First Catalytic Asymmetric Aldol-Tishchenko Reaction—Insight into the Catalyst Structure and Reaction Mechanism**

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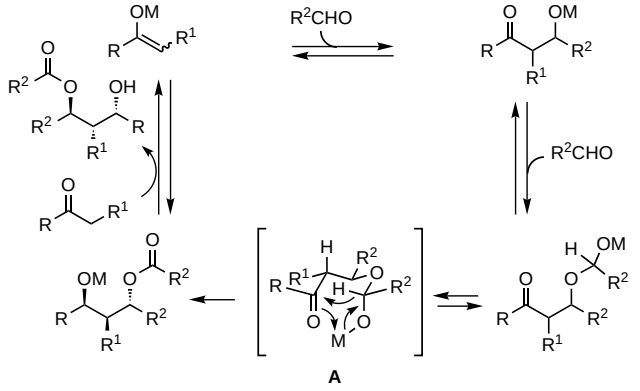
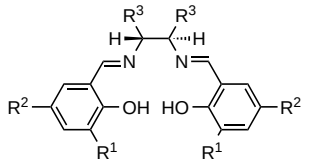
Since the comprehensive studies of Nord et al. in the 1940s,[1] the catalytic aldol-Tishchenko reaction has received much attention as a means to couple unactivated carbonyl compounds.[2] Only more recently have stoichiometric[3] and catalytic stereoselective reactions[4] become the focus of development. Mechanistic studies on stereoselective aldol-Tishchenko reactions suggest that the reaction occurs by the mechanism depicted in Scheme 1.[3a,d,e, 4a] After generation of



Scheme 1. Cycle for catalytic aldol-Tishchenko reactions.

the enolate, a reversible aldolization step is thought to precede a rate-determining reduction via transition state **A**.[5] The major product stereoisomer is derived from the stereoisomer of structure **A** wherein all substituents at the six-membered ring occupy equatorial positions. Despite the fact that stereocontrol in the aldol-Tishchenko reaction appears to result from a highly organized metal-centered transition state, this reaction has not been subject to enantioselective catalysis under the influence of chiral ancillary ligands. In this report, we describe the first catalytic enantioselective version of this process.[6]

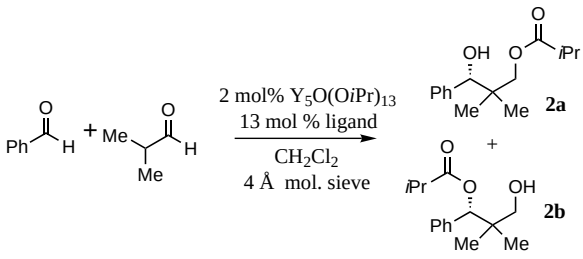
We recently reported that simple metal alkoxides can catalyze a diastereoselective hetero aldol-Tishchenko reaction thereby offering access to propionate equivalents directly from simple carbonyl compounds.[7] Expecting that de novo design of chiral metal alkoxide catalysts would be treacherous due to the inherent difficulty in predicting coordination numbers and aggregation states of metal alkoxides, we have used an arrayed catalyst evaluation[8] protocol to discover promising catalyst candidates. Initial studies with 96 independent complexes revealed the complex of $Y_5O(OiPr)_{13}$[9] and salen (**1a**)[10] as an effective catalyst for the enantioselective aldol-Tishchenko reaction.[11]



1a-f

We now examined the effect of ligand structure on this reaction [Eq. (1)]. As seen in Table 1, the aldol-Tishchenko adduct is obtained with ligand **1a** in 44% overall yield and in a 78:22 enantiomer ratio. The reaction provides two regioisomeric esters **2** in similar enantiopurity

Table 1. Analysis of the effect of ligand structure on the yttrium-catalyzed aldol-Tishchenko reaction (1). In all reactions the ratio of *i*PrCHO:PhCHO was 6:1, and they were performed under an inert atmosphere.



(1)

Ligand	R^1	R^2	R^3	Yield [%] (**2a**:**2b**)[a]	e.r. of **2a**[b]
1a	*t*Bu	*t*Bu	$(CH_2)_4$	44 (3.4:1)	78:22
1b	*t*Bu	H	$(CH_2)_4$	36 (3.0:1)	87:22
1c	Me	H	$(CH_2)_4$	54 (1.6:1)	57:43
1d	adamantyl	Me	$(CH_2)_4$	42 (3.2:1)	83:17
1e	*t*Bu	*t*Bu	Ph	48 (3.3:1)	82:18
1f	adamantyl	Me	Ph	70 (>15:1)	87:13

