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

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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 pre-activation of the pronucleophile using biological catalysts[2a–g] and non-biological 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). Enantio-enriched 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 pre-cataylst was prepared as previously reported by treating ligand **1** with 2 equiv of Et_2Zn in THF at RT. Subjection of this pre-catalyst (10 mol %) to a mixture of MVK, cyclohexane carboxaldehyde, 4A molecular sieve, and *i*-propanol (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 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.[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 4A molecular sieve. The reaction was generally faster in THF or (Method A, table 1) than in toluene (Method B), though 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 of bulkier,

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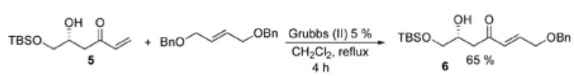
non-coordinating silyl protecting group seem to give better turnover as well as better chiral recognition (entry 3 vs. 4 and entry 8 vs. 9). Entry 7 deals with the issue of catalyst-controlled diastereo-selectivity. In a matched case (entry 7a), exclusive Felkin-Anh product (1,2-*anti*-diol) was obtained 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 7/1) in modest yield. Some β-branched aldehydes can also be employed to give modest yield and excellent % ee (entry 10), though α-branched aliphatic aldehydes gave better results. As shown in Fig. 1, the reaction shows a slight negative non-linear effect.

We envisioned propagation of the existing stereocenter created in the aldol addition through successive highly diastereoselective transformations. The obtained β-hydroxy enones were diastereo-selectively 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 pre-formed 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 effective method for convergent fragment coupling.

In contrast to alkynylmethyl ketones,[3e] 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).



(1).

In conclusion, we have demonstrated dinuclear Zn-complex **2** catalyze 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References

1. Roush, WR. Comprehensive Organic Synthesis. Trost, BM.; Fleming, I.; Heathcock, CH., editors. 2. Pergamon; Oxford, U.K: 1991. Carreira, EM. Comprehensive Asymmetric Catalysis. Jacobsen, EN.; Pfaltz, A.; Yamamoto, H., editors. 3. Springer; Heidelberg: 1999. p. 998 (c) Yamamoto Y, Asao N.

Chem Rev 1993;93:2207. (d) Marshall JA. Chem Rev 1996;96:31. [PubMed: 11848743] (e) Mahrwald R. Chem Rev 1999;99:1095. [PubMed: 11749441]

2. For biological catalysts, see (a)WongC-HEnzyme Catalysis in Organic Synthesis220022931 (b) Curtis ADM. Biotechnology 2000;8b:5. (c) Matsumoto K, Shimagaki M, Nakata T, Oishi T. Tetrahedron Lett 1993;34:4935. (d) Bednarski MD, Simon ES, Bischofberger N, Fessner WD, Kim MJ, Lees W, Saito T, Waldmann H, Whitesides GM. J Am Chem Soc 1989;111:627. (e) Fessner WD, Sinerius G, Schneider A, Dreyer M, Schulz GE, Badia J, Aguilar J. Angew Chem, Int Ed 1991;30:555. (f) List B, Shabat D, Barbas CF III, Lerner RA. Chem Eur J 1998;4:881. (g) Hoffmann T, Zhong G, List B, Shabat D, Anderson J, Gramatikova S, Lerner RA, Barbas CF III. J Am Chem Soc 1998;120:2768.. For non-biological catalyst, see (h) Trost BM, Ito H. J Am Chem Soc 2000;122:12003. (i) List B, Lerner RA, Barbas CF III. J Am Chem Soc 2000;122:2395. (j) Kumagai N, Matsunaga S, Yoshikawa N, Ohshima T, Shibasaki M. Org Lett 2001;3:1539. [PubMed: 11388861]

