheme 1, path a).[4] Thus, tremendous effort has been devoted only recently to develop catalytic asymmetric methodologies which combine high chemo- and enantioselectivity with powerful atom economy[5] of the aldol reaction.[6]

Such transformations are realized in Nature where enzymes transform nonpreactivated substrates into more complex molecules. Biochemical aldol reactions such as those catalyzed by aldolases perfectly meet the atom economy principle by employing unmodified carbonyl donors. Their

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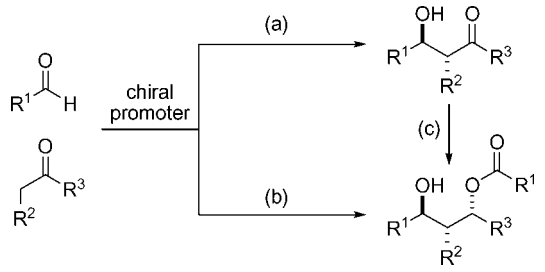
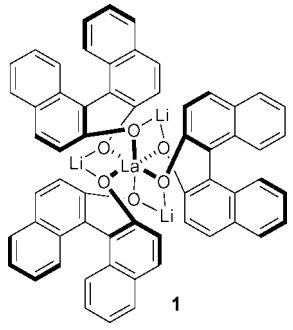


Scheme 1. Enantioselective direct aldol condensation (a) versus enantioselective aldol-Tishchenko reaction (b); carbonyl group reduction (c).

application is still, however, incipient in chemical practice mostly because of their narrow substrate scope.[7]

The first report on the use of a metal-based chemical catalyst for a direct enantioselective aldol reaction appeared from Shibasaki and coworkers.[8] The catalyst design is based on the general principle of two-center catalysis (Scheme 2). The multifunctional catalyst $LaLi_3$tris(binaphthoxide) (LLB-**1**) promotes the direct asymmetric aldol reaction of aldehydes with unmodified ketones by activation of both acceptor aldehyde and donor ketone. The synergistic functions of the active metal sites make substrates more reactive and control their positions in the transition state, so that functional groups are proximal to each other. Heterobimetallic complex **1** can be thus regarded as an enzyme mimic of the metal-containing aldolases of type II.[7a]



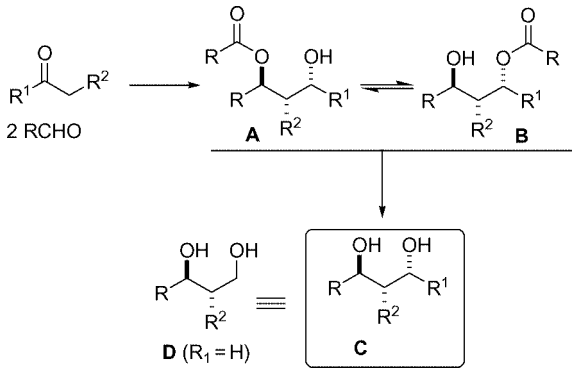
Scheme 2. Structure of Shibasaki's bifunctional catalyst (*S*)-LLB.

The remarkable success of this concept[9] inspired many scientists to devote more interest in this potentially advantageous strategy. Thus, the direct aldol addition of aldehydes and unmodified ketones to aldehydes in a catalytic, asymmetric manner with both metal-based catalysts[10] and organocatalysts[11] has been intensively developed over the last few years in many leading research groups.

From a practical perspective, however, there remains much room for improvement in the available methodology with respect to catalyst amount, stereoselectivity and substrate scope.[6b] In this regard, the aldol-Tishchenko reaction, defined as the domino condensation of aldehyde–ketone–aldehyde, appears to be complimentary in its methodology (Scheme 1, path b). While the aldol addition can create up to two new stereogenic carbon atoms, three adjacent stereogenic centers can be obtained by means of the aldol-Tishchenko reaction.

