Asymmetric Mukaiyama-Aldol Reaction in Aqueous Media Promoted by Zinc-Based Chiral Lewis Acids

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Abstract: Asymmetric aldol reactions in aqueous media have been realized by using zinc-based chiral Lewis acids. The aldol products have been obtained with high yield, diastereocontrol and a good level of enantioselectivity. The reactivity of both acetophenone and propiophenone enol ether surrogates was tested with a range of aldehydes.

Keywords: asymmetric catalysis; homogeneous catalysis; Lewis acids; Mukaiyama-aldol reaction; N ligands; water

Among the Lewis acid-catalyzed carbon-carbon bond forming reactions, the aldol-type reaction of silyl enol ethers with carbonyl compounds (the Mukaiyama reaction) has been recognized as one of the most valuable. It is therefore not surprising that a large number of methods have been developed in order to achieve this goal.[1]

In recent years, stereoselective organic reactions in aqueous media have attracted a great deal of attention.[2] To replace classical Lewis acids acting only in rigorously dried solvents, their water-tolerant substitutes have been screened with more or less satisfactory results in aldol and aldol-type reactions.[3] The very first catalytic asymmetric aldol reactions in aqueous media were performed with $Cu(OTf)_2$ as catalyst and bis(oxazolines) as chiral counterpart.[4] Other metals, e.g., lead[5] and particularly gallium[6] have been used with some success in enantioselective aqueous Mukaiyama-aldol reactions. Recently, Kobayashi and co-workers developed the combination of $RE(OTf)_3$ and chiral bis-pyridino-18-crown-6 for the asymmetric Mukaiyama-aldol reaction in aqueous ethanol [ee up to 85% for aromatic enol ether when $Pr(OTf)_3$ was used as Lewis acid].[7] In general, the state-of-the-art in this area provides aldol products in good ees (70–80%). The scope and limitation of this reaction is still not well recognized, and for ee exceeding 80% special ligands have to be chosen.[6,7] In general, the elaborated methods fail when aliphatic aldehydes are substrates, although Kobayashi recently presented an excellent example of hydroxymethylation of silicon enolates using an aqueous solution of formaldehyde.[8]

In this paper we demonstrate the utility of a zinc-based chiral Lewis acid for the enantioselective Mukaiyama-aldol reaction in aqueous media.

In spite of some promising examples of direct aldol condensations promoted by chiral Zn-complexes[9] in anhydrous solutions, little is know about the Zn-supported Mukaiyama-aldol condensation both in anhydrous and aqueous media. The initial attempt by Kobayashi's group employing a combination of $Zn(OTf)_2$ and chiral crown ether can hardly by regarded as promising.[5] On the other hand, the good results obtained by the same group with asymmetric silyl enol ether-based Mukaiyama–Mannich type reactions in aqueous media[10] strongly encourage intensive exploration of the subject.

The successful application of a zinc salt to asymmetric reactions in water-containing solutions must rely on its fit into the chiral ligand. Keeping in mind the well known kinship of the Zn^{2+} cation with *N*-donor ligands we decided to test various *N*-binding compounds (**1**–**7**) as potential sources of chirality.

As for first-step substrates, we focused on benzaldehyde and the *Z*-silyl enol ether **8**. Preliminary experiments revealed that the combination of zinc triflate with pybox-type ligands was the couple of choice for this process.

When (*S,S*)-**1** (22 mol %) and $Zn(OTf)_2$ (20 mol %) were used, the reaction of benzaldehyde with silyl enol ether **8** in THF/H_2O (9/1) at 0 °C for 10 h gave the desired aldol adduct **10** in good yield and with good diastereo- and enantioselectivity (Table 1, entry 1). Importantly, similar yield and stereoselectivity were observed when THF/H_2O (1/1) was applied as solvent. The same reaction in ethanol-water was visibly faster but less enantioselective (entry 1 *vs.* 11). From the practical point of view, it was exciting to find that the reaction does not require a large excess of silyl enol ether, and typically 1.2 equivs. are sufficient to obtain reasonable yields.

The key results from the reaction optimization are summarized in Table 1. Among the many members of the pybox-type ligand family,[11] OH-pybox **2** revealed better conversion with poor enantioselectivity and its Ph analogue **3** failed miserably (Table 1, entries 5 and 6).

