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Tetrahedron Letters 45 (2004) 7549–7552
Tetrahedron Letters

# The first example of a catalytic asymmetric aldol-Tishchenko reaction of aldehydes and aliphatic ketones

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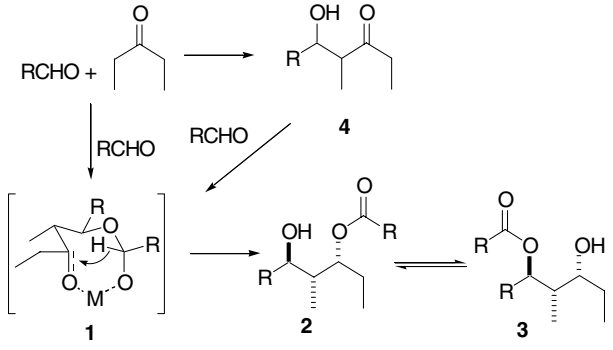
Received 6 July 2004; revised 19 August 2004; accepted 23 August 2004

**Abstract**—A number of combinations of Lewis acids and chiral ligands has been screened for the enantioselective direct tandem aldol condensation—Evans–Tishchenko reduction of aldehydes and ketones. Chiral ytterbium complexes were found to catalyze the condensation of aromatic aldehydes with 3-pentanone (and other ketones) giving rise to the *anti*-1,3-diol monoesters in good yield, and with high diastereocontrol and moderate levels of enantioselectivity. Three adjacent stereogenic centers are created in one reaction sequence in acyclic systems.


The control of stereochemistry during aldol addition is a crucial problem as the aldol addition is a fundamental method for construction of carbon–carbon bonds.[1]

A remarkable enhancement of efficiency of the aldol reaction was achieved recently when both chiral metal complexes and small chiral organic molecules were found to catalyze the direct aldol addition of unmodified ketones to aldehydes.[1b,2] Particularly, metal-based catalysts, inspired by the type II aldolases, have found their place in asymmetric synthesis. The multifunctional catalyst developed by Shibasaki[3] and the chiral semi-crown/Zn catalyst designed by Trost[4] have proved their efficiency, although there is still much room for improvement. To date, the scope of possible substrates and the selection of applicable catalytic systems remains restricted.[1b] In general, the methodology elaborated offers versatile access to aldol-type products from methyl ketones but the development of catalytic systems applicable to their methylene analogues is more challenging.[5,1b] Only selected α-substituted methyl ketones (particularly α-hydroxy) work efficiently.[6] The bulkiness of methylene ketones was found to inhibit the abstraction of α-hydrogen by the catalyst. As a result, low yields and low to moderate ees were observed during the simultaneous formation of both *syn*- and *anti*-aldols from these substrates.[5a] On the other hand, methylene ketones are efficient substrates for the tandem aldol-Tishchenko reaction.[7] As a result of such reactions 1,3-diol monoesters were formed with the simultaneous creation of three adjacent stereogenic centers (Scheme 1).[8] Designing this process in an enantioselective manner would be attractive in terms of both atom and chiral economy[9] as it offers unique one-step stereocontrol of three contiguous chiral centers in acyclic systems.

The high *anti*-stereoselectivity of this reaction unambiguously suggests the existence of a metal-centered transition state of type **1** with equatorially oriented bulky substituents. This observation encouraged us to search




**Scheme 1.** Postulated mechanism of the aldol-Tishchenko reaction.[8]

*Keywords*: Direct aldol condensation; Tishchenko reaction.
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doi:10.1016/j.tetlet.2004.08.134

for a metal-based chiral catalyst capable of promoting the reaction in an enantioselective way.

This challenge must be seen, however, in the context of the apparently high complexity of this process. Apart from the possibility of the formation of different diastereoisomers, the main 1,2-*anti*-1,3-*anti* product can be formed as an *O*-3-ester **2** and *O*-1-ester **3**. Both of these products can be obtained with different ratios of enantiomers, assuming that their formation is not a result of 1,3-acyl migration.[8] Finally, the problem with the rational design of chiral ligands seems convoluted because it is not clear whether the reaction proceeds through the aldol product **4** or directly through the concurrently generated intermediate **1**.