In 1906, Tishchenko reported the dimerization of aldehydes to their corresponding esters in the presence of Al- and Mg alkoxides.[12] Since then, this reaction has been used as an efficient method for the preparation of dimeric esters.[13] A complimentary transformation − the aldol-Tishchenko reaction[14] − has occupied a prominent position in organic chemistry as a highly effective method for the coupling of unactivated carbonyl compounds.[15]

The classic aldol-Tishchenko reaction is known to deliver 1,3-diol monoesters by the dimerization of aldehydes (Scheme 3, R^1 = H) having at least one α-hydrogen atom. In the first step of the reaction, two aldehyde molecules are condensed to the aldol product, which is further reduced by a third aldehyde molecule to give 1,3-diol monoester **A**. This, in turn, could isomerize through a 1,3-acyl migration.



Scheme 3. General scheme for the aldol-Tishchenko reaction.

Aldehydes and ketones also undergo tandem aldol-Tishchenko condensation with the simultaneous creation of three adjacent stereogenic centers (Scheme 3, product **C**).

Formation of diols in the aldol reaction is a valuable outcome that broadens the scope of the classic direct aldol methodology to include the asymmetric synthesis of various diol-type building blocks. The high selectivity of the aldol-Tishchenko reaction is also promising for stereoselective synthesis of *anti*-1,3-diols. Most of the methods use the stereoselective reduction of the corresponding β-hydroxy ketones, which is often the result of the aldol condensation (Scheme 1, path a–c). In this regard, the tandem aldol-Tishchenko reaction seems to be the method of choice for raising the whole economy process (Scheme 1, path b versus a/c).

Because of all the reasons discussed above, designing these reactions in an enantioselective manner would be attractive in terms of atom- and chiral economy, as they offer unique one-step stereocontrol of contiguous chiral centers in acyclic systems. Although the aldol-Tishchenko reaction had its genesis in the late 1890s,[14] its enantioselective variant has not been recorded until recently. This situation is now undergoing a highly significant change because of the enormous interest in the synthesis of enantiomerically pure compounds, but enantioselective direct condensation leading to 1,3-diols is still immature.[16]

The challenge of the asymmetric aldol-Tishchenko reaction has to be seen in the context of the apparent high com-

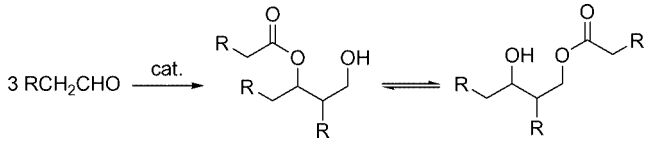
plexity of this process. Apart from the possibility of the formation of different diastereoisomers, the main product can be formed as *O*-1-ester **A** or *O*-3-ester **B** (Scheme 3). Both **A** and **B** can be obtained with different ratios of enantiomers, by assuming that their formation is not only a result of 1,3-acyl migration. Finally, the problem with the rational design of chiral ligands seems convoluted because the optimal catalyst must activate both partners in the direct aldol reaction as well as the resulting aldol in the Evans-Tishchenko reduction step.

Excellent reviews exhaustively cover the growing progress of the stereoselective aldol-Tishchenko reaction.[15,17] This overview is intended to represent the most recent aspects of the enantioselective variant of this methodology.

Asymmetric Aldol-Tishchenko Condensation of Three Aldehydes

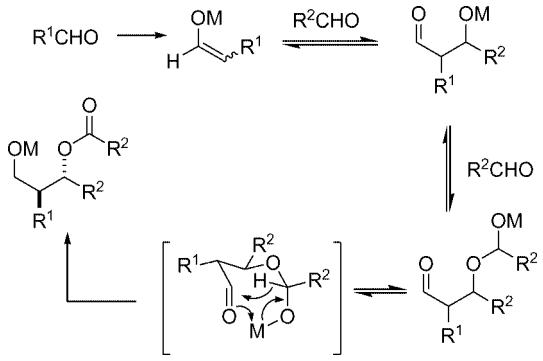
Aldol addition and the aldol-Tishchenko reaction are two major possible pathways for the dimerization of enolizable aldehydes. While the presence of a basic site in the catalyst is necessary for enolization of the aldehyde and subsequent aldol addition to another aldehyde, the Tishchenko reaction requires the presence of both acidic and basic sites in the catalyst.[18]

Initially, the aldol-Tishchenko reaction was demonstrated as a method for the coupling of three identical aldehydes (Scheme 4)[14c] catalyzed by either aluminium ate complexes of the general formula $Mg[Al(OR)_4]_2$[19] or magnesium- and calcium alkoxides.[20] Later, diastereoselective homo- and cross aldol-Tishchenko reactions were initiated by Sm-[21] and lithium[22] enolates.



