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Catalytic enantioselective Mukaiyama aldol reaction via a chiral indium(III)–pybox complex

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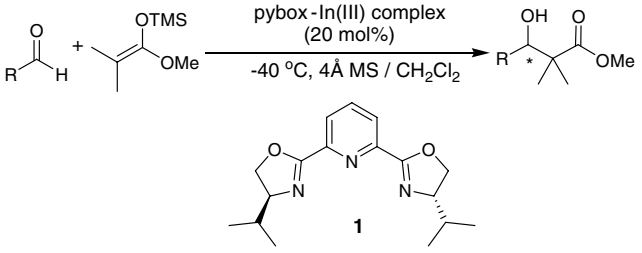
Abstract—A chiral indium(III) complex prepared from indium triflate and a pybox ligand has been developed to give good yields and enantioselectivities (up to 92% ee) in the addition of (1-methoxy-2-methyl-propenyloxy)-trimethylsilane to various aromatic and aliphatic aldehydes via the Mukaiyama aldol reaction.

The asymmetric Mukaiyama aldol[1] reaction between enolsilane derivatives and aldehydes constitutes one of the most versatile synthetic methodologies for the stereoselective construction of optically active β-hydroxy carbonyl units which are important building blocks for the construction of many natural products and pharmaceuticals.[2] Therefore, intense research in this area has been carried out in recent years leading to the development of numerous Lewis acid catalysts bound to chiral ligands.[3] However, to the best of our knowledge, enantioselective Mukaiyama aldol reactions employing a chiral indium(III) catalyst have not been reported. Herein, we report the first asymmetric Mukaiyama aldol reaction between (1-methoxy-2-methyl-propenyloxy)-trimethylsilane and various aldehydes catalyzed by a chiral indium(III)–pybox complex (Eq. 1).



(1)

Recently, we have reported a practical catalytic asymmetric allylation of aldehydes with allyltributylstannanes in the presence of an indium(III)–pybox catalyst as a chiral Lewis acid which has proven to be efficient and especially convenient.[4] Based on this precedent, extension of this chiral indium(III) catalytic system to the Mukaiyama aldol reaction was undertaken. In our initial study, we investigated the merits of various pybox ligands for their ability to promote the enantioselective Mukaiyama aldol reaction of benzaldehyde with (1-methoxy-2-methyl-propenyloxy)-trimethylsilane using a standard protocol. The chiral indium complexes were prepared by reacting indium triflate (0.2 equiv) and a series of bis-oxazoline ligands **1**–**8** (0.22 equiv) in dichloromethane at room temperature in the presence of 4 Å MS. After stirring for 1 h, benzaldehyde (1.0 equiv) was added followed by (1-methoxy-2-methyl-propenyloxy)-trimethylsilane (1.2 equiv). The product was obtained by aqueous work-up and column chromatography. The results are shown in Table 1.

Investigation into the utility of the In(III)–pybox complexes demonstrated that tridentate bis(oxazolinyl)-pyridines (pybox) (Table 1, entries 1, 6, 7 and 8) were effective catalysts for the enantioselective Mukaiyama aldol reaction. Variation of the ligand substituent revealed that the (*S*,*S*)-*i*-Pr-pybox–In(III) complex **1** was the optimal catalyst in this series, affording the (*S*)-β-hydroxy ester in 65% ee and 86% yield (entry 1). The bidentate (*S*,*S*)-bis-oxazoline ligands **2**–**5** were ineffective catalysts for enantiocontrol of this reaction (entries 2–5) probably due to ineffective binding of the ligand to indium.

Keywords: Catalytic; Chiral indium complex; Enantioselective Mukaiyama aldol.
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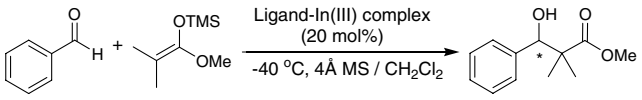
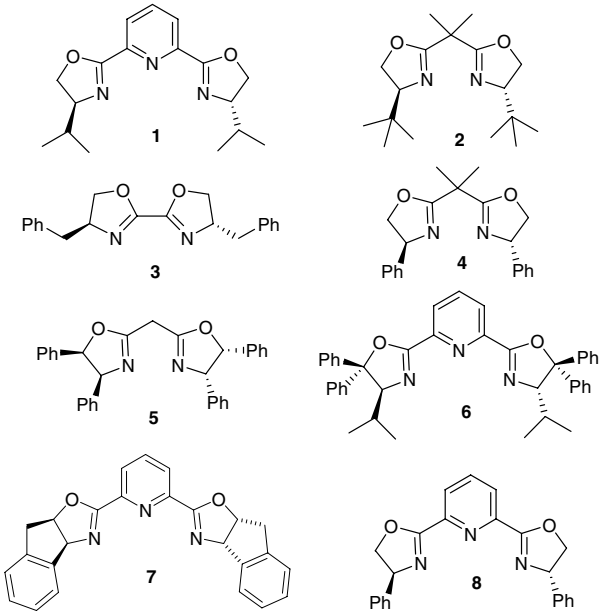
Table 1. Evaluation of various bis-oxazoline ligands for the enantioselective Mukaiyama aldol reaction[a]





