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Zn(pybox)-Complex-Catalyzed Asymmetric Aqueous Mukaiyama-Aldol Reactions

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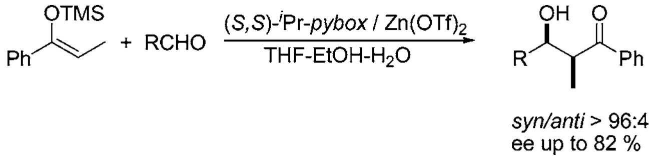

Catalytic asymmetric aldol reactions in aqueous media have been developed using chiral zinc complex. The aldol products have been obtained in high yields, high diastereocontrol, and good level of enantioselectivity. Various aromatic and α,β-unsaturated aldehydes and silyl enol ethers derived from ketones can be employed in this reaction to provide the aldol adducts in good to high yield. The elaborated catalytic system has been found as selective for aliphatic aldehydes as well.

Introduction

The aldol reaction is well recognized as one of the most important carbon−carbon bond-forming methods in organic synthesis. Up to two stereogenic centers are generated in the reaction, and thus a useful protocol must fulfill satisfactory levels of the reaction yield, diastereoselectivity, and enantioselectivity.[1] Among other recently elaborated methods,[2] aldol reaction of aldehydes with silicon enolates, the Mukaiyama reaction,[3] has been recognized as one of the most convenient and valuable.[4] Although several successful examples of chiral Lewis acid catalyzed Mukaiyama reactions have been developed, most of them have to be conducted at low temperatures in aprotic anhydrous solvents.

Stereoselective organic transformations in aqueous media have recently attracted a great deal of attention because environmental protection demands clean reaction processes that do not use damaging and expensive organic solvents.[5] Many carbon−carbon bond-forming processes have been carried out in water[6] since Kobayashi showed that rare earth metal triflates can act as Lewis acid type catalysts in aqueous medium.[7] In this way a number of diastereoselective Mukaiyama-type aldol reactions were realized using lanthanide triflates[8] and other water-compatible metals salts,[9] avoiding the use of rigorously dried and potentially toxic solvents and allowing the easy recovery of the active Lewis acid catalyst.

Enantioselective versions of Lewis acid mediated reactions in aqueous solvents are challenging especially in the context of designing a chiral ligand with appropriate binding property to the metal cations.[6] The catalysts containing copper,[10] lead,[11] and gallium[12] have been used with some success in enantioselective aqueous Mukaiyama-aldol reactions. The most spectacular success in this area was the application of rare earth metal elements. Kobayashi and co-workers developed the combination of praseodymium triflate and chiral crown ethers for asymmetric

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[12] (a) Li, H.-J.; Tian, H.-Y.; Chen, Y.-J.; Wang, D.; Li, Ch.-J. *Chem. Commun.* **2002**, 2994. (b) Li, H.-J.; Tian, H.-Y.; Wu, Y.-Ch.; Chen, Y.-J.; Liu, L.; Wang, D.; Li, Ch.-J. *Adv. Synth. Catal.* **2005**, *347*, 1247.

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Mukaiyama-aldol reaction in aqueous ethanol.[13] Recently, the same group presented excellent example of hydroxymethylation of silicon enolates using scandium-[14] and bismuth-based Lewis acid.[15]

The scope and limitation of this reaction is still, however, not fully recognized, and attaining high enantioselectivity in aldol reaction in aqueous media is generally not easy. Special ligands have to be chosen to obtain ee reaching 80%[12,13] and diastereoselectivity in hitherto reported reactions is not excellent. Finally, the elaborated methodologies failed in application to aliphatic aldehydes for which a remarkable drop in the reaction enantioselectivity was commonly observed.

