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Direct Asymmetric Aldol Reactions of Acetone Using Bimetallic Zinc Catalysts

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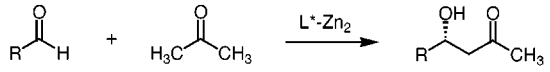
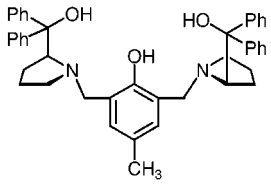
ABSTRACT

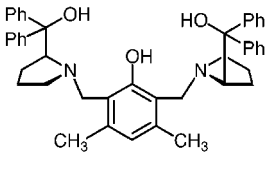


The enantioselective aldol reaction using a novel binuclear zinc catalyst of acetone with several aldehydes gave products in good yields (62–89%) with a high level of enantioselectivity (ee = 76–92%).

The aldol reaction[1] represents a very good example of an atom economic reaction.[2] However, in most cases, the transformation of the active methylene partner stoichiometrically to its enolate or an enol derivative is a necessary drawback.[3] Few examples exist of direct catalytic asymmetric aldol reactions, among them recent work by Shibasaki[4] et al., List[5] et al., and ourselves.[6,7] The work in our laboratories employing acetophenone and hydroxyacetophenone appears to involve two zincs organized in a chiral space by reacting diethylzinc with phenol **1**. Previous work has highlighted some of the difficulties in employing α-unbranched aldehydes in such direct aldol addition reactions with acetone and acetophenone.[5a] In this Letter, we explore the ability to use acetone as the active methylene partner, α-unbranched aldehydes as the carbonyl partner, and a second generation ligand **2**[8] in the dinuclear zinc catalyzed reaction.



1



2

The active catalyst **3**, prepared in situ by treatment of ligands **1** or **2** with 2 equiv of diethylzinc (see Scheme 1), involves initiation by liberation of 3 equiv of ethane followed by a fourth by reaction with the active methylene partner (acetone in this case). The chiral space derives from the conformational preferences of the diphenylcarbinol moieties. Thus, the two zincs act in concert to activate each of the two partners.[9]

(1) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 1.5 and 1.6. Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 1.7.

(2) Trost, B. M. *Science* **1991**, *254*, 1471. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(3) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. Mukaiyama, T.; Kobayashi, S. *Org. React.* **1994**, *46*, 1. Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, p 998. Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137.

(4) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466.

(5) (a) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (b) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (c) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

(6) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2000**, *123*, 3367.

(7) For a review of biological methods, see: Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. For leading references on the use of catalytic antibiotics, see: Turner, J. M.; Bui, T.; Lerner, R. A.; Barbas, C. F., III; List, B. *Chem. Eur. J.* **2000**, 2772. List, B.; Shabat, D.; Barbas, C. F., III; Lerner, R. A. *Chem. Eur. J.* **2000**, 881.

(8) Made from the known 2,6-di(hydroxymethyl)-3,5-dimethylphenol (Fitzgerald, J. S. *J. Appl. Chem.* **1995**, 289. Bertz, S. H. *Synthesis* **1980**, 708. Fahrni, C. J.; Pfaltz, A. *Helv. Chim. Acta* **1998**, *81*, 491**)** by sequential treatment with HBr, proline methyl ester, and phenylmagnesium bromide.

(9) The mechanism is related to the amino alcohol catalyzed asymmetric addition of organozinc reagents to aldehydes, cf. Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 2464.

