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Electronic and steric effects of bis(oxazolinyl)pyridine ligands on asymmetric Diels–Alder reactions

Hong Wang [a], Hongming Wang [b], Peng Liu [a], Hengquan Yang [a], Jianliang Xiao [a,c,*], Can Li [a,**]

[a] State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China
[b] State Key Laboratory of Molecular Reaction Dynamics, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China
[c] Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK

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Abstract

A series of bis(oxazolinyl)pyridine (Pybox) ligands with different electronic and steric properties were synthesized and evaluated in the Sc(III)-catalyzed asymmetric Diels–Alder reaction of alkenoyl-1,3-oxazolidin-2-ones with cyclopentadiene. The results show that electron-withdrawing groups increase the enantioselectivity, which is more significantly influenced by steric effects arising near the metal center. Up to 96% ee was obtained under mild reaction conditions when using a ligand containing the sterically bulky *t*Bu substituent and electron-withdrawing chloride.

Keywords: Diels–Alder reaction; Bis(oxazolinyl)pyridine ligands; Asymmetric catalysis; Electronic effects; Steric effects

1. Introduction

Enantioselective reactions catalyzed by chiral Lewis acid complexes are of great importance for the production of enantiopure pharmaceuticals and chemicals [1,2]. Among various chiral Lewis acid catalysts, chiral bis(oxazolinyl)pyridine (Pybox) ligands have shown many applications in asymmetric catalysis (Scheme 1) [3–9]. Evans et al. showed that Cu(II)-Pybox complexes are efficient catalysts in asymmetric Diels–Alder (ADA) reactions of monodentate acrolein dienophiles [4], and in recent years, catalysts prepared from the Pybox ligands and rare earth metal salts have also found applications in ADA reactions. For instance, Fukuzawa et al. found that the complex of Sc(III) and 4′-*i*Pr-Pybox is an efficient catalyst for ADA reaction of cyclopentadiene with the chelating dienophiles 3-acryloyl-1,3-oxazolin-2-one **1** and 3-((*E*)-2-butenoyl)-1,3-oxazolin-2-one **2**, affording more than 80% ee's [10]. The same complex catalyzed the ADA reaction of **2** with cyclopentadiene in supercritical CO_2, affording 88% ee; however, using Sc(III)-(4′-*t*Bu-Pybox) as catalyst, a much lower enantioselectivity and yield were obtained [11]. Extensive studies by Desimoni's group have established that both the diastereo- and enantio-selectivities of the ADA reactions depend on substituents on the Pybox ligands and on the lanthanide cations used, and in extreme cases, the sense of both selectivities could be reversed [12–15]. Similar effects were also noted by Aspinall and Greeves in asymmetric cyanation of aldehydes [6].

In a program aimed at developing immobilized Pybox catalysts, we needed to access 4-substituted Pybox ligands. Although Nishiyama et al. have previously studied the effect of substitution at the 4 position on the Rh(III)-Pybox-catalyzed asymmetric hydrosilyation and shown indeed that the reaction rates and enantioselectivies vary with the substituents [16,17], there appears to be no report on how the ADA reactions might be affected by similar variation in ligand. Herein we report the application of 4-substituted Pybox ligands in Sc(III)-catalyzed ADA reactions. Up to 96% ee was obtained under mild reaction conditions (0 °C) at a 5 mol% catalyst loading.

2. Experimental

2.1. General

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with $CDCl_3$ as solvent on a Bruker

* Corresponding author at: Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK. Tel.: +44 151 7942937; fax: +44 151 7943589.
** Corresponding author. Tel.: +86 411 84379070; fax: +86 411 84694447.
E-mail addresses: j.xiao@liv.ac.uk (J. Xiao), canli@dicp.ac.cn (C. Li).

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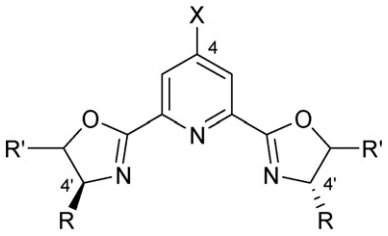

Scheme 1. Substituted Pybox ligands reported in the literature.

DRX-400 spectrometer with the chemical shift values referred to δ(TMS) = 0.00 ppm or $CDCl_3$ (δ 7.26 ppm). Dichloromethane was distilled over calcium hydride. Powdered molecular sieves 4 Å were heated at 350 °C for 8 h and kept in sealed vials in a dryer before use.

2.2. Synthesis of Pybox ligands *L1–L8*

2.2.1. Ligands *L1–L5*

2,6-Bis-[4′*S*-*iso*propyloxazolin-2′-yl]-4-chloropyridine (**L1**), 2,6-bis-[4′*S*-*iso*propyloxazolin-2′-yl]-4-bromopyridine (**L2**), 2,6-bis-[4′*S*-*iso*propyloxazolin-2′-yl]-4-methoxypyridine (**L4**) and 2,6-bis-[4′*S*-*iso*propyloxazolin-2′-yl]-4-dimethylaminopyridine (**L5**) were synthesized according to the literature methods [17-19]. 2,6-Bis-[4′*S*-*iso*propyloxazolin-2′-yl]-pyridine (**L3**) was obtained commercially. The ligands **L1**, **L4** and **L5** were synthesized in a manner very similar to Nishiyama's method [17]. However, we were not able to obtain **L2** using the literature procedure [18]. A modified method was adopted instead.

