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A chiral iron(II)–*pybox* catalyst stable in aqueous media. Asymmetric Mukaiyama–aldol reaction

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Abstract—Among various transition metals, iron is nontoxic, cheap and hence of great potential synthetic use. We report herein a water stable chiral Lewis acid containing an iron(II) ion and a *pybox*-type ligand. The resulting cationic aqua complex of C_2-symmetry is an effective Lewis acid catalyst for asymmetric Mukaiyama–aldol reactions in aqueous media. The aldol products have been obtained in good yields, *syn*-diastereoselectivities and ca. 70% levels of enantioselectivity.

The aldol reaction is considered as one of the most important carbon–carbon bond forming reactions in organic synthesis.[1] Its usefulness for the construction of natural products has promoted rapid evolution of efficient chiral catalysts.[2] Among other methodologies, the chiral Lewis-acid-catalyzed condensation of silyl enol ethers with aldehydes (the Mukaiyama reaction)[3] constitutes one of the most convenient and relevant variants of the classical aldol reaction.

In recent years, stereoselective organic reactions in aqueous media have attracted a great deal of attention.[4,5] In this respect, the enantioselective Mukaiyama reaction in aqueous solvents presents an important and challenging issue.[6] Since Kobayashi showed that a chiral copper complex can act as a water tolerant catalyst for the Mukaiyama–aldol reaction,[7] several other Lewis acids have been utilized in asymmetric aldol reactions in aqueous solvents.[8]

However, most of those catalysts are composed of heavy or rare earth metals which create drawbacks in their applications because of the toxicity or high price. In contrast, iron is the most abundant metal on earth, and consequently one of the cheapest and environmentally friendly. Interest in well-defined iron complexes as catalysts for bond forming reactions is an area of ongoing development.[9] In this respect enantioselective transformations promoted by iron complexes constitute precious and rare examples.[10]

Previously, dicarbonyl cyclopentadienyl iron halides[11] and cationic iron complexes[12] were demonstrated as catalysts in diastereoselective Mukaiyama-type additions of ketene acetals to aldehydes in anhydrous solvents. More recently, Kobayashi reported that Fe(II) and Fe(III) salts showed considerable activity in stereoselective Mukaiyama–aldol reactions in aqueous THF,[13] especially when the reaction was carried out in the presence of catalytic amounts of surfactants.[14] Thus, we considered iron salts to be interesting candidates for designing water compatible chiral Lewis acids. To the best of our knowledge, chiral iron-complexes have never been demonstrated as catalysts for asymmetric Mukaiyama–aldol reactions, not to mention in aqueous media, where the said catalytic system must meet much more stringent requirements.[5a,6b]

As a part of an ongoing program towards new asymmetric aldol methodologies, we reported recently the application of a zinc-based chiral Lewis acid in an asymmetric Mukaiyama–aldol reaction in aqueous media.[15] Here we present the first example of water compatible iron(II) complexes as non-toxic, environmentally benign catalysts for asymmetric Mukaiyama carbon–carbon bond forming processes.

We initially screened various chiral ligand-iron(II) chloride complexes for the best catalytic activity in the

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Keywords: Asymmetric synthesis; Mukaiyama reaction; Water; Iron complex.

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aqueous asymmetric Mukaiyama reaction. Our preliminary studies revealed that *pybox*-type ligands **1**[17] and **2**[18] were the most promising candidates for further studies.

The iron(II)–*pybox* complexes were prepared by stirring a deoxygenated EtOH/H_2O mixture of ligand and iron(II) chloride until all the solid was observed to dissolve. To the resulting dark red solution, benzaldehyde and silyl enol ether **3** were added under an argon atmosphere. The reaction in EtOH/H_2O (9/1) proceeded smoothly at 0 °C affording excellent selectivity (Table 1, entry 1).

The reaction outcome depended, however, on the solvent ratio giving the best enantioselectivity for EtOH/H_2O (4/1) (entry 2). We were delighted to find that the reaction proceeded in the same yield and good enantioselectivity using 10 mol % of the catalyst (entry 3). Below this level a lower yield and selectivity were observed (entry 4).