Scheme 4. The homo aldol-Tishchenko reaction with enolizable aldehydes, promoted by metal alkoxides.

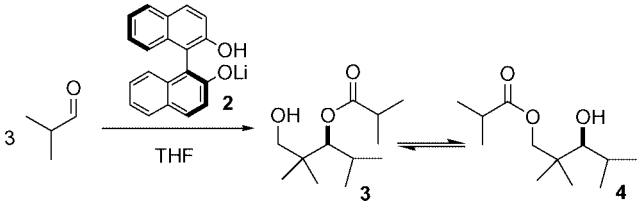
The mechanism of the classic aldol-Tishchenko reaction includes a base-induced enolization of one carbonyl partner and subsequent aldol addition to another aldehyde equivalent to furnish a metal aldolate, which upon reaction with a third aldehyde molecule forms a hemiacetal metal alkoxide. The plausible mechanism of the Tishchenko-reduction step was proposed independently in 1990 by Heathcock[23] and Evans.[24] Its idea is based on the formation of a bicyclic activated complex in which the hemiacetal hydrogen atom is transferred intramolecularly to the carbonyl moiety, eventually resulting in the reduction of the carbonyl group and oxidation of the hemiacetal to the ester moiety (Scheme 5).



Scheme 5. Plausible mechanism of the catalytic aldol-Tishchenko reaction.

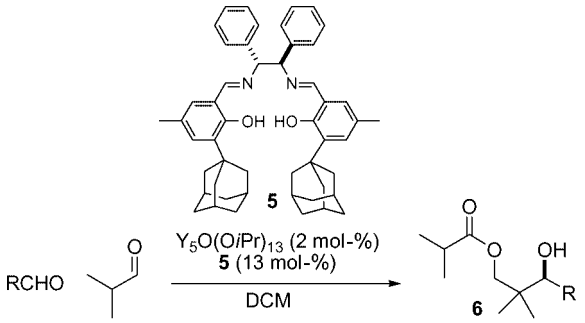
The higher level of stereochemical control observed in the reaction is supposed to be a result of the coordination of the metal catalyst to both the carbonyl- and the hemiacetal oxygen atoms. The rate-determining step of this sequence is believed to be the latter Tishchenko reduction of the hemiacetal metal alkoxide – the aldolization step is fast and reversible. The major stereoisomeric product is formed through the transition cyclic structure where all substituents of the six-membered structure occupy equatorial positions. The observation that stereocontrol in the aldol-Tishchenko reaction appears to be the result of a highly organized, metal-centered transition state encouraged the use of this reaction in an enantioselective manner under the influence of chiral ancillary ligands.

The use of chiral ligands in the asymmetric aldol-Tishchenko reaction was pioneered by Mäeorg et al.[25] Binaphtholate catalysts were used to gain insight into the stereochemistry of the self-condensation of 2-methylpropanal.[26] The shortest reaction time and the highest *ee*s were obtained with (*S*)-1,1′-binaphthalene-2-ol-2′-oxylithium (**2**) in THF (Scheme 6). Several steps of this condensation were found to be controlled by a homochiral catalyst, but with only low enantioselectivities (*ee* < 30%). The application of such a catalyst for this multistep condensation to prepare enantiomerically pure compounds appeared to be limited because of the various equilibrium reactions leading to opposite enantiomers.



Scheme 6. Self-condensation of 2-methylpropanal in the presence of binaphtholate catalysts **2**.

More recently Morken et al. discovered and developed the first catalytic enantioselective aldol-Tishchenko reaction of two different aldehydes.[27] The yttrium complex with salen-type ligand **5** was found to catalyze the condensation of 2-methylpropanal with various aromatic aldehydes. The results obtained are depicted in Scheme 7.



