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Toward Asymmetric Aldol-Tishchenko Reactions with Enolizable Aldehydes: Access to Defined Configured Stereotriads, Tetrads, and Stereopentads

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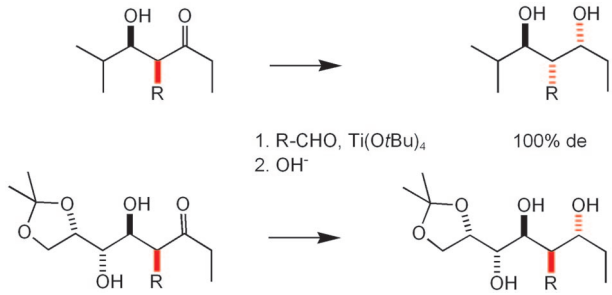

Asymmetric aldol-Tishchenko reactions of enolizable aldehydes and ketones in the presence of chiral BINOLTi(O*t*Bu)$_2$/cinchona alkaloids complexes are described. Different configurative outcomes of these reactions depend on an equilibration through a retro aldol/aldol sequence and can be influenced by the configurative architecture of substrates. The results are explained by means of transition state models and rate constants. These considerations offer a fine-tuning of diastereoselectivity in aldol-Tishchenko reactions. Extensions of this research give access to defined configured stereotriads, stereotetrads, and stereopentads.

Introduction

The aldol-Tishchenko reaction continues to be an attractive challenge for organic synthesis.[1] This transformation is an useful method for the construction of defined adjacent stereogenic centers and represents a valuable tool with regard to chiral economy. Three stereogenic centers can be created by aldol-Tishchenko reactions of an aldehyde with ethyl ketones. So-called stereotriads will be formed by only one reaction step of two prochiral starting compounds.[2] Nevertheless, there are many problems that still have to be solved. First of all, a general and enantioselective execution of the aldol-Tishchenko reaction with enolizable aldehydes in the propionate series does currently not exist.[3] In addition, only a limited number of publications describe enantioselective aldol-Tishchenko reactions.[4] In principal, there are two general methodologies to achieve this aim: the direct aldol-Tishchenko reaction (I) and domino aldol-Tishchenko reaction (II, Scheme 1).

By applying the direct aldol-Tishchenko reaction (I) the 1,2-*anti*-, 1,3-*anti*-configured Tishchenko products were isolated with high degrees of enantio- and diastereoselectivity. These

(1) (a) Mahrwald, R. In *Modern Aldol Reactions*; Mahrwald, R. Ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 327−344. (b) Mlynarski, J. *Eur. J. Org. Chem.* **2006**, 4779–4786. (c) Shibasaki, M.; Ohshima, T. In *Asymmetric Synthesis*; Christmann, M.; Bräse, S. Eds.; Wiley-VCH: Weinheim, 2007; pp 141−146.

(2) (a) Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. *Organometallics* **1990**, *9*, 30–44. (b) Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317–318. (c) Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087–1089. (d) For an intramolecular version, see: Uenishi, J.; Masuda, S.; Wakabayashi, S. *Tetrahedron Lett.* **1991**, *32*, 5097–5100. (e) Baramee, A.; Chaichit, N.; Intawee, P.; Thebtharononth, C.; Thebtharononth, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1016–1017. (f) Bodnar, P.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674–5675. (g) Mascarenhas, C. M.; Duffey, M. O.; Liu, S.-Y.; Morken, J. P. *Org. Lett.* **1999**, *1*, 1427–1429. (h) Delas, C.; Blacque, O.; Moise, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2265–2270. (i) Delas, C.; Blacque, O.; Moise, C. *Tetrahedron Lett.* **2000**, *41*, 8269–8272.

(3) Morken et al. described an asymmetric aldol Tishchenko reaction catalyzed by chiral yttrium-salen complexes: Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 601–603. During these investigations the authors used isobutyraldehyde as the ene component and aromatic aldehydes as carbonyl compounds.

(4) (a) Chiral BINOL-alkoxides: Loog, O.; Maeorg, U. *Tetrahedron: Asymmetry* **1999**, *10*, 2411–2415. (b) Chiral ytterbium complexes: Mlynarski, J.; Mitura, M. *Tetrahedron Lett.* **2004**, *45*, 7549–7552. (c) Mlynarsyki, J.; Rakiel, M.; Stodulski, A.; Suszcynska, A.; Frelek, J. *Chem.−Eur. J.* **2006**, *12*, 8158–8167. (d) Mlynarski, J.; Jankowska, J.; Rakiel, B. *Tetrahedron: Asymm.* **2005**, *16*, 1521–1526. (e) Mlynarski, J.; Jankowska, J.; Rakiel, B. *Chem. Comm.* **2005**, 4854–4856. (f) Stodulski, M.; Jazwinski, J.; Mlynarski, J. *Eur. J. Org. Chem.* **2008**, 5553–5562. (g) Chiral lanthan complexes: Gnanadesikan, V.; Horiuchi, Y.; Oshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7782–7783. (h) Horiuchi, Y.; Gnanadesikan, V.; Ohshima, T.; Masu, H.; Katagiri, K.; Sei, Y.; Yamaguchi, K.; Shibasaki, M. *Chem.−Eur. J.* **2005**, *11*, 5195–5204.

