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Direct Catalytic Asymmetric Aldol-Tishchenko Reaction

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Development of mild and catalytic methods for the stereo and enantioselective transformation of nonpreactivated functional groups is a topic of continuing interest.[1] In this regard, we[2] and others[3] have attempted the direct catalytic asymmetric aldol reaction of unmodified ketones. Most of the catalytic systems reported to date, however, are limited to rather simple donors such as methyl ketones,[2a,b,3a,b] α-hydroxymethyl ketones,[2c,3c,d] and easily enolizable aliphatic aldehydes.[3e] Direct aldol reaction of ethyl ketones[4] are viewed as a formidable synthetic challenge because of poor participation of the resulting aldolates in catalyst turnover and a strong tendency toward retro-aldol reactions. Tremendous effort has been focused on the propionate aldol reaction of carboxlic acid derivatives under silylating conditions.[5] Here, we report that this elusive aldol reaction can be accomplished using the aldol-Tishchenko reaction. By coupling an irreversible Tishchenko reaction to a reversible aldol reaction, the catalytic aldol-Tishchenko reaction provides high product yields and high ees from an aldol process and does not require stoichiometric preactivation of the ketone as a silyl enolate.

As part of ongoing studies of direct aldol reactions that have broad utility in asymmetric synthesis, we recently initiated studies toward a direct aldol reaction of ethyl ketones. Inspired by the earliest report of an SmI_2-catalyzed Tishchenko reaction of β-hydroxy ketone by Evans et al.[6a] and an yttrium−salen complex catalyzed asymmetric cross aldol-Tishchenko reaction by Morken et al.,[6b] we hypothesized that the metalated aldolates **1** derived from our lanthanoid-based heterobimetallic catalyst might be activated for the addition of another aldehyde molecule (Scheme 1). Accordingly, this activation−addition step would provide Evans intermediate **2**,[6a] which exhibits the appropriate orientation to rapidly undergo [3,3] bond reorganization to provide Tishchenko adduct **3**. Because of the number of established procedures,[7,8] we expected that this addition−rearrangement sequence would allow us to prevent the competitive retro-aldol reaction and provide an attractive platform for the development of highly enantio- and diastereoselective aldol-type adducts.

Preliminary studies using propiophenone (**4a**) with 4-chlorobenzaldehyde (**5a**) in the presence of 10 mol % of LLB, which was prepared from La(O-*i*-Pr)$_3$,[2] revealed that the anticipated sequential addition was possible with excellent diastereoselectivity and moderate enantiocontrol (>98:2 dr[9] and 64% ee for **3aa**); however, the catalytic efficiency was unsatisfactory (Table 1, entry 1). Assuming that lithium binaphthoxide would not be basic enough for deprotonation, we next examined the use of a metal salt additive, which might competitively coordinate and decrease the pK_a of the ketone. While a variety of lithium salts were productive in this context, 30 mol % LiOTf[10] provided the optimal reaction efficiency and high selectivity (entry 2). Keeping the 1:3:3 ratio of lanthanum, BINOL, and LiOTf in mind, we investigated whether the same catalytic system would be accomplished by mixing 6 equiv of BuLi to the mixture of the 1:3 ratio of La(OTf)$_3$ and BINOL. The commercial availability of La(OTf)$_3$, high tolerance to air and water, and

Scheme 1

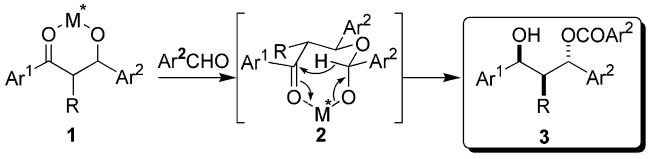
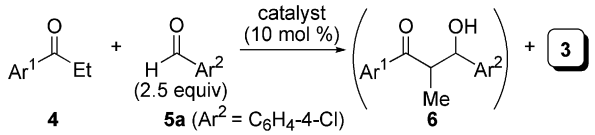


Table 1. Optimization Studies



entry	ketone[a]	catalyst[b]	conv.[c] (%)	**6**:**3**[d]	ee[e] (%)
1	**4a**	(*R*)-LLB	20	∼1:1	64
2	**4a**	(*R*)-LLB + LiOTf (1:3)	60	∼1:1	78
3	**4a**	La(OTf)$_3$ + (*R*)-BINOL + BuLi (1:3:6)	60	∼1:1	86
4	**4b**	La(OTf)$_3$ + (*R*)-BINOL + BuLi (1:3:6)	75	2:>98	88
5	**4b**	La(OTf)$_3$ + (*R*)-BINOL + BuLi (1:3:5.6)	80	2:>98	93

