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Direct Enantioselective Aldol−Tishchenko Reaction Catalyzed by Chiral Lithium Diphenylbinaphtholate

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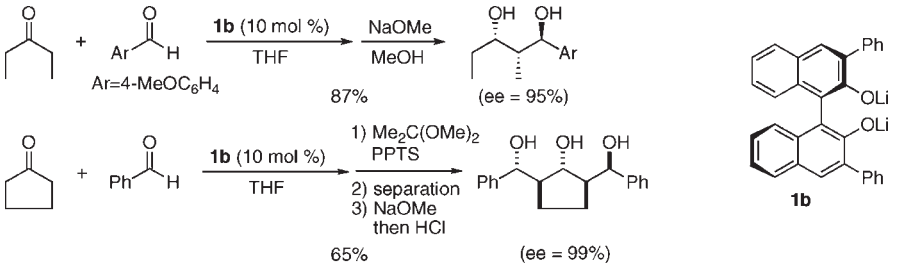
ABSTRACT

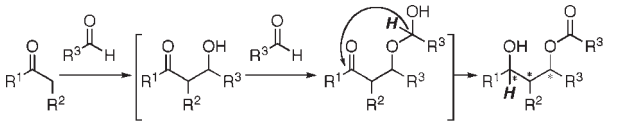


Chiral lithium diphenylbinaphtholate is an effective catalyst for the enantioselective aldol−Tishchenko reaction, affording 1,3-diol derivatives with three contiguous chiral centers and high stereoselectivities. Successive aldol−aldol−Tishchenko reactions gave a triol derivative with five consecutive chiral centers. The present reaction was applicable to highly enantioselective Evans−Tishchenko reduction.

The direct enantioselective aldol reaction is a powerful tool in organic synthesis because it constructs C−C bonds from two carbonyl compounds without the need to prepare silyl enol ethers.[1,2] Recently, a direct aldol reaction followed by acetalization and a hydride shift, which is called the direct aldol−Tishchenko reaction (Scheme 1),[3,4] has attracted much attention because it creates three contiguous asymmetric centers, affording monoacyl-protected 1,3-diols.[5]

An early attempt at the enantioselective aldol−Tishchenko reaction was reported by Mäeorg, who observed the first enantioselectivities in the self-condensation of 2-methylpropanal using the monolithium salt of binaphthol.[6] However, Morken, who obtained optically active monoacyl-protected 1,3-diol from two aldehydes using chiral yttrium complex as a catalyst, reported the successful examples of an enantioselective aldol−Tishchenko reaction in 2001.[7] Later, Shibasaki,[8]

Scheme 1. Aldol−Tishchenko Reaction



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(2) Reviews on the enantioselective direct aldol reaction: (a) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595–1601. (b) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570–579. (c) Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293. (e) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600–1632.

(3) Herein an "aldol−Tishchenko reaction" refers to an aldol reaction followed by acetalization and a hydride shift, while an "Evans−Tishchenko reduction" indicates the formation of β-acyloxy alcohol from β-hydroxy ketone with aldehyde.

(4) Reviews on the enantioselective direct aldol−Tishchenko reaction: (a) Mahrwald, R. *Curr. Org. Chem.* **2003**, *7*, 1713–1723. (b) Mlynarski, J. *Eur. J. Org. Chem.* **2006**, 4779–4786.

(5) Reviews on the stereoselective synthesis of 1,3-diols: Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557–588.

(6) An aldol−Tishchenko adduct was obtained in 21% yield with 33% ee: Loog, O.; Mäeorg, U. *Tetrahedron: Asymmetry* **1999**, *10*, 2411–2415.

(7) Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 601–603.

