

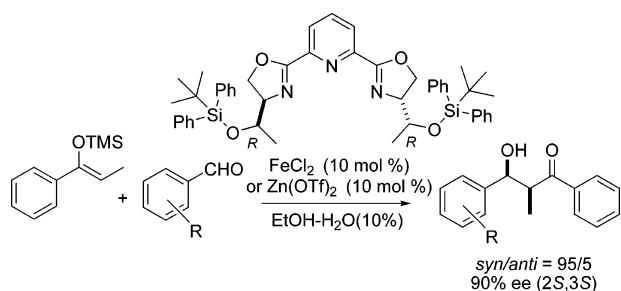
## Iron(II) and Zinc(II) Complexes with Designed *pybox* Ligand for Asymmetric Aqueous Mukaiyama-Aldol Reactions

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An iron(II) complex with a hindered hydroxyethyl-*pybox* (*hepybox*) ligand shows improved catalytic activity and enantioselectivity for asymmetric Mukaiyama-aldol reactions in aqueous media. This water-stable chiral Lewis acid promotes condensation of aromatic silyl enol ethers with a range of aldehydes with good yields, excellent *syn*-diastereoselectivity and up to 92% ee. The combination of the same ligand with Zn<sup>II</sup> salt is also demonstrated as a remarkably efficient and water-compatible chiral Lewis acid.

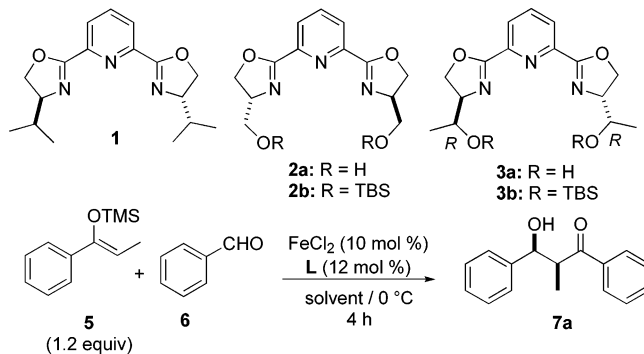
Organic reactions in which water is used as a solvent or cosolvent have attracted a great deal of attention recently because of the unique properties of water and its key role as a solvent for green chemistry.<sup>1</sup> Although various kinds of reactions have been developed in aqueous solvents recently,<sup>2</sup> asymmetric catalysis promoted by chiral Lewis acids in such media is still at an initial stage mostly because of the water incompatibility of known catalysts.<sup>3</sup> Moreover, enantioselective versions of Lewis acid mediated reactions in aqueous solvents are difficult to achieve because competitive ligand exchange between a chiral ligand and water molecules easily occurs, and this affects enantioselectivity.

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TABLE 1. Mukaiyama-Aldol Reaction Catalyzed by Fe<sup>II</sup> Salt: Effect of Solvents and Ligands



entry	solvent	ligand	yield (%) <sup>a</sup> ( <i>syn/anti</i> )	ee <i>syn</i> (%) <sup>b</sup>
1	EtOH–H <sub>2</sub> O(10%)	<b>1</b>	63 (93/7)	40 ( <i>S,S</i> ) <sup>c</sup>
2	EtOH–H <sub>2</sub> O(20%)	<b>1</b>	60 (95/5)	62 ( <i>S,S</i> )
3	EtOH	<b>1</b>	30 (81/19)	40 ( <i>S,S</i> )
4	EtOH–H <sub>2</sub> O(10%)	<b>2a</b>	70 (91/9)	68 ( <i>R,R</i> )
5	EtOH–H <sub>2</sub> O(20%)	<b>2a</b>	65 (85/15)	58 ( <i>R,R</i> )
6	EtOH–H <sub>2</sub> O(10%)	<b>3a</b>	65 (9/1)	27 ( <i>S,S</i> )
7	EtOH–H <sub>2</sub> O(10%)	<b>2b</b>	62 (96/4)	38 ( <i>R,R</i> )
8	EtOH–H <sub>2</sub> O(10%)	<b>3b</b>	75 (92/8)	70 ( <i>S,S</i> )
9	EtOH–H <sub>2</sub> O(10%)	<b>4<sup>d</sup></b>	82 (92/8)	<i>rac</i>

<sup>a</sup> Isolated yield after silica gel chromatography. <sup>b</sup> Determined by HPLC analysis using Chiralpak AD-H column. <sup>c</sup> The absolute configuration of the enol **7a** was determined by comparison of the HPLC analysis with literature data in ref 9. <sup>d</sup> *Ph-pybox*.

