Direct asymmetric aldol-Tishchenko reaction of aliphatic ketones catalyzed by *syn*-aminoalcohol–Yb(III) complexes†

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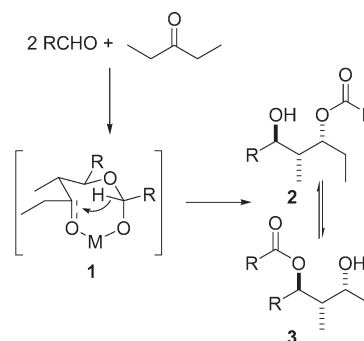
The asymmetric direct aldol condensation of aldehydes with ethyl- and propylketones is catalyzed by *syn-α-*aminoalcohol–Yb(OTf)₃ complexes, yielding the *anti-*1,3-diol monoesters with high diastereocontrol and good enantioselectivity. Three adjacent stereogenic centers are created in a simultaneous aldol condensation and Evans–Tishchenko reduction in an acyclic system.

The control of stereochemistry during aldol addition is a crucial problem as this reaction is a fundamental method for the construction of carbon–carbon bonds.[1] In this regard, the metal-catalyzed asymmetric direct aldol reaction of aldehydes with unmodified ketones still remains a challenge for synthetic chemists.[2] Remarkable success in this area is a result of Trost's[3] and Shibasaki's[4] outstanding work on homo- and heterobimetallic catalysts.[5–7] To date however, the scope of possible substrates and the selection of applicable catalytic systems still remains limited.[2b,c] In general, the elaborated methodology offers a versatile access to aldol-type products from methyl ketones,[3a,5a,b] while the development of catalytic systems applicable to their methylene analogues[8] is more challenging and restricted mainly to α-hydroxymethyl ketones.[3b,5c] The bulkiness of methylene ketones was anticipated to make it more difficult for the catalyst to abstract an α-hydrogen,[8c] and additionally, a strong tendency towards retro-aldol reactions was observed for such substrates.

In this regard, Shibasaki[9] and ourselves[10] have attempted the direct catalytic asymmetric aldol-Tishchenko reaction as a useful method for overcoming the problem of unreactivity of higher ketones. In the one-step process, aldehydes were reacted with methylene ketones to give 1,3-diol monoesters,[11] which were formed as a result of bond reorganization in a cyclic Evans-type[12] intermediate **1** (Scheme 1).

In contrast to the previously presented examples of a stereoselective Tishchenko reaction of two different aldehydes,[13] three adjacent stereogenic centers are created by use of a ketone as the substrate in the process, making this methodology very effective in terms of chiral economy.

Despite the clear potential of the aldol-Tishchenko reaction of unmodified ketones with aldehydes leading to protected 1,3-diols **2** and **3**, its enantioselective variant presents an unexplored problem that has only been preliminarily unravelled. In general,

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† Electronic Supplementary Information (ESI) available: Representative experimental procedures and full characterisation of all compounds as well as their stereochemical assignment. See http://dx.doi.org/10.1039/b509505k
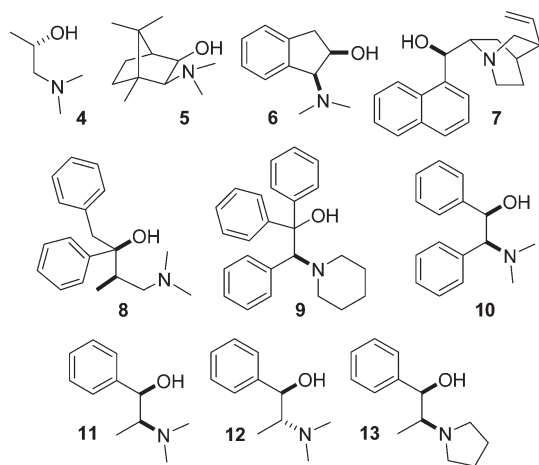

Scheme 1 Postulated mechanism of the aldol-Tishchenko reaction.[11]

the state-of-the-art in this area provides condensation products in good ee only for activated aromatic donors (typically, *p*-trifluoro-methyl propiophenone, for which the Tishchenko product was mixed with simple aldol in a 1 : 1 ratio).[9] Our laboratory has recently described the use of diol[10] and aminoester[14] ligands for the condensation of aliphatic ketones. Our catalytic systems were highly diastereoselective, but unsatisfactory levels of enantio-selectivity forced us to carry on with research.

Here, we report the first efficient application of a chiral aminoalcohol-based catalyst to the enantioselective aldol-Tishchenko reactions between aldehydes and aliphatic ketones. This process provides high product yields and good ee values, leading to *anti-*1,3-diols without tedious stoichiometric preactiva-tion of the ketones.