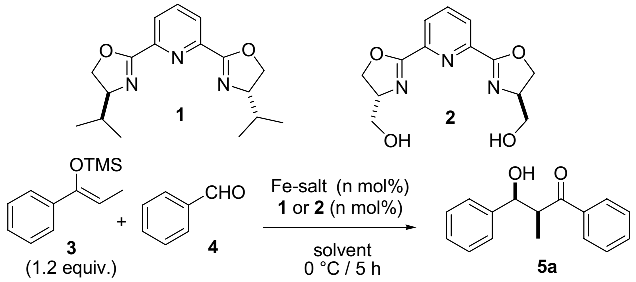
The use of $Fe(BF_4)_2{\cdot}6H_2O$ (entry 6) or $Fe(ClO_4)_2$ (entry 7) with **1** resulted in a slightly better reaction yields without significant change in the diastereoselectivity, but a drop in enantioselectivity was observed. $FeSO_4$-**1** was found to be an unpromising combination. Iron fluoride did not form a catalyst soluble in the reaction mixture.

The effect of the solvents was then examined. The aldol reaction proceeded most efficiently in water–ethanol solutions. The Fe(II)-based chiral Lewis acid was stable in alcohol-type solvents but the catalytic system decomposed rapidly when an aqueous mixture with aprotic solvents, such as THF and DME, was engaged as the reaction medium.

We have found that a water content exceeding 20% in the reaction medium resulted in a lower yield and selectivity. On the other hand, the essential role of water was proved by using dry ethanol. In this case, a lower yield and stereoselectivity were observed (entry 12). In dry dichloromethane, only traces of aldol product was formed in the reaction.

In all cases careful deoxygenation of the solvents played an essential role in obtaining satisfactory levels of ee and was crucial for reproducibility of the experiments. Although iron(III) chloride with **1** was an active Lewis acid, it delivered aldol **5a** as a racemate (entry 14). Formation of an iron(III) catalyst was thus expected to be

Table 1. Solvent and catalyst studies. Reaction of benzaldehyde with *Z*-enol silyl ether **3**



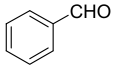
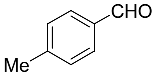
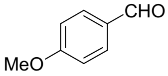
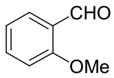
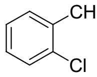
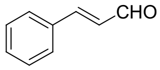
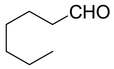
Entry	Solvent	Fe-salt	*n*	Yield[a] (%) (*syn*/*anti*)	ee[b] (%) (*syn*)
Ligand **1**					
1	EtOH/H_2O 9/1	$FeCl_2{\cdot}4H_2O$	20	66 (94/6)	40 (*S*,*S*)[c]
2	EtOH/H_2O 4/1	$FeCl_2{\cdot}4H_2O$	20	62 (96/4)	62
3	EtOH/H_2O 4/1	$FeCl_2{\cdot}4H_2O$	10	60 (95/5)	62
4	EtOH/H_2O 4/1	$FeCl_2{\cdot}4H_2O$	5	50 (92/8)	24
5	EtOH/H_2O 7/3	$FeCl_2{\cdot}4H_2O$	10	42 (94/6)	30
6	EtOH/H_2O 4/1	$Fe(BF_4)_2{\cdot}6H_2O$	10	65 (95/5)	45
7	EtOH/H_2O 4/1	$Fe(ClO_4)_2{\cdot}nH_2O$	10	69 (94/6)	38
8	MeOH/H_2O 4/1	$FeCl_2{\cdot}4H_2O$	10	55 (95/5)	33
9	*n*-PrOH/H_2O 4/1	$FeCl_2{\cdot}4H_2O$	10	50 (92/8)	28
10	*i*-PrOH/H_2O 4/1	$FeCl_2{\cdot}4H_2O$	10	45 (92/8)	28
11	DMF/H_2O 4/1	$FeCl_2{\cdot}4H_2O$	10	70 (85/15)	rac.
12	EtOH	$FeCl_2{\cdot}4H_2O$	10	30 (86/14)	47
13	EtOH	$FeCl_2$	10	30 (81/19)	40
14	EtOH/H_2O 4/1	$FeCl_3$	10	39 (86/14)	rac.
Ligand **2**					
15	EtOH/H_2O 9/1	$FeCl_2{\cdot}4H_2O$	10	68 (91/9)	70 (*R*,*R*)[c]
16	EtOH/H_2O 4/1	$FeCl_2{\cdot}4H_2O$	10	66 (85/15)	58

[a] Isolated yield after silica gel chromatography.