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Scheme 1. Proposed Catalytic Cycle of the Asymmetric Aldol Reaction

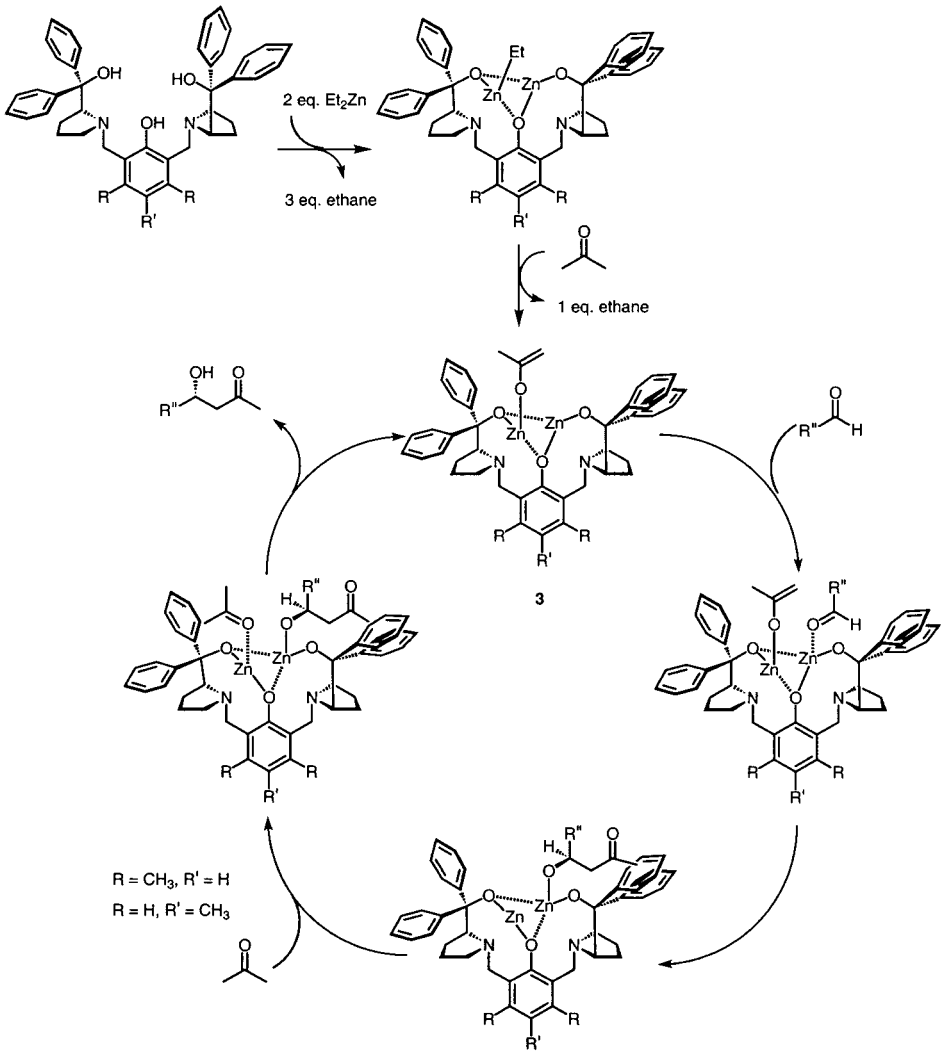
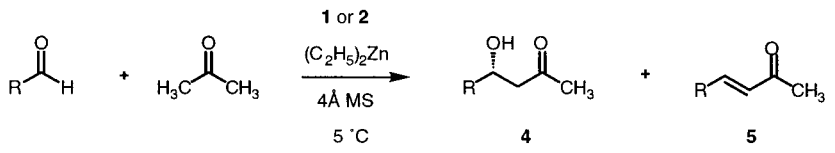


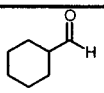
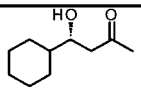
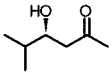
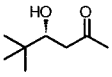
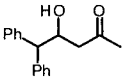
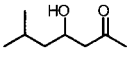
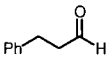
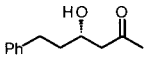
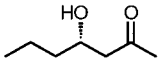
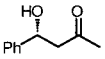
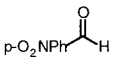
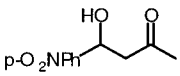
Table 1. Optimization of the Reaction between Acetone and Cyclohexanecarboxaldehyde[a]