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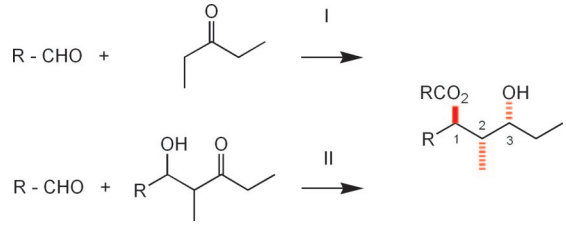
SCHEME 1. General Pathways of Aldol-Tishchenko Reactions



reactions are limited to the use of aromatic aldehydes and cannot be generalized to the use of enolizable aldehydes.

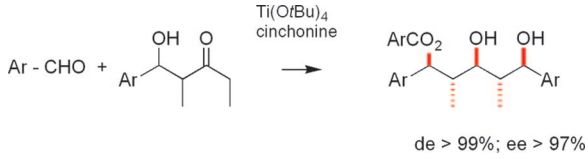
This challenge can be overcome by the deployment of the Nevalainen protocol (II).[5] Retro aldol-Tishchenko processes of ketone aldol adducts were utilized for the stereoselective synthesis. The Tishchenko products of enolizable aldehydes were isolated with moderate enantioselectivities (ee < 60%); they have been reported in the acetate aldol series so far.[6]

Furthermore, the control of simple diastereoselectivity has not yet been solved. The classical yield of base-catalyzed aldol-Tishchenko reactions is 1,2-*anti*, 1,3-*anti*-configured stereotriads. Only a few publications describe other configured stereotriads, and moreover, they cannot be generalized.[7] Herein, we report and discuss results of asymmetric aldol-Tishchenko reactions of enolizable aldehydes.

Results and Discussion

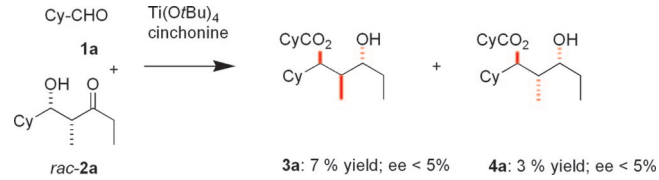
Recently, we have reported a highly asymmetric direct aldol-Tishchenko reaction mediated by ligand exchange of titanium(IV) alkoxides and chiral amino alcohols.[8] Stereopentads were isolated with a high degree of diastereo- as well as enantioselectivity. This transformation is limited to the use of aromatic aldehydes (Scheme 2).

SCHEME 2. Formation of Stereopentads by Aldol-Tishchenko Reaction



In order to extend this transformation to aldol-Tishchenko reactions of enolizable aldehydes, we tested cyclohexanecarboxaldehyde **1a** and the corresponding racemic aldol adduct **2a** (ratio of *syn*/*anti* = 95:5) as model substrates. A complex of $Ti(OtBu)_4$ and cinchonine was used in these initial studies to give a mixture of differently configured aldol-Tishchenko 1-esters **3a** and **4a**. These Tishchenko products were obtained with low yields and no enantioselectivities (Scheme 3).

SCHEME 3. Aldol-Tishchenko Reaction in the Presence of $Ti(OtBu)_4$/Cinchonine Complex[a]

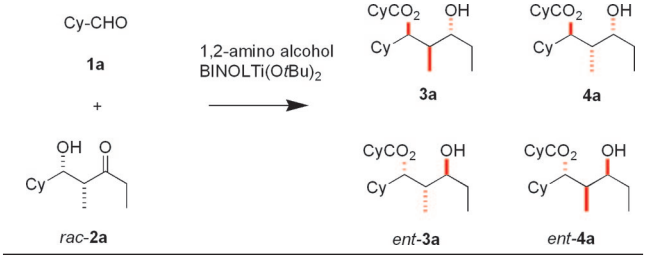


[a] Reaction conditions: 1 equiv of $Ti(OtBu)_4$ and cinchonine, 1 equiv of aldol adduct **2a**, 5 equiv of aldehyde **1a**, rt, CH_2Cl_2, 24 h.

The formation of 1,2-*syn*-, 1,3-*anti*-configured 1-ester **3a** was unexpected, since 1,2-*anti*, 1,3-*anti*-configured 1-ester **4a** represents the "classical" configurative outcome of an aldol-Tishchenko reaction.[1] The ratio of products **3a** to **4a** did not depend on reaction time (7/3 for **3a**/**4a**).

A successful asymmetric aldol-Tishchenko reaction with enolizable aldehydes could be realized by increasing the steric bulkiness of the titanium(IV) complexes. For that reason BINOL-titanium(IV) complexes of 1,2-amino alcohols (cinchona alkaloids) were examined.[9] Yields and selectivities increased by application of these titanium(IV) complexes. Moreover, shorter reaction times were observed; reactions were completed within 4−6 h at room temperature (Table 1). The Tishchenko products were obtained with moderate to good enantioselectivities.

