ORGANIC
LETTERS

1999
Vol. 1, No. 9
1427−1429

Simple Metal Alkoxides as Effective Catalysts for the Hetero-Aldol–Tishchenko Reaction

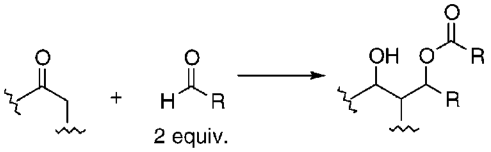
**Cheryl M. Mascarenhas, Matthew O. Duffey, Shih-Yuan Liu, and
James P. Morken***

*Department of Chemistry, Venable and Kenan Laboratories,
University of North Carolina, Chapel Hill, North Carolina 27599-3290*

morken@unc.edu

Received August 23, 1999

ABSTRACT

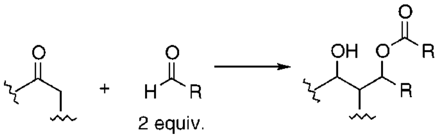


(1)

This paper reports the utility of simple metal alkoxides for the catalytic, stereoselective hetero-aldol–Tishchenko reaction (eq 1). Choice of metal alkoxide is crucial to achieving high efficiency and stereoselectivity. Whereas NaO-*t*-Bu is an effective catalyst, delivering one product in 68% yield and 99:1 stereoselection, $Sm(O\text{-}i\text{-}Pr)_3$ is less effective and delivers the same product in 42% yield with 4:1 stereoselection.

Development of mild and catalytic methods for the stereo- and enantioselective transformation of unactivated functional groups has significant practical implications. In this regard, we are studying the catalytic aldol−Tishchenko reaction (Scheme 1) as a method for production of nonracemic propionate equivalents directly from unmodified carbonyl substrates. By coupling an irreversible Tishchenko reaction to a reversible aldol reaction,[1] the catalytic aldol−Tishchenko reaction provides high product yields from an aldol process while not requiring stoichiometric preactivation of starting material ketone as a metal enolate. Since Nord's work in the 1940s,[2] the homo-aldol−Tishchenko reaction has received considerable attention in the literature;[3] only recently, have studies focused on development of the hetero-aldol−Tishchenko process. In addition to reports on the stoichiometric stereoselective hetero-aldol−Tishchenko reaction,[4] Mahrwald[5] and Fang[6] have reported catalytic reactions employing titanium and samarium catalysts, respectively. Herein, we disclose our preliminary studies with regard to the utility of various metal alkoxides for catalysis of the stereoselective aldol−Tishchenko reaction. These studies reveal the synthetic utility of the alkoxide-catalyzed aldol−Tishchenko reaction and should have consequence for future design of effective chiral catalysts.

Scheme 1



We have been attracted to the seminal observation of Mahrwald and Costisella that n-BuLi/$Ti(O\text{-}i\text{-}Pr)_4$ is effective for the catalytic diastereoselective hetero-aldol−Tishchenko reaction.[5] Our investigation of this catalyst system suggests that lithium isopropoxide, generated from addition of n-BuLi to $Ti(O\text{-}i\text{-}Pr)_4$,[7] is the active constituent when n-BuLi/$Ti(O\text{-}i\text{-}Pr)_4$ is used as the precatalyst. As can be seen in Scheme 2, we have found that LiO-*i*-Pr exhibits reactivity that is comparable to that of n-BuLi/$Ti(O\text{-}i\text{-}Pr)_4$ in hetero-aldol−

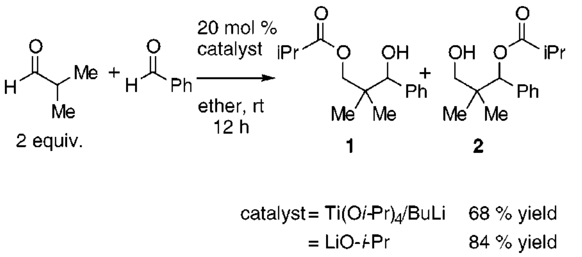
---

[1] For a discussion on the reversibility of the aldol reaction, see: Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, 1991; Vol. 2, pp 133−179.