Despite the clear potential of this reaction, its enantioselective variant has apparently never been recorded in the literature. An insight into the enantioselective reaction of aldehydes leading to products with only one stereocenter was presented by Morken and co-workers.[10] The work of Schneider and Hansch[11] provided additional details, although it concentrated on ketone aldols, and does not include a direct condensation.

Herein, we would like to present the first instance of a chiral Lewis acid-based approach toward the solution of the problem of stereo-induction in the aldol-Tishchenko reaction of unmodified aldehydes and ketones. To uncover a way to induce stereoselectivity in this reaction we screened a number of metal source–chiral ligand combinations (Fig. 1). All of the materials tested were commercial, except for the compound **9**, which was easily prepared in three steps from available materials.[12]

Early experiments revealed that the most promising catalysts for this condensation were the combinations of ytterbium(III) triflate **D** with chiral diols **5**, **7**, and **9** supported by a tertiary amine. When benzaldehyde (1 mmol) and 3-pentanone (1 mmol) were treated with an equimolar amount of the catalyst prepared from

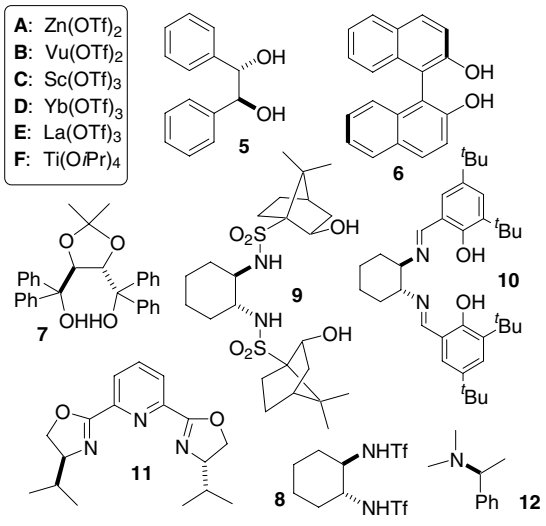
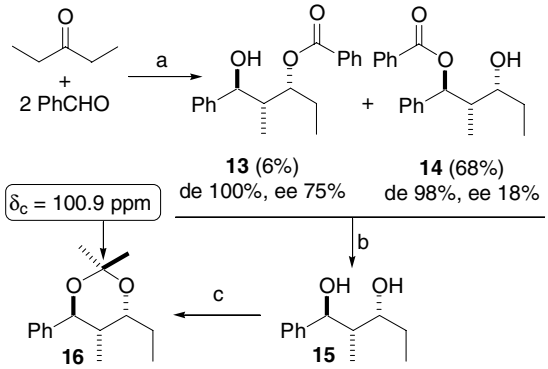



**Figure 1.**




**Scheme 2.** Reagents and conditions: (a) $Yb(OTf)_3$ (100 mol%), **5** (100 mol%), $Et^iPr_2N$ (200 mol%), THF, rt, 4 h; (b) NaOMe, MeOH; (c) DMP, acetone, CSA, rt, 30 min.

(*S*,*S*)-hydrobenzoin[13] the desired product was obtained as a mixture of two regioisomeric-esters **13** and **14** in 6% and 68% yields, respectively (Scheme 2).

The reaction was highly diastereoselective and the major 1,2-*anti*-1,3-*anti* products were accompanied by only traces (less then 3%) of 1,2-*syn*-1,3-*anti* co-products.[14] The main product **14** was formed with 18% ee. Surprisingly, both esters **13** and **14** showed a different enantiomeric excess—75% (1*R*,2*R*,3*S*)[15] and 18% (1*S*,2*S*,3*R*), respectively. This observation, while being a contradiction to the previous studies of the Tishchenko reaction,[10,11] indicated that the formation of both regioisomeric esters is not a result of a simple acyl migration.