To address all of these deficiencies and develop new methodologies, we wish to report a novel chiral zinc catalyst with pybox-type ligand for asymmetric Mukaiyama-aldol reaction in aqueous media.[16] Previously, synthetic Zn^{2+} coordination complexes have been studied extensively as simplified models for various biological processes,[17] e.g., aldol reactions catalyzed by type II aldolases, natural aldol reaction catalysts,[18] containing Zn^{2+} cofactor in the active site. The studies on aldol reactions in aqueous media may serve to some extent as a model for enzymatic processes in living organisms where water is a "life solvent" because the same metal cofactor is responsible for the substrate activation in both genuine enzymatic and laboratory processes.[17g] Here, we describe the detailed studies on our catalyst and further improvements of the asymmetric aldol reactions in aqueous media. Emphasis is placed on aliphatic aldehydes, usually unsuitable substrates for such reactions.

Results and Discussion

Despite some promising examples of the direct aldol condensation promoted by chiral Zn-complexes,[19] little is known about zinc-supported Mukaiyama-aldol condensation in either anhydrous or aqueous media. It was found previously that Lewis acids based on Zn^{2+} were both stable and active in Mukaiyama reaction in wet THF, although they gave moderate yields of the aldol products.[9a] Planning our screening for an enantioselective zinc-based catalyst for the reaction, we considered published unpromising examples of enantioselective aldol reaction promoted by zinc triflate and chiral crown ether combination,[11] as well as spectacular results obtained by the same group with asymmetric silyl enol ether based Mukaiyama–Mannich-type reaction in aqueous media.[20]

Successful application of zinc salt to asymmetric reaction in aqueous solutions must rely on its possibly best fit into the chiral ligand. Keeping in mind the well-known kinship of a zinc cation with the nitrogen atom lonely electron pair, surpassing binding constants of Zn^{2+} with water molecules,[21] we found it reasonable to test various types of *N*-binding ligands. Our initial studies began with an evaluation of zinc complexes with ligands containing one, two, and three nitrogen atoms. The enantioselectivity of ligands was assessed in the catalytic aldol reaction of propiophenone silyl enol ether **4** and benzaldehyde as common substrates for the first stage optimization of the Mukaiyama process.[16] Of the complexes surveyed, the $Zn(OTf)_2$-pybox catalysts with ligands **1**−**3**[22] provided superior levels of asymmetric inductions (Table 1).

When (*S*,*S*)-**1** (22 mol %) and $Zn(OTf)_2$ (20 mol %) were used, the reaction between benzaldehyde and silyl enol ether **4** in THF/H_2O (9/1) at 0 °C gave the desired aldol adduct **6** in good yield and good diastereo- and enantioselectivity (entry 1). It is important to mention that the homogeneous reactions does not need any stirring and the same yield and selectivity was observed when the whole reaction mixture was alowed to stay in the fridge at the appropriate temperature. Interestingly, similar stereoselectivity was observed when THF/H_2O (1/1) was applied as a solvent (entry 2). In this case, however, the yield dropped probably because of limited contact between phases in the nonhomogeneous mixture. The same reaction in ethanol/water was visibly faster but less enantioselective (entry 1 vs 3). From the practical point of view, it was exciting to find out that the reaction does not require a large excess of silyl enol ether and 1.2 equiv is sufficient to obtain reasonable yield.

N-Mono- and bidentate ligands were less promising sources of chirality in tested reactions. This observation confirmed strong preferences of Zn^{2+} toward formation of chiral complexes stabilized by three nitrogen atoms in the aldol reactions in aqueous media. This is a conspicuous analogy to type II aldolases in which zinc ion is tightly coordinated by three histidine residues in the reaction active site.[23]

Application of ethanol instead of THF resulted in better conversion yet affected enantioselectivity. Unlike wet THF, in which $Zn(OTf)_2$/**1** was insoluble below −10 °C, application of ethanol gave opportunity in lowering the reaction temperature. Thus, at −20 °C both diastereo- and enantioselectivities of the reaction improved noticeably, leading to 68% ee and 93% yield (entry 7).

