ORGANIC LETTERS

2005
Vol. 7, No. 20
4499−4501

Enantioselective Direct Aldol-Tishchenko Reaction: Access to Chiral Stereopentads

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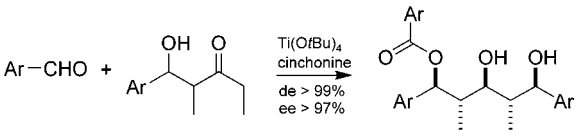
Received July 26, 2005 *(Revised Manuscript Received August 29, 2005)*

ABSTRACT



The aldol-Tishchenko reaction of aromatic aldehydes in the presence of titanium(IV) tertbutoxide and amino alcohols is described. When used with cinchona alkaloids, stereopentads were isolated for the first time with a high degree of diastereo- and enantioselectivity.

Stereochemical control is the most important aspect in the synthesis of organic molecules that contain one or more stereogenic elements. The introduction of new stereogenic centers into a target molecule is most commonly achieved by addition to one face of a double bond. Most synthetic processes involve stereoselective additions of nucleophiles to aldehydes and ketones. Seen from this point of view, the aldol-Tishchenko reaction is a very valuable method with respect to chiral economy.[1]

For classical C−C bond formation there are a number of known limitations. With reactions of carbanions with carbonyl functionalities (aldehydes or ketones), the alkylation of a carbonyl compound can produce only one new stereogenic carbon center. An aldol addition can create two new stereogenic carbon atoms depending on the choice of enolate substituent and the aldehyde or ketone. By means of the Tishchenko reaction, three adjacent stereogenic centers can be obtained. These so-called stereotriads are produced in a single reaction step with an exceptional high degree of diastereoselectivity.

Examples of the enantioselective performance of the aldol-Tishchenko reaction are rare. There are only a limited number of publications describing the enantioselective execution of this important C−C bond formation process.

Early attempts of an asymmetric aldol-Tishchenko reaction were published by Loog and Mäeorg, who observed the self-addition of isobutyraldehyde in the presence of chiral BINOL complexes.[2] Morken et al. described for the first time a successful asymmetric aldol-Tishchenko reaction, catalyzed by an yttrium-salen complex.[3] Addition results were obtained by cross aldol-Tishchenko reactions of isobutyraldehyde with aromatic aldehydes. Mlynarski et al. described aldol-Tishchenko reactions of diethyl ketone with aromatic aldehydes in the presence of chiral lanthanide complexes with moderate enantioselectivities.[4] Schneider et al. used chiral zirconium alkoxides in aldol-Tishchenko reactions[5] and obtained products with moderate enantioselectivities. Recently Shibasaki et al. demonstrated the usefulness of $La(OTf)_3$−BINOL catalysts in enantioselective aldol-Tishchenko reactions of propiophenone and aromatic aldehydes.[6] The Tishchenko stereotriads were isolated by the authors in a high degree of enantioselectivity.

Herein we describe our preliminary results of the enantioselective execution of the aldol-Tishchenko reaction. Inspired by the ligand exchange mediated aldol addition,[7] we were able to determine conditions for an aldol-Tishchenko

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(2) Loog, O.; Mäeorg, U. *Tetrahedron: Asymmetry* **1999**, *10*, 2411−2415.

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

(4) Mlynarski, J.; Jankowska, J.; Rakiel, B. *Tetrahedron: Asymmetry* **2005**, *16*, 1521−1526.

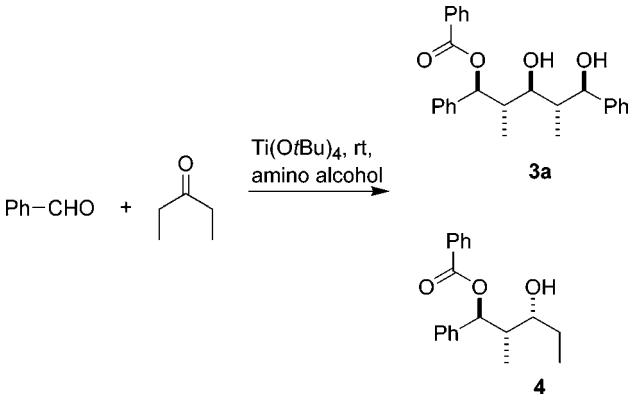
(5) Schneider, C.; Hansch, M. *Synlett* **2003**, 837−841.

(6) Gnanadesikan, V.; Horiuchi, Y.; Oshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7782−7783.