TABLE 1. Asymmetric Aldol-Tishchenko Reaction with Cyclohexanecarboxaldehyde in the Presence of $BINOLTi(OtBu)_2$ and Different Cinchona Alkaloids



entry	1,2-amino alcohol	compound: yield (%) (ee %)[c,d]	
1[a]	cinchonine	**3a**: 27 (42)	**4a**: 17 (78)
2[b]	cinchonine	*ent*-**3a**: 27 (21)	*ent*-**4a**: 16 (26)
3[a]	cinchonidine	**3a**: 30 (30)	**4a**: 11 (38)
4[b]	cinchonidine	*ent*-**3a**: 22 (40)	*ent*-**4a**: 15 (60)

[a] Reaction conditions: 1 equiv of a preformed complex of (*R*)-$BINOLTi(OtBu)_2$ and 1,2-amino alcohol, 1 equiv of aldol adduct **2a**, 5 equiv of aldehyde **1a**, rt, CH_2Cl_2. [b] Reaction conditions: 1 equiv of a preformed complex of (*S*)-$BINOLTi(OtBu)_2$ and 1,2-amino alcohol, 1 equiv of aldol adduct **2a**, 5 equiv of aldehyde **1a**, rt, CH_2Cl_2. [c] Enantioselectivities were determined by ^1H NMR analysis using the Mosher ester technique.[10] [d] The absolute configurations of the stereotriads were determined by ^1H NMR studies using the Mosher ester technique.[11]

The choice of chiral BINOL ligand as well as chiral 1,2-amino alcohol is crucial for the stereochemical outcome of these reactions. The results of Table 1 clearly indicate the existence

(5) Nevalainen, V.; Simpura, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3422–3425.

(6) (a) Simpura, I.; Nevalainen, V. *Tetrahedron Lett.* **2001**, *42*, 3905–3907. (b) Simpura, I.; Nevalainen, V. *Tetrahedron* **2003**, *5*, 7535–7546. (c) Schneider, C.; Hansch, M. *Chem. Commun.* **2001**, 1218–1219. (d) Schneider, C.; Hansch, M.; Weide, T. *Chem.−Eur. J.* **2005**, *11*, 3010–3021. (e) Schneider, C.; Hansch, M. *Synlett* **2003**, 837–840. (f) Schneider, C.; Hansch, M.; Sreekumar, P. *Tetrahedron: Asymmetry* **2006**, *17*, 2738–2742. (g) For very early studies of this method, see also: Fouquet, G.; Merger, F.; Platz, R. *Liebigs Ann. Chem.* **1979**, 1591–601.

(7) (a) Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 843–853. (b) Enders, D.; Ince, S. J.; Bonnekessel, M.; Runsink, J.; Raabe, G. *Synlett* **2002**, 962–966. (c) Markert, M.; Mahrwald, R. *Synthesis* **2004**, 1429–1433.

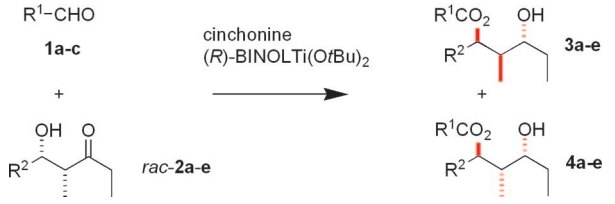
(8) Rohr, K.; Herre, R.; Mahrwald, R. *Org. Lett.* **2005**, *7*, 4499–4501.

(9) In the very first experiments the catalysts were generated in situ and used in the reactions at 10 mol %, but after optimization it turned out that the catalyst has to be prepared and used in equimolar amounts. See Supporting Information.

(10) See Supporting Information.

(11) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096. For a comprehensive overview, see: Seco, J. M.; Qinoa, E.; Giguera, R. *Chem. Rev.* **2004**, *104*, 17–117. For more details see Supporting Information.

TABLE 2. Aldol-Tishchenko Reactions of Enolizable Aldehydes in the Presence of Cinchonine and (*R*)-BINOLTi(O*t*Bu)$_2$[a]

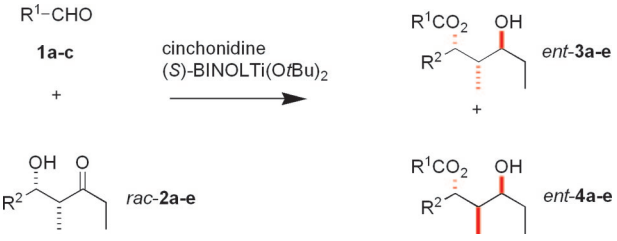


entry	R^1	R^2	compound: yield (%) (ee %)	
1	Cy	Cy	**3a**: 27 (42)	**4a**: 17 (78)
2	*i*Pr	*i*Pr	**3b**: 23 (36)	**4b**: 29 (62)
3	Et	Et	**3c**: 50 (18)	**4c**: 45 (42)
4	*i*Pr	Ph-$(CH_2)_2$-	**3d**: 10 (10)	**4d**: 7 (30)
5	*i*Pr	*n*Pr	**3e**: 28 (20)	**4e**: 13 (38)