3. For aldol reactions: (a) Trost BM, Ito H, Silcoff ER. J Am Chem Soc 2001;123:3367. [PubMed: 11457073] (b) Trost BM, Silcoff ER, Ito H. Org Lett 2001;3:2497. [PubMed: 11483044] (d) Trost BM, Yeh VSC. Org Lett 2002;4:3513. [PubMed: 12323057] (e) Trost BM, Fettes A, Shireman BT. J Am Chem Soc 2004;126:2660. [PubMed: 14995157] Henry reactions: (f) Trost BM, Yeh VSC. Angew Chem Int Ed 2002;41:861. (g) Trost BM, Yeh VSC, Ito H, Bremeyer N. Org Lett 2002;4:2621. [PubMed: 12153193]Mannich-type reactions: (h) Trost BM, Terrell LR. J Am Chem Soc 2003;125:338. [PubMed: 12517138]Diol desymmetrization: (i) Trost BM, Mino T. J Am Chem Soc 2003;125:2410. [PubMed: 12603126]

4. (a) Joo JM, Kwak HS, Park JH, Song JH, Lee E. Bioorg Med Chem Lett 2004;14:1905. [PubMed: 15050624] (b) Trost BM, Hanson PR. Tetrahedron Lett 1994;35:8119. (c) Boukouvalas J, Fortier G, Radu II. 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 SE, Stavenger RA. J Am Chem Soc 2000;122:8837. However, for a successful reaction using lanthanides see Hong BC, 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. [PubMed: 15686381]

6. See Supporting Information for details.

7. (a) Chen KM, Hardtmann GE, Prasad K, Repic O, Shapiro MJ. Tetrahedron Lett 1994;28:155. (b) Evans DA, Chapman KT, Carreira EM. 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 JW, Fraefel N, Muri D, Carreira EM. Angew Chem Int Ed 2001;40:2082.

9. For cross metathesis, see (a) Connon SJ, Blechert S. Angew Chem, Int Ed 2003;42:1900. (b) Chatterjee AK, Morgan JP, Scholl M, Grubbs RH. J Am Chem Soc 2000;122:3783. (c) Chatterjee AK, Choi TL, Sanders DP, Grubbs RH. J Am Chem Soc 2003;125:11360. [PubMed: 16220959]

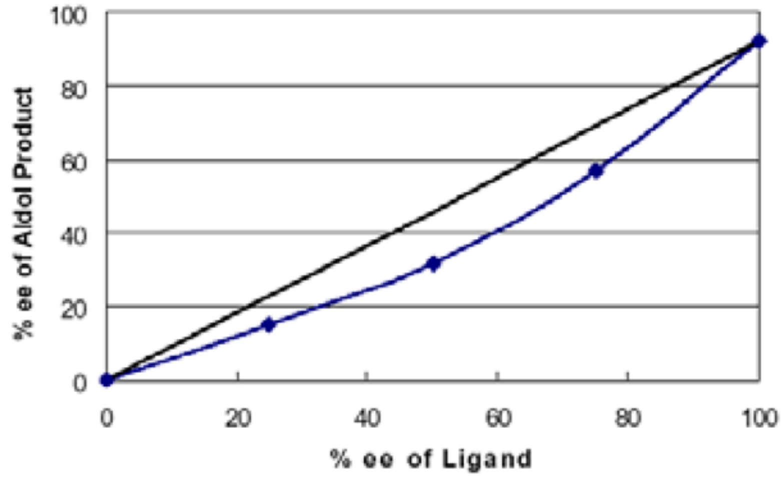
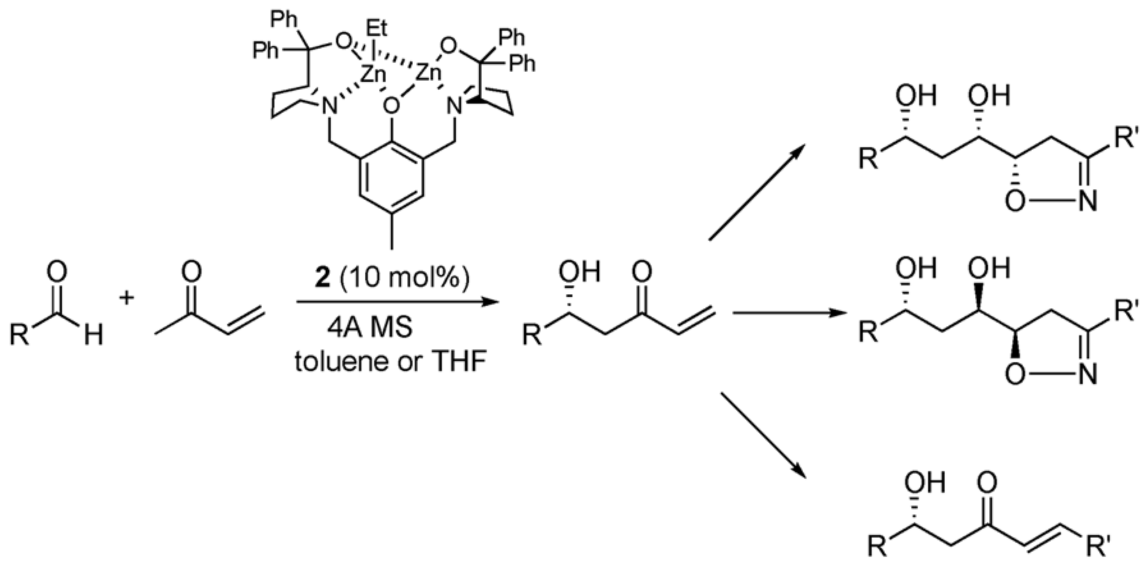