[a] Combined yield, after purification by flash chromatography; ratio of **2a**:**2b** determined by ^{1}H NMR spectroscopy; identity of major enantiomer determined by comparison to authentic material. [b] Enantiomer ratio determined by GLC (β-Dex column by Supelco).

suggesting a nonselective intramolecular acyl migration after formation of the aldol-Tishchenko adduct. Bulky substituents *ortho* to the salen oxygen atom (R^1) are necessary for reactivity and selectivity, whereas the presence of *para* substituents (R^2) is not essential for asymmetric induction. Also of note is that the diphenylethylene-derived ligand **1e** displays greater enantioselection than the corresponding diaminocyclohexane-derived ligand **1a**. With some of the structural requirements for effective ligands exposed, we prepared salen **1f** containing both a bulky *ortho* adamantyl unit and the diphenyl backbone. The use of **1f** in the aldol-Tishchenko reaction (1) results in 70% yield and an 87:13 ratio of enantiomers, the highest selectivity of all ligands examined.

Reaction generality was examined through experiments with different aldehydes as reaction substrates [Eq. (2),

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[+] Crystallography

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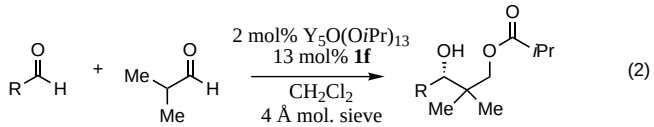
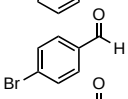
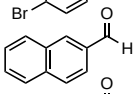
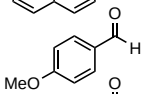
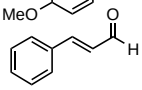
Table 2]. All substrates gave useful product yields, except for the less electrophilic anisaldehyde (entry 4) as might be expected. While comparable levels of enantioselection were obtained with all aromatic aldehydes, α,β-unsaturated aldehydes (entry 5) appear to be less useful under the current reaction conditions.

Table 2. Utility of the catalytic asymmetric aldol-Tishchenko reaction (2).

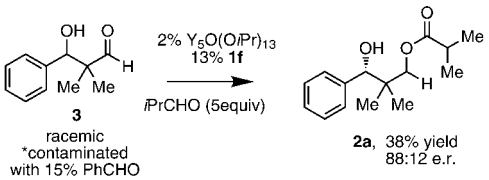


(2)

Entry	Substrate	Yield [%][a]	e.r. (configuration)[b]
1		70	87:13 (*S*)
2		55	85:15 (*S*)
3		50	82:18
4		21	86:14
5		50	55:45

[a] Yield, after purification by column chromatography. [b] Enantiomer ratio determined by GLC (β-Dex column) or by HPLC (Chiracel OD or Chiracel OJ). The identity of the major enantiomer, where indicated, was determined by comparison to authentic material.

To ascertain whether this catalyzed reaction operates under similar Curtin–Hammett conditions as described in Scheme 1, we prepared racemic **3** (contaminated with 15% benzaldehyde) and subjected it to the catalytic reaction conditions in the presence of isobutyraldehyde [Eq. (3)].



(3)

With ligand **1f**, aldol-Tishchenko adduct **2a** was obtained from **3** in 38% yield and with an 88:12 enantiomer ratio. These results strongly indicate that, with the yttrium–salen catalyst, the Tishchenko reduction is slower than the retro-aldol reaction and a similar kinetic profile operates as that described previously.

Time-course experiments show that the enantiomer ratio does not change as the aldol-Tishchenko reaction proceeds, indicating that the 1,3-glycol monoester product does not modify the oxophilic yttrium center in any detrimental way during the course of the reaction. Additional experiments in which the enantiomeric excess of ligand **1a** was varied show a linear relationship between ligand enantiopurity and reaction enantioselectivity thereby suggesting the possibility of a monomeric catalyst structure.[12] Vapor pressure osmometry experiments provided more definitive evidence of a monomeric aggregation state of the metal complex; a solution prepared to be 0.050 M each in metal and ligand was measured to be (0.057 ± 0.005) M in solute versus a calibration curve prepared for the known monomer triphenylmethane.[13]

To elucidate the architecture of the catalyst complex, a crystal structure analysis was performed for the complex prepared from $Y_5O(OiPr)_{13}$ and ligand **1a** (Figure 1).[14] It