The synthesis of enantiopure molecules via aldol-type reactions constitutes another interesting problem,<sup>4</sup> and the development of efficient aldol methods in aqueous solvents is an intensively investigated topic nowadays.<sup>5</sup> The Mukaiyama-aldol reaction in aqueous media has also been a subject of current importance.<sup>6</sup> Only a few catalysts containing copper,<sup>7</sup> lead,<sup>8</sup> praseodymium,<sup>9</sup> or gallium<sup>10</sup> have been used in their enantioselective variants. Recently, excellent examples of the hydroxymethylation of silicon enolates using scandium<sup>11</sup> and bismuth-based<sup>12</sup> Lewis acids have been reported.

The scope and limitation of this reaction is still, however, not fully recognized. Attaining high enantioselectivity in aldol

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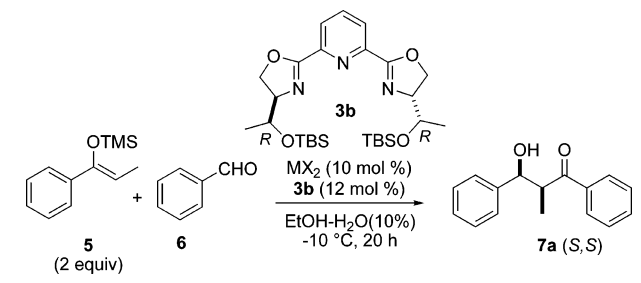
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TABLE 2. Effect of Metal Salt on Reaction Yield and Selectivity



entry	MeX <sub>n</sub>	yield (%) <sup>a</sup> (syn/anti)	ee syn (%) <sup>b</sup>
1	Zn(OTf) <sub>2</sub>	84 (92/8)	68 (2S,3S)
2	Zn(OTf) <sub>2</sub>	84 (94/6)	62 <sup>c</sup>
3	Cu(OTf) <sub>2</sub>	17 (82/18)	13
4	In(OTf) <sub>3</sub>	78 (95/5)	rac
5	Pr(OTf) <sub>3</sub>	84 (65/35)	34
6	Bi(OTf) <sub>3</sub>	40 (95/5)	9
7	NiCl <sub>2</sub>	trace	
8	RuCl <sub>2</sub>	trace	
9	CeCl <sub>3</sub>	67 (65/35)	30
10	<b>FeCl<sub>2</sub></b>	<b>75 (95/5)</b>	<b>72</b>

<sup>a</sup> Isolated yield after silica gel chromatography. <sup>b</sup> Determined by HPLC analysis using Chiralpak AD-H column. <sup>c</sup> *pybox* **1** was used instead of **3b**.<sup>13</sup>

reactions in aqueous media is generally not easy, and diastereoselectivity in hitherto reported reactions is not excellent. Moreover, most reported catalysts are composed of heavy or rare earth metals, which creates some drawbacks for their applications because of toxicity or high price. To address this issue, we have recently discovered zinc-<sup>13</sup> and iron-based<sup>14</sup> chiral Lewis acids as cheap, nontoxic, and environmentally benign catalysts for the asymmetric Mukaiyama carbon-carbon bond-forming process.

Application of iron-based chiral Lewis acids to asymmetric synthesis seems to be particularly exciting as iron is one of the most abundant metals on earth and consequently one of the cheapest and most environmentally acceptable. Interest in well-defined iron complexes as catalysts for bond-forming reactions is an area of ongoing development.<sup>15</sup>

Our group recently reported the first example of water-compatible iron-based chiral Lewis acids for the Mukaiyama reaction.<sup>14</sup> We showed that application of iron complexes with convenient chiral ligands is possible yet problematic because of some instability of iron complexes in aqueous media. Moreover, the catalytic system was capricious and very sensitive to many reaction factors. Thus, reproducibility of the reaction was far more problematic when compared to other known catalysts. Finally, the enantioselectivity of the catalyst left room for further improvement.