The structural assignment of the esters **13** and **14** obtained was corroborated by high-resolution NMR experiments and is in a full agreement with previously published data.[7] The assigned 1,2-*anti*-1,3-*anti* stereochemistry of **13** and **14** was supported in both cases by an NMR analysis of the diols **15**[7] as well as rigid derivative **16**.[14,16] It is important to stress that the structures of **13** and **14** were established unequivocally, since our assignments differ from those published in the literature.[14,17]

Next, we attempted to reduce the catalyst loading. Decreasing the amount of Yb-complex to 20 mol% resulted in a diminished overall yield (59% after 10 h) as well as a reduced enantiomeric excess (Table 1, row 1). A similar outcome was observed with 10 mol% of the catalyst after the reaction time was extended for few days.

Other diols tested in this reaction gave either less satisfactory results (TADDOL—**7**) or failed to react altogether (**6** and **10**). Ligands with phenolic OH-groups although useful in classical aldol condensation (**6**)[3] and also in the aldol-Tishchenko reaction of two aldehydes (**10**)[10] may not be appropriate to the aldol-Tischenko reaction of aldehydes and ketones under the tested conditions. In our hands, both **6** and **10** were completely unreactive even when BuLi was used as a base. Limited catalytic activity of compounds with NH centers (**8** and

**Table 1.** The reaction was performed by the addition of 3-pentanone (1 mmol) and benzaldehyde (1 mmol) to a mixture of $Yb(OTf)_3$ (0.20 mmol), ethyldiisopropylamine (40 mmol), and **5** (0.20 mmol) in the appropriate solvent at rt, 20 h

| Entry | Solvent | Yield of **14** (%) | ee (%) |
|---|---|---|---|
| 1 | THF | 59 | 12 (1*S*,2*S*,3*R*) |
| 2 | DCM[a] | 17 | −8[b] |
| 3 | Dioxane | 58 | 9 |
| 4 | DME | 35 | 9 |
| 5 | MeCN | ND | — |
| 6 | $Et_2O$[a] | 18 | 5 |

[a] Catalyst only partially soluble in the reaction mixture.
[b] The use of '+/−' signs is only a convention to designate opposite enantiomers.

**9**) was observed, but unfortunately all of the ligands tested gave only the racemic esters **13** and **14**. The combination of hydrobenzoin with the pybox ligand **11** as a base was successful only when an equimolar amount of catalyst was used. In the latter case, however, the desired product was formed with a less than satisfactory yield (18%) but with higher ee (>90%).

The catalyst reactivity was strongly dependent on the metal center. Most of the metal salts showed catalytic activity toward the aldol condensation but only rare-earth elements gave the desired aldol-Tishchenko products. Interestingly, only the combination of ytterbium salt and hydrobenzoin ensured a good level of conversion. When the reaction was catalyzed by scandium, praseodymium, or lanthanum salts, significant amounts of simple *syn*- and *anti*-aldols **4** were isolated from the reaction mixture. Among all the solvents tested the most promising turned out to be THF, leading to the ester **14** with a higher ee, when compared to other solvents. DCM, usually the solvent of choice for the simple aldol condensations, gave surprisingly poor results leading to a product with a low (17%) yield (Table 1).

With a suitable metal and ligand in hand we decided to optimize the reaction with regard to the minor product **13** formed with a higher ee. It is important to point to our separate experiments, which revealed that the acyl migration between regioisomeric-esters **13** and **14** during the reaction is negligible even after a few days (less then 5%). We tested several catalytic systems with different tertiary amines. Table 2 indicates that the choice of amine influenced both the ee observed as well as the overall yield.

The highest ee (66%) was obtained when 10 mol% of *N*-methylimidazole (NMI) was used as an additive. The use of Hünig's base gave, however, better overall results as it delivered the product in a better chemical yield and with a similar level of ee (Table 2). Interestingly, the use of the chiral amine **12** did not affect the ee suggesting that this part of the catalyst structure is not responsible for the asymmetric induction.