Entry	R	Yield [%]	*ee* [%]
1	phenyl	70	74
2	4-bromphenyl	55	70
3	naphtyl	50	64
4	4-methoxyphenyl	21	72
5	cinnamyl	50	10

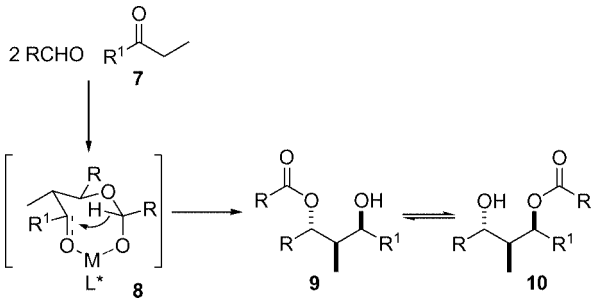
Scheme 7. Condensation of aromatic aldehydes with 2-methylpropanal, catalyzed by a yttrium–salen complex.

The reaction provided two regioisomeric esters in similar enantiopurity, which suggests nonselective intramolecular acyl migration after formation of aldol-Tishchenko adduct **6**. The relation between ligand structure and reaction enantioselectivity was also studied. Additional experiments proved that, with the yttrium–salen catalyst, the Tishchenko reduction step, which is slower than the retro-aldol reaction, is the stereo-determining step.

The reactions presented above constitute the first published examples of catalytic enantioselective aldol-Tishchenko reactions.

Condensation of Aldehydes to Ketones and Ketone Aldols

The scope of the aldol-Tishchenko reaction can be widespread with the use of aldehydes and ketones as suitable substrates. As a result, 1,3-diol monoesters **9** and **10** can be formed with the simultaneous creation of three adjacent stereogenic centers from the bond reorganization of cyclic Evans' intermediate **8** (Scheme 8). To design this process in an enantioselective manner would be attractive both in terms of atom- and chiral economy as it offers stereocontrol of three contiguous chiral centers in acyclic systems in one unique step.



Scheme 8. Aldol-Tishchenko condensation of ethyl ketones with aldehydes.

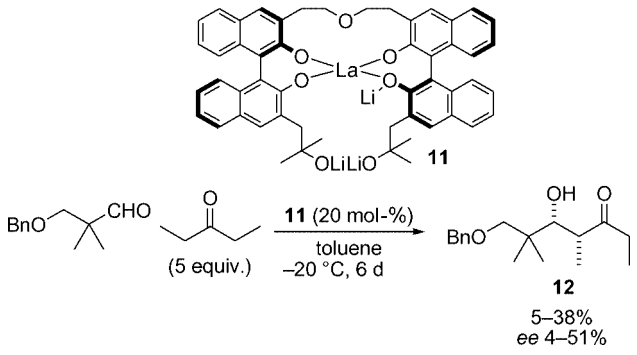
The importance of the catalytic asymmetric aldol-Tishchenko reaction of aldehydes with ketones comes from its potent usefulness in the direct asymmetric condensation of aldehydes with methylene ketones **7**, which are perceived as difficult substrates under classic direct aldol condensation conditions. Thus, problems with the direct aldol condensation of ethyl ketones will be briefly presented.

Direct Aldol Condensation of Ethyl Ketones

Since the first artificial metal complex was documented to be capable of promoting direct asymmetric aldol reactions,[8] some other metal-based and purely organic molecules were reported to activate unmodified donors under catalytic conditions.[2] To date, the substrate scope for these catalytic systems is, however, relatively narrow, and continuous effort is devoted to develop more general methodologies.