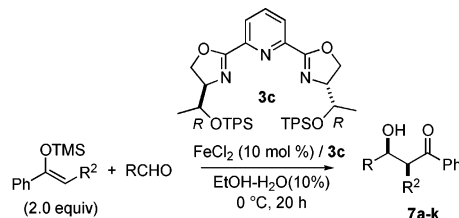
Herein we describe studies on the application of an iron complex composed of iron(II) chloride and tuned, lipophilic *pybox* ligand as stable, efficient, and reliable iron-based chiral Lewis acids for aqueous asymmetric Mukaiyama-aldol reactions.

Our initial aim was to identify the best-suited chiral ligand in terms of both reaction conversion and enantioselection. At first, *Z*-silyl enol ether **5** was reacted with benzaldehyde in

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TABLE 3. Examples of Fe<sup>II</sup>-3c-Catalyzed Mukaiyama-Aldol Reactions

entry	product	yield (%) <sup>a</sup> (syn/anti)	ee syn (%) <sup>b</sup>
1	<b>7a</b>	84 (96/4)	84
2	<b>7b</b>	27 (3/2)	27 <sup>c</sup>
3	<b>7c</b>	94 (94/6)	92
4	<b>7d</b>	83 (96/4)	80
5	<b>7e</b>	95 (95/5)	84
6	<b>7f</b>	81 (87/13)	79
7	<b>7g</b>	88 (91/9)	78
8	<b>7h</b>	50 (85/15)	74
9	<b>7i</b>	95 (5/1)	rac
10	<b>7j</b>	98 (8/2)	64
11	<b>7k</b>	25 (7/3)	60
11	<b>7k</b>	39	60

<sup>a</sup> Isolated yield after silica gel chromatography. <sup>b</sup> Determined by HPLC analysis using Chiralpak AD-H and AS-H columns. <sup>c</sup> Carried out in anhydrous ethanol.

aqueous ethanol in the presence of iron(II) chloride and various *pybox* ligands. The results are summarized in Table 1.

A series of modified *pybox* ligands was evaluated in association with  $\text{FeCl}_2$  to identify the most enantioselective and reliable system. Although in all cases the reaction proceeded smoothly to give the aldol product **7a** in good yields and diastereoselectivities, the enantioselectivities depend on the structure of *pybox* ligands. In a deoxygenated aqueous system, commercial *pybox* **1**<sup>16</sup> provides aldol **7a** in up to 62% ee. Application of hydroxymethyl-*pybox* **2a**<sup>17</sup> slightly increased the ee (68%), while its hydroxyethyl analogue **3a** resulted in decreased selectivity (27%). Further, we decided to test more hindered analogues of **2a** and **3a**. Whereas protection of the hydroxymethyl-*pybox* by

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TABLE 4. Examples of Zn<sup>II</sup>-3c-Catalyzed Mukaiyama-Aldol Reactions

entry	product	solvent	temp.	time	yield (%) ( <i>syn/anti</i> ) <sup>a</sup>	ee <i>syn</i> (%) <sup>b</sup>	
1		<b>7a</b>	EtOH-THF(1/1)-H <sub>2</sub> O(10%)	-20 °C	20 h	90 (93/7)	90
			EtOH-H <sub>2</sub> O(10%)	-20 °C	20 h	80 (95/5)	91
			EtOH-H <sub>2</sub> O(10%)	0 °C	10 h	92 (93/7)	88
			EtOH-H <sub>2</sub> O(20%)	0 °C	10 h	85 (92/8)	87
		THF-H <sub>2</sub> O(10%)	0 °C	10 h	47 (85/15)	73	
2		<b>7b</b>	EtOH-THF(1/1)-H <sub>2</sub> O(10%)	-20 °C	20 h	89 (9/1)	92
			EtOH-H <sub>2</sub> O(10%)	-20 °C	20 h	90 (93/7)	95
3		<b>7c</b>	EtOH-H <sub>2</sub> O(10%)	-20 °C	20 h	85 ( <i>syn</i> )	80
4		<b>7d</b>	EtOH-H <sub>2</sub> O(10%)	-20 °C	20 h	92 (92/8)	90
5		<b>7f</b>	EtOH-H <sub>2</sub> O(10%)	-20 °C	20 h	82 (85/15)	77
6		<b>7i</b>	EtOH-THF(1/1)-H <sub>2</sub> O(10%)	-20 °C	20 h	94 (9/1)	86
			EtOH-H <sub>2</sub> O(10%)	-20 °C	20 h	98 (9/1)	87
7		<b>7j</b>	EtOH-THF(1/1)-H <sub>2</sub> O(10%)	-20 °C	72 h	40 (85/15)	85
			THF-H <sub>2</sub> O(10%)	0 °C	72 h	35 (85/15)	64

<sup>a</sup> Isolated yield after silica gel chromatography. <sup>b</sup> Determined by HPLC analysis using Chiralpak AD-H and AS-H columns.