[a] Reaction conditions: 1 equiv of a preformed complex of (*R*)-BINOLTi(O*t*Bu)$_2$ and cinchonine, 1 equiv of aldol adduct **2a**−**e**, 5 equiv of aldehydes **1a**−**c**, rt, CH_2Cl_2.

of an optimal combination of 1,2-amino alcohols and chiral BINOL ligands used (compare entries 1 and 2, 3 and 4, Table 1). After altering the chirality of 1,2-amino alcohols and chirality of the BINOL ligands, we observed a change of direction as well as of degree of enantioselectivity. These results have encouraged us to explore the dominating influences on the stereocontrol of this reaction more intensively. Following this protocol we investigated the influence of different enolizable aldehydes. Results of Tables 2 and 3 clearly demonstrate that the levels of enantioselectivities of 1-esters **3a**−**e** and **4a**−**e** depend on the bulkiness of the aldehydes **1a**−**c** deployed in these experiments (compare entries 1, 2, and 3, Table 2 and 3). Bulky aldehydes resulted in Tishchenko products with good enantioselectivities but with low yields. On the other hand, when used with propionaldehyde, the corresponding Tishchenko products were obtained with quantitative yields but with low degrees of enantioselectivity (entry 3, Table 2).

TABLE 3. Aldol-Tishchenko Reaction of Enolizable Aldehydes in the Presence of Cinchonidine and (*S*)-BINOLTi(O*t*Bu)$_2$[a]



entry	R^1	R^2	compound: yield (%) (ee %)	
1	Cy	Cy	*ent*-**3a**:22 (40)	*ent*-**4a**:17 (60)
2	*i*Pr	*i*Pr	*ent*-**3b**:45 (48)	*ent*-**4b**:19 (68)
3	Et	Et	*ent*-**3c**:28 (22)	*ent*-**4c**:37 (44)
4	*i*Pr	Ph-$(CH_2)_2$-	*ent*-**3d**: 8 (20)	*ent*-**4d**:10 (36)
5	*i*Pr	*n*Pr	*ent*-**3e**:25 (28)	*ent*-**4e**:26 (32)

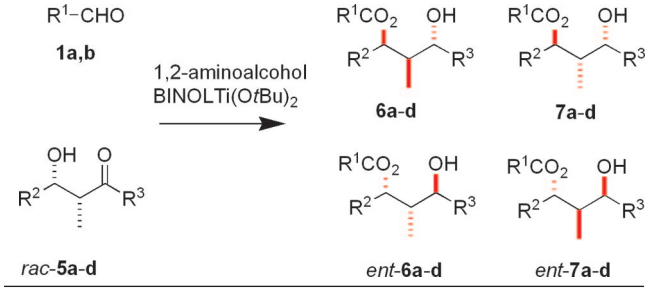
[a] Reaction conditions: 1 equiv of a preformed complex of (*S*)-BINOLTi(O*t*Bu)$_2$ and cinchonidine, 1 equiv of aldol adduct **2a**−**e**, 5 equiv of aldehydes **1a**−**c**, rt, CH_2Cl_2.

Also, different enolizable aldehydes can be used successfully for aldol-Tishchenko reaction independently of the aldehydes used for the formation of starting aldol adducts **2a**−**e**. Mixed aldol-Tishchenko products are accessible ($R^1 \neq R^2$; entries 4 and 5, Tables 2 and 3). Cross aldol-Tishchenko products could not be detected under these reaction conditions.

The enantioselectivities reported did not change during the reaction time. In addition, the enantioselectivities did not depend on the diastereomeric configuration of the aldol adducts. The same enantioselectivities were obtained when used with *anti*- or *syn*-configured aldol adducts. In contrast the diastereomeric ratio depends on the configuration of the starting aldol adducts **2a**−**e**. When *syn*-configured aldol adducts were employed, 1,2-*syn*-, 1,3-*anti*-configured Tishchenko products were isolated as main products. When starting with aldol adducts **2a**−**e** with a *syn*/*anti* ratio of 95:5, the Tishchenko products **3a**−**e**/**4a**−**e** were obtained in a ratio of 7:3 to 1:1. When a 1:1 mixture of *syn*/*anti*-configured aldol adducts was used, the diastereoselectivity of **3a**−**e**/**4a**−**e** decreased to 1:1.[12]

Next, we explored the steric influence of substituted ketones in these transformations. To this end we reacted aldol adducts **5a**−**d** (prepared from unsymmetrical ethyl ketones) with the corresponding enolizable aldehydes. There is a small improvement of enantioselectivities detected in this series (compare results of entries 1 and 2 of Table 2 with entries 1 and 3 of Table 4). Experiments with aldol adducts of *tert*-butyl ethyl ketone failed (entry 4, Table 4).