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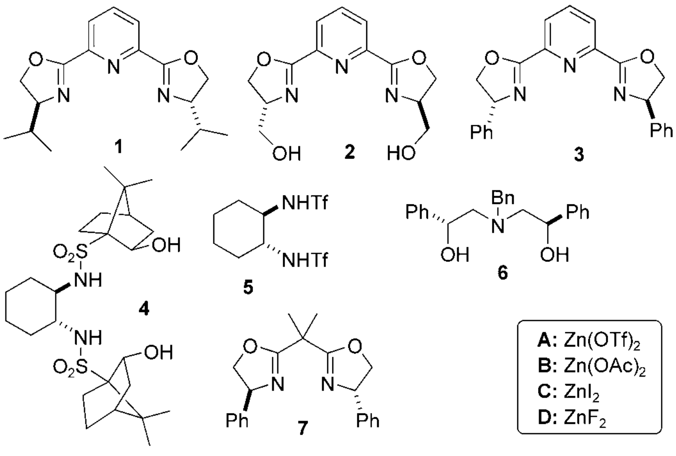
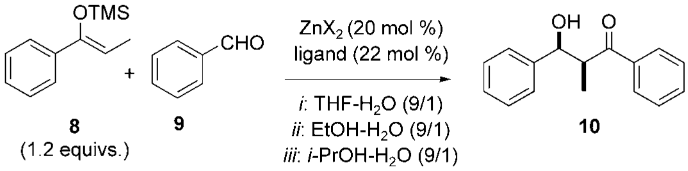
Table 1. Metal sources and some selected chiral ligands used in the initial studies.



A: $Zn(OTf)_2$
B: $Zn(OAc)_2$
C: ZnI_2
D: ZnF_2



Entry	Catalyst	Solvent	Temp. [°C]	Time [h]	Yield[a] (*syn/anti*)	Ee[c] *syn*
a) ligand and anion effects						
1	**A1**	*i*	0	10	73 (9/1)	53 (*S,S*)[12]
2	**B1**	*i*	0–rt	20	14	10
3	**C1**	*i*	0–rt	20	trace	–
4	**D1**	*i*	0	20	53	50
5	**A2**	*i*	0	10	82	–24
6	**A3**	*i*	0	96	56	–13
7	**A4**	*i*	0	20	67	–3
8	**A5**	*i*	0	20	59	0
9	**A6**	*i*	0–rt	40	25	0
10	**A7**	*ii*	0	20	58	–27
b) solvent and temperature effects						
11	**A1**	*ii*	0	10	80 (9/1)	39
12	**A1**	*ii*	–10	48	97[b]	62
13	**A1**	*i*+*ii* (2:1)	–10	48	66[b]	73
14	**A1**	*iii*	–10	48	30	65
15	**A1**	*ii*	–20	72	88 (95/5)	69
16	**A1**	*ii*	–20	24	93 (95/5)[b]	69
17	**A1**	*i*+*ii* (1:1)	–20	72	43 (95/5)	75
18	**A1**	*i*+*ii* (2:1)	–20	72	34 (96/6)	77
19	**A1**	*i*+*ii* (1:1)	–25	48	**86** (96/4)[b]	**75**
20	**A1**[d]	*i*+*ii* (1:1)	–25	48	88 (93/7)[b]	72

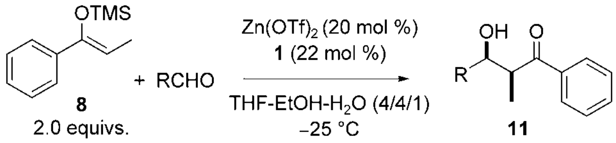
[a] Isolated yield.
[b] 2.0 equivs. of **8** were used.
[c] The ees were determined on a Daicel Chiralpak AD-H column.
[d] 10 mol % of the catalyst was used.

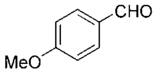
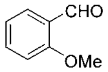
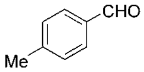
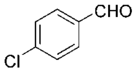
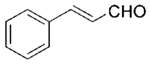
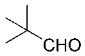
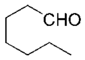
The combination of box **7** with zinc was not as efficient as in the case of the Cu salt[4] (Table 1, entry 10). All other amino ligands failed in the elaborated reaction.

Zinc fluoride as a catalyst led to a somewhat poorer results while the application of zinc acetate and iodide was simply disappointing.

Next, we examined the effect of solvents in the reaction. Application of ethanol instead of THF gave a better conversion but affected the enantioselectivity (Table 1, entry 11). In this case, however, decreasing of reaction temperature was more promising, and at –10 °C the ee improved visibly. At the same tempera-

Table 2. Mukaiyama-aldol condensation with the **A1** catalytic system.



Entry	Aldehyde	Product	Time [h]	Yield[a] (*syn/anti*)	ee[b] (*syn*)
1		**11a**	72	77 (92/8)	70
2		**11b**	24	85 (98/2)	72
3		**11c**	48	62 (94/6)	74
4		**11d**	48	86 (95/5)	72
5		**11e**	24	79 (91/9)	72
6		**11f**	72[c]	16 (*syn* only)	45
7		**11g**	72	65 (95/5)	74

[a] Isolated yield.