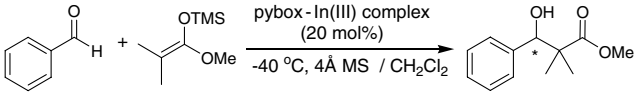
Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	**1**	86	65
2	**2**	68	0
3	**3**	56	0
4	**4**	33	0
5	**5**	24	0
6	**6**	11	11
7	**7**	14	15
8	**8**	12	20

[a] Unless otherwise specified, the reaction was carried out with (1-methoxy-2-methyl-propenyloxy)-trimethylsilane (0.6 mmol) and benzaldehyde (0.5 mmol) in the presence of the chiral indium(III) catalyst prepared from chiral ligands (22 mol %) and $In(OTf)_3$ (20 mol %) in the presence of 15 mg powdered activated 4 Å molecular sieves in 1.5 mL of CH_2Cl_2. The reaction mixture was kept for 24 h at −40 °C.
[b] Isolated yield.
[c] Refer to Supplementary data for enantiomeric excess determination.

With these encouraging results, an optimization study to enhance both the enantiomeric excess and yield of the reaction was initiated. The merits of various indium salts, temperature and the effects of additives were investigated. The results are shown in Table 2.

The reaction catalyzed by the (*S*,*S*)-*i*-Pr-pybox–**1**–In-$(OTf)_3$ complex exhibited the best conversion and enantiomeric excess (Table 2, entry 1). The corresponding halide complexes were inferior catalysts for the reaction and resulted in low yields and enantioselectivities. Moreover, a temperature study revealed that the reaction

Table 2. Optimization studies for the enantioselective Mukaiyama aldol reaction catalyzed by chiral (*S*,*S*)-*i*-Pr-pybox–**1**–In(III) complex[a]



(2)

Entry	Indium reagent	Temperature (°C)	Yield[b] (%)	ee[c] (%)
1	$In(OTf)_3$	−40	86	65
2	InF_3	−40	0	—
3	$InCl_3$	−40	23	0
4	$InBr_3$	−40	19	5
5	$In(OTf)_3$	−20	84	50
6	$In(OTf)_3$	−60	<10	—
7	$In(OTf)_3$	−40	85	0[d]
8	$In(OTf)_3$	−40	72	62[e]
9	$In(OTf)_3$	−40	82	63[f]

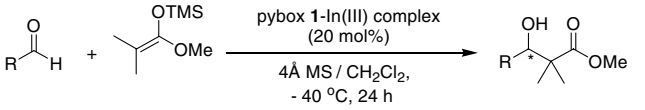
[a] Unless otherwise specified, the reaction was carried out with (1-methoxy-2-methyl-propenyloxy)-trimethylsilane (0.6 mmol) and benzaldehyde (0.5 mmol) in the presence of a chiral indium(III) catalyst prepared from pybox (22 mol %) and $In(OTf)_3$ (20 mol %) in the presence of 15 mg powdered activated 4 Å molecular sieves in 1.5 mL of CH_2Cl_2. The reaction mixture was kept for 24 h at −40 °C.
[b] Isolated yield.
[c] Refer to Supplementary data for enantiomeric excess determination.
[d] The reaction was carried out with 1.2 equiv of TMSCl.
[e] The reaction was carried out with 1.2 equiv of 2,6-di-*tert*-butyl-4-methylpyridine.
[f] The reaction was carried out with 1.2 equiv of isopropanol.

carried out at −60 °C afforded a very low yield (entry 6) while a significant decrease in enantioselectivity was observed at −20 °C (entry 5). Attempts to increase the yield and enantioselectivity through the employment of additives were also unsuccessful. The addition of TMSCl probably results in the formation of a catalytically active silicon intermediate (Me_3SiX), which affords an avenue for a competing achiral catalytic process hence leading to a loss of enantioselectivity (entry 7).[5] Moreover, the addition of 2,6-di-*tert*-butyl-4-methylpyridine and isopropanol did not afford any significant increase in enantioselectivity or yield.