[a] **4a**: Ar^1=C$_6$H$_5$, **4b**: Ar^1=C$_6$H$_4$-4-CF$_3$. [b] All reactions were performed in tetrahydrofuran (1.0 M) at room temperature (48 h for **4a**, 24 h for **4b**). [c] Total yield of **6** and **3** was determined by ^{1}H NMR analysis of the crude sample. [d] Determined by ^{1}H NMR analysis of the crude sample. [e] ee of **3** was determined by HPLC analysis after hydrolysis using NaOMe/MeOH to the corresponding diol **7**. Diastereoselectivity was generally below the detection limit of 500 MHz ^{1}H NMR (>98:2).

superior levels of asymmetric induction and efficiency (entry 3) exhibited by this modified procedure prompted us to further explore this catalytic condition. Switching to ketone **4b** had a significant effect on the reactivity and Tishchenko selectivity, while maintaining the similar enantiocontrol (entry 4). Superior levels of asymmetric induction were realized by decreasing the amount of BuLi. Thus, 1:3:5.6 La(OTf)$_3$/BINOL/BuLi was the appropriate ratio for a broad range of substrates (entry 5).

Experiments to probe the scope of the aldehyde substrate are summarized in Table 2.[11] A variety of alkyl and heteroatom substituents can be incorporated on the phenyl ring at both the meta and para positions (Table 2, entries 1−7, 85−95% ee, 65−96% yield). The aryl framework can be successfully extended to naphthalene and heteroaromatic derived systems (entries 8−10, 88−94% ee, 67−82% yield). In addition, a number of aromatic ketones can also be used without loss of reaction efficiency or enantiocontrol (entries 11−15, 84−88% ee, 60−81% yield). Importantly, the α,β-unsaturated enone resulting from β-elimination of the hydroxyl group was not formed, confirming the mild reaction conditions employed in this asymmetric process. Furthermore, reactions were performed at room temperature, demonstrating the practical utility of the present catalytic system. We next examined the capacity of

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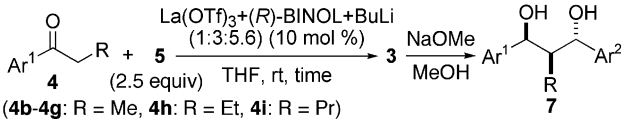
Table 2. Direct Aldol-Tishchenko Reactions: Substrate Scope



entry	ketone **4** Ar^1	aldehyde **5** Ar^2	time (h)	ee[a] (%)	yield[b] (%)
1	**4b**: 4-$F_3C-C_6H_4$	**5a**: 4-$Cl-C_6H_4$	60	93	95
2	**4b**: 4-$F_3C-C_6H_4$	**5b**: 4-$Br-C_6H_4$	48	95	96
3	**4b**: 4-$F_3C-C_6H_4$	**5c**: 4-$F-C_6H_4$	72	92	85
4	**4b**: 4-$F_3C-C_6H_4$	**5d**: 4-Me-C_6H_4	94	92	67
5	**4b**: 4-$F_3C-C_6H_4$	**5e**: C_6H_5	84	91	95
6	**4b**: 4-$F_3C-C_6H_4$	**5f**: 3-$Br-C_6H_4$	48	86	92
7	**4b**: 4-$F_3C-C_6H_4$	**5g**: 3-$MeO-C_6H_4$	72	85	65
8	**4b**: 4-$F_3C-C_6H_4$	**5h**: 2-naphthyl	80	88	67
9	**4b**: 4-$F_3C-C_6H_4$	**5i**: 3-furyl	84	93	77
10	**4b**: 4-$F_3C-C_6H_4$	**5j**: 3-thienyl	84	94	82
11	**4c**: 4-$Br-C_6H_4$	**5b**: 4-$Br-C_6H_4$	48	85	70
12	**4d**: 3-$Cl-C_6H_4$	**5a**: 4-$Cl-C_6H_4$	48	84	60
13	**4e**: 3,4-$Cl_2-C_6H_4$	**5a**: 4-$Cl-C_6H_4$	48	88	81
14	**4f**: 3,5-$Cl_2-C_6H_4$	**5a**: 4-$Cl-C_6H_4$	48	85	73
15	**4g**: 3,5-$F_2-C_6H_4$	**5a**: 4-$Cl-C_6H_4$	48	87	77
16	**4h**: 4-$F_3C-C_6H_4$	**5b**: 4-$Br-C_6H_4$	90	88	90
17	**4i**: 4-$F_3C-C_6H_4$	**5b**: 4-$Br-C_6H_4$	90	87	88

[a] Determined by HPLC analysis after converting to the corresponding diol. The diastereoselectivity was generally below the detection limit of 500 MHz ^{1}H NMR (>98:2).[9] [b] Isolated yield of the corresponding diol **7**.

