J|A|C|S
COMMUNICATIONS

Published on Web 05/24/2005

Direct Asymmetric Zn−Aldol Reaction of Methyl Vinyl Ketone and Its Synthetic Applications

Barry M. Trost,* Seunghoon Shin, and Joseph A. Sclafani

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received March 9, 2005; E-mail: bmtrost@Stanford.edu

The aldol reaction is one of the most widely utilized C−C bond-forming reactions in organic chemistry, because of the importance of β-hydroxy carbonyl compounds in many natural products.[1] Recently, several groups have reported a direct catalytic enantioselective version without resorting to preactivation of the pronucleophile using biological catalysts[2a−g] and nonbiological transition-metal catalysts,[2h−j] including our own dinuclear Zn complex **2**.[2h,3] Typically, however, successful donors have included simple ketones, such as methyl, and hydroxylmethyl ketones, and limited progress has been made in catalytic enantioselective aldol reactions of more functionalized or functionalizable nucleophiles, such as methyl vinyl ketone (MVK). Enantioenriched β-hydroxyketones derived from MVK are particularly interesting, because stereocenters created in the aldol reactions can be propagated further in a sequence of highly diastereoselective transformations, where MVK functions as a bifunctional building block (Scheme 1).

Despite tremendous synthetic potential,[4] base instability of MVK and its aldol products has hampered its development.[5] To the best of our knowledge, there is no general asymmetric aldol reaction of MVK reported to date. Herein we report an atom-economical and direct route to the hydroxy ketones from MVK as well as synthetic applications of resulting hydroxy enones.

Initially, on the basis of the promising catalytic activity displayed by dinuclear Zn complex **2**,[3] we set out to examine the reaction of MVK as an aldol donor. The precataylst was prepared as previously reported by treating ligand **1** with 2 equiv of Et_2Zn in THF at RT. Subjection of this precatalyst (10 mol %) to a mixture of MVK, cyclohexane carboxaldehyde, 4Å molecular sieve, and isopropyl alcohol (5 equiv) in THF at −35 °C led to irreproducible yields of the desired aldol product (10−30%) and dehydration product, resulting from removal of the β-hydroxy stereocenter (60−80%). Although the reaction was highly enantioselective (90−95% ee), the product profile was time dependent, and more dehydration byproduct formed upon longer reaction time. The effect of additives and change of reaction parameters (temperature/time) did not much improve the result. On the other hand, we found that there is significant negative nonlinear effect in accord with an aggregation effect (see Figure 1).[6]

Along this line, the effect of concentration and solvent was examined. Gratifyingly, we observed an improved yield of the desired aldol addition vs elimination (entry 1, Table 1) with excellent enantioselectivity by using an increased concentration of MVK. Catalyst (10 mol %) prepared in THF or toluene (0.5 mL) was added to a combination of freshly distilled MVK (1 mL), cyclohexane carboxaldehyde (0.5 mmol), *i*-PrOH (5 equiv), and 4Å molecular sieve. The reaction was generally faster in THF (Method A, Table 1) than in toluene (Method B), although toluene had better control over the elimination problem. As shown in Table 1, a variety of aliphatic aldehydes led to the corresponding β-hydroxy vinyl ketones in reproducible yields and high enantioselectivities. In the case of α- or β-hydroxyaldehydes, the presence

Scheme 1. Utility of Zn−Aldol Addition

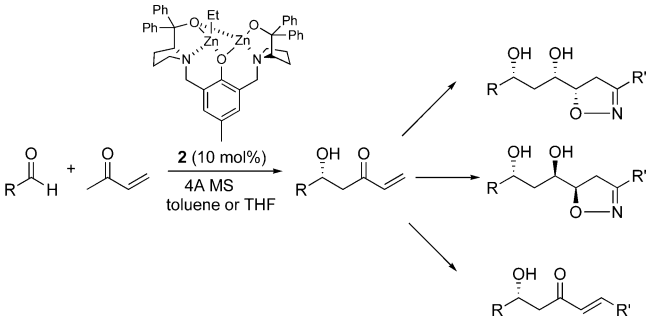
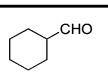
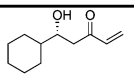
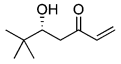
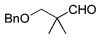
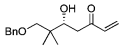
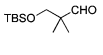
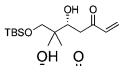
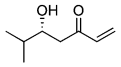
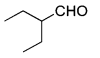
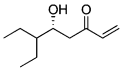
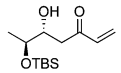
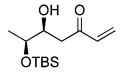
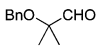
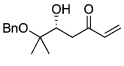
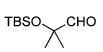
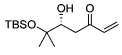
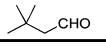
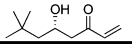