[2] (a) Kulpinski, M. S.; Nord, F. F. *J. Org. Chem.* **1943**, *8*, 256−270. (b) Villiani, F. J.; Nord, F. F. *J. Am. Chem. Soc.* **1946**, *68*, 1674−1675. (c) Villiani, F. J.; Nord, F. F. *J. Am. Chem. Soc.* **1947**, *69*, 2605−2608.

10.1021/ol990246c CCC: $18.00

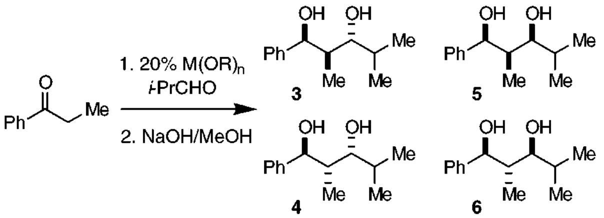
Scheme 2



Tishchenko reactions.[8] In the presence of 20 mol % LiO-*i*-Pr, isobutyraldehyde is effectively condensed with benzaldehyde to furnish the respective 1,3-diol monoesters **1** and **2** (1:2 ratio) derived from a hetero-aldol−Tishchenko process. Notably, the product yield with LiO-*i*-Pr compares favorably to that when *n*-BuLi/Ti(O-*i*-Pr)$_4$ is used as the catalyst.[9]

To examine the effect of alkoxide metal counterion on reaction efficiency and selectivity, we performed a series of experiments with propiophenone and isobutyraldehyde as reaction substrates (2:1 aldehyde:ketone). As can be seen in Table 1, with 20 mol % catalyst in ether at room temperature, a number of simple metal alkoxides can catalyze or promote the aldol−Tishchenko reaction. The alkali metal and alkaline earth alkoxides tended to be the most efficient out of those alkoxides examined. Under the reaction conditions, the highest degree of stereocontrol was obtained with either commercial LiO-*i*-Pr (99:1) or NaO-*t*-Bu (98:1), which delivers stereoisomer **3** (after ester methanolysis) derived from a net tandem *anti*-aldol/*anti*-Tishchenko reaction. Commercial NaO-*t*-Bu exhibits the highest catalytic efficiency delivering the aldol−Tishchenko product in 68% yield. It merits mention that the 1,2-*syn*-2,3-*anti* isomer is always the major product diastereomer and that low stereoselection results from erosion of 1,2 diastereocontrol: in all cases 1,3 relative stereocontrol is maintained with high fidelity (≥10:1 *anti* [**3** + **4**]:*syn* [**5** + **6**]).

Table 1. Alkoxide-Catalyzed Aldol−Tishchenko Reaction[a]

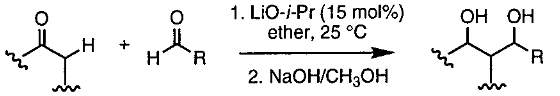


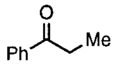
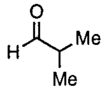
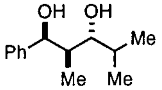
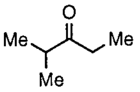
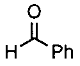
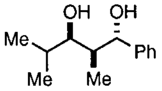
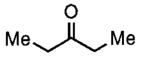
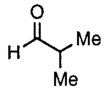
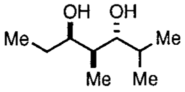
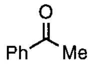
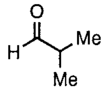
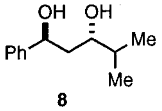
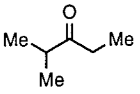
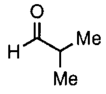
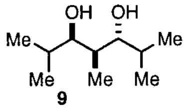
M(OR)$_n$	% Yield major isomer[b]	stereoselection[c] 3	: 4	: 5	: 6
LiO-*i*-Pr (*in situ*)	54	28	1	0.3	0.3
LiO-*i*-Pr (Aldrich)	37	99	1	0.1	0.3
Mg(O-*i*-Pr)$_2$	15	4	1	0.1	0.2
NaO-*t*-Bu	68	98	1	2.2	0.9
La(O-*i*-Pr)$_3$	27	6	1	0.1	0.2
Sm(O-*i*-Pr)$_3$	23	4	1	0.1	0.2
Zr(O-*t*-Bu)$_4$	14	5	1	0.2	0.2
Yb(O-*i*-Pr)$_3$	6	2	1	0.1	0.2
Cu(O-*i*-Pr)$_2$	8	49	1	<0.1	<0.1
Zn(O-*t*-Bu)$_2$	7	19	1	0.5	<0.1
Ca(OMe)$_2$	5	32	1	0.5	0.5
Al(O-*t*-Bu)$_3$	0		———		