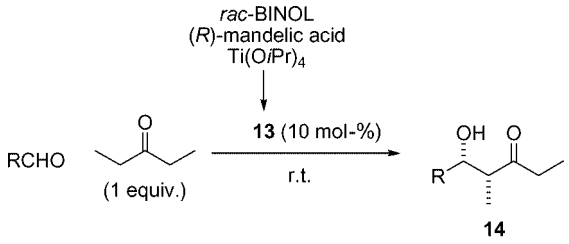
The direct aldol reaction between aldehydes and methylene ketones should provide a powerful tool for the formation of new carbon–carbon bonds and the construction of two continuous chiral centers. In contrast to well-documented transformations of methyl ketones,[8,10a,10c,10d] their methylene analogues, however, remain a formidable synthetic challenge.[4a] Only some α-substituted methyl ketones, particularly α-hydroxy ketones, work nicely in reactions promoted by known polymetallic catalysts.[10b,10e,10h] Diastereo- and enantioselective synthesis of aldols, starting from methylene ketones (e.g. 3-pentanone), by means of the direct catalytic asymmetric aldol reaction is still immature. The bulkiness of methylene ketones was expected to make it more difficult for the catalysts to abstract an α-hydrogen from the donor. A strong tendency towards the retro-aldol reaction creates another disadvantage for the direct aldol reaction of ethyl ketones that is promoted by chiral polymetallic complexes.

The initial study of this issue was presented by Shibasaki,[28] who reported the application of a strong basic La-Li-**11** complex that incorporates a Li alkoxide moiety. The catalyst promoted the direct aldol reaction of 3-pentanone with *anti* selectivity. However, the reported yields and *ee*s of the desired aldols were only modest (Scheme 9).



Scheme 9. Direct catalytic asymmetric aldol reactions of 3-pentanone, promoted by the La-Li-**11** complex.

The most promising example of the asymmetric condensation of 3-pentanone was reported by Mahrwald.[29] The titanium-based catalyst obtained by combining racemic BINOL, titanium(IV)alkoxide, and (*R*)-mandelic acid was suitable for promoting the cross aldol reaction of 3-pentanone and aldehydes. As depicted in Scheme 10, aldol adducts were obtained with *syn* selectively in moderate to good yields and with good *ee*s. The plausible structure of the active catalytic species was also proposed.



Entry	Substrate	Yield [%]	*ee* [%]
1	phenyl	85	91
2	*tert*-butyl	71	93
3	phenylacethylene	68	78
4	*iso*-propyl	43	71
5	ethyl	78	74

Scheme 10. Direct catalytic asymmetric aldol reactions of 3-pentanone, promoted by the *rac*-(BINOL)$_2$Ti$_2$(O*i*Pr)$_3$/(*R*)-**13** complex.

Unfortunately, with (*S*)-mandelic acid, the opposite enantiomer (*syn*-**14**) of the aldol adducts was observed only with low enantioselectivities (*ee* < 20%).[29a]

Despite the high demand for the development of a direct aldol reaction of ethyl ketones, this problem still remains largely uninvestigated. One possible solution to minimize the retro-aldol reaction problem is the aldol-Tishchenko condensation. Thus, by coupling an irreversible Tishchenko reaction with a reversible aldol reaction of ethyl ketones, this issue can be overcome.

Aldol-Tishchenko Condensation of Ketones and Aldehydes

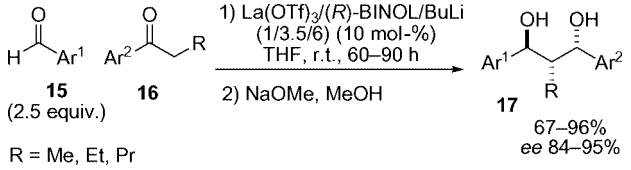
The first example of a stereoselective aldol-Tishchenko reaction of ketones with aldehydes was presented by Heathcock et al. in 1990.[23] Isolated nickel ketone enolates reacted with benzaldehyde to deliver products resulting from the aldol-Tishchenko reaction. The configuration of the resulting diol monoesters was established as 1,2-*anti*-1,3-*anti* and was explained by plausible model **8** (Scheme 8) in which all bulky substituents occupy an energetically preferred equatorial position.

Further, the stereoselective syntheses of 1,3-diols in the aldol-Tishchenko condensation of aldehydes with ethyl ketones were intensively studied.[21,22,30] Isomeric diol monoesters **9** and **10** were isolated with a high degree of the same 1,2-*anti*-1,3-*anti* stereoselectivity. In all cases, only one of four possible diastereoisomers was predominantly formed in the condensation of ketone or ketone metal-enolate.