TABLE 4. Aldol-Tishchenko Reaction of Enolizable Aldehydes with Unsymmetrical Ethyl Ketones



entry	R^1	R^2	R^3	compound: yield (%) (ee %)	
1[a]	*i*Pr	*i*Pr	Ph	**6a**: 30 (40)	**7a**: 11 (86)
2[a]	Cy	Cy	*i*Pr	**6b**: 40 (52)	**7b**: 29 (60)
3[a]	Cy	Cy	Ph	**6c**: 28 (54)	**7c**: 12 (80)
4	Cy	Cy	*t*Bu	**6d**: -	**7d**: -
5[b]	*i*Pr	*i*Pr	Ph	*ent*-**6a**: 25 (54)	*ent*-**7a**: 14 (78)
6[b]	Cy	Cy	Ph	*ent*-**6b**: 26 (56)	*ent*-**7b**: 20 (72)
7[b]	Cy	Cy	*i*Pr	*ent*-**6c**: 55 (42)	*ent*-**7c**: 29 (54)

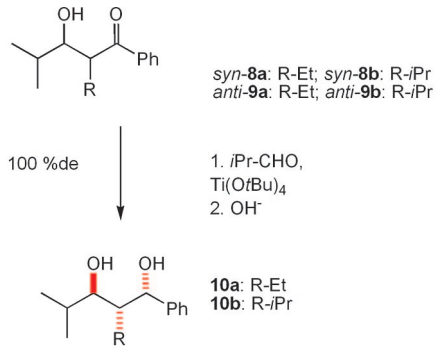
[a] Reaction conditions: 1 equiv of a preformed complex of (*R*)-BINOLTi(O*t*Bu)$_2$ and cinchonine, 1 equiv of aldol adduct **5a**−**d**, 5 equiv of aldehydes **1a**,**b**, rt, CH_2Cl_2 [b] Reaction conditions:1 equiv of a preformed complex of (*S*)-BINOLTi(O*t*Bu)$_2$ and cinchonidine, 1 equiv of aldol adduct **5a**−**d**, 5 equiv of aldehydes **1a**,**b**, rt, CH_2Cl_2.

In order to obtain more information on the configurative course of this reaction, we tested aldol adducts of propyl and *iso*-butyl phenyl ketones. For that reason we have reacted aldol-Tishchenko reactions of defined *syn*- and *anti*-configured aldol adducts **8a**, **8b**, **9a**, and **9b** with isobutyraldehyde in the presence of titanium(IV) alkoxides (Scheme 4).

During these reactions we were able to detect equilibrations of the starting aldol adducts depending on the configuration. When used with *anti*-configured aldol adducts **9a** or **9b**, an equilibration to only a small extent was detected. The Tishchenko reaction started immediately, and within 1 or 3 days the transformation was completed. 1,2-*syn*-, 1,3-*anti*-Configured Tishchenko products could not be observed in these reactions.

(12) These results correspond to those described by Schneider, C.; Klapa, K.; Hansch, M. *Synlett* **2005**, 91–94.

SCHEME 4. Aldol-Tishchenko Reactions of *syn*- and *anti*-Configured Aldol Adducts in the Presence of Ti(O*t*Bu)$_4$ or (*R*)-BINOLTi(O*t*Bu)$_2$/Cinchonine Complexes



syn-**8a** → **10a**	55 %, 3 days; Ti(O*t*Bu)$_4$
syn-**8b** → **10b**	51 %, 7 days; Ti(O*t*Bu)$_4$
anti-**9a** → **10a**	57 %, 1 day; Ti(O*t*Bu)$_4$
anti-**9b** → **10b**	49 %, 3 days; Ti(O*t*Bu)$_4$
syn-**8a** → **10a**	53 %, 6 days, 88 %ee; (*R*)-BINOLTi(O*t*Bu)$_2$ / cinchonine
syn-**8b** → **10b**	48 %, 7 days, 83 %ee; (*R*)-BINOLTi(O*t*Bu)$_2$ / cinchonine
anti-**9a** → **10a**	54 %, 3 days, 80 %ee; (*R*)-BINOLTi(O*t*Bu)$_2$ / cinchonine
anti-**9b** → **10b**	52 %, 4 days, 81 %ee; (*R*)-BINOLTi(O*t*Bu)$_2$ / cinchonine