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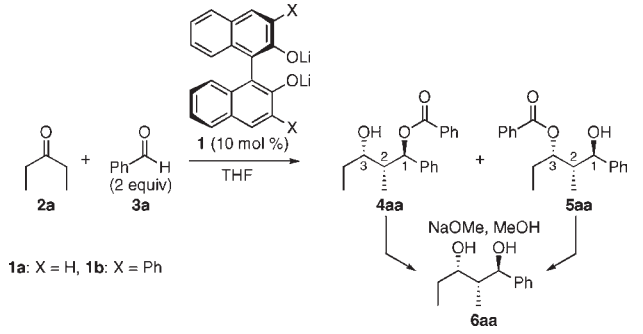
Mlynarski,[9] and Mahrwald[10] independently reported enantioselective aldol−Tishchenko reactions of ketones with aldehydes using lanthanum, ytterbium or titanium complexes, enabling three or more contiguous chiral centers with high selectivities to be created. Herein we report a highly enantioselective aldol−Tishchenko reaction with wide range of substrates using a simple lithium base, chiral lithium diphenylbinaphtholate.[11]

We initially investigated the aldol−Tishchenko reaction of 3-pentanone (**2a**) and benzaldehyde (**3a**) (2 equiv) in the presence of lithium binaphtholate[12] (**1a**) (10 mol %) prepared from binaphthol and butyllithium (Scheme 2).

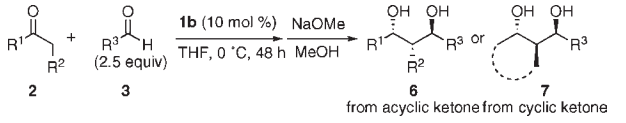
Scheme 2. Aldol−Tishchenko Reaction Catalyzed by Lithium Binaphtholate



The reaction proceeded to give the product as a mixture of 1-*O*-ester **4aa** and 3-*O*-ester **5aa**, but the chemical yields and selectivities were unsatisfactory (13% yield, 24% ee for **4aa** and 20% yield, 24% ee for **5aa**). After screening binaphthol derivatives, we found that the dilithium salt of 3,3′-diphenylbinaphthol (**1b**) gave monobenzoyl diols as a mixture of **4aa** (44%) and **5aa** (23%) with enantioselectivities of 85% ee.[13] Isolated **4aa** easily isomerized into a mixture of **4aa** and **5aa** without losing enantioselectivities, suggesting that **5aa** was produced by the acyl migration of the original aldol−Tishchenko product **4aa**.[14]

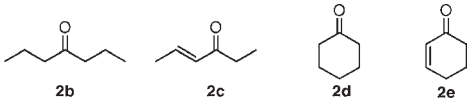
The aldol−Tishchenko reaction of **2a** and **3a** at 0 °C and subsequent debenzoylation gave the 1,3-diol as a single product **6aa** (1,2-*anti*-1,3-*anti*) with high enantioselectivity (Table 1, entry 1). Transition-state model **A**

Table 1. Aldol−Tishchenko Reaction Catalyzed by **1b**



entry	ketone	R^3 (aldehyde)	product	yield,[a] %	ee,[b] %
1	**2a**	Ph (**3a**)	**6aa**	81	93
2	**2a**	4-MeC_6H_4 (**3b**)	**6ab**	81	95
3	**2a**	4-MeOC_6H_4 (**3c**)	**6ac**	87	95
4	**2a**	4-BrC_6H_4 (**3d**)	**6ad**	80	88
5	**2a**	PhCH=CH (**3e**)	**6ae**	61	94
6	**2b**	Ph (**3a**)	**6ba**	71	93
7	**2c**	Ph (**3a**)	**6ca**	80	87
8	**2d**	Ph (**3a**)	**7da**	91	90
9[c]	**2e**	Ph (**3a**)	**7ea**	88	85

[a] Isolated yield. [b] Determined by HPLC. [c] −23 °C.



proposed by early pioneers can explain the formation of the 1,2-*anti*-1,3-*anti* isomer.[7−10,15] Although slight decreased selectivity was observed in the reaction of bromobenzaldehyde (**3d**) (entry 4), tolualdehyde (**3b**), and anisaldehyde (**3c**) gave similar selectivities of 95% ee were obtained in the reaction with **2a** (entries 2 and 3). The reaction of cinnamaldehyde **3e** gave a slightly lower chemical yield but with high selectivity (entry 5).