10.1021/ol0517675 CCC: $30.25
Published on Web 09/07/2005

reaction in the presence of titanium(IV) alkoxides and amino alcohols. Initial studies, using diethyl ketone and benzaldehyde in the presence of titanium(IV) isopropoxide and 1,2-amino alcohols, revealed that ligand exchange of titanium(IV) alkoxides and amino alcohols also promote the aldol-Tishchenko reaction. The reactions were carried out at room temperature. The Tishchenko products **4** were isolated with a high degree of diastereoselectivity. In addition, compounds were detected that were produced both by an aldol-Tishchenko reaction and by a second aldol addition. 1,3,5-Triol monoesters **3**, so-called stereopentads, were obtained with a high degree of stereoselectivity (Scheme 1). Different

Scheme 1. Aldol-Tishchenko Reaction in the Presence of Ti(O*t*Bu)$_4$ and Amino Alcohols.



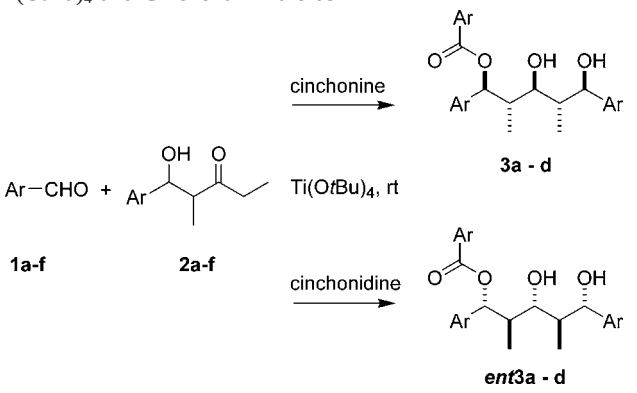
titanium(IV) alkoxides were tested in these reactions. Highest yields were obtained by using titanium(IV) tertbutoxide. Additional byproducts derived from reduction and aldol condensation were observed by application of titanium(IV) alkoxides containing an α-hydrogen.

A variety of amino alcohols are useful for this transformation. Nevertheless, it was observed that only amino alcohols containing a tertiary nitrogen atom are suitable for a clean reaction with satisfactory yields. Further optimization studies revealed that by the use of the corresponding aldol adducts **2a**−**d** as starting compounds, instead of separated aldehydes and diethyl ketone, resulted in higher yields and a cleaner reaction. In addition, by employing cinchona alkaloids as 1,2-amino alcohols the stereopentads **3a**−**d** were isolated with an exceptional high degree of diastereo- and enantioselectivity (Table 1).

A set of substituted aldehydes were tested in these reactions in order to explore scope and limitation of the aldehyde substrate. The use of aromatic aldehydes with electron-withdrawing substituents decreases yields and homogeneity of this reaction (entries 7 and 8, Table 1). No triol monoesters **3** were detected by applying disubstituted aldehydes **1e** and **1f** in these reactions. Best results were obtained by using aldehydes with electron-donating substituents (entries 1−6, Table 1). Access to both enantiomers of

(7) Mahrwald, R. *Org. Lett* **2000**, *2*, 4011−4012. Mahrwald, R.; Ziemer, B. *Tetrahedron Lett*. **2002**, *43*, 4459−4461.

Table 1. Aldol-Tishchenko Reaction in the Presence of Ti(O*t*Bu)$_4$ and Cinchona Alkaloids



entry	Ar	compd	conditions[a]	yield (%)[b]	ee (%)[c]
1	Ph	**3a**	method A	52	>98
2	Ph	***ent*3a**	method B	59	97
3	4-MeOC$_6$H$_4$	**3b**	method A	61	96
4	4-MeOC$_6$H$_4$	***ent*3b**	method B	65	>98
5	4-MeC$_6$H$_4$	**3c**	method A	72	98
6	4-MeC$_6$H$_4$	***ent*3c**	method B	61	>98
7	4-NO$_2$C$_6$H$_4$	**3d**	method A	36	97
8	4-NO$_2$C$_6$H$_4$	***ent*3d**	method B	32	>98
9	2.4-(MeO)$_2$C$_6$H$_3$	**3e**			
10	2.4-Me$_2$C$_6$H$_3$	**3f**			