Fig. 1.
Non-linear Effect (%ee of aldol product vs. % ee of ligand 1



Scheme 1.
Utility of Zn-Aldol Addition

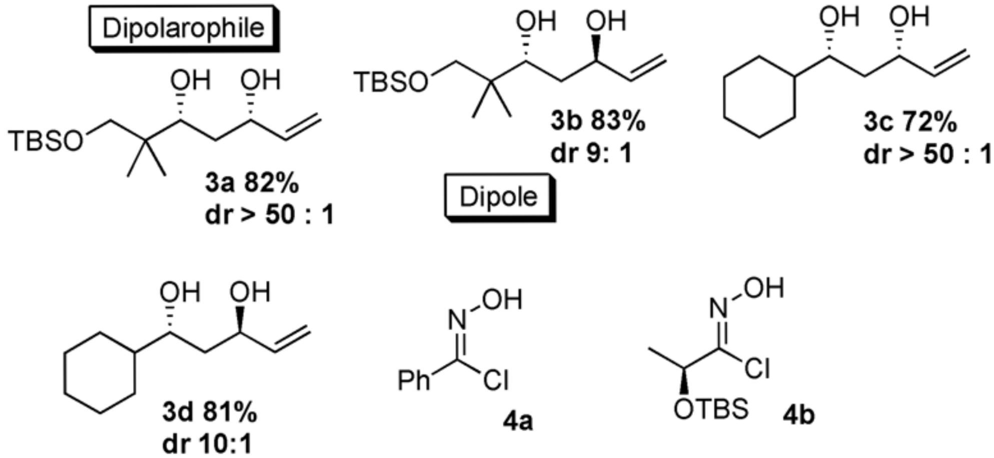
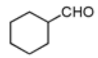
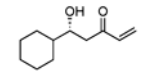
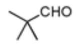
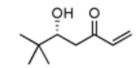
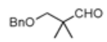
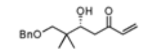
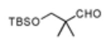
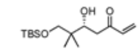
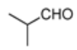
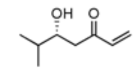
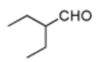
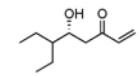
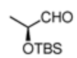
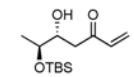
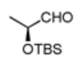
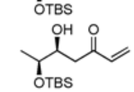
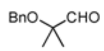
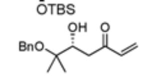
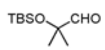
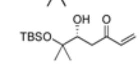
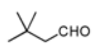
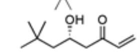


Chart 1.
Cycloaddition Partners

Table 1

Reactions of Various Aldehydes

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

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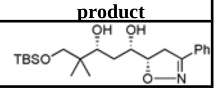
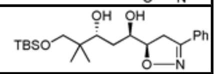
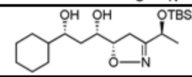
Table 2

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)