2.2.2. Synthesis of 2,6-bis-[4′*S*-isopropyloxazolin-2′-yl]-4-bromopyridine (*L2*)

Chelidamic acid (1.18 g, 5.9 mmol) and phosphorus pentabromide (16.49 g, 38.3 mmol) were heated at 90 °C for 3 h. The mixture was cooled to room temperature and then following addition of $CHCl_3$ (23 mL), it was filtered. The filtrate was cooled to 0 °C; MeOH (33 mL) was added slowly. The mixture was concentrated and crystallized in methanol to give 4-bromopyridine-2,6-dicarboxylic acid dimethyl ester as yellow solid (1.37 g, 85% yield).

The above solid was treated with 5 M NaOH (12 mL) and the resulting solution was refluxed for 1 h. After cooling to room temperature, the mixture was acidified with hydrochloric acid to pH 2 and then filtered. The resulting white solid was dried in vacuum at 60 °C to give 4-bromopyridine-2,6-dicarboxylic acid (584 mg, 95% yield). The subsequent procedures were the same as those in the literature [19].

2.2.3. Synthesis of 2,6-bis-[4′*S*-phenyloxazolin-2′-yl]-4-chloropyridine (*L6*)

Chelidamic acid (422 mg, 2.1 mmol) was treated with $SOCl_2$ (11 mL) and a drop of DMF at reflux for 2 days. The excess $SOCl_2$ was then removed under reduced pressure to give the acid chloride as a white solid. To a solution of (*S*)-phenyl glycinol (444 mg, 4.3 mmol) and triethylamine (1.7 mL, 12.9 mmol) in $CHCl_3$ (9 mL) was slowly added a solution of the acid chloride in $CHCl_3$ (15 mL) at 0 °C. The mixture was stirred for 1 day at room temperature and water was then added. The mixture was extracted with CH_2Cl_2 (3× 20 mL) and then dried over $MgSO_4$. The residue was purified by silica gel chromatography with ethyl acetate and hexane (1:2) to give a white solid in 90% yield (830 mg, 1.9 mmol).

To the above solid (300 mg, 0.68 mmol), TsCl (286 mg, 1.5 mmol) was added. This was followed by introducing CH_2Cl_2 (5 mL) and Et_3N (0.9 mL), and the mixture was refluxed for 24 h. Then water (0.5 mL) and dichloromethane (15 mL) were added and the reflux was continued for an additional 1 h. After cooling to room temperature, the organic solution was washed with water (3× 10 mL) and then dried over Na_2SO_4. After evaporation, the crude product was purified by crystallization from ethanol to yield **L6** as white solid (137 mg, 50%). The ^{1}H NMR and ^{13}C NMR spectra were the same as those reported [9].

2.2.4. Synthesis of 2,6-bis-[4′*S*-tert-butyloxazolin-2′-yl]-4-chloropyridine (*L7*)

The preparation was similar to that of **L1**, with (*S*)-*tert*-leucinol replacing (*S*)-valinol. The ligand was obtained as a white solid in 61% yield. Although this ligand was reported by Clark et al. [20], the synthetic method and spectroscopic data were not available. $[\alpha]_D^{31} = -133.3$ (c = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 2H), 4.49 (dd, J = 9.1, 10.1 Hz, 2H), 4.34 (t, J = 8.7 Hz, 2H), 4.12 (dd, J = 8.7, 10.1 Hz, 2H), 0.97 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 148.3, 145.5, 126.3, 76.3, 70.1, 34.3, 26.2; HRMS Calcd. for $C_{19}H_{26}N_3O_2Cl$ (M) 363.1714; found 363.1714.

2.2.5. Synthesis of 2,6-bis-[4′*S*-benzyloxazolin-2′-yl]-4-chloropyridine (*L8*)

The preparation was similar to that of **L1**, with (*S*)-phenylalaninol replacing (*S*)-valinol. The ligand was obtained as white solid in 49% yield. $[\alpha]_D^{32} = -20.9$ (c = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 2H), 7.34–7.22 (m, 10H), 4.67–4.64 (m, 2H), 4.47 (t, J = 9.1 Hz, 2H), 4.26 (t, J = 8.2 Hz, 2H), 3.25 (dd, J = 5.3, 13.8 Hz, 2H), 2.75 (dd, J = 8.8, 13.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 148.3, 145.7, 137.8, 129.4, 128.9, 126.9, 126.2, 73.1, 68.4, 41.8; HRMS Calcd. for $C_{25}H_{22}N_3O_2Cl$ (M) 431.1401; found 431.1404.

2.3. General procedure for the ADA reaction

Anhydrous CH_2Cl_2 (3 mL) was added to a mixture of $Sc(OTf)_3$ (15 mg, 0.03 mmol), a Pybox ligand (0.03 mmol) and 4 Å molecular sieves (90 mg). The mixture was cooled to 0 °C and stirred for 0.5 h, and substrate **1** or **2** (0.6 mmol) and cyclopentadiene (1.8 mmol) were then added in sequence. After a period of time, the product was isolated by filtration through silica and eluted with ethyl acetate/hexane (1:1). The conversion was determined by ^{1}H NMR. The *endo/exo* ratio and ee value of the *endo* isomer were analyzed by chiral HPLC [Chiralcel-OD column, with hexane/2-propanol (95/5) as the eluant for substrate **1** and hexane/ethanol (98/2) as the eluant for substrate **2**].