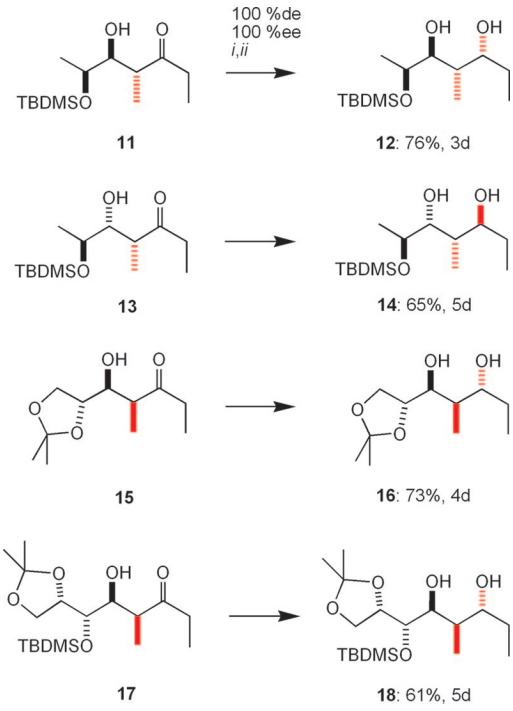
By treatment of *syn*-configured aldol adduct **8a** or **8b** with isobutyraldehyde in the presence of Ti(O*t*Bu)$_4$, only an equilibration to *anti*-configured aldol adducts **9a** or **9b** was observed within the first 24 h. Aldol-Tishchenko products could not be detected at this initial stage. An aldol-Tishchenko reaction occurred with yields and stereoselectivities comparable to those of the *anti*-series once *anti*-configured aldol adducts **9a** or **9b** were formed in substantial amounts. Extremely high diastereoselectivities were noticed in both series; 1,2-*anti*, 1,3-*anti*-configured Tishchenko products **10a** or **10b** were isolated as a single stereoisomer. 1,2-*syn*-, 1,3-*anti*-Configured Tishchenko products could not be detected in any case.

Similar results with regard to stereoselectivity were obtained in the enantioselective series when applying (*R*)-BINOL-Ti(O*t*Bu)$_2$/cinchonine complexes. Starting with *syn*-configured aldol-adducts **8a** or **8b**, an equilibration to *anti*-configured aldol adducts **9a** or **9b** was observed in the first 24 h. Subsequent Tishchenko reactions yielded 1,2-*anti*-, 1,3-*anti*-configured products **10a** or **10b**. The products were isolated with high degrees of enantioselectivity (Scheme 4).

Differences were observed with regard to reaction rates. Bulky substituted phenyl ketones require longer reaction times (e.g., **8a** → **10a** = 3 days (R-Et) and **8b** → **10b** = 7 days (R-*i*Pr) (Scheme 4).[13] Furthermore, bulky reagents require also longer reaction times (compare **8a** → **10a** = 3 days (Ti(O*t*Bu)$_4$) and **8a** → **10a** = 6 days (BINOLTi(O*t*Bu)$_2$/cinchonine) (Scheme 4). When used with comparatively sterically unassuming reagents such as Ti(O*t*Bu)$_4$, a complete reaction to 1,2-*anti*-, 1,3-*anti*-configured products is observed within 1 or 3 days.

To explore the substrate-induced stereoselectivity, we tested several chiral oxygen-substituted aldol adducts in Ti(O*t*Bu)$_4$-mediated aldol-Tishchenko reactions. In this series we did not observe any equilibration of the corresponding aldol adducts. Even when used with an excess of titanium(IV) *tert*-butoxide (10 equiv), equilibrations or retro aldol reactions could not be detected. *syn*- or *anti*-Configured aldol adducts are configuratively stable under these conditions (this is probably due to a chelation of titanium(IV) alkoxides to the additional oxygen functionalities in these substrates). This observation could be extended to a general access to defined, differently configured stereopentads or stereotetrads. Aldol adducts of several optically active aldehydes and diethyl ketone were reacted with isobutyraldehyde in aldol-Tishchenko reactions (Scheme 5). Independently of the configuration of the starting aldol adducts **11**, **13**, **15**, and **17**, the Tishchenko products were formed with 1,3-*anti*-configuration as a single stereoisomer. The 1,2-configurations of the starting aldol adducts were not changed.

SCHEME 5. Chiral Stereotetrads and Stereopentads by Tishchenko Reactions[a]



[a] Reaction conditions: (i) Ti(O*t*Bu)$_4$, *i*Pr-CHO, rt CH_2Cl_2; (ii) NaOMe/MeOH.

The configurative outcomes of the reported experiments can be explained by well-accepted transition state models[14] in Figure 1 and kinetic considerations in Figure 2. They are influenced by several aspects: 1,3-diaxial interactions in the transition state steric interactions between substituents R^1/R^2 and R^2/R^3 steric interactions between substituent R^2 and the titanium complex.

The steric hindrances between substituents R^2 and R^3 are decreasing in the order **5a** < **8a** < **8b** (R^2: Me < Et < *i*Pr) in reactions with substituted phenyl ketones (R^3 = Ph, Figure 1). The bulky phenyl group drives the ethyl and isopropyl group into the equatorial position. The formation of 1,2-*anti*, 1,3-*anti*-configured Tishchenko products is the consequence. On the other hand, the methyl group (R^2 = Me) is configuratively more flexible. Repulsive interactions to the bulky titanium complex can predominate, and weak steric interactions allow the unfavored axial position of the methyl group (transition state **A,**

(13) In some cases no reactions were observed (entry 4, R^3-*t*Bu, Table 4).

(14) Mahrwald, R. *Curr. Org. Chem.* **2003**, *7*, 1713–1723.