[b] Determined by HPLC analysis using a chiralpak AD-H column.

[c] The absolute configuration of the aldol product **5a** was determined by comparing the optical rotation and HPLC analyses with the literature data.[16,8c]

Table 2. Asymmetric aldol reaction of silyl enol ether **3** with various aldehydes catalyzed by $FeCl_2$/*hm-pybox* **2** (10 mol %)[19]

Entry	Aldehyde	Product	Yield[a] (%) (*syn*/*anti*)	ee[b] (%) (*syn*)
1		**5a**[20]	72 (91/9)	70 (*R*,*R*)
2		**5b**	75 (92/8)	70
3		**5c**	65 (93/7)	75
4		**5d**	87 (93/7)	70
5		**5e**	79 (9/1)	72
6		**5f**	72 (7/3)	44
7		**5g**	25 (8/2)[c]	23

[a] Isolated yield after silica gel chromatography.

[b] Determined by HPLC analysis using a chiralpak AD-H column.

[c] Reaction time 72 h.

responsible for the decrease in the reaction selectivity in nondeoxygenated solvents.

Interestingly, other *pybox*-type ligands delivered essentially different results. Application of (*R*,*R*)-diphenyl-*pybox* resulted in the formation of a racemic aldol product. On the other hand, the yield and selectivity were improved by application of 10 mol % of (*R*,*R*)-*hm-pybox* **2** and Fe(II) chloride (entry 15). This catalytic system was more stable and thus a far more attractive combination than iron(II)–*pybox* **1**.

Finally, it was revealed that the aldol product **5a** was obtained in 72% yield with 70% ee using 10 mol % of $FeCl_2{\cdot}4H_2O$ and **2** (Table 2, entry 1). It is noteworthy that the same level of selectivity was attained using $FeCl_2{\cdot}4H_2O$ and anhydrous $FeCl_2$. For practical reasons, we chose for further experiments $FeCl_2$ which is easier to handle and is less prone to air oxygenation.[19]

Several other substrates were subjected to this catalytic system, and the results are summarized in Table 2. In the case of aromatic aldehydes all the reactions provided good yields (65–87%), diastereoselectivities (*syn*/*anti* = 91/9–93/7) and enantioselectivities for the *syn* isomer of 70–75%. α,β-Unsaturated cinnamaldehyde gave a relatively lower ee of aldol product **5f** (44%). An aliphatic aldehyde (entry 7) was less compatible with the reaction conditions (25% yield, 23% ee).

In summary, we have shown that the $FeCl_2$–*pybox* complex is an efficient chiral catalyst for asymmetric aldol reactions in aqueous media. To the best of our knowledge, this is the first example of a chiral iron complex being active in aqueous asymmetric Mukaiyama reactions. Although the stereoselectivity remains to be improved further, the present work provides a useful concept for the design of chiral catalysts composed of iron(II) salts which function effectively in aqueous media.[21]