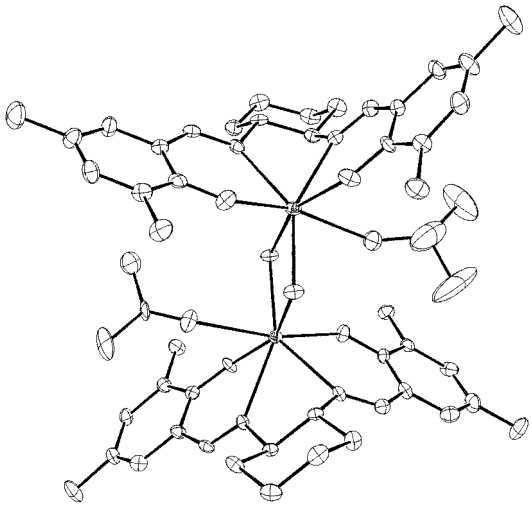


Figure 1. ORTEP diagram of the complex prepared from **1a** and $Y_5O(OiPr)_{13}$ and crystallized from acetone/CH_2Cl_2; *tert*-butyl substituents have been truncated for clarity.

revealed the complex to be a dimer where each yttrium is seven-coordinate, complexed to acetone (crystallization co-solvent) and bridged by two hydroxide ions to a second yttrium center.[15] Whereas in most salen complexes of d transition and main group metals the ligand structure is planar, the yttrium ion causes significant bending in the four-coordinate ligand. Addition of the crystalline complex to a solution of isobutyraldehyde and benzaldehyde is not sufficient to catalyze the aldol-Tishchenko reaction. We suspect that this catalytic inactivity may be due either to the stability of the dimeric solid-state structure relative to the monomeric structure observed in solution or to the replacement of isopropoxides with hydroxides. Regardless, because the structure shows a salen coordination geometry that is similar to that reported for a salen(amido)yttrium complex,[16] we expect that the structure is relevant (vide infra).

Considering the correlation between product and ligand configuration, the structural requirements for enantioselection, the evidence for a monomeric yttrium–salen complex and evidence for rate-determining hydride transfer, we propose a predictive model for enantioselection in the aldol-Tishchenko reaction (Scheme 2). Chelate-controlled organization of the intramolecular Tishchenko transition state positions the hemiacetal substituent (*i*Pr) in a pseudoequatorial position about the cyclic transition structure. With a salen ligand coordinated to yttrium, the major product is derived from a structure where the isopropyl group is positioned away

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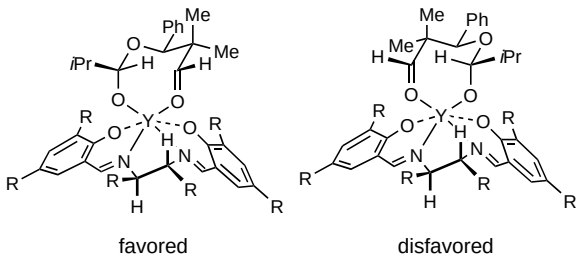

Scheme 2. Predictive model for enantioselection in the aldol-Tishchenko reaction catalyzed by Y–salen complexes.

from the axial salen hydrogen; presumably the diastereomeric transition structure suffers from this steric interaction thereby yielding less of the minor enantiomer.

In conclusion, we have discovered and developed the first catalytic enantioselective aldol-Tishchenko reaction. The mechanistic studies presented herein should provide a useful starting point for the development of more effective catalytic asymmetric aldol-Tishchenko reactions.

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[12] See Supporting Information for this data.

[13] These experiments do not rule out the possibility of a monomeric catalyst in solution with participation of two Y–salen complexes in the transition state. Kinetic studies addressing this issue will be reported.

[14] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-150468. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[15] Crystals were obtained by allowing acetone to diffuse into a 1:1 (metal:ligand) mixture of $Y_5O(O\mathit{i}Pr)_{13}$ and ligand **1a** in dichloromethane. The bridging hydroxides likely result from adventitious moisture. According to the X-ray analysis, one acetone is pyramidalized such that it might be construed as an isopropoxide. We feel that this is unlikely since it requires one bridging ligand to be a water molecule in order to maintain the Y^{III} oxidation state.

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Total Synthesis of the Callipeltoside Aglycon**

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The callipeltosides were isolated by Minale and co-workers from the shallow-water lithistid sponge *Callipelta* sp., collected off the east coast of New Caledonia.[1a,b] Callipeltoside A (**1** in Scheme 1, obtained in 1.4×10^{-4}% yield) was found to inhibit in vitro the proliferation of KB and P388 cells (IC_{50} values of 11.26 and 15.26 $\mu g\,mL^{-1}$, respectively). Results indicate this activity to be cell-cycle dependent, blocking proliferation in the G1 phase, highlighting callipeltoside A as a putative, mechanism-based lead.[1a] Similarly, callipeltosides B and C, differing only in the sugar portion of their structures, also exhibited marked cytotoxic activity.[1b]

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