A Direct Catalytic Enantioselective Aldol Reaction via a Novel Catalyst Design

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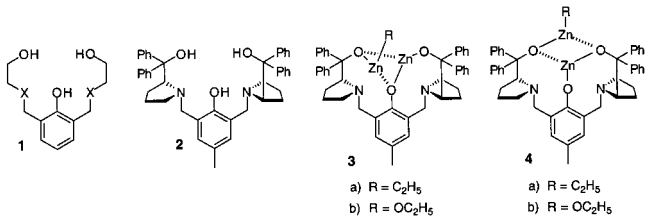
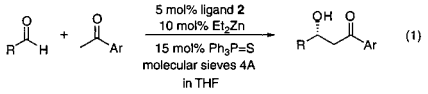
Few chemical reactions have reached the promise of the aldol reaction in its importance in the synthesis of complex molecules.[1] Almost all of the reactions are performed by preformation of an enolate, enol, or an equivalent with one of the most important versions being the Mukaiyama aldol reaction involving enol silyl ethers. In these cases, stoichiometric amounts of base and/or adjunct reagents (such as silylating agents to form the enol silyl ethers) are required—thus decreasing the atom efficiency of the process. The classical aldol reaction is highly atom economic[2] but suffers from selectivity, notably chemo- and regioselectivity problems. A further challenge is to perform these reactions asymmetrically. Indeed, most of the asymmetric versions of the aldol reaction rely upon the use of chiral auxiliaries;[3] however, it must be noted that there have been some successes of using asymmetric catalysts although they normally rely on a Mukaiyama type process.[4] An exciting challenge to enhance the efficiency of the aldol reaction is to find a compound that will catalyze the direct aldol addition without prior stoichiometric formation of the nucleophile and to do so asymmetrically. Biological-type catalysts (enzymes and antibodies) have had selected successes.[5] The first reports of chemical catalysts for this process from the groups of Shibasaki et al.[6] and List et al.[7] have just appeared.[8]

In developing a semi-rational strategy for designing catalysts for this process, the use of crown compounds seemed very attractive.[9] Their ability to tightly bind metal ions and to achieve high levels of molecular recognition in binding events suggested that they might serve as good templates on which to construct asymmetric catalysts. Surprisingly, very few catalytic asymmetric processes based upon chiral crown complexes have been developed.[10] One of the issues may be the different requirements associated with high binding affinities versus catalysis. For catalysis, turnover at reasonable rates must accompany the molecular recognition events. To approach both requirements, a semi-crown design would provide the opportunity for good chiral recognition and might also provide a path for facile exchange of product to overcome problems of product inhibition. This contribution reports the realization of this goal in a direct asymmetric aldol reaction.

The design incorporated a phenoxide as a base as depicted in **1** to promote a catalytic process whereby the alkoxide generated in the aldol reaction would rapidly be protonated by the phenol fragment but the phenoxide might still be adequate to form the enolate. To regain any loss in binding energy by going to the less well-organized semi-crown design, replacing oxygen (i.e., **1**, X = O) by stronger coordinating elements for some metals such as nitrogen (i.e., **1**, X = NR) was envisioned. Chiral ligand



2, readily synthesized in four steps from *p*-cresol, meets these design criteria. Thus, the known 2,6-bis(bromomethyl)-*p*-cresol, prepared in two steps from *p*-cresol using formaldehyde followed by HBr,[11] reacts smoothly with the hydrochloride of methyl prolinate in the presence of triethylamine in methylene chloride at room temperature (85% yield). Addition of phenylmagnesium chloride in THF at room temperature completes the synthesis of **2** (>99.5% ee by chiral HPLC) in 74% yield. In a series of preliminary experiments examining lithium, magnesium, and zinc, zinc appeared to give the highest ee. The solution formed by treating the ligand **2** in THF with a solution of diethylzinc in hexane was used as the catalyst for the aldol reaction of eq 1.



(1)

The addition of molecular sieves increased the turnover frequency but was still rather slow. Adding a weak coordinating agent for zinc that might help displace the product was explored. A phosphate such as trimethyl phosphate did improve the turnover frequency in contrast to a phosphine oxide such as tri-*n*-butylphosphine oxide which hindered the reaction. The best results were obtained with triphenylphosphine sulfide in terms of turnover and ee. Thus, the reaction conditions stated in eq 1 were adopted as our standard to explore a range of substrates.