References and notes

1. *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004.
2. (a) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595; (b) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65; (c) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.
3. (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011; (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203; (c) Mukaiyama, T.; Matsuo, J. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; p 127.
4. *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998.
5. (a) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751; (b) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221; (c) Li, Ch.-J. *Chem. Rev.* **2005**, *105*, 3095.
6. (a) Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2002**, *8*, 4095; (b) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209.
7. Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* **1999**, *55*, 8739.
8. For a lead-based catalyst see: (a) Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 11531; for a gallium-based catalyst see: (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; for rare earth metal catalysts see: (c) Hamada, T.; Manabe, K.; Ishikawa, S.; Nagayama, S.; Shiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 2989; (d) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 12236; for a recent example of a bismuth-based catalyst see: (e) Kobayashi, S.; Ogino, T.; Shimizu, H.; Ishikawa, S.; Hamada, T.; Manabe, K. *Org. Lett.* **2005**, *7*, 4729.
9. Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.
10. For examples of asymmetric Diels–Alder reactions, see: (a) Kündig, E. P.; Saudan, C. M.; Viton, F. *Adv. Synth. Catal.* **2001**, *343*, 51, and references cited therein; (b) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.-i.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074; (c) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807; (d) Khiar, N.; Fernandez, I.; Alcudia, F. *Tetrahedron Lett.* **1993**, *34*, 123; (e) Matsukawa, S.; Sugama, H.; Imamoto, T. *Tetrahedron Lett.* **2000**, *41*, 6461; for enantioselective sulfide oxidation see: (f) Legros, J.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4225; for other examples see: (g) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978; (h) Trost, B. M.; Lee, Ch. B. *J. Am. Chem. Soc.* **2001**, *123*, 3671; (i) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2752; (j) Scheafer, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4606.
11. Colombo, L.; Ulgheri, F.; Prati, L. *Tetrahedron Lett.* **1989**, *30*, 6435.

12. Bach, T.; Fox, D. N. A.; Retz, M. T. *J. Chem. Soc. Chem. Commun.* **1992**, 1634.
13. Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.
14. Aoyama, N.; Manabe, K.; Kobayashi, S. *Chem. Lett.* **2004**, *33*, 312.
15. (a) Mlynarski, J.; Jankowska, J. *Adv. Synth. Catal.* **2005**, *347*, 521; (b) Jankowska, J.; Mlynarski, J. *J. Org. Chem.* **2006**, *71*, 1317.
16. Denmark, S.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333.
17. Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119.
18. Iwasa, S.; Nakamura, H.; Nishiyama, H. *Heterocycles* **2000**, *52*, 939.
19. Representative procedure: a mixture of *hm-pybox* ligand **2** (17 mg, 0.06 mmol) and iron(II) chloride (6.5 mg, 0.05 mmol, 10 mol %) in deoxygenated EtOH/H_2O (9/1, 1.5 mL) was stirred at 0 °C under an Ar atmosphere until all the solid had dissolved (15–20 min). To the resulting deep-red solution, silyl enol ether **3** (230 μL, 1.0 mmol, 2 equiv) and appropriate aldehyde (0.5 mmol) were added and the resulting solution was stirred at 0 °C for 5 h under an argon atmosphere. The reaction was diluted with methyl *tert*-butyl ether (30 mL) and washed with water and brine. The organic phase was dried, evaporated to dryness and the residue was purified by silica gel chromatography (typically, AcOEt/hexane, 1/4).
20. Data for *(2R,3R)-3-hydroxy-2-methyl-1,3-diphenyl-propan-1-one* (**5a**): ^{1}H NMR (200 MHz) δ (*syn*): 1.19 (d, 3H, J 7.2 Hz), 3.67 (d, 1H, OH, J 1.7 Hz), 4.11 (dq, 1H, J 3.0, 7.3 Hz), 5.23 (br s, 1H), 7.20–7.65 (m, 8H), 7.85–8.20 (m, 2H); ^{13}C NMR (50 MHz) δ: 11.1, 47.1, 73.0, 125.9, 127.3, 128.2, 128.4, 128.7, 133.5, 135.6, 141.7, 205.8.; $[\alpha]_D$ −3.5 (c 1.00 in $CHCl_3$, ee 70%), lit.[16] for *syn*-(2*S*,3*S*): $[\alpha]_D$ +11.7 (c 1.03 in $CHCl_3$, 95% ee); HPLC Daicel Chiralpak AD-H, hexane/*i*-PrOH = 9/1, flow rate = 1 mL/min; *syn* isomer: $t_1 = 9.9$ min (major), $t_2 = 12.2$ min (minor), *anti* isomer: $t_1 = 14.6$ min, $t_2 = 16.0$ min.
21. During the evaluation of this manuscript we encountered a more efficient catalyst composed of an iron salt and a tuned *pybox* ligand. These results will be published soon.