Having optimized the reaction parameters, we extended this catalytic enantioselective Mukaiyama aldol reaction to a series of aldehydes (Eq. 3). The results are shown in Table 3.

Among the aromatic aldehydes employed, 4-nitro-benzaldehyde underwent the catalytic process to afford the β-hydroxy ester with an excellent enantiomeric excess of 92% and a yield of 75% (Table 3, entry 2). In addition, the Mukaiyama aldol reaction of 1-naphthyl and 2-naphthylaldehyde under the influence of the chiral indium catalyst **1** furnished the products in comparable enantiomeric excesses of 77% and 76%, respectively (entries 5 and 6). The reaction of 3-phenyl-propionaldehyde under the influence of the chiral indium catalyst also afforded the product in 51% ee (entry 7). The absolute configuration of the β-hydroxy esters was determined by comparison of the sign of optical rotation and the HPLC data with literature values.[6]

Table 3. Enantioselective Mukaiyama aldol reaction of various aldehydes catalyzed by chiral (*S*,*S*)-*i*-Pr-pybox (**1**)–In(III) complex[a]



(3)

Entry	R	Yield[b] (%)	ee[c] (%)
1	Ph	86	64
2	4-$NO_2C_6H_4$	75	92
3	4-$MeOC_6H_4$	71	57
4	4-MeC_6H_4	73	65
5	1-Naphthyl	50	77
6	2-Naphthyl	56	76
7	$PhCH_2CH_2$	40	51

[a] Unless otherwise specified, the reaction was carried out with (1-methoxy-2-methyl-propenyloxy)-trimethylsilane (0.6 mmol) and benzaldehyde (0.5 mmol) in the presence of the chiral indium(III) catalyst prepared from pybox (**1**) (22 mol %) and $In(OTf)_3$ (20 mol %) in the presence of 15 mg powdered activated 4 Å molecular sieves in 1.5 mL of CH_2Cl_2. The reaction mixture was kept for 24 h at −40 °C.

[b] Isolated yield.

[c] Refer to Supplementary data for enantiomeric excess determination.

In conclusion, we have demonstrated an enantioselective Mukaiyama aldol reaction between (1-methoxy-2-methyl-propenyloxy)-trimethylsilane and various aldehydes using a catalytic amount of (*S*,*S*)-*i*-Pr-pybox–**1**–In(III) complex. The main features of this reaction are as follows: (1) the procedure[7] is operationally simple and can furnish a variety of β-hydroxy esters in good yields and enantioselectivities; (2) the reaction can be performed exclusively using commercially available chemicals. Continuing investigations into the identity of the catalytic species and further extension of the catalytic system to other enantioselective organic transformations are in progress.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.029.

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7. Representative procedure for the enantioselective Mukaiyama aldol reaction of aldehydes: Preparation of (*S*)-methyl-3-hydroxy-2,2-dimethyl-3-phenylpropanoate. To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $In(OTf)_3$ (56.2 mg, 0.1 mmol, 0.2 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL × 2) prior to the addition of 1.5 mL of dichloromethane. (*S*,*S*)-*i*-Pr-pybox **1** (33.2 mg, 0.11 mmol, 0.22 equiv) was added to the mixture which was then stirred under nitrogen at room temperature for 1 h. Benzaldehyde (0.05 mL, 0.5 mmol, 1 equiv) was added to the resulting mixture which was then stirred for 10 min to afford a white suspension. The reaction mixture was then cooled to −40 °C for 15 min followed by slow addition of (1-methoxy-2-methyl-propenyloxy)-trimethylsilane (0.12 mL, 0.6 mmol, 1.2 equiv). The reaction mixture was stirred at −40 °C for 24 h and then quenched with 5 mL of saturated sodium bicarbonate solution. The aqueous layer was extracted with ether (3 × 10 mL) and the combined organic extract was concentrated in vacuo and treated with a mixture of THF–1 M HCl (5:1 mL) solution for 20 min. The mixture was extracted with ether (3 × 10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residual crude product was purified via silica gel chromatography to afford the β-hydroxy ester as a colourless oil. (65%); $[\alpha]_D$ +13.43 (*c* 8.43 w/v%, CH_2Cl_2). The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiralcel OJ column (hexane:*i*-propanol, 98:2, 1 mL/min: $t_1 =$ 13.8 min for the *S* enantiomer, $t_2 = 16.67$ for the *R* enantiomer). It had been established from literature that the *S* enantiomer elutes first.[6]