Initial examples of the catalytic aldol-Tishchenko reactions of unmodified ketones and aldehydes to yield 1,3-diol monoesters were presented by Mahrwald,[30c] Fang,[21b] and Morken[22] through the use of titanium complexes, samarium iodide, and simple metal alkoxides, respectively.

The stereochemical potential of this process was demonstrated recently when the aldol-Tishchenko condensation was executed under asymmetric control. In 2004, Shibasaki[31] and we[32] independently presented the application of the aldol-Tishchenko reaction in an attempt to overcome the retro-aldol condensation problem in the direct asymmetric condensation of ethyl ketones.

Shibasaki et al. demonstrated the usefulness of La(OTf)$_3$/(*R*)-BINOL/BuLi catalysts in the enantioselective condensation of propiophenones to aromatic aldehydes.[31] The Tishchenko stereotriads were isolated by these authors with a high degree of enantioselectivity (Scheme 11).



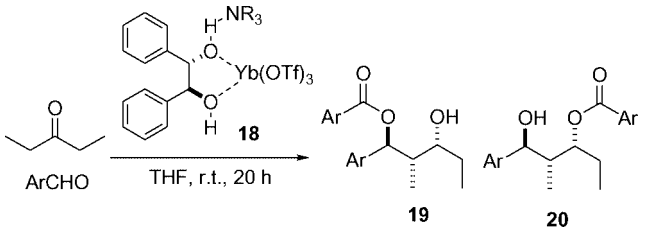
Scheme 11. Direct catalytic asymmetric aldol-Tishchenko reaction catalyzed by La(OTf)$_3$/(*R*)-BINOL/BuLi.

Superior levels of asymmetric induction were realized after careful optimization of the reagents ratio. Thus, a ratio of 1:3:5.6 for La(OTf)$_3$/(*R*)-BINOL/BuLi was the best ratio for a broad range of *para*-substituted ketones and aromatic aldehydes. Under the optimized conditions, the direct catalytic asymmetric aldol-Tishchenko reactions of a variety of both aldehydes **15** and ketones **16** smoothly proceed to give aldols and, after hydrolysis with NaOMe in MeOH, the corresponding diols **17** were obtained in up to 96% isolated yield and up to 95% *ee*. It is worth noting that the reaction proceeded with the same efficiency even for propyl- and butyl ketones, and therefore, the asymmetric direct aldol-type reaction of these substrates was achieved for the first time.

Application of propiophenone in the condensation caused the desired Tishchenko product to be admixed with the simple aldol product in a 1:1 ratio. Thus, the presented catalytic system can be regarded as useful for activated aromatic donors only.

Further mechanistic studies proved that LiOTf promoted a dynamic structural change of LLB to generate a novel binuclear complex [La$_2$Li$_4$(binaphthoxide)$_5$]. The results of spectroscopic analysis and of the experiments involving the concentration effects suggest that the active species has a defined oligomeric structure.[33]

At around the same time, we reported the first example of the aldol-Tishchenko reaction of aliphatic diethyl ketone with aromatic aldehydes in the presence of a chiral lanthanide complex.[32] Simple combination of (*S*,*S*)-hydrobenzoin, ytterbium triflate, and a tertiary amine promoted the condensation reaction with moderate enantioselectivities (Scheme 12).

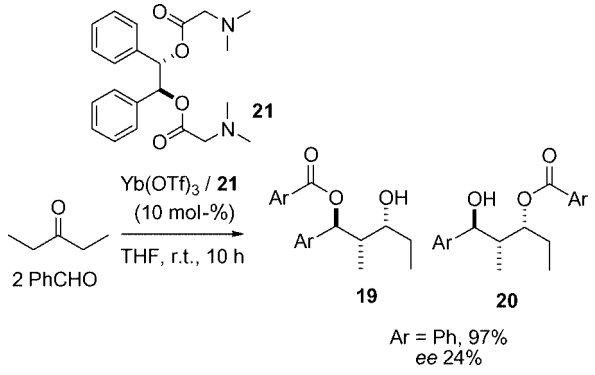


Scheme 12. Direct catalytic asymmetric aldol-Tishchenko reaction of 3-pentanone with aromatic aldehydes.