[b] The ees were determined on a Daicel Chiralpak AD-H column.

[c] Reaction temperature 0 °C.

ture the catalytic system **A1** was insoluble in THF/H_2O. Further decreasing of the reaction temperature resulted in increases of both diastereo- and enantioselectivities, leading to 69% ee at −20 °C (entry 15).

In this case, however, the main condensation product **10** was accompanied by some amount of α-hydroxypropiophenone (less than 10%). To find the optimal balance between yield and stereoselectivity we have tested mixed solvents. In the case of a wet ethanol-THF mixture (1:1) we obtained 86% yield when 2 equivs. of **8** were used. Substrate loading does not affect the observed ee (entries 17 and 19). We were delighted to find that the reaction proceeded in high yield with good enantioselectivity even using 10 mol % of the catalyst (entry 20). Five mol % also worked well, although with slightly lower ee (70%).

In water-based aldol reactions we observed a predominance of *syn*-aldol products which is in full agreement with previously published results.[4–7] This, as a rule, is in contrast with the analogous reactions run under anhydrous conditions where the *anti*-isomer is usually the major product.[2a]

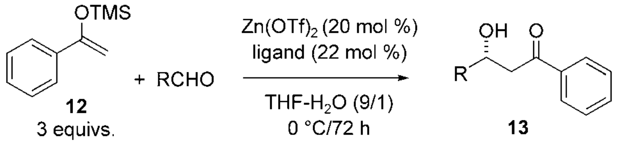
Encouraged by the enhanced selectivity, we started to explore the reaction scope. In the catalytic asymmetric aldol reaction using $Zn(OTf)_2$ and **1** (**A1** system), other aldehydes were tested, and the results are summarized in Table 2.

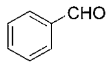
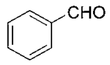
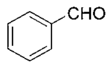
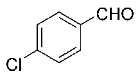
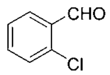
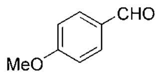
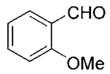
Surprisingly, the hindered *o*-anisaldehyde was more reactive as compared to its *para* counterpart, probably because of interaction of the methoxy function with the metal core of catalyst. Not only aromatic aldehydes (entries 1–4) but also α,β-unsaturated aldehydes, e.g., cinamaldehyde (entry 5) gave good yields as well as high stereoselectivity. Aliphatic aldehydes were good substrates as well in the presented catalytic system. Pivalaldehyde was obviously less reactive leading, however, to the desired product only at 0 °C which resulted in the loss of reaction selectivity. Heptanal, in spite of a slightly lower reactivity, showed the same level of stereoselectivity as aromatic aldehydes. Retention of the ee level in the reaction with aliphatic aldehydes is a valuable observation as some previously demonstrated catalytic systems lost stereosectivity with these important substrates.[4,6,7]

The reasonable outcome in the condensation of enol ether **8** encouraged us to test the reactivity of its shorter analogue **12**. Such a variant of the Mukaiyama-type reaction in aqueous media to the best of our knowledge has never been presented in the literature. Substrate **12** was previously demonstrated to be moderately reactive in Mukaiyama–Mannich reactions in aqueous solution with some success (ee up to 90%).[10]

Again, we tested combination of all three pybox ligands **1–3** with zinc triflate. In this case, because of

Table 3. Mukaiyama-aldol condensation of acetophenone silyl enol ether.



Entry	Aldehyde	Ligand	Product	Yield[a]	ee[b]
1		**1**	**13a**	22	27 (*S*)[13]
2		**2**	**13a**	38	64 (*R*)
3		**3**	**13a**	33	17 (*R*)
4		**2**	**13b**	48	43
5		**2**	**13c**	85	56
6		**2**	**13d**	15	56
7		**2**	**13e**	60	77

[a] Isolated yield.

[b] The ees were determined on a Daicel Chiralpak AS column.

the much lower reactivity of the substrate, the best results were obtained with as much as 3 equivs. of **12** at 0 °C when THF-H_2O was used as medium. In ethanol-based solvents we observed a faster hydrolysis of enol ether substrate. Surprisingly, for the condensation of **12** the most promising source of chirality turned out to be OH-pybox **2** (Table 3, entry2).

In the case of the condensation of **12** with aromatic aldehydes the same rules were observed favoring *o*-substituted aldehydes, e.g., *o*-anisaldehyde was a far more reactive and selective substrate when compared to *p*-anisaldehyde.