Table 1. Reactions of Various Aldehydes

entry	RCHO	method	temp /time (h)	yield[a] (%)	Ee[b] (%)	product
1		A B	-35/48 -25/21	53 56	92 91	
2		A B	-30/48 -15/7	57 74	77 86	
3		A B	-30/48 -15/22	64 46	83 87	
4		A B	-15/8 -15/14	52 66	93 92	
5		A B	-35/36 -20/10	51 56	90 91	
6		A B	-35/36 -20/10	47 37	83 85	
7a		B	-15/17	59	>99 de	
7b		B	-15/18	33	71 de	
8		B	-15/15	33	44	
9		B	-15/14	50	91	
10		A	-35/36	49	98	

[a] All yields are for isolated pure product. [b] The ee's were determined by chiral HPLC.

of bulkier, noncoordinating silyl protecting group seem to give better turnover as well as better chiral recognition (entry 3 vs 4 and entry 8 vs 9). Entry 7 deals with the issue of catalyst-controlled diastereoselectivity. In a matched case (entry 7a), exclusive Felkin−Anh product (1,2-*anti*-diol) was obtained with excellent selectivity and good yield, where intrinsic bias is reinforced by the catalyst in the same direction. In a mismatched case (entry 7b), 1,2-*syn*-diol formed with catalyst-controlled diastereoselectivity (dr 6/1) in modest yield. Some β-branched aldehydes can also be employed

10.1021/ja051526s CCC: $30.25

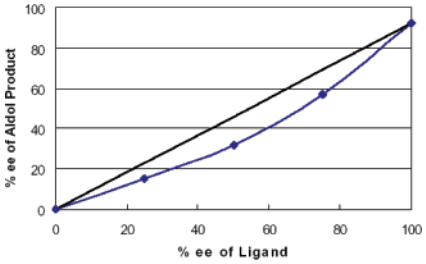


Figure 1. Nonlinear effect (% ee of aldol product vs % ee of ligand **1**).

Chart 1. Cycloaddition Partners

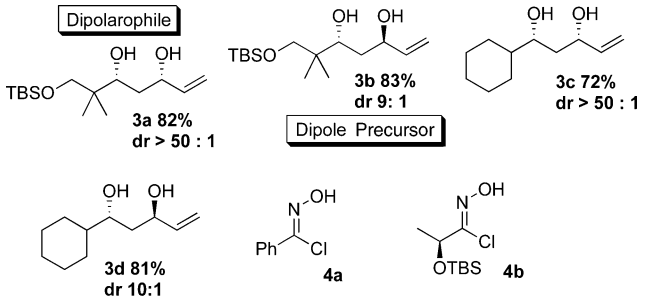
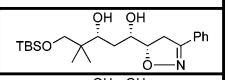
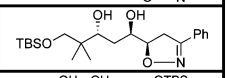
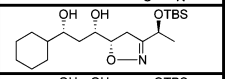
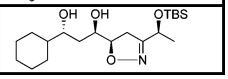


Table 2. Mg-Mediated Cycloaddition of Nitrile Oxide

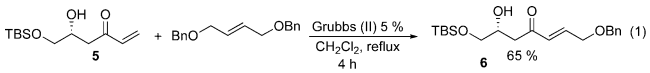
Dipolaro-phile	dipole	condition	yield(dr)[a]	product
3a	**4a**	-25 °C, 10 h	59 % (>95:5)	
3b	**4a**	-20 °C, 9 h	71 % (>95:5)	
3c	**4b**	-25 °C, 11 h	69 % (>95:5)	
3d	**4b**	-30 °C, 18 h	60 % (>95:5)	

to give modest yield and excellent % ee (entry 10), although α-branched aliphatic aldehydes gave better results.