Surprisingly, under elaborate conditions both regioisomeric esters were formed as opposite enantiomers, which indicates that the formation of both products **19** and **20** is not the result of a simple acyl migration.

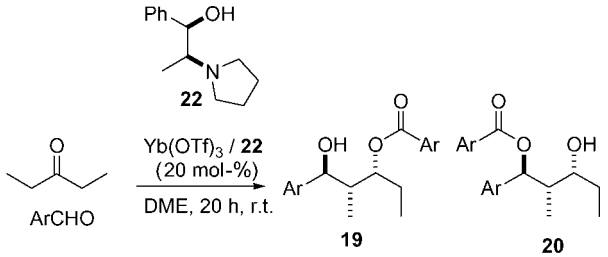
Binding of the amine to the hydroxy group through a hydrogen bond (type-**18** structure) was supposed to be essential for catalytic activity.[34] We presumed that the amino group fixed to the molecule would exhibit catalytic activity as well, and that such a defined architecture would form a more efficient catalyst.[35] To realize this concept and make use of the general principle of the two-center ligand, we reported the synthesis of a catalyst composed of ytterbium triflate and a bis(aminoester)-type ligand **21**. Chiral hybrid *O*,*N*-donor ligands were prepared by the condensation of (*S*,*S*)-hydrobenzoin and amino acid moieties. A catalyst loading of 5–10 mol-% was sufficient to obtain high yields of Tishchenko stereotriads **19/20**.

A systematic evaluation of $RE(OTf)_3$ in the condensation of benzaldehyde with 3-pentanone revealed a consistent increase in enantioselectivity as a function of the lanthanide atomic number – the highest *ee* of 24% was obtained with $Yb(OTf)_3$ (Scheme 13).



Scheme 13. Direct catalytic asymmetric aldol-Tishchenko reaction of 3-pentanone with aromatic aldehydes, promoted by $Yb(OTf)_3$/**21**.

Recently we presented a more promising catalytic system composed of *syn*-aminoalcohols as chiral ligands.[36] The asymmetric direct aldol condensation of aromatic aldehydes with ethyl- and propyl ketones, which is catalyzed by the ephedrine-type amino alcohol–$Yb(OTf)_3$ complex, yielded the *anti*-1,3-diol monoesters with high diastereocontrol and up to 86% enantioselectivity (Scheme 14).



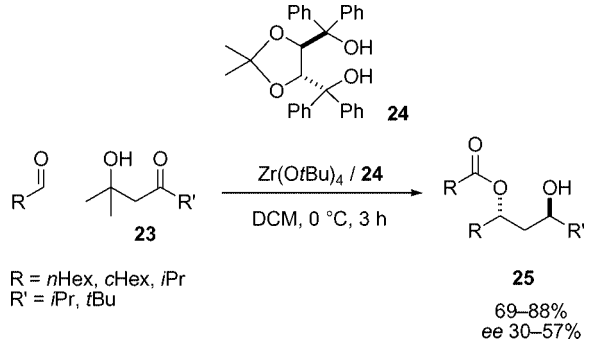
	Aldehyde Ar	Ketone	Overall yield **19**/**20** [%]	*ee* **19**/**20** [%]
1	Ph	3-pentanone	81	75
2	4-OMe-Ph	3-pentanone	60	86
3	4-Me-Ph	3-pentanone	76	80
4	4-Cl-Ph	3-pentanone	76	55
5	Ph	4-heptanone	77	65
6	Ph	propiophenone	85	75

Scheme 14. Direct catalytic asymmetric aldol-Tishchenko reaction catalyzed by $Yb(OTf)_3$/(1*R*,2*S*)-**22**.

However, the catalytic activity of these catalysts is quite low, and to achieve a good yield in a reasonable time, quite large loadings of the catalyst (15–20 mol–%) is required.