The highest reaction enantioselectivity was observed when a DME/water mixture was applied. In this case ee exceeded 80%, but observed yield was unsatisfactory, even when 2 equiv of enol ether **4** was engaged (entry 9). It was found that the addition of 2,6-di-*tert*-butyl-4-methylpyridine[13b] was indifferent and did not improve observed yield (entries 9 and 10).

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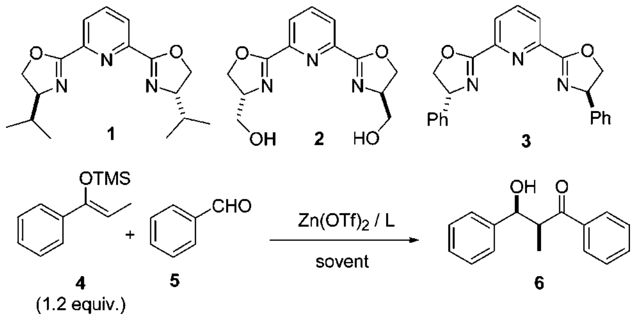
TABLE 1. Mukaiyama-Aldol Reaction of Silyl Enol Ether 4; Solvent Studies



	L	catalyst mol %	solvent	temp (°C)	time (h)	yield[a] (*syn*/*anti*)	ee[c] (*syn*)
1	**1**	20	THF−H_2O(10%)	0	20	73 (9/1)	58 (*S,S*)
2	**1**	20	THF−H_2O(50%)	0	72	38 (93/7)	60 (*S,S*)
3	**1**	20	EtOH−H_2O(10%)	0	10	80 (9/1)	39 (*S,S*)
4	**1**	20	CH_2Cl_2	0	20	13 (7/3)	rac
5	**2**	20	THF−H_2O(10%)	0	20	82	24 (*R,R*)
6	**3**	20	THF−H_2O(10%)	0	96	56	13 (*R,R*)
7	**1**	20	EtOH−H_2O(10%)	−20	24	93 (96/4)[b]	68
8	**1**	20	DMF−H_2O(10%)	−25	96	52 (93/7)[b]	76
9	**1**	20	DME−H_2O(10%)	−25	96	18 (92/8)[b]	82
10	**1**	20	DME−H_2O(10%)	−25	48	18 (95/5)[b,d]	79
11	**1**	20	THF/EtOH(1/1)−H_2O(10%)	−25	72	43 (96/4)	75
12	**1**	**20**	**THF/EtOH(1/1)−H_2O(10%)**	**−25**	**72**	**84 (96/4)[b]**	**75**
13	**1**	**10**	**THF/EtOH(1/1)−H_2O(10%)**	**−25**	**48**	**88 (94/6)[b]**	**72**
14	**1**	**5**	**THF/EtOH(1/1)−H_2O(10%)**	**−25**	**48**	**84 (93/7)[b]**	**71**
15	**1**	20	DME/THF(1/1)−H_2O(10%)	−25	48	25 (92/8)[b]	74
16	**1**	20	DME/EtOH(1/1)−H_2O(10%)	−25	48	63 (94/6)[b]	78

[a] Isolated yield. [b] 2.0 equiv of **4** was used. [c] ee values were determined on a Daicel Chiralpak AD-H column. [d] 100 mol % of 2,6-di-*tert*-butyl-4-methylpyridine was admixed.

To find the optimal balance between the reaction yield and stereoselectivity, we have tested mixed solvents. In the case of wet ethanol/THF mixture (1:1) we obtained 84% yield when 2 equiv of **4** was used. Substrate loading did not affect observed ee (entries 11 and 12). We were delighted to find that the reaction proceeded in high yield with good enantioselectivity even when 10 mol % of the catalyst was used (entry 13). In general, 10 mol % of the catalyst delivered aldol products with better yields; 5 mol % of the catalyst also worked well (entry 14) but when less than 20 mol % of the catalyst was used both stereoselectivity and enantioselectivity were, however, a little lower. Aldol reaction conducted in DME-containing solvents was still selective yet less efficient (entries 15 and 16).

