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# Bis(oxazoline) derived cationic aqua complexes: highly effective catalysts for enantioselective Diels–Alder reactions

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#### Abstract

Cationic aqua complex derived from bidentate inda-box ligand and  $Cu(ClO_4)_2 \cdot 6H_2O$  is an excellent catalyst (5–10 mol%) for enantioselective (92–99% *ee*) Diels–Alder reactions of cyclopentadiene and various bidentate dienophiles. © 1998 Elsevier Science Ltd. All rights reserved.

#### 1. Introduction

The versatility of chiral bis(oxazoline)-metal complexes has been documented in numerous asymmetric syntheses.<sup>1</sup> Particularly notable is the utility of bis(oxazoline)-metal complexes in enantioselective Diels-Alder reactions.<sup>2</sup> Recently, metal complexes of *cis*-1-aminoindan-2-ol derived conformationally constrained bis(oxazoline) ligand (inda-box) have been shown to undergo enantioselective Diels-Alder reactions of cyclopentadiene with various bidentate dienophiles.<sup>3,4</sup> Of various metal-ligand complexes we have examined, inda-box-Cu(OTf)<sub>2</sub> complex consistently exhibited excellent enantioselectivities compared to phenylglycinol derived Ph-box– $Cu(OTf)_2$  complex.<sup>3</sup> While the *cis*-1-aminoindan-2-ol is structurally related to phenylglycinol, the corresponding inda-box is conformationally more constrained since the aromatic ring and the alcohol moiety are linked by a methylene group, thereby restricting the rotational freedom of the aromatic ring completely. As a consequence, inda-box-metal complexes are expected to limit transition state geometries far more effectively than the corresponding phenylglycinol derived Ph-box-metal complexes. This may explain the difference in observed enantioselectivity. While the inda-box–Cu(OTf)<sub>2</sub> complex provided quite impressive enantioselectivity and isolated yields, this catalytic system is far from satisfactory because of a number of limitations which include low reaction temperature, longer reaction time and air sensitivity of the catalyst complexes. In view of these limitations, the recent report by Kanemasa and Curran on the development of various air stable cationic aqua complexes of tridentate ligand (R,R)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) (1)

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(Fig. 1) and various metal perchlorates is very intriguing to us.<sup>5</sup> In an effort to examine the effectiveness of cationic aqua complexes derived from constrained bidentate ligands to carry out enantioselective Diels–Alder reactions, we have prepared various aqua complexes of inda-box ligand and investigated Diels–Alder reactions. Among various metal perchlorates examined, inexpensive commercially available  $Cu(ClO_4)_2 \cdot 6H_2O$  turned out to be the most effective. Herein, we report that the reaction of cyclopenta-diene with various bidentate dienophiles in the presence of 5–10 mol% of aqua complexes derived from (1S,2R)-inda-box ligand  $2^3$  and  $Cu(ClO_4)_2 \cdot 6H_2O$  afforded excellent *endo/exo* selectivity as well as *endo* enantioselectivity. Of particular note, other bidentate bis(oxazoline) ligands such as *t*-Bu-box (3) and Ph-box (4) ligands are considerably less efficient (6–41% *ee*) under similar reaction conditions.