entry	ligand	L:$ZnEt_2$	addivite	temp	yield (%)	*ee* (%)
1[b]	10 mol% **1**	1:1	None	0°	39	45
2[b]	10 mol% **1**	1:1	None	r.t.	44	67
3[b]	10 mol% **1**	1:1		0°	74	40
4	10 mol% **1**	1:1	None	r.t.	12	76
5	10 mol% **1**	1:1		r.t.	36	74
6	10 mol% **1**	1:1	4Å MS, 	0	65	78
7	10 mol% **1**	1:1	4Å MS, $(CH_3O)_3PO$ $(CH_3)_2CHOH$	-5°	64	82
8	10 mol% **1**	1:1	4Å MS, Ph_3PS	-8°	64	84
9	10 mol% **2**	1:1	4Å MS, Ph_3PS	-8°	48	86
10	5 mol% **1**	1:2	4Å MS	r.t.	74[c]	54
11	5 mol% **1**	1:2	4Å MS	5°	64	87
12	5 mol% **1**	1:2	4Å MS	-25°	69[c]	89
13	5 mol% **1**	1:2	4Å MS, Ph_3PS	5°	54	87
14	10 mol% **1**	1:2	4Å MS	5°	85	93
15	2.5 mol% **1**	1:2	4Å MS	5°	42	83
16	10 mol% **2**	1:2	4Å MS	5°	89	92
17	10 mol% **2**	1:2	4Å MS, Ph_3PS	5°	70	81

[a] All reactions performed in 10 vol % acetone in THF for 48 h except where noted otherwise. [b] Reaction performed in neat acetone. [c] In addition to 12% of dehydration product obtained.

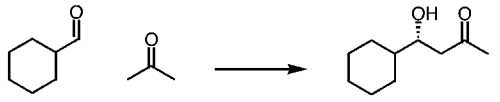
Table 2. Catalytic Asymmetric Aldol Reactions of Acetone with Aldehydes[a]



entry	aldehyde	catalyst	product	ratio **4** / **5**[j]	yield **4** (%)[i]	*ee* (%)
1		1[e]		ONLY 4	62	87
		1[f]		ONLY 4	85	93
		2[f]		ONLY 4	89	92
2		1[e]		ONLY 4	80	87
		2[f]		ONLY 4	89	91
3		1[e]		ONLY 4	76	86
		2[f]		ONLY 4	72	94
4		1[e]		ONLY 4	79	82
		1[f]		ONLY 4	72	87
		2[f]		ONLY 4	84	91
5		1[e]		ONLY 4	24	76
		2[f]		ONLY 4	59	84
6		1[e]		6:1	59	89
		1[f]		1:3	24	89
		2[f]		15:1	76	82
7		1[e]		ONLY 4	56	84
		1[g]		15:1	55	87
		2[f]		ONLY 4	69	89
		2[h]		ONLY 4	72	84
8		1[e]		3:1	55	88
		1[g]		3:1	57	85
		2[e]		ONLY 4	78[b]	83
		2[f]		1:4	12	79
9		1[e]		2:1	36	74
		1[e]		ONLY 4	62[c]	78
		2[f]		8:1	54	76

[a] Standard conditions were 0.5 mmol aldehyde, 0.5 mL of acetone, 100 mg of 4 Å molecular sieves, and the catalyst added as a 0.1 M solution in THF. [b] 82% conversion. [c] 80% conversion. [d] ee's determined by chiral HPLC using chiracell OD or OJ columns. [e] 5% catalyst used. [f] 10% catalyst used. [g] 5% catalyst and 5 equiv (per catalyst) of PPh_3S used. [h] 10% catalyst and 5 equiv (per catalyst) of PPh_3S used. [i] Isolated yield. [j] Determined by ^1H NMR spectroscopy on the crude mixture.