[a] Reaction conditions: 2 equiv of aldehyde, 1 equiv of ketone, 20 mol % catalyst, 12 h. [b] Determined by ^{1}H NMR spectroscopy versus an internal standard. [c] Stereoselectivity determined by GLC (HP1701 column) in comparison to authentic material.

To explore the synthetic utility of the alkoxide-catalyzed aldol−Tishchenko reaction, a number of ketone and aldehyde substrates were examined with LiO-*i*-Pr as the catalyst (15 mol % catalyst derived from *n*-BuLi and 2-propanol; 3:1 aldehyde:ketone). As shown in Table 2 (product configuration determined unambiguously), efficient and stereoselective catalytic conversion can be achieved with aromatic and nonaromatic ethyl ketones. With ethyl ketones, 2-substituted-1,3-diols are obtained in moderate yield and good selectivity

Table 2. Utility of Catalytic Hetero-Aldol−Tishchenko Reaction[a]



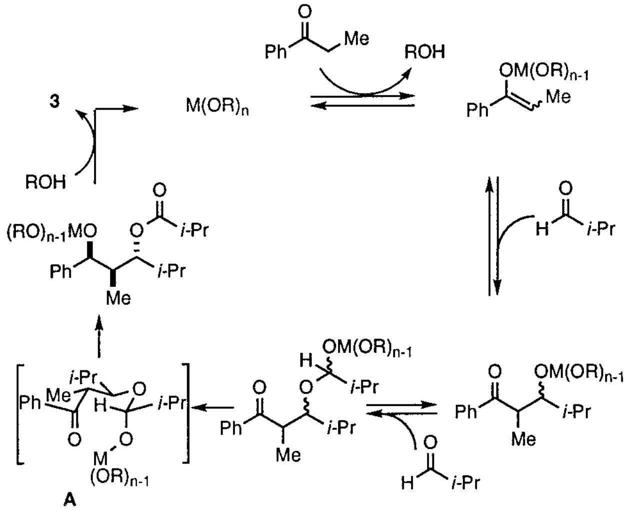
entry	Carbonyl	Aldehyde	Product[b]	Yield (%)[c]	d.r.[d]
1			 **3**	74	96:4
2			 **4**	45[e]	6:1
3			 **7**	61	5:1
4[f]			 **8**	29[g]	>95:5
5			 **9**	55	>95:5

[a] Reaction conditions: 3 equiv of aldehyde, 1 equiv of ketone, 15 mol % catalyst, 14 h. [b] Identity of major product established by comparison to authentic materials. [c] Isolated yield after purification by column chromatography. [d] Diastereoselection determined by GLC (HP1701 column) or ^{1}H NMR spectroscopy. [e] Remaining mass balance is unconverted starting material. [f] Reaction carried out with 20 mol % Mg(O-*i*-Pr)$_2$ as catalyst. [g] Remainder of mass balance is homotrimer derived from iso butyraldehyde aldol−Tishchenko reaction.

from the aldol−Tishchenko reaction/hydrolytic workup sequence. While most efficient product formation occurs with propiophenone as the substrate (entry 1), aliphatic ketones also provide useful product yields with selectivity ranging from 5:1 (entry 3) to >20:1 (entry 5). Notably, hetero-aldol−Tishchenko reactions, with nonsymmetric aliphatic ketones (entries 2 and 5), result in product formation with high regiocontrol: C−C bond formation occurs exclusively at the less substituted α-carbon. Low product yields result from methyl ketones with lithium isopropoxide catalyst (data not shown); in this case, ^{1}H NMR analysis of the unpurified reaction mixture indicates that the major product arises from aldol condensation. Although product yield is still low (29%, entry 4), competitive aldol condensation is avoided when Mg(O-*i*-Pr)$_2$ is employed as the reaction catalyst. In accord with Table 1, Mg(O-*i*-Pr)$_2$ is able to deliver reaction product **8** with good 1,3 relative stereocontrol.