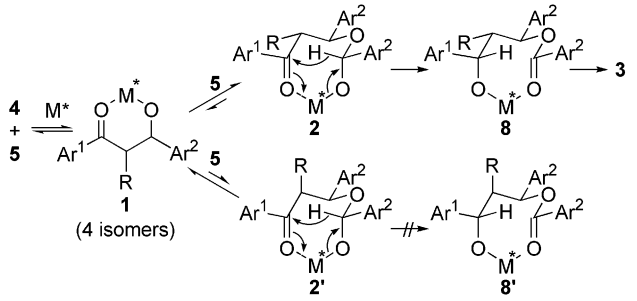
the present catalytic system to catalyze asymmetric aldol-Tishchenko reactions of propyl and butyl ketones (**4h** and **4i**). As highlighted, the catalyst exhibited similar efficiency without considerable deterioration of enantiocontrol (entries 16 and 17, 87−88% ee, 88−90% yield). Despite the single previous use of diethyl ketone in the direct aldol reaction,[4] to our knowledge, this is the first example of an asymmetric aldol-type reaction of propyl and butyl ketones.

The uncertain mechanism[12] of this direct aldol-Tishchenko reaction prompted us to inspect the relation between the aldol product and the Tishchenko product, as well as their stereoselectivities. The aldol byproduct **6aa** obtained by the reaction of **4a** (Table 1, entry 3) was with no enantio- or diastereoselectivity. To obtain further insight, we attempted a deliberate retro-aldolization of independently prepared racemic aldol adducts **6aa** (syn/anti = 7:3 or syn/anti = 3:7) under representative reaction conditions (10 mol % of La catalyst, room temperature, 72 h). The same mixtures of **4a**, **6aa** (syn/anti = 4:6, racemic), and **3aa** (>98:2 dr,[9] 70% ee)[13] were obtained starting with either a 7:3 or a 3:7 syn/anti ratio of aldol adducts **6aa**. These results are consistent with the rapid retro-aldol cleavage of metal aldolate and *confirm the essential role of the Tishchenko reaction in controlling the stereoselectivity.*

These unique observations offered us a reasonable mechanistic explanation as depicted in Scheme 2. Metal enolate reacts reversibly with aldehyde, yielding all possible isomeric metal aldolates **1**.[14] An anti-aldolate proceeds through a bicyclic transition state **2** to give **8**. A syn-aldolate can undergo a similar reaction with a slower rate through transition state **2′**, the alkyl group of which occupies an energetically unfavorable axial position. In such cases, a fast isomerization from syn-aldolate to anti-aldolate might surpass the rate of the Tishchenko reaction. Thus, a syn-aldolate might isomerize to anti-aldolate through a retro-aldol reaction and undergo the Tishchenko reaction via the more favorable transition state **2**, giving rise to anti-aldol anti-Tishchenko product **3** in high efficiency and diastereoselectivity.

In conclusion, we established the Tishchenko reaction as one of the useful methods for overcoming the retro-aldol reaction problem

Scheme 2



for aromatic donors and acceptors. Moreover, this is the first example of a direct aldol-Tishchenko reaction of propionate equivalent. Further studies on broadening the substrate scope to aliphatic donors and acceptors, useful precursors for the synthesis of polypropionate natural products, and determining the mechanism and catalyst structure are ongoing.

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Supporting Information Available: Experimental procedures and characterization of the products with ^{13}C NMR of diol **7**; other detailed results and discussion (PDF); X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Other metal salts such as NaOTf, KOTf, CuOTf, and $Mg(OTf)_2$ produced less satisfactory results.
(11) Relative and absolute configurations were determined by chemical correlation and X-ray analysis. See Supporting Information for more details.
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(13) Slightly lower ee would be ascribed to the different starting materials used. See Supporting Information for details.
(14) Presumably, the low aldol selectivities are due to strong retro-aldolization.

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