(15) Ide, A.; Scholtis, S.; Mahrwald, R. *Org. Lett.* **2006**, *8*, 5353–5355. The energetically unfavoured axial position of the phenyl group of mandelic acid ester in the transition state explains the formation of *anti*-configured aldol adducts under thermodynamic control.

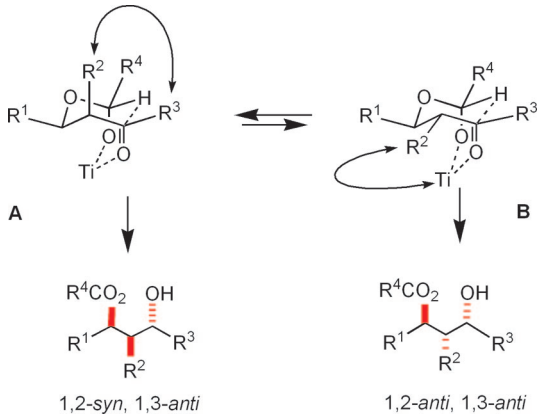


FIGURE 1. Proposed transition state model. Ti = Ti(O*t*Bu)$_4$ or BINOLTi(O*t*Bu)$_2$/cinchona alkaloids.

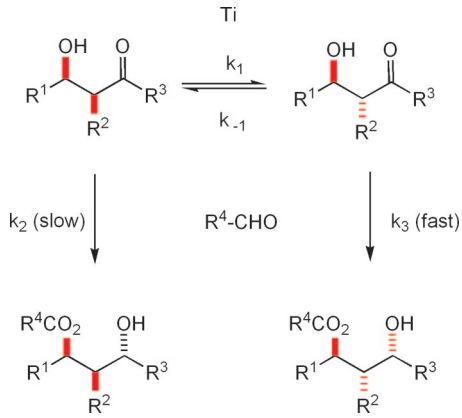


FIGURE 2. Possible mechanistic reaction pathway. Ti = Ti(O*t*Bu)$_4$ or BINOLTi(O*t*Bu)$_2$/cinchonine.

Figure 1). 1,2-*syn*-, 1,3-*anti*-Configured products were isolated as the main products (see results of Tables 1−4). Also, these results indicate that the 1,3-diaxial interactions are very weak and can be overriden by steric interactions of R^2, R^3 and of the titanium complex. For similar observations in asymmetric aldol additions of mandelic acid esters see, ref 15.

It is assumed that a fast and reversible retro aldol interconversion of *syn*- and *anti*-configured aldol adducts occurs in the presence of titanium complexes via the intermediate titanium enolates (R^2 = Et and *i*Pr, Scheme 4).[16] Subsequent stereoselective Tishchenko reaction is irreversible and fixes the configuration of the aldol adduct mixture with the rate constants k_2 and k_3 (Figure 2). The rate differences determine the configurative outcome of the reaction. The exclusive formation of 1,2-*anti*, 1,3-*anti*-configured Tishchenko products can be explained by the fast reaction with aldehyde R^4-CHO via transition state **B** (k_1, $k_{-1} > k_3 \gg k_2$, Figures 1 and 2).

In the case of substituent R^2 = Me, the ratio of equilibration rates and Tishchenko reaction rates become more equal (k_1, $k_{-1} > k_2 \gg k_3$). Thus the *syn*-configuration of starting aldol adducts can be preserved in the Tischenko products substantially. These considerations are consistent with previous reports.[6d,e,17]

When used with oxygen-substituted aldol adducts, an equilibration was not observed (k_1 and $k_{-1} \rightarrow 0$). The stereochemical integrity of the substrates is not affected. 1,3-*anti*-Configured Tishchenko products were isolated as a single stereoisomer. Similar results were obtained in samarium-catalyzed Tishchenko reductions of β-hydroxy ketones. In these reactions the configuration of substrates remains unaffected.[18]

Conclusions

With these experiments we have demonstrated the utility of chiral BINOL-titanium/cinchona alkaloid complexes in asymmetric aldol-Tishchenko reactions. Several aspects of the substituent architecture of the starting aldol adducts dictate the stereochemical outcome of these reactions:

• By application of propionate aldol adducts (R^2 = Me), diastereomeric mixtures of 1,2-*anti*, 1,3-*anti*- and 1,2-*syn*, 1,3-*anti*-configured Tishchenko products can be isolated with good enantioselectivities (ee's up to 86%). An initial equilibration of starting aldol adducts is overlapped by the competing Tishchenko reaction. For this reason the exact ratio of equilibration of the aldol adducts cannot be determined. This retro aldol reaction was monitored by NMR experiments and works with reaction rates similar to those of the Tishchenko reaction.

• By deploying racemic and diastereomeric mixtures of starting aldol adducts (R^2 = Et, *i*Pr) Tishchenko products can be obtained with high degrees of enantio- and diastereoselectivities (ee's up to 80−88%, de = 100%). A full equilibration by retro aldol reactions can be observed during these reactions.