Various aqua complexes (6) were prepared by reaction of an equimolar mixture of metal perchlorate and (1S,2R)-inda-box in CH<sub>2</sub>Cl<sub>2</sub> at 23°C for 8–10 h (Scheme 1). While the metal perchlorates are insoluble in CH<sub>2</sub>Cl<sub>2</sub>, in the presence of bis(oxazoline) ligand the resulting metal-ligand complexes fully dissolve in CH<sub>2</sub>Cl<sub>2</sub> at 23°C. For example, suspension of Cu(ClO<sub>4</sub>)·6H<sub>2</sub>O and (1S,2R)-inda-box 2 in CH<sub>2</sub>Cl<sub>2</sub> resulted in a clear lime green solution after stirring at 23°C for 8 h. The ligand–metal complexes so prepared (5–10 mol%), were cooled to the specified temperature and 1 equiv. of dienophile (5a-c)followed by 4-6 equiv. of freshly cracked cyclopentadiene were added. The progress of the reaction was monitored by TLC. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> solution. After workup and chromatography over silica gel, the resulting Diels-Alder cycloadducts were analyzed by <sup>1</sup>H NMR (400 MHz) and chiral HPLC analysis (Daicel Chiralcel OD column,<sup>6</sup> 10% isopropanol:hexane as the eluent). The Diels-Alder reactions of acryloyl-N-oxazolidinone (5a) and cyclopentadiene in the presence of cationic complexes derived from various metal perchlorates [M(ClO<sub>4</sub>) $_2$ ·6H<sub>2</sub>O; M=Cu, Co, Zn, Ni, Mg] and (15,2R)-inda-box (2) ligand were first examined. Among various metal perchlorates,  $Cu(ClO_4)_2 \cdot 6H_2O$  exhibited the best enantioselectivities (98% *ee*, entry 2) while  $Zn(ClO_4)_2$  and Mg(ClO<sub>4</sub>)<sub>2</sub> have shown almost no enantioselectivity (<10% ee) at 0°C. However, cationic complexes derived from  $Cu(ClO_4)_2 \cdot 6H_2O$  and other bidentate bis(oxazoline) ligands (3 and 4; Fig. 1) were ineffective, providing considerably lower endo enantioselectivities (6% ee and 41% ee, respectively) of the cycloadduct **7a**. As tridentate ligand DBFOX **1** has been shown<sup>5</sup> to provide excellent *endo* enantio-

Enantioselective Diels–Alder reaction of Dienophile 5 with cyclopentadiene						
Entry	Dienophile	Ligand-Metal salt (mol %)	Temp (Time, h)	% Yield <sup>a</sup>	endo/exo <sup>c</sup>	<i>endo</i> ee (config.) <sup>d</sup>
1.	5a	2-Cu(ClO <sub>4</sub> ) <sub>2</sub> .6H <sub>2</sub> O (5)	-78°C (11)	80 <sup>b</sup>	97 : 3	92 (2 <i>S</i> )
2.	5a	2-Cu(ClO <sub>4</sub> ) <sub>2</sub> .6H <sub>2</sub> O (10)	-78°C (10)	88	>99 : 1	98 (2 <i>S</i> )
3.	5a	2-Ni(ClO <sub>4</sub> ) <sub>2</sub> .6H <sub>2</sub> O (10)	-30°C (4)	90	92 : 8	68 (2 <i>S</i> )
4.	5a	2-Cu(ClO <sub>4</sub> ) <sub>2</sub> .6H <sub>2</sub> O (10)	-30°C (3)	87	>99 : 1	98 (2 <i>S</i> )
5.	5a	2-Cu(ClO <sub>4</sub> ) <sub>2</sub> .6H <sub>2</sub> O (10)	0°C (1)	91	98 : 2	95 (2 <i>S</i> )
6.	5a	3-Cu(ClO <sub>4</sub> ) <sub>2</sub> .6H <sub>2</sub> O (10)	0°C (5)	85	97 : 3	6 (2 <i>S</i> )
7.	5a	4-Cu(ClO <sub>4</sub> ) <sub>2</sub> .6H <sub>2</sub> O (10)	0°C (1)	84	97 : 3	41 (2 <i>S</i> )
8	5a	$2 - C_0(C(0_1)) - 6H_0(10)$	0°C (3)	60	92 . 8	30 (25)

85<sup>b</sup>

88

95

95:5

94:6

92:8

99 (2S)

84 (2S)

92  $(2R)^{e}$ 

-30°C (36)

23°C (6)

-78°C (7)

 Table 1

 Enantioselective Diels–Alder reaction of Dienophile 5 with cyclopentadiene

<sup>a</sup>Isolated yield after chromatography. <sup>b</sup>Based on recovered (20-25%) starting material. <sup>c</sup>*Endo/exo* ratios were determined by <sup>1</sup>H-NMR and HPLC. <sup>d</sup> Determined by chiral

HPLC. <sup>e</sup>Determined by comparison of known optical rotation.