*O*-*tert*-butyldimethylsilyl group<sup>17b</sup> did not improve the selectivity and even resulted in a drop of enantioselectivity (38%), application of the TBS-hydroxyethyl-*pybox* **3b**<sup>17c</sup> increased selectivity as reflected in the higher ee (70%).

Subsequently, various metal salts were examined in the asymmetric aldol reaction using the best ligand so far, **3b** (Table 2). We screened some water-compatible Lewis acids as potential catalysts for the Mukaiyama-aldol reaction. Although almost all salts that were studied catalyzed the formation of **7a** in good yield, the complexes derived from Zn(OTf)<sub>2</sub> and FeCl<sub>2</sub> afforded substantially higher enantioselectivity. Only for an iron salt, application of deoxygenated solvents was necessary because of an unwelcome tendency toward oxidation of the Fe(II) to Fe(III), which catalyzes the reaction but produces racemates.

As can be seen from the previous study, the readily available combination of hindered hydroxyethyl-*pybox* **3b** and iron(II) chloride turned out to be the most selective couple in the aqueous asymmetric Mukaiyama-aldol reaction. These considerations led us to prepare a new, designed analogue. We decided to test a more hindered and lipophilic *pybox* family member. We assumed that more bulky ligand substituents can effectively shield one of the sites of nucleophilic attack, resulting in the higher enantioselectivity. On the other hand, recent findings suggest that selective hydrophobic acceleration can play an interesting and important part in organic synthesis in water.<sup>2c</sup> Thus, we decided to equip hydroxyethyl-*pybox* with bulky and lipophilic substituents. Using a modified literature procedure<sup>17c</sup> we prepared *O*-*tert*-butyldiphenylsilyl-hydroxyethyl-*pybox* (TPS-he-*pybox*) **3c**.<sup>18</sup>

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(18) For the synthesis of **3c** from (2*S*,3*R*)-L-threonine methyl ester hydrochloride and pyridinedicarbonyldichloride, see Supporting Information.

The enantioselectivity of this ligand was assessed in the catalytic aldol reaction of **5**. As expected, the more bulky substituents had a profound effect on enantioselectivity (Table 3, entry 1). Aqueous ethanol proved to be the optimal solvent, providing aldol product in 84% yield and 84% ee at 0 °C.

The generality of the reaction was examined in detail using 10 mol % of the catalyst, and the results are summarized in Table 3. The Mukaiyama-type reactions proceeded well using various substrates. The reaction has broad applicability with respect to the aldehyde. Both good enantioselectivity (70–90%) and excellent *syn*-selectivity were obtained when silyl enol ether **5** and aromatic aldehydes were employed. Heteroaromatic 2-pyridinecarboxyaldehyde delivered racemates (entry 8). Although the aldol reaction of  $\alpha,\beta$ -unsaturated (entry 9) and aliphatic (entry 10) substrates proceeded in aqueous solvent, the enantioselectivity was moderate. For all reactions catalyzed by Fe(II) complexes, deoxygenated solvents were used. In the case of the complex composed of Fe(II) with **3c**, the resulting species was far more stable under the reaction conditions when compared to previously elaborated systems.<sup>14</sup> As a result the catalyst was observed to be more convenient and reliable. This resulted in better reproducibility of the reaction yield and ee. To explain this tendency, we assume that bulky silyl groups in the ligand better shield the central iron cation, which suppress the Fe(II) to Fe(III) oxidation process.

The catalytic utility and flexibility of ligand **3c** was demonstrated as well in the reaction promoted by Zn<sup>II</sup> salt. To our delight this zinc-based chiral Lewis acid showed high activity in aqueous Mukaiyama-aldol reactions. Thus, the selectivity of the process was improved by replacing commercial ligand **1**<sup>13</sup> with TPS-he-*pybox* **3c**. Moreover, zinc catalyst seems to be the more convenient for such reaction as this complex is not air-sensitive.