Since our initial studies had revealed that, in particular, Yb complexes combined with diol/amine and aminoalcohols can catalyze the aldol-Tishchenko reaction, we tested combinations of ytterbium triflate with a representative family of ligands **4–13** (L) (Fig. 1). All of the materials tested were commercial, except for compound **5**.[15] Our experiments showed that ligands having free amino functions, unreactive in the desired process, must be excluded. Thus, unprotected amines—precursors of **5**, **6** and **10**—were efficiently methylated using formaldehyde and formic acid.[16]

Preliminary studies using benzaldehyde with 3-pentanone in the presence of 20 mol% of the catalyst, which was prepared from Yb(OTf)₃ and (*S*)-3-dimethylamino-2-propane **4** in the 1 : 2 ratio, revealed that the anticipated sequential reaction is achievable with excellent diastereoselectivity (> 95 : 5) and low enantiocontrol (Table 1, entry 1).† Unfortunately, the observed catalytic efficiency was unsatisfactory (34% yield). Similarly, our experiments with other aliphatic alcohols, *i.e.* (−)-DAIB (**5**) and 1-amino-2-indanol derivative **6**, were disappointing.

Fig. 1 Selected chiral ligands used in the initial studies.

In contrast, the condensation promoted by a catalyst containing the Cinchona ligand with benzyl-type OH **7** was much more effective (83% yield) but unselective (Table 1, entry 4). This observation confirms our previous conclusion that a benzyl-type hydrogen atom is necessary in the catalyst structure.[14]

Next, a series of benzyl-type aminoalcohols were tested to find an optimal ligand. Reactive α-aminoalcohol **8** was unselective, presumably because of having the N-center removed from the oxygen atom by three carbon atoms. Shorter analogues **10** and **11** showed some level of enantioselectivity, retaining a good level of reactivity. Comparison of *syn*-**11** and *anti*-**12** N-methylephedrines proved that the *syn*-orientation of substituents is necessary for both reactivity and selectivity (Table 1, entry 8 *vs.* 9).

Structural variations in the amino function had significant effects on the enantioselectivity of the reaction. In particular, more bulky amino-protection enhanced the enantioselectivity, with the

2-pyrrolidynyl substituted (1R,2S)-propanol **13** giving the best result with 42% ee (Table 1, entry 10).

With the best catalyst in hand, we turned our attention to other reaction aspects. Changing the reaction medium to a more coordinating one resulted in further increasing the enantioselectivity (Table 2). 1,2-dimethoxyethane (DME) proved to be the best solvent, giving the product in 66% yield with 60% ee (Table 2, entry 6). Decreasing the reaction temperature to 0 °C only slightly increased the ee, albeit at the expense of the overall yield.

In an effort to study the influence of the metal–ligand ratio on the enantioselectivity of the reaction, we tested many combinations of Yb(OTf)$_3$ with ligand **13** (Table 2). These experiments revealed the best reaction enantioselectivity for (4 : 1) complex architecture. Such ligands-reach complex(es) were previously recorded in the literature.[17]

Next, we attempted to reduce the catalyst loading. Decreasing the amount of Yb complex to 10 mol% resulted in a diminished overall yield (33%), while the ee stayed at almost the same level (Table 2, entry 13). We were glad to find, however, that 15 mol% of the catalyst promoted the reaction with a comparable yield and ee. We kept this loading in further experiments.

The structural assignment of the obtained esters **14** was corroborated by high-resolution NMR experiments, and is in full agreement with previously published data.[18] The assigned 1,2-*anti*-1,3-*anti* stereochemistry of **14** was supported in both cases by the NMR analysis of separately-derived diols as well as a sterically rigid O-isopropylidene derivative.†[19]

Experiments to probe the scope of the aldehyde substrate are summarized in Table 3. Reactions were performed at room temperature, demonstrating the practical utility of the elaborated catalytic system.

Resulting mixtures of 1-*O*- and 3-*O*-esters could be easily saponified to deliver appropriate *anti*-1,3-diols[9,18a] with huge synthetic potential. For this detailed study however, we decided to separate and characterize all ester-type products.

Substituted aromatic aldehydes are acceptable substrates, and conspicuously the reaction selectivity depends on the electron acceptor character of the substituents. For instance, *p*-chlorobenzaldehyde was more reactive but a worse substrate (76% yield,

Table 1 Ligand studies: Reaction of 3-pentanone with benzaldehyde promoted by various chiral ligands **4**–**13**

Entry	L	Overall yield **14a** + **14b** (%)[a]	ee (%)[b]
1	**4**	34[c]	9
2	**5**	20	−3[d]
3	**6**	16	7
4	**7**	83	rac.
5	**8**	90	rac.
6	**9**	23	rac.
7	**10**	70	8
8	**11**	69	10
9	**12**	n.d.	—
10	**13**	88	42
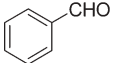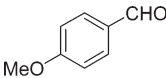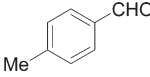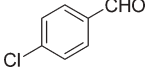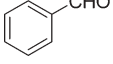
[a] Isolated yield. [b] The ee values of esters and diols were determined by HPLC (Chiralpak AD-H column). [c] Major *anti*-aldol *anti*-Tishchenko isomer (1,2-*anti*-1,3-*anti*) **14** formation was accompanied by some traces (less then 3%) of 1,2-*syn*-1,3-*anti* co-products. [d] The use of '±' signs is only a convention to designate opposite enantiomers.