Table 1 summarizes our results. Recovery of 96% of excess acetophenone has been demonstrated in entry 4. Using a chiral but racemic aldehyde, 2-phenylpropenal, a 2:1 diastereomeric mixture of adducts with both having high ee was obtained (entry

(1) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.7, pp 239. Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, part B, p 111.

(2) For a general discussion of atom economy in organic synthesis, see: Trost, B. M. *Science* **1991**, *254*, 1471; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(3) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995; Chapter 6, pp 306−361.

(4) For the general review on enantioselective Mukaiyama aldol reaction, see: 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. Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. Bach, T. *Angew. Chem., In. Ed. Engl.* **1994**, *33*, 417. Also see: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(5) Takayama, S.; McGarvey, G. J.; Wong, C. H. *Chem. Soc. Rev.* **1997**, *26*, 407. Rasor, J. P. *Chim. Oggi.* **1995**, *13*, 9. Barbas, C. F., III; Heine, A.; Zhory, G.; Hoffmann, T.; Gramatikova, S.; Björnestedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, E. A.; Lerner, R. A. *Science* **1997**, *278*, 2085. Also see: Kajimoto, T. *Yakugaku Zasshi* **2000**, *120*, 42; *Chem. Abstr.* **2000**, *132*, 194551. Hiratake, J.; Oda, J. *Yuki Gosei Kagaku Kyokaishi* **1997**, *55*, 452; *Chem. Abstr.* **1997**, *127*, 17218.

(6) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561. Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. For a review, see: Shibasaki, M., Sasai, H. *Top. Stereochem.* **1999**, *22*, 201.

(7) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. For an intramolecular variant differentiating prochiral carbonyl groups, see: Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, 358.

(8) For an early examination using a zinc complex of α-amino esters which, however, did not report any ee's, see: Nakayawa, M.; Nakao, H.; Watanabe, K. *Chem. Lett.* **1985**, 391.

(9) Lehn, J.-M. *Supramolecular Chemistry*; VCH Verlagsgesellschaft: Weinheim, 1995 and references therein.

(10) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, *1981*, 625. Cram D. J.; Sogah, G. D. Y *J. Am. Chem. Soc.* **1985**, *107*, 207. Tõke, L.; Bakó, P.; Keseru, G. M.; Albert, M.; Fenichel, L. *Tetrahedron* **1998**, *54*, 213 and references therein.

(11) Van der Boom, M. E.; Liou, S.-Y.; Ben-David, Y.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **1998**, *120*, 6531. Arnaud, N.; Picard, C.; Cazaux, L.; Tisnès, P. *Tetrahedron* **1997**, *53*, 13757.

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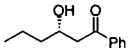
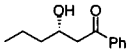
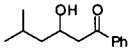
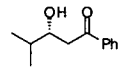
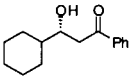
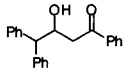
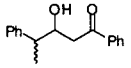
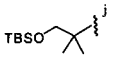
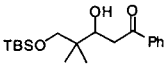
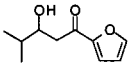
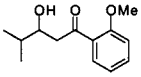
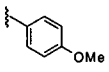
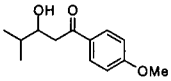
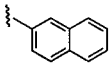
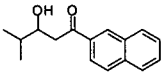
Table 1. Enantioselective Aldol Reaction of Aryl Methyl Ketone[a]

RCHO	O Ar	Product[b]	yield %	ee[c] %
 [d]	-Ph		33	56
 [e]	-Ph		24	74
 [d]	-Ph		49	68
	-Ph		62[f]	98
	-Ph		60	98
	-Ph		79	99
	-Ph		67[g] (2:1)	94[h] (98)[i]
 [j]	-Ph		61	93
			66	97
			48	97
			36[k]	98
			40[k]	96