The reaction in pure CH_2Cl_2 gave lower yield and diastereoselectivity, and the product was found to be a racemate (entry 4). The desired product **6** was not detected when dry THF was used as reaction medium. Thus water plays an essential role for attaining good yield and enantioselectivity in the reaction. This observation encouraged us to take under consideration the existence of water molecules in further stereochemical discussion.

Next we checked the recyclability of the catalytic system Zn(OTf)$_2$-**1**. After the first cycle (ee 68%, Table 1, entry 7) the active species was extracted to the water phase and concentrated. We repeated the same reaction using EtOH/H_2O (9/1) as a solvent. The observed yield was high (98%), but selectivities were dramatically decreased (ee 6%, de 46%). These results suggested that although pybox ligand can be effectively recycled as hydrophilic Zn-complex, some active intermediates were extracted into the organic phase.

In aqueous aldol reactions we observed a predominance of *syn*-aldol products, which is in full agreement with previously published results.[10,12,13] This, as a rule, is in contrast with the analogous reactions run under anhydrous conditions where the *anti*-isomer is usually the major product.[2,6a]

We were delighted to find that the elaborated catalytic system turned out to be highly diastereoselective (dr, 96/4, entry 12) when compared to hitherto published examples. Diastereoisomeric ratios in previously presented reactions rarely exceeded 9/1 value and only for a narrow range of tested substrates.[11,13] Reported diastereoselectivities were modest for Cu(II)[10] (3/1−5/1) and Ga(III)[12] (8/2−9/1) based catalysts.

The absolute configuration of the aldol product **6** resulted from configuration of the ligand used. Thus (*S*,*S*)-**1**-pybox produced aldol with (2*S*,3*S*)-configuration, whereas (*R*,*R*)-**2** and **3** delivered the opposite enantiomer of **6**. In all cases the absolute configuration of the alcohol **6** was determined by comparison of the HPLC analysis and optical rotation value with literature data.[13b]

The stereochemical course of the reaction can be rationalized by the model shown in Scheme 1. We assume that before an aldehyde binding, the catalyst exists as an octahedral triaqua-complex, as was proven during the investigation of bis(indanol)-pybox with zinc triflate complex.[24] To rationalize the observed sense of induction, a complexation of the aldehyde to the zinc ion to give a square pyramidal reacting complex is proposed. This was previously shown for benzyloxyacetaldehyde with Cu(pybox)[25] and glyoxylate with Sc(pybox)[26] complexes. In both cases bidentate aldehydes occupied apical and equatorial positions of the complex, replacing the vicinal triflates and the water molecule. When an aldehyde coordinates to the Zn cation

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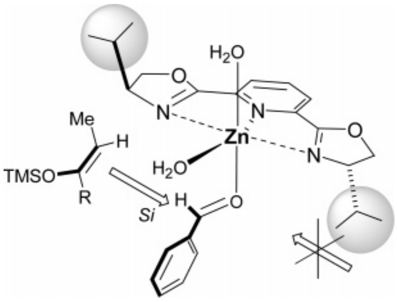
(24) Jiang, M.; Dalgarno, S.; Kilner, C. A.; Halcrow, M. A.; Kee, T. P. *Polyhedron* **2001**, *20*, 2151.

SCHEME 1. Assumed Transition State Model in the Asymmetric Aldol Reaction



complexed with (*S*,*S*)-pybox **1**, in the fashion shown in Scheme 1, the *re* face of the coordinated aldehyde carbonyl is shielded by the isopropyl substituent of **1**, allowing nucleophilic attack of silyl enol ether predominantly from the *si* face. It is possible that the water molecule coordinated to the zinc cation can additionally fix this structure by hydrogen bond formation or steric crowding. Such a structure with tridentate ligands was observed when urea and two molecules of water coordinate to the zinc cation.[27] The (2*S*,3*S*)-adduct is considered to be formed selectively in this manner.