In summary, we present the successful application of zinc-based chiral Lewis acids to the enantioselective Mukaiyama-aldol condensation in aqueous media. The catalytic asymmetric aldol reaction using $Zn(OTf)_2$ and chiral ligand proceeded with good to high yields and stereoselectivities, when several aldehydes and two silyl enol ethers were tested. The same stereoselectivity was observed in wet to aqueous solutions (containing 10–50% water), and aliphatic aldehydes were found to be acceptable substrates. To the best of our knowledge this is the first example of an enantioselective variant of this reaction executed with the zinc salt-pybox ligand combination. Further experiments to define the scope and limitations of this process, especially with aliphatic substrates, are in progress in our laboratory.

Experimental Section

General Remarks

Reactions were controlled using TLC on silica alu-plates [Merck (0.2 mm)]. All reagents and solvents were purified and dried according to common methods. All organic solutions were dried over Na_2SO_4. Reaction products were purified by flash chromatography using Merck silica gel 60 (240–400 mesh). The diastereomer ratios were determined using a ^1H NMR technique. Enantiomer ratios were measured on chiral HPLC columns (Chiralpak AS and AD-H) with hexane/2-propanol (9:1).

Typical Procedure for the Asymmetric Aldol Reaction

To a solution of pybox ligand **1** (18 mg, 0.06 mmol) and zinc trifluoromethanesulfonate (18 mg, 0.05 mmol) in THF-EtOH-H_2O (1/1/0.2; 1.5 mL) at −25 °C were added silyl enol ether **8** (250 μL, 1 mmol) and the appropriate aldehyde (0.5 mmol). The whole solution was stirred for 24 h at the same temperature (maintaining the entire homogeneous reaction mixture in the fridge at an appropriate temperature led to desired products with only slightly poorer results). The reaction mixture was diluted with MTBE and washed with water and brine. The organic solution was dried, evaporated to dryness and the residue was purified by silica gel chromatography (AcOEt/hexane, 1/4).

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References and Notes

The author (JJ) is a student of Warsaw University of Technology, and this work is a part of her M.Sc. Thesis.

[1] a) T. D. Machajewski, Ch.-H. Wong, *Angew. Chem. Int. Ed.* **2000**, *39*, 1352–1374; b) C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Soc. Rev.* **2004**, *33*, 65–75.

[2] a) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751–2772; b) D. Sinou, *Adv. Synth. Catal.* **2002**, *344*, 221–237; c) K. Manabe, S. Kobayashi, *Chem. Eur. J.* **2002**, *8*, 4095–4101; d) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209–217.

[3] a) F. Fringuelli, O. Piermatti, F. Pizzo, in: *Organic Synthesis in Water*, (Ed.: P. A. Grieco), Blackie Academic & Professional, London, **1998**, pp. 250–261; b) S. Kobayashi, in: *Organic Synthesis in Water*, (Ed.: P. A.

Grieco), Blackie Academic & Professional, London, **1998**, pp. 262–302.

[4] S. Kobayashi, S. Nagayama, T. Busujima, *Tetrahedron*, **1999**, *55*, 8739–8746.

[5] S. Nagayama, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 11531–11532.

[6] H.-J. Li, H.-Y. Tian, Y.-J. Chen, D. Wang, Ch.-J. Li, *Chem. Commun.*, **2002**, 2994–2995.

[7] T. Hamada, K. Manabe, S. Ishikawa, S. Nagayama, M. Shiro, S. Kobayashi, *J. Am. Chem. Soc.* **2003**, *125*, 2989–2996.

[8] S. Ishikawa, T. Hamada, K. Manabe, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 12236–12237.

[9] a) N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2169–2178; b) B. M. Trost. H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004; c) B. M. Trost. H. Ito, E. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367–3368; d) B. M. Trost. E. Silcoff, H. Ito, *Org. Lett.* **2001**, *3*, 2497–2500.

[10] a) S. Kobayashi, T. Hamada, K. Manabe, *J. Am. Chem. Soc.* **2002**, *124*, 5640–5641; b) T. Hamada, K. Manabe, S. Kobayashi, *Angew. Chem. In. Ed.* **2003**, *42*, 3927–3930; c) T. Hamada, K. Manabe, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 7768–7769.

[11] G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.*, **2003**, *103*, 3119–3154.

[12] The absolute configuration of the alcohol **10** was determined by comparison of the HPLC analysis with literature data in ref.[7]

[13] The absolute configuration of the alcohol **13a** was determined by comparison of optical rotation with literature data: S. H. Mashraqui, R. M. Kellogg, *J. Org. Chem.* **1984**, *49*, 2513–2516.