[a] Method A: 5 equiv of aldehyde, 1 equiv of aldol adduct, 1 equiv of cinchonine, 1 equiv of Ti(O*t*Bu)$_4$, rt. Method B: 5 equiv of aldehyde, 1 equiv of aldol adduct, 1 equiv of cinchonidine, 1 equiv of Ti(O*t*Bu)$_4$, rt. [b] Isolated yields. [c] The enantiomeric excess was determined by ^{1}H NMR analysis of the corresponding Mosher esters.[8]

the stereopentads **3a**−**d** and ***ent*3a**−**d** can be realized by the optional use of cinchonine (Method A) or cinchonidine (Method B) during these reactions (Table 1).[8] Similar high enantioselectivities were detected by using both methods. It is very noteworthy that almost exclusively only one product was formed, although 31 other stereoisomers of the 1,3,5-triol monoester **3** are statistically possible. The 1,3-diol monoesters **4** were found as minor byproducts during these transformations without any enantioselectivity.

These surprising results encouraged us to more intensively analyze the relationship between the stereoselectivities obtained and the configuration of the starting aldol adducts **2a**−**d**. For that reason we reacted defined mixtures of *syn*- and *anti*-configurated aldol adducts **2a**−**d** with an excess of aldehydes in the presence of titanium(IV) tertbutoxide and cinchona alkaloids. The same diastereo- and enantiomeric ratios were obtained in the isolated stereopentads **3a**−**d**, independent of the diastereomeric ratio of the starting aldol adducts **2a**−**d**. These findings verify results we obtained in previously works.[9] They indicate a clean retro-aldol cleavage

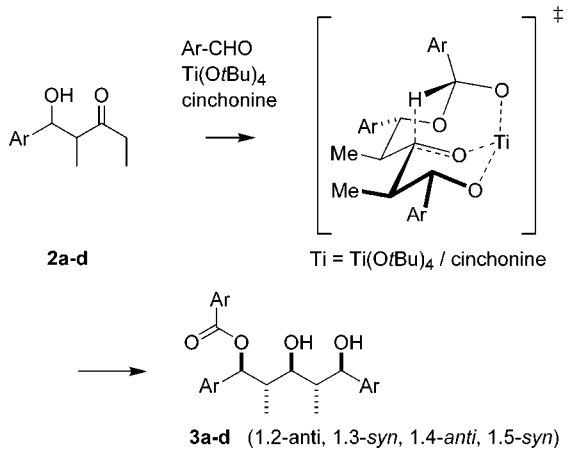
(8) The absolute configuration of the stereopentads **3a**−**d** and ***ent*3a**−**d** were determined by ^{1}H NMR studies using the Mosher ester technique: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092−4096. For a comprehensive review, see: Seco, J. M.; Qinoa, E.; Riguera, R. *Chem. Rev*. **2004**, *104*, 17−118. For more details see Supporting Information.

(9) Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087−1090.

and demonstrate that the control of stereoselectivity is realized during the Tishchenko reaction.[6,9] This seems to be true for both diastereo- and enantioselectivity.

Stereopentads **3a**−**d** were found with a "nonclassical" Tishchenko configuration. An explanation for the exceptional high stereoselectivities is given by the assumption of a tricyclic transition state model as shown in Scheme 2. This

Scheme 2. Proposed Transition State.



is the first report of an enantioselective approach to chiral 1,3,5-triol monoesters by an aldol-Tishchenko reaction. Only two publications appeared so far describing the direct synthesis of racemic stereopentads.[10,11] For the employment of silylenolethers and ketones in Tishchenko reactions see ref 12.

These experiments demonstrate that the ligand exchange of titanium(IV) alkoxides and 1,2-amino alcohols mediate the aldol-Tishchenko reaction. This simple and useful process is applicable to the diastereo- and enantioselective formation of 1,3,5-triol monoesters. Further studies to extend this method to enolizable aldehydes are ongoing.

Acknowledgment. The authors would like to thank the Deutsche Forschungsgemeinschaft for its financial support.

Supporting Information Available: Experimental procedures and characterization of the products by ^{13}C and ^{1}H NMR spectroscopy and mass spectroscopy. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674−5675. The authors isolated and characterized the *rac*-1,2-*anti*, 1,3-*anti*, 1,4-*anti*, 1,5-*anti*-configured 1,3,5-triol monobenzoates by X-ray structure analysis.

(11) Markert, M.; Mahrwald R. *Synthesis* **2004**, 1429−1433. The *rac*-1,2-*syn*, 1,3-*syn*, 1,4-*syn*, 1,5-*anti*-configured 1,3,5-triol monoesters were characterized by X- ray structure analysis.

(12) Delas, C.; Blacque, O.; Moïse, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2265−2270. Delas, C.; Moïse, C. *Synthesis* **2000**, 251−254.