2-Cu(ClO<sub>4</sub>)<sub>2</sub>.6H<sub>2</sub>O (10)

2-Cu(ClO<sub>4</sub>)<sub>2</sub>.6H<sub>2</sub>O (10)

2-Cu(ClO<sub>4</sub>)<sub>2</sub>.6H<sub>2</sub>O (10)

9.

10.

11.

5b

5b

5c

selectivity with a range of metal perchlorates, cationic aqua complex derived from  $Cu(ClO_4)_2 \cdot 6H_2O$  and bidentate inda-box ligand has exhibited comparable enantioselectivities.

The results of various Diels-Alder reactions are summarized in Table 1. As shown, reaction of cyclopentadiene and variously substituted acryloyl-N-oxazolidinone (5a-c) in the presence of  $Cu(ClO_4)_2 \cdot 6H_2O$  derived aqua complex proceeded with excellent *endo* selectivity as well as *endo* enantioselectivity over a range of temperatures. Acrylovl-N-oxazolidinone (5a) exhibited excellent endo/exo selectivity (>99:1), endo enantioselectivity (98% ee, entry 4) at -30°C and excellent isolated vield (87%).<sup>7</sup> The reaction time was considerably shorter (3 h at  $-30^{\circ}$ C) than the reaction at  $-78^{\circ}$ C (10 h). The reaction was virtually complete within 1 h at 0°C providing very high endo enantioselectivity (95% ee, entry 5). The Diels-Alder reaction of crotonyl oxazolidinone (5b) and fumaroyl-N-oxazolidinone (5c) with 10 mol% catalyst complex (entries 9 and 11) also provided excellent enantioselectivity (99% *ee* at  $-30^{\circ}$ C for **7b** and 92% *ee* at  $-78^{\circ}$ C for **7c**). The enantiomeric excess of *endo* adduct 7c could not be determined by direct HPLC analysis using Daicel Chiralcel OD column since products peaks are inseparable under a variety of solvent systems and assay conditions. However, the enantioselectivity of 7c was determined after its conversion to the corresponding iodolactone 8 and comparison of optical rotation. As shown in Scheme 2, treatment of cycloadduct 7c with iodine, KI and NaHCO<sub>3</sub> in aqueous CH<sub>2</sub>Cl<sub>2</sub> at 23°C for 16 h afforded 8 ( $[\alpha]_D^{23}$  +38.1 (c 0.84; CHCl<sub>3</sub>); lit.<sup>3</sup>;  $[\alpha]_D^{23}$ -39.2 (c 4.65; CHCl<sub>3</sub>); 94% ee) in 62% yield after silica gel chromatography. The reaction of isoprene and fumaroyl-N-oxazolidinone  $(5d)^8$  was also investigated with 10 mol% aqua complex derived from  $Cu(ClO_4)_2 \cdot 6H_2O$  and inda-box. The reaction proceeded at 23°C for 24 h to provide the cycloadduct 9 in 75% yield and 72% enantiomeric excess ( $[\alpha]_D^{23} - 125$  (c 1.0; CH<sub>2</sub>Cl<sub>2</sub>); lit.<sup>9</sup>;  $[\alpha]_D^{23} - 161$  (c 1.1; CH<sub>2</sub>Cl<sub>2</sub>); 93% ee).<sup>10</sup>

In summary, cationic aqua complex of inexpensive  $Cu(ClO_4)_2 \cdot 6H_2O$  and readily prepared constrained bidentate bis(oxazoline) (2) provided a highly effective catalytic system for enantioselective Diels–Alder reactions over a range of temperatures. The observed enantioselectivities with aqua Cu(II)-complex are comparable to the tridentate DBFOX 1 ligand designed by Kanemasa and Curran, and co-workers.<sup>5</sup>



The present protocol further broadens the scope and synthetic utility of readily prepared inda-box ligands. Synthetic application of the current catalytic system is in progress. The following example is representative of this procedure.