Condensation of Aldehydes with Ketone Aldols

In 2001, Navalainen et al.[37] and Schneider et al.[38] independently established the cross aldol-Tishchenko reaction of ketone aldols with aldehydes with either an Al- or Zr-based catalyst. Subsequently, Schneider reported the first catalytic, enantioselective aldol-Tishchenko reaction that employs Zr-TADDOLates as chiral catalysts.[39] $Zr(OtBu)_4$ was shown to be the catalyst of choice in the condensation process, and it catalyzed a rapid retro-aldol cleavage of **23** to furnish a ketone enolate in situ, which underwent the aldol-Tishchenko reaction with aliphatic aldehydes. 1,3-*anti*-Diol monoesters were typically obtained in good yields and with complete diastereoselectivity. Up to 57% enantiomeric excess was reached when TADDOL **24** was used as a chiral ligand (Scheme 15).

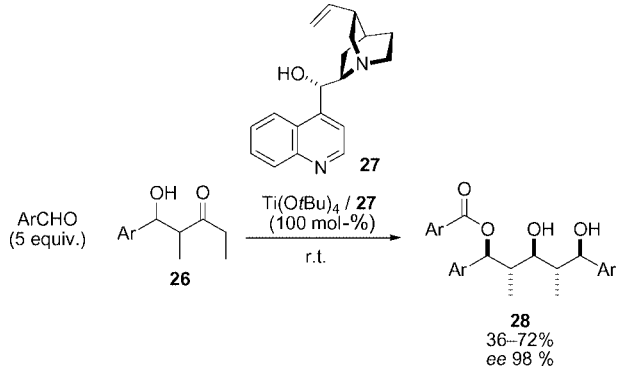


Scheme 15. Zr-TADDOLAate catalyzed aldol-Tishchenko reactions of ketone aldols **23** with aldehydes.

Control experiments proved that the enantioselectivity of the overall reaction originates from the initial retro-aldol/aldol step.

Chandrasekhar demonstrated that although L-proline – a natural small amino acid metal-free catalyst – could promote such an asymmetric aldol transfer, the reaction incidentally did not yield any aldol-Tishchenko product.[40]

Recently, Mahrwald presented the aldol-Tishchenko reaction of aromatic aldehydes in the presence of titanium(IV)*tert*-butoxide and a chiral amino alcohol.[41] In the condensation of 3-pentanone that is promoted by $Ti(OtBu)_4$ and an amino alcohol, the authors observed the formation of ester **20** (Ar = Ph) and compounds produced both by an aldol-Tishchenko reaction and by a second aldol addition, i.e. 1,3,5-triol monoesters **28**. These so-called stereopentands were obtained with a high degree of stereoselectivity (Scheme 16).



Scheme 16. Direct catalytic asymmetric aldol-Tishchenko reaction in the presence of $Ti(OtBu)_4$ and cinchonine.

Further optimization studies revealed that by the use of corresponding aldols **26** as starting compounds, instead of separated aldehydes and diethyl ketone, the reaction resulted in the clean and efficient formation of stereopentands.[42] Moreover, by employing cinchonine or cinchonidine alkaloids as ligands, the stereopentands **28** were isolated with an exceptional degree of diastereo- and enantioselectivity (Scheme 15).

Although this reaction requires stoichiometric addition of the chiral catalyst, it is a noteworthy example of the asymmetric Tishchenko condensation. Compounds with five new adjacent stereocenters are created in one domino reaction sequence with high enantioselectivity.

Summary and Outlook

The diastereoselective and enantioselective aldol-Tishchenko reaction has emerged recently as an efficient tool for the control of the stereochemistry during the domino-type reaction of three aldehydes or aldehyde–ketone–aldehyde to prepare 1,3-diols with up to three continuous chiral centers in acyclic systems.

This reaction can be executed in an enantioselective manner, as only one single diastereoisomer is formed during the condensation in all cases. Indeed, asymmetric synthesis of *anti*-1,3-diols by condensation of aldehydes and ketones to aldehydes were realized with catalytic amounts of a chiral promoter. Enantioselective methods, and in particular the use of chiral rare-earth-element complexes, have proven to be the most selective and versatile so far. Enantioselective direct couplings of unmodified ethyl ketones to aldehydes by means of aldol-Tishchenko reactions have recently emerged as viable and more promising alternatives to classical direct aldol condensations.

Inherent difficulties such as low catalyst efficiency and important substrate dependency still limit a broad use of this methodology as an everyday tool. Future directions in the control of enantioselectivity and widening of substrate scope might include further ligand design.

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