In an effort to expand the scope of the zinc-promoted Mukaiyama aldol process, various aldehydes and other silyl enol ethers were then examined, and the results are summarized in Tables 2 and 3.

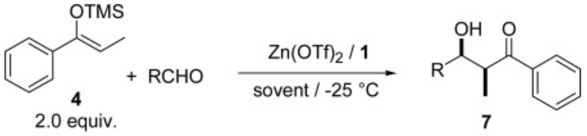
Not only aromatic aldehydes (Table 2, entries 1−5) but also α,β-unsaturated, e.g., cinamaldehyde (entry 6), and aliphatic substrates (entries 7−14) gave good yields as well as stereoselectivity. In most cases observed stereoselectivity was high and surpassing (9/1) diastereomers ratio when 20 mol % of the catalyst was used. Its higher values were characteristic for *o*-substituted aldehydes, for instance, (98/2) for 2-chlorbenzaldehyde (entry 4), and reached the top for *o*-anisaldehyde, for which the *anti*-aldol was not observed in the reaction mixture (entry 2). Moreover, 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 the catalyst.

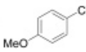
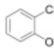
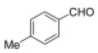
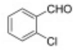
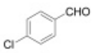
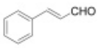
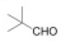
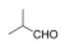
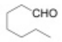
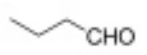
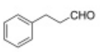
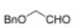
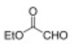
Diminishing the catalyst loading to 10 mol % did not affect reaction yield but decreased diastereoselectivity (entries 1−5).

We did not observe, however, correlation between the enantioselectivity of an Mukaiyama-aldol reaction and the nature of the *para*-substituent of a benzaldehyde substrate. Although usually increasing ee with increasing electron-donating character of the substituent was observed for a metal-catalyzed addition to carbonyl group,[29] it was not previously observed in aqueous Mukaiyama reaction.[12,13]

We were delighted to find out that the elaborated catalytic system can be successfully applied for aliphatic aldehydes without significant loss of diastereo- and enantioselectivity of the aldol coupling process (entries 7−12). Pivalaldehyde was

TABLE 2. Examples of Zn(OTf)$_2$(pybox-1)-Catalyzed Mukaiyama-Aldol Reactions



	aldehyde		cat. mol%	solvent	time [h]	yield (*syn/anti*)	ee (*syn*)[a]
1		**7a**	20	THF/EtOH(1/1)-H$_2$O(10%)	72	77 (92/8)	70
			10	THF/EtOH(1/1)-H$_2$O(10%)	72	56 (84/16)	68
			20	DME/EtOH(1/1)-H$_2$O(10%)	48	75 (93/7)	74
2		**7b**	20	THF/EtOH(1/1)-H$_2$O(10%)	24	85 (*syn*)	72
			10	THF/EtOH(1/1)-H$_2$O(10%)	24	85 (*syn*)	68
			20	DME-EtOH(1/1)-H$_2$O(10%)	48	77 (*syn*)	76
3		**7c**	20	THF/EtOH(1/1)-H$_2$O(10%)	48	62 (94/6)	74
			10	THF/EtOH(1/1)-H$_2$O(10%)	48	70 (91/9)	68
4		**7d**	20	THF/EtOH(1/1)-H$_2$O(10%)	48	83 (98/2)	69
			10	THF/EtOH(1/1)-H$_2$O(10%)	48	98 (89/11)	62
5		**7e**	20	THF/EtOH(1/1)-H$_2$O(10%)	48	85 (95/5)	72
			10	THF/EtOH(1/1)-H$_2$O(10%)	48	88 (91/9)	66
6		**7f**	20	THF/EtOH(1/1)-H$_2$O(10%)	24	79 (91/9)	72
7		**7g**	20	THF/EtOH(1/1)-H$_2$O(10%)	72	16 (*syn*)[b]	45
8		**7h**	20	THF/EtOH(1/1)-H$_2$O(10%)	24	22 (4/1)	73
9		**7i**	20	THF-H$_2$O(10%)	96	50 (86/14)[b]	74
			20	THF/EtOH(1/1)-H$_2$O(10%)	48	45 (95/5)	74
			20	THF/EtOH(4/1)-H$_2$O(10%)	168	62 (94/6)[c]	70
10		**7j**	20	THF/EtOH(1/1)-H$_2$O(10%)	48	21 (94/6)	75
			20	THF/EtOH(4/1)-H$_2$O(10%)	168	60 (94/6)[c]	73
11		**7k**	20	THF/EtOH(1/1)-H$_2$O(10%)	168	35 (9/1)	75
			20	THF/EtOH(4/1)-H$_2$O(10%)	168	55 (93/7)[c]	72
12		**7l**	20	THF-H$_2$O(10%)	168	80 (4/1)[b]	54
13		**7m**	20	THF/EtOH(1/1)-H$_2$O(10%)	192	86 (7/3)[b]	34
14	HCHO	**7n**	20	EtOH-H$_2$O(9/1)	48	16	rac.