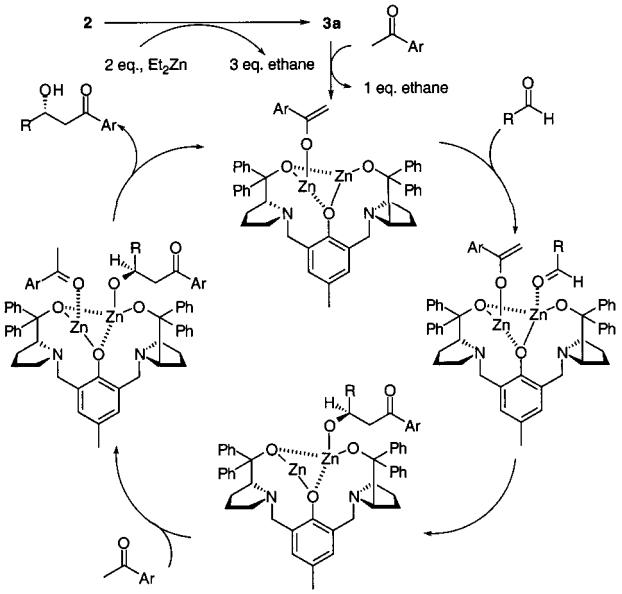
[a] Reactions performed according to eq 1 at 5 °C for 2 d using aldehyde:ketone ratio of 1:10 unless otherwise noted. [b] Absolute stereochemistries were determined by the comparison with optical rotation value of literature value[12]. [c] Enantiomeric excess was determined with chiral HPLC column (Chiracel OD column). [d] Reaction performed at −5 °C. [e] Reaction performed at −15 °C. [f] A 96% recovery of excess acetophenone was demonstrated in this case. [g] Diastereomers were not separated. [h] ee of major diastereomer. [i] ee of minor diastereomer. [j] Reaction time of 4 d. [k] Aldehyde:ketone ratio of 1:5 was employed.

7). The absolute configurations for the aldol adducts of entries 1, 4, and 5 are assigned by comparison to the literature.[12] It is likely that the absolute configuration for the remaining examples can be assigned by analogy as the same.

To establish the nature of the catalyst, the stoichiometry of the metal to ligand was examined by the evolution of ethane gas. The presence of three active hydrogens suggests the possible involvement of more than one zinc. Indeed, addition of 2 equiv of diethylzinc per ligand **2** liberates 3 equiv of ethane to form **3a** or **4a**. That one additional alkylmetal bond remained was revealed by addition of water which liberated the fourth equivalent. These

(12) Narasaka, K.; Miwa, T.; Hayashi, H.; Ohta, M. *Chem. Lett.* **1984**, *1984*, 1399. Veeraraghavan Ramachandran, P.; Xu, W.-C.; Brown, H. C. *Tethrahedron Lett.* **1996**, *37*, 4911.

Scheme 1. Proposed Catalytic Cycle



observations support structures such as **3a** and **4a** invoking a bimetallic catalyst as the initial species which reacts with ketone to liberate the fourth equivalent of ethane and initiate the catalytic cycle as depicted in Scheme 1. X-ray structures of somewhat related aminoether complexes suggest that N coordination to zinc might be included.[13] The role of two proximal zinc species is to provide both a zinc to form the requisite enolate and a second zinc to function as a Lewis acid to coordinate the aldehyde. The picture that emerges for the catalytic cycle then parallels proposals for the ability of amino alcohols to effect the asymmetric addition of organozinc reagents to aldehyde partners.[14]

To determine which catalyst, **3** or **4**, is favored, we calculated the energy of both using an MM2 force field on the CAChe system. Since in the catalytic cycle, an alkoxy group not an ethyl group is envisioned to be on zinc, the calculation were performed on the structures **3b** and **4b** wherein ethyl was replaced by ethoxy. The calculations indicate that **3b** is about 7 kcal/mol more stable than **4b** and leads us to favor structure **3** at present. This structure suggests the enolate approaches the *re* face of the aldehyde to give the observed products. This new catalyst design offers much opportunity for variation—a task under current investigation.

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Supporting Information Available: Characterization data for all the aldol adducts, typical experimental procedure, and Figure 1, Proposed Intermediate Responsible for Asymmetric Induction (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Sakiyama, H.; Mochizuki, R.; Sugawara, A.; Sakamoto, M.; Nishida, Y.; Yamasaki, M. *J. Chem. Soc., Dalton Trans.* **1999**, 997. For other zinc complexes derived from 2,6-di(dialkylaminomethyl)-*p*-cresol, see: Uhlenbrock, S.; Wegner, R.; Krebs, B. *J. Chem. Soc., Dalton Trans.* **1996**, 3731. For bis-ligated dinuclear zinc complexes, see: Fahrni, C. J.; Pfaltz, A.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1998**, *81*, 507.

(14) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.