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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 $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ is an excellent catalyst (5–10 mol%) for enantioselective (92–99% *ee*) Diels–Alder reactions of cyclopentadiene and various bidentate dienophiles.

1. Introduction

The versatility of chiral bis(oxazoline)–metal complexes has been documented in numerous asymmetric syntheses.¹ Particularly notable is the utility of bis(oxazoline)–metal complexes in enantioselective Diels–Alder reactions.² 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.^{3,4} Of various metal–ligand complexes we have examined, inda-box– $\text{Cu}(\text{OTf})_2$ complex consistently exhibited excellent enantioselectivities compared to phenylglycinol derived Ph-box– $\text{Cu}(\text{OTf})_2$ complex.³ 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– $\text{Cu}(\text{OTf})_2$ 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**) (Fig. 1) and various metal perchlorates is very intriguing to us.⁵ 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 $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ turned out to be the most effective. Herein, we

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report that the reaction of cyclopentadiene with various bidentate dienophiles in the presence of 5–10 mol% of aqua complexes derived from (1*S*,2*R*)-inda-box ligand **2**³ and Cu(ClO₄)₂·6H₂O 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 (1*S*,2*R*)-inda-box in CH₂Cl₂ at 23°C for 8–10 h (Scheme 1). While the metal perchlorates are insoluble in CH₂Cl₂, in the presence of bis(oxazoline) ligand the resulting metal–ligand complexes fully dissolve in CH₂Cl₂ at 23°C. For example, suspension of Cu(ClO₄)₂·6H₂O and (1*S*,2*R*)-inda-box **2** in CH₂Cl₂ 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 NaHCO₃ solution. After workup and chromatography over silica gel, the resulting Diels–Alder cycloadducts were analyzed by ¹H NMR (400 MHz) and chiral HPLC analysis (Daicel Chiralcel OD column,⁶ 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(ClO₄)₂·6H₂O; M=Cu, Co, Zn, Ni, Mg] and (1*S*,2*R*)-inda-box (**2**) ligand were first examined. Among various metal perchlorates, Cu(ClO₄)₂·6H₂O exhibited the best enantioselectivities (98% *ee*, entry 2) while Zn(ClO₄)₂ and Mg(ClO₄)₂ have shown almost no enantioselectivity (<10% *ee*) at 0°C. However, cationic complexes derived from Cu(ClO₄)₂·6H₂O 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 shown⁵ to provide excellent *endo* enantio-selectivity with a range of metal perchlorates, cationic aqua complex derived from Cu(ClO₄)₂·6H₂O 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(ClO₄)₂·6H₂O derived aqua complex proceeded with excellent *endo* selectivity as well as *endo* enantioselectivity over a range of temperatures. Acryloyl-*N*-oxazolidinone (**5a**) exhibited excellent *endo/exo* selectivity (>99:1), *endo* enantioselectivity (98% *ee*, entry 4) at –30°C and excellent isolated yield (87%).⁷ The reaction time was considerably shorter (3 h at –30°C) than the reaction at –78°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°C for **7b** and 92% *ee* at –78°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 NaHCO₃ in aqueous CH₂Cl₂ at 23°C for 16 h afforded **8** ([α]_D²³ +38.1 (*c* 0.84; CHCl₃); lit.³; [α]_D²³ –39.2 (*c* 4.65; CHCl₃); 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(ClO₄)₂·6H₂O and inda-box. The reaction proceeded at 23°C for 24 h to provide the cycloadduct **9** in 75% yield and 72% enantiomeric excess ([α]_D²³ –125 (*c* 1.0; CH₂Cl₂); lit.⁹; [α]_D²³ –161 (*c* 1.1; CH₂Cl₂); 93% *ee*).¹⁰