Table 2 Solvent and catalyst studies: Reaction of 3-pentanone with benzaldehyde promoted by ligand **13**

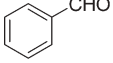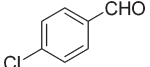| Entry	Solvent	Yb(OTf)$_3$: **13**	Overall yield **14a** + **14b** (%)[a]	ee (%)[b]
20 mol% of the catalyst:				
1	THF	1 : 1	0	—
2	THF	1 : 2	88	42
3	CH$_2$Cl$_2$	1 : 2	trace	—
4	Dioxane	1 : 2	35	52
5	MeCN	1 : 2	16	35
6	DME	1 : 2	66	60
7	THF	1 : 3	76	55
8	THF	1 : 4	86	62
9	DME	1 : 4	82	76
10	THF	1 : 5	86	61
11	THF	1 : 10	83	50
10 mol% of the catalyst:				
12	THF	1 : 4	60	55
13	DME	1 : 4	33	67

[a] Isolated yield. [b] The ee values of esters and diols were determined by HPLC (Chiralpak AD-H column).

Table 3 Substrate studies: Condensation of ethyl and propyl ketones with various aldehydes promoted by Yb(OTf)$_3$ and (1R,2S)-**13** (1 : 4, 15 mol%)

Entry	Aldehyde	Ketone	Yield (%)^a	ee (%)^b
1	PhCHO	O (ethyl ketone)	3-O-ester **14a**: 42 1-O-ester **14b**: 39	75
2	MeO–C$_6$H$_4$–CHO	O (ethyl ketone)	3-O-ester **15a**: 9 1-O-ester **15b**: 49	86
3	Me–C$_6$H$_4$–CHO	O (ethyl ketone)	3-O-ester **16a**: 25 1-O-ester **16b**: 51	80
4	Cl–C$_6$H$_4$–CHO	O (ethyl ketone)	3-O-ester **17a**: 37 1-O-ester **17b**: 39	55
5	PhCHO	O (dipropyl ketone)	3-O-ester **18a**: 23 1-O-ester **18b**: 54	65
6	PhCHO	O, Ph (propiophenone)	3-O-ester **19a**: n.d. 1-O-ester **19b**: 85	75
7	Cl–C$_6$H$_4$–CHO	O, Ph (propiophenone)	1-O-ester **20a**: 40 3-O-ester **20b**: 29	70

^{a} Isolated yield. ^{b} The ee values of esters and diols were determined by HPLC (Chiralpak AD-H and AS-H columns).
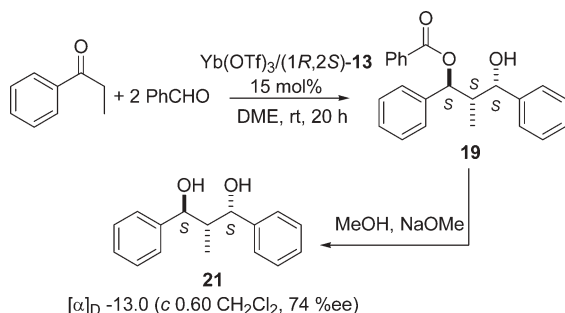
Scheme 2 Condensation of propiophenone with benzaldehyde.

55% ee) than *p*-anisaldehyde, which gave the condensation product in 86% ee. *p*-Methylbenzaldehyde condensed smoothly, leading to the desired product in 76% overall yield and 80% ee.

Dipropyl ketone was reactive under the tested catalytic system (77% yield, 65% ee), but its isopropyl counterpart was unreactive, probably because of steric interaction of the substrate with the active metal species in cyclic system **1**.

To assign the sense of the asymmetric induction we deprotected ester **19** and compared its optical rotation, as well as comparing the HPLC analysis of the obtained diol **21**, with published data (Scheme 2).[9] The same experiments in the case of the *p*-chloro-substituted diol (condensation of propiophenone and *p*-chloro-benzaldehyde, Table 3, entry 7) confirmed the same (1S,2S,3S) orientation of asymmetric carbon atoms.†

In conclusion, we established a new catalyst for the enantiose-lective aldol-Tishchenko reaction between aldehydes and aliphatic ketones (diethyl and dipropyl ketones) to give aldol-Tishchenko products with a dramatic increase in molecular complexity, created in a single operation. 1,3-Diol monoesters were formed in good to excellent yields with high *anti*-diastereocontrol and up to 85% ee. The ligand studies presented herein should provide a useful starting point for the development of more effective catalytic asymmetric aldol-Tishchenko reactions. Experiments on the scope and limitation of this reaction, as well as on further elucidation of the reaction mechanism, are in progress in our laboratory.

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