Several examples of the catalytic asymmetric aldol reactions of silyl enol ether **5** with aldehydes are shown in Table 4. The best solvent for a range of aldehydes was ethanol–water. In general, the amount of water did not affect selectivity. However, the catalyst used is not applicable to solvents with more than 25% water because of solubility problems. A good level of ee, reaching 90%, was maintained for aromatic (entries 1–5),  $\alpha,\beta$ -unsaturated (entry 6), and aliphatic aldehydes (entry 7).

Despite the bulky substituent in ligand **3c**, the same geometry of the resulting complex can be postulated as it was observed

for other metal-*pybox* complexes.<sup>16</sup> Zinc ion coordinates to three nitrogen atoms (in the planar geometry) resulting in the octahedral structure of the whole complex where octahedron positions are held by water molecules.<sup>19</sup> Due to the bulky silyl group the attack toward the coordinated carbonyl group is more effectively shielded from the one face. As a result the higher enantioselectivity of the reaction was observed when compared to the same process catalyzed by zinc complex with less hindered *pybox* ligands.<sup>13</sup>

In summary, the application of the iron(II)-*pybox* complexes as reliable and water-compatible chiral Lewis acids for the Mukaiyama-aldol reactions has been accomplished. The use of 10% of this chiral catalyst allowed better reactivity and enantioselectivity than with commercial ligands. Moreover, the stability of the catalytic system is far more satisfactory when compared to previously described iron(II) catalysts. An easy-to-prepare *pybox*-type ligand showed high selectivity in the reaction catalyzed by both Fe<sup>II</sup> and Zn<sup>II</sup> chiral Lewis acids. The developed zinc-based chiral Lewis acid seems to be the most efficient and enantioselective catalyst for the aqueous Mukaiyama condensation.<sup>20</sup>

## Experimental Section

**General Procedure for Asymmetric Aldol Reactions Catalyzed by Fe<sup>II</sup> Salt.** A mixture of TPS-he-*pybox* (**3c**) (47 mg, 0.06 mmol, 12 mol %) and iron(II) chloride (6.5 mg, 0.05 mmol, 10 mol %) in 1.5 mL of deoxygenated EtOH/H<sub>2</sub>O (9/1) was stirred at 0 °C under Ar until all solid was observed to dissolve (15–20 min). To the resulting deep-red solution were added silyl enol ether **5** (230  $\mu$ L, 1.0 mmol, 2 equiv) and the appropriate aldehyde (0.5 mmol), and resulting solution was stirred at 0 °C for 5 h under Ar. The reaction was diluted with MTBE and washed with water and brine. The organic phase was dried and evaporated to dryness, and the residue was purified by silica gel chromatography (typically, AcOEt/hexane, 1:4).

**General Procedure for Asymmetric Aldol Reactions Catalyzed by Zn<sup>II</sup> Salt.** A mixture of TPS-he-*pybox* (**3c**) (23 mg, 0.03 mmol, 12 mol %) and zinc(II) trifluoromethanesulfonate (9 mg, 0.025 mmol, 10 mol %) in 1 mL of EtOH/H<sub>2</sub>O (9/1) was stirred at –20 °C (15–20 min). To the resulting homogeneous solution were added silyl enol ether **5** (115  $\mu$ L, 0.5 mmol, 2 equiv) and the appropriate aldehyde (0.25 mmol), and resulting homogeneous solution was left in the refrigerator at –20 °C overnight without stirring. The reaction mixture was poured onto a silica gel column and eluted by AcOEt/hexane (1:4) to yield the desired aldols.

**Supporting Information Available:** General experimental procedure for Fe<sup>II</sup>- and Zn<sup>II</sup>-based catalysts, full characterization of compounds **7a–k**, and synthesis of ligand **3c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(20) For comparison see the following. Reference 9: **7a** 90% yield, 78% ee; **7b** 91% yield, 75% ee; **7i** 77% yield, 76% ee; **7j** 53% yield, 47% ee. Reference 10: **7a** 85% yield, 85% ee; **7b** 80% yield, 84% ee; **7i** 90% yield, 86% ee. Reference 13: **7j** 55% yield, 72% ee.