High enantioselectivities were also obtained using other ketones as substrates. 4-Heptanone **2b** gave a similar result with **2a** (entry 6). Cyclic ketones, cyclohexanone (**2d**), and cyclohexenone (**2e**) (entries 8 and 9) gave diols of 1,2-*syn*-1,3-*anti* isomers **7da**, **7ea** in high enantioselectivities as a single product, probably via tricyclic transition state **B** proposed by Fang (Figure 1).[15f] It is noteworthy that this is the highest level of enantioselectivity for the aldol−Tishchenko reaction using simple aliphatic ketones.

In the case of cyclopentanone (**2f**), which is a highly reactive aldol donor, the byproduct derived from the

(9) (a) Mlynarski, J.; Mitura, M. *Tetrahedron Lett.* **2004**, *45*, 7549–7552. (b) Mlynarski, J.; Jankowska, J.; Rakiel, B. *Chem. Commun.* **2005**, 4854–4856. (c) Mlynarski, J.; Jankowska, J.; Rakiel, B. *Tetrahedron: Asymmetry* **2005**, *16*, 1521–1526. (d) Mlynarski, J.; Rakiel., B.; Stodulski, M.; Suszczynska, A.; Frelek, J. *Chem.—Eur. J.* **2006**, *12*, 8158–8167.

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(12) Recent examples of using lithium binaphtholate as a catalyst:(a) Schiffers, R.; Kagan, H. B. *Synlett* **1997**, 1175–1178. (b) Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett.* **2000**, *41*, 7453–7456. (c) Hatano, M.; Ikeno, T.; Miyamoto, T.; Ishihara, K. *J. Am. Chem. Soc.* **2005**, *127*, 10776–10777. (d) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Synth. Catal.* **2008**, *350*, 1776–1780. (e) Hatano, M.; Horibe, T.; Ishihara, K. *J. Am. Chem. Soc.* **2010**, *132*, 56–57.

(13) Selectivities using catalysts derived from other 3,3′-disubsituted binaphthols: dimethyl; 28% ee, dichloro 58% ee.

(14) Acyl migration of the products is often observed in the aldol−Tishchenko reaction; see ref 15.

(15) Mechanistic studies of the aldol−Tishchenko reaction: (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449. (b) Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. *Organometallics* **1990**, *9*, 30–44. (c) Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087–1089. (d) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674–5675. (e) Abu-Hasanayn, F.; Streitwieser, A. *J. Org. Chem.* **1998**, *63*, 2954–2960. (f) Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 843–853. (g) Mascarenhas, C. M.; Duffey, M. O.; Liu, S.-Y.; Morken, J. P. *Org. Lett.* **1999**, *1*, 1427–1429. (h) Markert, M.; Mahrwald, R. *Synthesis* **2004**, 1429–1433.

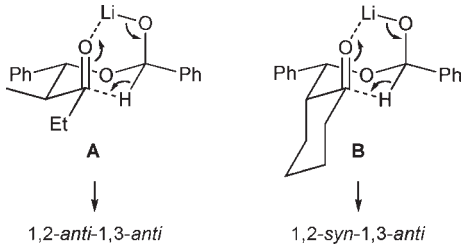
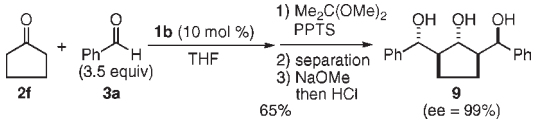


Figure 1. Plausible transition-state models.

double aldol reaction was significant even using a stoichiometric amount of benzaldehyde (**3a**) (Scheme 3). Hence, we employed 3.5 equiv of benzaldehyde (**3a**) as an aldol acceptor to afford inseparable two diastereomers, which were converted to acetonides for the separation of the isomers and the following deprotection afforded triol **9** with five consecutive chiral centers[10] with extremely high enantioselectivity. The relative configuration of **9** was determined by X-ray crystallographic analysis.