• When used with oxygen-functionalized optically pure aldol adducts the aldol-Tishchenko products were isolated as a single stereoisomer (de = 100%, ee = 100%). An equilibration of the starting aldol adducts could not be detected under these reaction conditions. These transformations offer a simple access to chiral stereotetrads and stereopentads of aliphatic and enolizable aldehydes.

Further investigations on catalytic execution and determination of structure of titanium complexes are in progress.

Experimental Section

Starting Materials. The deployed aldol adducts **2a**−**k** were synthesized by aldol reactions in the presence of $TiCl_4$[19] or $TiCl_4$/Et_3N.[20]

(1*R*,2*R*,3*R*)-1-Cyclohexyl-3-hydroxy-2-methyl-pentyl Cyclohexanecarboxylate (3a) and (1*R*,2*S*,3*R*)-1-Cyclohexyl-3-hydroxy-2-methyl-pentyl Cyclohexanecarboxylate (4a). Ti(O*t*Bu)$_4$ (2.0 mL, 5.0 mmol), cinchonine (1.5 g, 5.0 mmol) and (*R*)-BINOL (1.4 g, 5.0 mmol) were dissolved in dry dichloromethane and stirred for 2−3 h at rt. The solvents were removed in vacuo, and the residue was co-evaporated three times with dry toluene. The remaining brown-orange solid was dissolved in 20 mL of dry dichlormethane. Next, 990 mg of aldol adduct **2a** (5.0 mmol) and 6.0 mL of freshly distilled cyclohexanecarboxaldehyde **1a** (50.0 mmol) were dissolved in 20.0 mL of CH_2Cl_2 under inert conditions. This solution was carefully added to the prepared titanium(IV) complex. The reaction was continuously monitored by thin layer chromatography. At the end of the reaction, the reaction mixture was diluted with diethylether, filtered over Celite, and extracted successively by saturated

(16) For similar equilibrations in the propionate series during aldol-Tishchenko reactions see the following. (a) Total synthesis of rapamycin: Yang, W.; Digits, C. A.; Hatada, M.; Narual, S.; Rozamus, L. W.; Huestis, C. M.; Wong, J.; Dalgarno, D.; Holt, D. A. *Org. Lett.* **1999**, *1*, 2033–2035. (b) Intramolecular aldol-Tishchenko reaction in the total synthesis of octalactine: Aird, J. I.; Hulme, A. N.; White, J. W. *Org. Lett.* **2007**, *9*, 631–634.

(17) (a) Reutrakul, V.; Jaratarooonphong, J.; Tuchinda, P.; Kuhakarn, C.; Kongsaeree, P.; Prabpai, S.; Pohmakotr, M. *Tetrahdron Lett.* **2006**, *47*, 4753–4757. (b) Schneider, C.; Klapa, K.; Hansch, M. *Synlett* **2005**, 91–94.

(18) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.

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(20) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049.

aqueous NH_4Cl and $NaHCO_3$ solution. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexane/EtOAc) to give pure product **3a** (420 mg, 27%) and **4a** (265 mg, 17%) as a colorless oil. **3a**: R_f 0.7 (8:2 hexane/EtOAc); ^{1}H NMR δ 4.84 (dd, 1H, J = 1.1, 9.4 Hz), 3.52 (br, 1H, OH), 2.86 (m, 1H), 2.26 (ddq, 1H, J = 3.8, 7.2, 11.3 Hz), 1.02−1.86 (m, 25H), 0.87 (t, 3H, J = 7.2 Hz), 0.71 (d, 3H, J = 7.2 Hz); ^{13}C NMR δ 177.4, 77.3, 72.7, 43.4, 39.3, 38.4, 29.5, 29.2, 28.9, 28.6, 26.4, 26.0, 25.6, 25.5, 25.4, 25.3, 25.2, 9.7, 9.3; HRMS (ESI) calcd for $C_{19}H_{34}O_3Na$ 333.2406, found 333.2401. **4a**: R_f 0.6 (8:2 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.75 (dd, 1H, J = 3.8, 8.9 Hz, CH), 3.40 (ddd, 1H, J = 1.5, 5.3, 7.2 Hz, CH), 2.36 (ddq, 1H, J = 3.6, 7.0, 7.5 Hz), 1.97−1.04 (m, 24H, CH_2, CH_{cHex}, $CH_{2,cHex}$), 0.91 (t, 3H, J = 7.4 Hz, CH_3), 0.83 (d, 3H, J = 6.8 Hz, CH_3); ^{13}C NMR (75 MHz) δ 177.2, 79.3, 71.3, 43.6, 38.5, 35.5, 30.3, 29.3, 29.2, 28.7, 26.9, 26.1, 26.0, 25.7, 25.6, 25.4, 25.3, 11.0, 8.7; HRMS (EI) calcd for $C_{19}H_{34}O_3$ 310.2508, found 310.2508.

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Supporting Information Available: Details of the procedures, spectral data for all compounds, proof of configuration, corresponding diols and acetonides, spectral data of Mosher esters, and results of X-ray structure analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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