The reaction of acetone with cyclohexanecarboxaldehyde was explored as a test (eq 1). Initial experiments were


(1)

performed using a 1:1 ratio of ligand **1** to diethylzinc (Table 1, entries 1−9). Reactions proceeded bettter in THF than in pure acetone in terms of ee; however, conversions and thus yields were low. Additives such as 4 Å MS, 2-propanol, phosphate, or phosphinethioxide seem to increase rate as reflected in the higher yields. Switching to a 1:2 ratio of ligand to diethylzinc (entries 10−17) in THF did increase conversions within the same time period. Use of 10% gave a yield boost compared to 2.5 and 5 mol % with little effect on ee. Switching to ligand **2** showed little effect (Table 1, entry 14 vs 16). Addition of Ph_3PS slowed the reaction while retaining high ee.

Using 4 Å MS (100 mg per 0.5 mmol of aldehyde) at 0.1 M in THF with 10−15 equiv of acetone at 5 °C as standard conditions, the examples shown in Table 2 were performed with both ligands **1** and **2**.[10] Except for entry 1, somewhat improved results were obtained using ligand **2** over **1** under otherwise identical conditions. For an α-branched aldehyde (Table 2, entry 4), a slight improvement in yield and a significant improvement in ee was obtained. In the difficult cases of α-unbranched and aryl aldehydes, significant improvements arose using ligand **2**. In all cases (entries 5−9), improvements in yields were obtained. In many cases, the improved yields arose because the amount of the elimination product **5** decreased. Attempts to reduce the amount of elimination by adding triphenylphosphine sulfide with ligand **1** (entries 7 and 8) failed. In some cases, the ee's were also higher with ligand **2**, notably entry 5. The absolute configuration in many cases was assigned by comparison to the literature and assumed to be the same in the other cases.[10b]

For α-unbranched aldehyde partners, the catalysts derived from ligands **1** and **2** with 2 equiv of diethylzinc give the best recorded results to date. Using proline with such aldehydes, yields and ee's ranged from 22 to 35% and 36 to 73%, respectively.[3] In the present case for similar aldehyde partners using ligand **2**, yields and ee's range from 59 to 76% and 82 to 89% ee. Furthermore, the results are considerably improved over the use of Ipc-X (X = Cl or OSO_2CF_3) which is required, stoichiometrically, as a chiral auxiliary.[11] More generally, the enantioselectivities observed with acetone are lower than with acetophenone as the aldol donor with branched aldehydes. For example, the ee's for the aldehydes of entries 1, 2, and 4 in their reactions with acetophenone were 98−99%. The absolute configuration with the same ligand is the same for both acetone and acetophenone. A rationale derives from the role the phenyl rings of the diphenylcarbinol moiety play in the chiral recognition (see Scheme 1). The planar aryl rings of acetophenone and related ketones cause less steric distortion of the chiral pocket than the bulk of a tetrahedral carbon such as methyl in the case of acetone. The improved results obtained with ligand **2** over **1** may result from, in the former, minimization of the distortion of the chiral pocket in the case of acetone because of the buttressing effects with the 3,5-dimethyl groups of the phenol ring. It appears this new catalyst will prove more generally useful for the direct aldol reaction.

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Supporting Information Available: Sample experimental procedure and characterization data of aldol adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) New compounds have been fully characterized spectroscopically and elemental composition established by high-resolution mass spectrometry and/or combustion analysis. (b) The absolute configurations of the aldol products of entry 1 [Silverman, I. R.; Edington, C.; Eliott, J. D.; Johnson, W. S. *J. Org. Chem.* **1987**, *52*, 180], entry 2 [ref 5b and 11], entry 3 [ref 11a], entry 6 [Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649], and entries 7 and 8 [ref 11b]. The products of entries 5 (ref 5a) and 9 [Grayson, D. H.; Tuite, M. R. J. *J. Chem. Soc., Perkin Trans. I* **1986**, 2137] are known although the absolute configurations are not identified.

(11) (a) Ramachandran, P. V.; Xu, W.-C.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 4911; (b) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997.