On the basis of previously proposed reaction mechanisms,[4c,d,5,6] a plausible catalytic cycle for the stereoselective formation of 1,3-glycol monoesters is depicted in Scheme 3 and may account for our observed lack of selectivity with certain metal alkoxide catalysts. Mahrwald has elegantly shown that in the catalytic reaction with *n*-BuLi/Ti(O-*i*-Pr)$_4$ as the catalyst, an initial reversible aldolization step is likely followed by rate- and stereochemistry-determining Tishchenko reduction through the Evans−Tishchenko[10] transition state (**A**, Scheme 3). We expect that when LiO-*i*-Pr is used as the catalyst, a similar kinetic profile is operative and thereby provides reaction product in high stereoselectivity. It is reasonable to expect that with less selective catalysts, erosion of 1,2 stereocontrol results from a change in reaction kinetics such that the hydride transfer step is accelerated relative to the rate of retroaldol transformation. In such cases the aldol step becomes rate-determining and the Tishchenko reaction no longer controls product configuration. This observation is critical to the future design of enantioselective aldol−Tishchenko reactions where one wishes to use chiral catalysts that are designed to prohibit reaction through one of the enantiomeric Evans−Tishchenko transition structures.

Scheme 3



Acknowledgment. The authors thank the donors of the Petroleum Research Fund administered by the American Chemical Society for partial support and to Amoco Chemicals for unrestricted research funding. J.P.M. acknowledges receipt of an NSF CAREER award, a Packard Foundation Fellowship, and a DuPont Young Professor Grant.

Supporting Information Available: Characterization data for all compounds and experimental details are available. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990246C

---

(3) For representative examples of homo-aldol−Tishchenko reactions, see: (a) Casnati, G.; Pochini, A.; Salerno, G.; Ungaro, R. *Tetrahedron Lett.* **1974**, 959−962. (b) Fouquet, G.; Merger, F.; Platz, R. *Liebigs Ann. Chem.* **1979**, 1591−1601. (c) Villacorta, G.; San Filippo, J. *J. Org. Chem.* **1983**, *48*, 1151−1154. (d) Okano, T.; Satou, Y.; Tamura, M.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1879−1885. (e) Miyano, A.; Tashiro, D.; Kawasaki, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1998**, *39*, 6901−6902.

(4) For stoichiometric, stereoselective aldol−Tishchenko reactions, see: (a) Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317−318. (b) Baramee, A.; Chaichit, N.; Intawee, P.; Thebtaranonth, C.; Thebtaranonth, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1016−1017. (c) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674−5675. (d) Abu-Hasanayn, F.; Streitwieser, A. *J. Org. Chem.* **1998**, *63*, 2954−2960.

(5) Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087−1089.

(6) Lu, L.; Chang, H. Y.; Fang, J. M. *J. Org. Chem.* **1999**, *64*, 843−853.

(7) For an analogous stoichiometric reaction of Ti(O-*n*-Pr)$_4$ with BuMgCl to generate Ti(III) and, presumably, *n*-PrOMgCl, see: Herman, D. F.; Nelson, W. K. *J. Am. Chem. Soc.* **1953**, *75*, 3882−3887.

(8) With certain substrates, we do notice subtle differences in selectivity when LiO-*i*-Pr is used versus *n*-BuLi/Ti(O-*i*-Pr)$_4$. This may be attributed to the presence of Ti(IV) alkoxides.

(9) Calculated yield with Ti(O-*i*-Pr)$_4$/BuLi as catalyst assumes that 0.2 equiv of benzaldehyde is converted to stilbene diol (which can be isolated from these experiments) in accord with a pinacol reaction mediated by titanium that has been reduced according to ref 7.

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