[a] ee values were determined on a Daicel Chiralpak AD-H column. [b] Reaction temperature 0 °C. [c] Reaction temperature −10 °C.

obviously less reactive, leading however to the desired product at 0 °C with the loss of reaction enantioselectivity. Heptanal despite slightly lower reactivity showed the same level of stereoselectivity as aromatic aldehydes (entry 9). For aliphatic aldehydes special conditions have to be applied because of lower substrate reactivity. In aqueous ethanol, hydrolysis of enol ether **4** was faster than the desired addition and low yield was observed. We solved this problem by application of medium composed of wet THF with 20 vol % of EtOH at −10 °C (entry 9). Under the elaborated conditions heptanal, butanal, and phenylpropanal provided aldols **7i**−**k** in acceptable yields and good levels of stereocentrol. Retention of the good level of ee in the reaction with aliphatic aldehyde is a valuable observation as the application of the most previously demonstrated catalytic systems resulted in lower stereosectivity with those important substrates.

Benzyloxyacetaldehyde was reactive only at 0 °C, which resulted in only a moderate level of ee (entry 12). Initial studies on ethyl glyoxalate showed that this important substrate[26,28] delivered product in good yield but with low stereoselection

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(27) Komen, R. P.; Miskelly, G. M.; Oliver, A.; Rickard, C. E. P. *Acta Crystallogr., Sect. C* **1999**, *55*, 1213.

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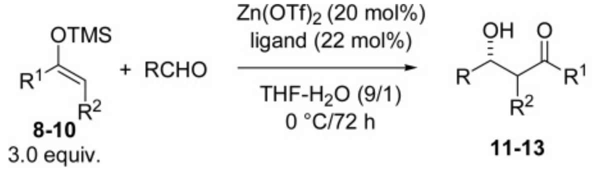
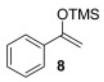
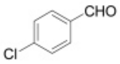
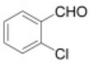
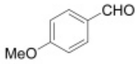
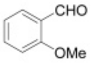
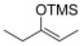
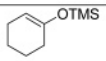
TABLE 3. Mukaiyama-Aldol Condensation of Acetophenone and Cyclohexanone Silyl Enol Ethers



	enol ether	aldehyde	ligand	product	yield (*syn/anti*)[a]	ee (*syn*)[b]
1	 **8**	benzaldehyde	**1**	**11a**	22	27 (*S*)
2	**8**	benzaldehyde	**2**	**11a**	38	64 (*R*)
3	**8**	benzaldehyde	**3**	**11a**	33	17 (*R*)
4	**8**		**2**	**11b**	48	43
5	**8**		**2**	**11c**	85	56
6	**8**		**2**	**11d**	22	56
7	**8**		**2**	**11e**	60	77
8	 **9**[c]	benzaldehyde	**1**	**12**	82 (7/3)	rac
9	**10** 	benzaldehyde	**1**	**13**	76 (1/1)	22
10	**10**	benzaldehyde	**2**	**13**	92 (3/2)	10

[a] Isolated yield. [b] ee values were determined on a Daicel Chiralpak AS column. [c] *E*/*Z* = 7/3.