The different results obtained with catalytic systems containing either 1 or 2 equiv of amine may indicate the presence of structurally different active species. It is possible to postulate the two structures **17** and **18**, by analogy to Kobayashi's catalyst composed of binol, $Ln(OTf)_3$, and amines.[18] A structure like **17**, which can be considered as more 'asymmetric' leads to the product with higher enantiomeric excess. The better solubilities and activities of complexes **17** and **18** in THF suggest the possibility of coordination of the solvent with the central metal atom as is common for structures possessing lanthanide elements (Fig. 2).[19]

**Table 2.** The reaction was performed by the addition of 3-pentanone (1 mmol) and benzaldehyde (1 mmol) to a mixture of $Yb(OTf)_3$ (0.20 mmol), appropriate amine (20/40 mmol), and **5** (0.20 mmol) in THF at rt, 20 h

| | Amine | **13** [%] (ee) | **14** ee [%] |
|---|---|---|---|
| *Amine (40 mol%)* | | | |
| 1 | $Et^iPr_2N$ | 8 (−38) | 57 (11) |
| 2 | TEA | 9 (−17) | 68 (11) |
| 3 | NMI | 15 (−58) | 62 (rac.) |
| 4 | BuLi | ND | 56 (23) |
| *Amine (20 mol%)* | | | |
| 5 | $Et^iPr_2N$ | **36** (−58) | 56 (7) |
| 6 | TEA | 38 (−57) | 51 (7) |
| 7 | NMI | 18 (−**66**) | 60 (8) |
| 8 | BuLi | 4 (−50) | 42 (rac.) |

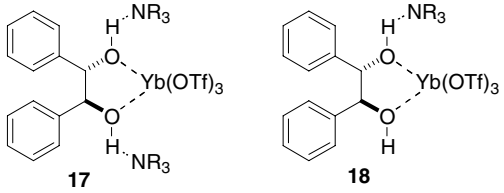
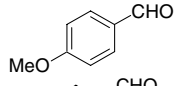
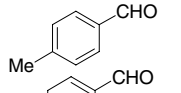
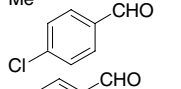
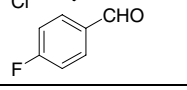



**Figure 2.**

Continuing our studies we conducted reactions with a series of substituted aromatic aldehydes (Table 3). Conspicuously, the reaction efficiency depends on the electron acceptor character of the aldehyde. In the substituent order F–Cl–Me–OMe, the decrease in yield of product with the 3-*O*-ester function is accompanied by simultaneous increase of its ee.

**Table 3.** The reaction was performed by the addition of 3-pentanone (1 mmol) and aldehyde (1 mmol) to a mixture of $Yb(OTf)_3$ (0.20 mmol), ethyldiisopropylamine (20 mmol), and **5** (0.20 mmol) in THF at rt, 20 h

| | Aldehyde | Product | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 |  | 3-*O*-Ester | 2 | — |
| | | 1-*O*-Ester | 45 | 18 |
| 2 |  | 3-*O*-Ester | 10 | 74 |
| | | 1-*O*-Ester | 64 | 17 |
| 3 |  | 3-*O*-Ester | 38 | −53 |
| | | 1-*O*-Ester | 58 | 38 |
| 4 |  | 3-*O*-Ester | 51 | −28 |
| | | 1-*O*-Ester | 30 | 24 |

In an attempt to gain some insight into the reaction mechanism we prepared a racemic sample of aldol **4** (R = Ph). Its reaction with benzaldehyde under the previously elaborated reaction conditions gave only racemic ester **14**. Such a result supports the expectation that the Evans–Tishchenko reduction step does not determine the stereochemistry of the products. On the other hand, the much lower yield of this reaction as compared to the direct process suggests that the formation of intermediate **1** is essential for the condensation to occur.

In conclusion, we present the first enantioselective example of the tandem aldol condensation—Evans–Tishchenko reduction reaction of aldehydes and ketones. We have shown that selectively protected *anti*-1,3-diols with three asymmetric carbons are formed. This kind of reaction is totally unexploited, and it is notable that the diol product was obtained with up to 70% ee, albeit in moderate chemical yield. The reaction does not require an excess of the ketonic substrate and the catalyst is composed from accessible, commercial materials. 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.

## Acknowledgements

Financial support from the Polish State Committee for Scientific Research (KBN Grant 3 T09A 126 27) is gratefully acknowledged. The author (J.M.) thanks the Alexander von Humboldt Foundation for a Return Fellowship.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.134. Representative experimental procedures and full characterization of all novel compounds as well as their stereochemical assignment are available.

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