We envisioned propagation of the existing stereocenter created in the aldol addition through successive highly diastereoselective transformations. The obtained *β*-hydroxy enones were diastereoselectively reduced to 1,3-*syn*- (dr > 99:1) or 1,3-*anti*-diols (dr > 90:10) in excellent yields using $Et_2B(OMe)/NaBH_4$ and $Me_4NBH(OAc)_3$, respectively (Chart 1).[6,7] These diols were used directly without protection in a Mg-mediated diastereoselective cycloaddition of nitrile oxide.[8] When the 1,3-diols were treated with 3 equiv of EtMgBr in CH_2Cl_2 followed by a preformed solution of a nitrile oxide at −25 °C, the corresponding dihydro-isoxazoles formed smoothly in excellent diastereoselectivities and good yields (Table 2). Notably, the obtained diastereoselectivity depends only on the stereocenter of the allylic alcohol in the dipolarophile, and stereocenters elsewhere had no stereo-directing effect, thus providing an effective method for convergent fragment coupling.

In contrast to alkynylmethyl ketones,[3d] vinylmethyl ketone donors require their use in excess, thus necessitating readily available donors. Resolution of this issue resides in the recent developments in the cross-metathesis reaction which allows a liberal modification on the terminal olefin end also reinforcing the bifunctionality of MVK as a synthetic building block.[9] As shown in eq 1, the desired vinyl-modified ketone **6** was obtained from **5** in 65% yield with excellent *E*/*Z* selectivity (>15:1).

In conclusion, we have demonstrated dinuclear Zn complex **2** catalyzes the aldol reaction of methyl vinyl ketone in good yield and excellent % ee. The resulting product could be transformed



via stereoselective reactions into a variety of useful intermediates, showcasing MVK as a useful bifunctional building block.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences (GM-13598), for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California-San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental procedures for the preparation of new compounds as well as characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, UK, 1991; Vol. 2. (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, p 998. (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (d) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (e) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.

(2) For biological catalysts, see (a) Wong, C.-H. *Enzyme Catalysis in Organic Synthesis*, 2nd ed. Drauz, K, Waldmann, H., Eds.; Wiley-VCH: New York, 2002; Vol. 2, p 931. (b) Curtis, A. D. M. *Biotechnology* **2000**, *8b*, 5. (c) Matsumoto, K.; Shimagaki, M.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1993**, *34*, 4935. (d) Bednarski, M. D.; Simon, E. S.; Bischofberger, N.; Fessner, W.-D.; Kim, M.-J.; Lees, W.; Saito, T.; Waldmann, H.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 627. (e) Fessner, W.-D.; Sinerius, G.; Schneider, A.; Dreyer, M.; Schulz, G. E.; Badia, J.; Aguilar, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 555. (f) List, B.; Shabat, D.; Barbas, C. F., III; Lerner, R. A. *Chem. Eur. J.* **1998**, *4*, 881. (g) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2768. For nonbiological catalyst, see: (h) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (i) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (j) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539.

(3) For aldol reactions: (a) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (b) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497. (c) Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513. (d) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660. Henry reactions: (e) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861. (f) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621. Mannich-type reactions: (g) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. Diol desymmetrization: (h) Trost, B. M.; Mino, T. *J. Am. Chem. Soc.* **2003**, *125*, 2410.

(4) (a) Joo, J. M.; Kwak, H. S.; Park, J. H.; Song, J. H.; Lee. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1905. (b) Trost, B. M.; Hanson, P. R. *Tetrahedron Lett.* **1994**, *35*, 8119. (c) Boukouvalas, J.; Fortier, G.; Radu, I.-I. *J. Org. Chem.* **1998**, *63*, 916.

(5) One account was described on Mukaiyama-type aldol reaction of MVK where instability was noted for the adduct derived from benzaldehyde and MVK: Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837. However, for a successful reaction using lanthanides, see: Hong, B. C.; Chin, S.-F. *Synth. Commmun* **1997**, *27*, 1191. Antibody-catalyzed retro-aldol reaction (kinetic resolution) of racemic *β*-hydroxy ketone has recently been published. However, no enantioselectivity was observed for *β*-hydroxy ketone derived from MVK: Baker-Glenn, C.; Hodnett, N.; Reiter, M.; Ropp, S.; Ancliff, R.; Gouverneur, V. *J. Am. Chem. Soc.* **2005**, *127*, 1481.

(6) See Supporting Information for details.

(7) (a) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1994**, *28*, 155. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(8) (a) Kanemasa, S.; Masaki, N.; Kamimira, A.; Kenzi, H. *J. Am. Chem. Soc.* **1994**, *116*, 2324. (b) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082.

(9) For cross metathesis, see: (a) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

JA051526S