(entry 13). Application of aqueous formaldehyde was unsuccessful (entry 14).

Experiments to probe the scope of the enol ether substrates are summarized in Table 3. First, the reactivity of acethophenone surrogate **8** was investigated. Such a variant of Mukaiyama-type reaction is problematic because of a stronger tendency toward hydrolysis affecting reaction yield. Again, we tested the combination of all three pybox ligands **1**−**3** with zinc triflate. Because of the much less reactivity of substrate, the best results were obtained with as much as 3 equiv of **8** at 0 °C when THF/H_2O was used as a medium. In ethanol-based solvent we observed faster hydrolysis of the enol ether substrate. Surprisingly, for condensation of **8** the most promising source of chirality turned out to be *hm*-pybox **2**[22b] (Table 3, entry 2).

The absolute configuration of the alcohol **11a** was determined by comparison of the optical rotation with literature data.[30]

In the case of the condensation of **8** with aromatic aldehydes the same rules were observed, favoring *o*-substituted aldehydes. For example, *o*-anisaldehyde was a far more reactive and selective substrate when compared to *p*-anisaldehyde (entry 6 vs 7).

Silyl enol ethers **9** and **10** derived from 3-pentanone and cyclohexanone, respectively, were not good substrates in the present catalytic system (entries 8−10). While reaction with enol ether **9** afforded the aldol product in racemic form, the cyclohexanone derivative **10** led to formation of *syn*-aldol in 10% ee (entry 10) and *anti*-aldol in 40% ee.

In summary, we have developed $Zn(OTf)_2$-pybox as an efficient chiral catalyst for asymmetric Mukaiyama-aldol condensation in aqueous media. Under the elaborated conditions the reaction of aldehydes and silyl enol ethers proceeds with good to high yields and stereoselectivity. High enantioselectivity in the aldol reaction in aqueous media is difficult to achieve, but compared to hitherto reported reactions the selectivity is good, and readily available combination of Lewis acid and chiral ligand demonstrate practical utility of presented catalytic system. Newly elaborated catalyst allows to increase the water content in the reaction mixture up to 50% what would have important advantages to environmental issues.

Experimental Section

General Methods. Reactions were controlled using TLC on silica alu-plates (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 silicagel 60 (240−400 mesh). Diastereomeric ratio was detected using ^1H NMR technique. Enantiomer ratios were measured using chiral HPLC columns (Chiralpak AS-H and AD-H) with hexane/2-propanol solvent gradient.

Typical Procedure for Asymmetric Aldol Reactions. To a solution of pybox ligand **1** (37 mg, 0.125 mmol) and zinc trifluoromethanesulfonate (36 mg, 0.10 mmol) in 1.5 mL of THF/EtOH(1/1)−H_2O(10%) at −25 °C were added silyl enol ether **4** (250 μL, 1 mmol, 2 equiv) and the appropriate aldehyde (0.5 mmol). The reaction mixture was stirred for 20 min at the same temperature, and then the homogeneous solution was left standing in the fridge at the appropriate temperature for 10−168 h. The reaction was diluted with MTBE and washed with water and brine. Organic solution was dried and evaporated to dryness, and the residue was purified by silica gel chromatography (AcOEt/hexane, 1/4).

Acknowledgment. We thank the Alexander von Humboldt Foundation for generous donation of the HPLC system.

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

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