In summary, cationic aqua complex of inexpensive Cu(ClO₄)₂·6H₂O 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. 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(ClO₄)₂·6H₂O (91 mg, 0.25 mmol) in CH₂Cl₂ (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(ClO₄)₂·6H₂O completely dissolved providing a lime green solution. The resulting cationic aqua complex was cooled to –78°C, and fumaroyl-*N*-oxazolidinone **5c** (526 mg, 2.47 mmol) in CH₂Cl₂ (0.5 ml) was added. Freshly cracked cyclopentadiene (1 ml, 15 mmol) was added dropwise at –78°C and the resulting mixture was stirred for 7 h. After this period, the reaction was quenched with aqueous NaHCO₃ solution. The mixture was extracted with chloroform (2×10 ml) and the combined organic layer was washed successively with water and brine, and dried over anhydrous Na₂SO₄. Evaporation of the solvents under reduced pressure afforded a crude residue which was purified by column chromatography over silica 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. ¹H NMR (400 MHz, CDCl₃) δ 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); ¹³C NMR (100 MHz, CDCl₃) δ 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^{–1}; mass (CI): *m/z* 280 (M⁺+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 CH₂Cl₂ (4 ml) were added water (1 ml), solid NaHCO₃ (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 Na₂SO₄ 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). [α]_D²³ +38.1 (*c* 0.84; CHCl₃); lit.³, [α]_D²³ -39.2 (*c* 4.65; CHCl₃); 94% *ee* (2*S*-isomer). ¹H NMR (400 MHz, CDCl₃) δ 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); ¹³C NMR (100 MHz, CDCl₃) δ 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⁻¹; mass (CI): *m/z* 337 (M⁺+H).

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Fig. 1.

Scheme 1.

Scheme 2.

Table 1

Enantioselective Diels-Alder reaction of Dienophile 5 with cyclopentadiene

Entry	Dienophile	Ligand-Metal salt (mol %)	Temp (Time, h)	% Yield ^a	endo/exo ^c	endo ee (config.) ^d
1.	5a	2-Cu(C10 ₄) ₂ ·6H ₂ O (5)	−78°C (11)	80 ^b	97:3	92 (2 <i>S</i>)
2.	5a	2-Cu(C10 ₄) ₂ ·6H ₂ O (10)	−78°C (10)	88	>99:1	98 (2 <i>S</i>)
3.	5a	2-Ni(C10 ₄) ₂ ·6H ₂ O (10)	−30°C (4)	90	92:8	68 (2 <i>S</i>)
4.	5a	2-Cu(C10 ₄) ₂ ·6H ₂ O (10)	−30°C (3)	87	>99:1	98 (2 <i>S</i>)
5.	5a	2-Cu(C10 ₄) ₂ ·6H ₂ O (10)	0°C (1)	91	98:2	95 (2 <i>S</i>)
6.	5a	3-Cu(C10 ₄) ₂ ·6H ₂ O (10)	0°C (5)	85	97:3	6 (2 <i>S</i>)
7.	5a	4-Cu(C10 ₄) ₂ ·6H ₂ O (10)	0°C (1)	84	97:3	41 (2 <i>S</i>)
8.	5a	2-Co(C10 ₄) ₂ ·6H ₂ O (10)	0°C (3)	60	92:8	30 (2 <i>S</i>)
9.	5b	2-Cu(C10 ₄) ₂ ·6H ₂ O (10)	−30°C (36)	85 ^b	95:5	99 (2 <i>S</i>)
10.	5b	2-Cu(C10 ₄) ₂ ·6H ₂ O (10)	23°C (6)	88	94:6	84 (2 <i>S</i>)
11.	5c	2-Cu(C10 ₄) ₂ ·6H ₂ O (10)	−78°C (7)	95	92:8	92 (2 <i>R</i>) ^e

^a isolated yield after chromatography^b Based on recovered (20–25%) starting material^c *Endo/exo* ratios were determined by ¹H-NMR and HPLC^d Determined by chiral HPLC.^e determined by comparison of known optical rotation.