## 2. Preparation of cycloadduct 7c

To a stirred suspension of  $Cu(ClO_4)_2 \cdot 6H_2O$  (91 mg, 0.25 mmol) in  $CH_2Cl_2$  (2 ml) at 23°C, (1*S*,2*R*)inda-box 2 (98 mg, 0.3 mmol) was added. The resulting mixture was stirred for 10 h until the  $Cu(ClO_4)_2 \cdot 6H_2O$  completely dissolved providing a lime green solution. The resulting cationic aqua complex was cooled to  $-78^{\circ}$ C, and fumaroyl-N-oxazolidinone 5c (526 mg, 2.47 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml) was added. Freshly cracked cyclopentadiene (1 ml, 15 mmol) was added dropwise at  $-78^{\circ}$ C and the resulting mixture was stirred for 7 h. After this period, the reaction was quenched with aqueous NaHCO<sub>3</sub> solution. The mixture was extracted with chloroform  $(2 \times 10 \text{ ml})$  and the combined organic layer was washed successively with water and brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvents under reduced pressure afforded a crude residue which was purified by column chromatography over silca gel (25% ethyl acetate:hexane as eluent) to provide the cycloadduct 7c (635 mg, 95% yield) and its exo isomer as a mixture (92:8) by HPLC. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.31 (dd, 1H, J=3.2, 5.6 Hz), 5.87 (dd, 1H, J=2.8, 5.6 Hz), 4.39 (t, 2H, J=8.1 Hz), 4.30 (t, 1H, J=4.1 Hz), 4.13–3.89 (m, 4H), 3.39 (br s, 1H), 3.15 (br s, 1H), 2.84 (dd, 1H, J=1.6, 4.7 Hz), 1.71 (br d, 1H, J=8.8 Hz), 1.45 (dd, 1H, J=1.6, 8.8 Hz), 1.22 (t, 3H, J=7.2 Hz);  ${}^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.08, 172.70, 153.14, 138.09, 133.19, 62.00, 60.63, 48.26, 47.56, 47.38, 46.57, 46.32, 42.82, 14.10; IR (neat) 2983, 1779, 1741, 1694 cm<sup>-1</sup>; mass (CI): *m/z* 280 (M<sup>+</sup>+H).

## 3. Determination of optical purity of the endo-isomer 7c

Enantiomeric excess of *endo* adduct was calculated from the known optical rotation of the iodolactone **8** derived from **7c**. The above mixture of cycloadducts (mixture of *endo* and *exo*) was converted to iodolactone **8** as follows: to a stirred solution of the mixture of cycloadducts (58 mg, 0.208 mmol) in  $CH_2Cl_2$  (4 ml) were added water (1 ml), solid NaHCO<sub>3</sub> (125 mg, 1.49 mmol), KI (66 mg, 0.4 mmol) and

solid iodine (777 mg, 3.06 mmol). The resulting mixture was stirred at 23°C for 16 h. After this period, the reaction was quenched with saturated sodium thiosulfate solution and the mixture was extracted with chloroform (2×10 ml). The combined organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude iodolactone was purified by silica gel chromatography (25% ethyl acetate:hexane as the eluent) to afford **8** (44 mg, 62% yield).  $[\alpha]_D^{23}$  +38.1 (*c* 0.84; CHCl<sub>3</sub>); lit.<sup>3</sup>,  $[\alpha]_D^{23}$  -39.2 (*c* 4.65; CHCl<sub>3</sub>); 94% *ee* (2*S*-isomer). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.13 (d, 1H, *J*=5.0 Hz), 4.20–4.15 (m, 2H), 3.88 (d, 1H, *J*=2.7 Hz), 3.22–3.20 (m, 1H), 3.10 (d, 1H, *J*=4.5 Hz), 3.01 (br s, 1H), 2.82 (br s, 1H), 2.32 (dd, 1H, *J*=1.3, 12.0 Hz), 1.96 (dd, 1H, *J*=2.2, 11.9 Hz), 1.29–1.24 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  177.16, 170.01, 88.37, 61.87, 50.46, 50.28, 46.08, 40.80, 34.94, 27.88, 14.06; IR (neat) 2979, 2928, 2848, 1783, 1729, 1555, 1236, 1194, 1007 cm<sup>-1</sup>; mass (CI): *m/z* 337 (M<sup>+</sup>+H).

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