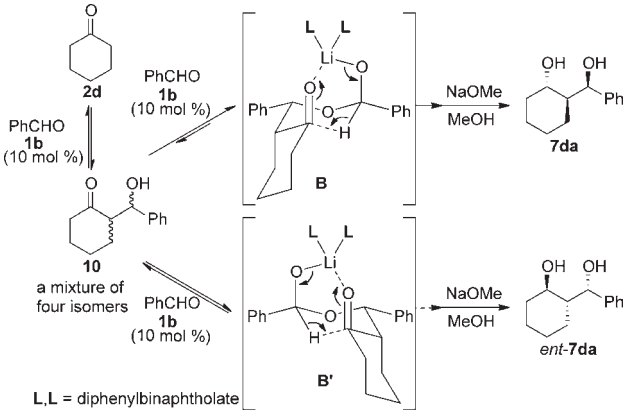
Scheme 3. Construction of Five Contiguous Chiral Centers



According to the early pioneers' reports,[7−10,15] the enantioselectivity in the aldol-Tishchenko reaction is controlled by the stability of the cyclic transition state of the hydride shift step because the aldolization process is reversible. To confirm this mechanism, we added benzaldehyde (**3a**) to the mixture of aldol adducts prepared from cyclohexanone (**2d**) and benzaldehyde (**3a**) (**10** *syn*/*anti* = 1/2, racemic) in the presence of catalyst **1b** (Scheme 4). As expected, 1,3-diol **7da** with the same stereochemistry as entry 8 was produced as a single diastereomer in high yield (1,2-*syn*-1,3-*anti* 86% ee vs 90% ee in entry 8). These results suggest the cyclic transition state of hydride shift step **B**, which is more stable than the other transition state **B′**, controls the stereochemistry.

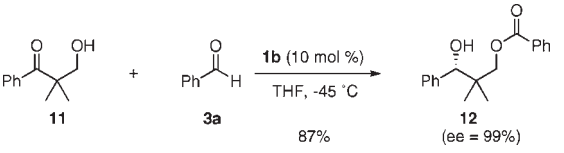
The reaction of β-hydroxy ketone and aldehyde (the so-called Evans−Tishchenko reduction), which produces β-acyloxy alcohol, is often used as a chemical tool in natural product syntheses due to its high diastereoselectivities.[16] However, the enantioselective version of this reaction is still being developed.[17] Our reaction could easily be

Scheme 4. Plausible Reaction Pathway



expanded to the Evans−Tishchenko reduction. In the presence of catalyst **1b**, β-hydroxy ketone **11** reacted with benzaldehyde (**3a**) to afford acyloxy alcohol **12** in high chemical and optical yields (Scheme 5).

Scheme 5. Enantioselective Evans−Tishchenko Reduction



In conclusion, we have demonstrated that chiral lithium diphenylbinaphtholate is an effective catalyst for the highly enantioselective aldol−Tishchenko reaction. The catalyst is easily prepared from common reagents and does not contain rare metals. In the case of cyclopentanone, a single manipulation controlled five successive chiral centers. The present reaction was applicable to a highly enantioselective Evans−Tishchenko reduction. Studies on the mechanism as well as the design of chiral catalysts to further enhance enantioselectivity are currently in progress.

Supporting Information Available. Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Schneider, C.; Hansch, M. *Synlett* **2003**, 837–840. (b) Schneider, C.; Hansch, M.; Sreekumar, P. *Tetrahedron: Asymmetry* **2006**, *17*, 2738–2742.