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

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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

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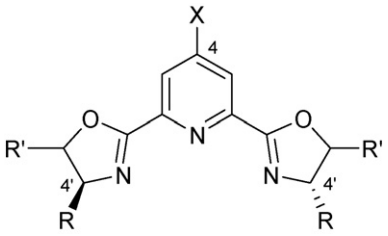


Scheme 1. Substituted Pybox ligands reported in the literature.

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*)

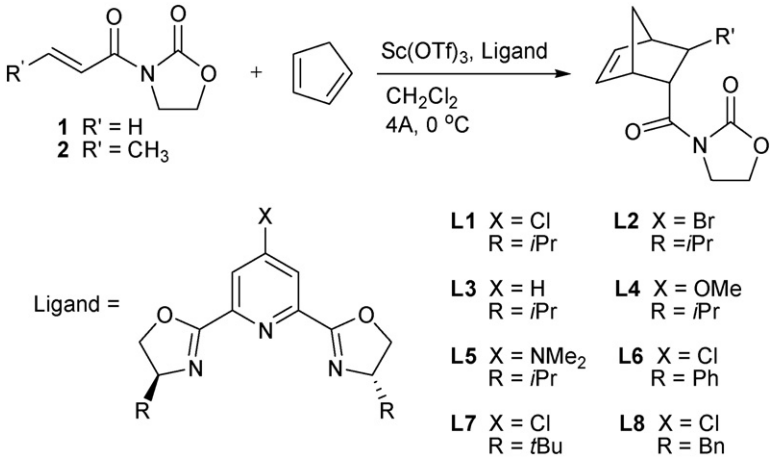
The preparation was similar to that of **L1**, with (*S*)-*tert*-leucinol replacing (*S*)-valinol. The ligand was obtained as a white solid in 61% yield. Although this ligand was reported by Clark et al. [20], the synthetic method and spectroscopic data were not available. $[\alpha]_D^{31} = -133.3$ (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**].



Scheme 2. ADA reaction catalyzed by Sc(III) in combination with a ligand **L1**–**L8**.

3. Results and discussion

The Pybox ligands (**L1**–**L8**) employed in this study are shown in Scheme 2. Although some of these ligands (**L1**–**L6**) have been studied in asymmetric hydrosilylation by Nishiyama et al. [17] and in asymmetric epoxidation by Beller and co-workers [9], they have not been applied to ADA reactions. In this study, they were either obtained commercially or prepared with modified literature methods [17–19]. **L6** was prepared by modifying Beller's method [9]. Thus, by using the readily available TsCl and Et_3N, the intermediate hydroxyamide was transformed into **L6**, simplifying the ligand synthesis [9]. Using this modified procedure, the ligands **L7** and **L8** were then made easily accessible. Judging by the Hammett substituent constants [21,22], the –Cl and –Br substituents are expected to play an electron-withdrawing role, while the –OMe and $–NMe_2$ moieties will be electron-donating. The corresponding catalysts **C1**–**C8** were prepared *in situ* by reacting an equimolar ligand **L1**–**L8** with $Sc(OTf)_3$ in the presence of MS-4 Å. The resulting catalysts were then evaluated in the benchmark ADA reaction of 3-acryloyl-1,3-oxazolin-2-one **1** with cyclopentadiene (Scheme 2). The experimental results are summarized in Table 1.

Focusing on the catalysts **C1**–**C5**, we can see that all the reactions are completed within 5 min. Although the catalyst loadings in most ADA reactions catalyzed by Pybox complexes were around 10 mol%, we found that 5 mol% catalyst is sufficient to give fast cyclization. To the best of our knowledge, this is the highest activity reported in similar reactions [3,10–15]. Table 1 also shows that there is no significant difference in diastereoselectivity among all these catalysts. However, the enantioselectivities are clearly affected by the substituents at the 4 position of ligand. Thus, on going from **C1** through **C2**–**C4** to **C5**, a gradual decrease in the enantioselectivity is manifest, with the difference in ee's being more than 10%. Since this is less likely to be a steric effect, it demonstrates that more electron-withdrawing groups at the 4-position of the Pybox skeleton benefit the enantioselection. A more electrophilic Sc(III) center would be expected to bind **1** more tightly; this could in turn enhance the steric discriminating capability of the ligand, leading to a higer ee. This may explain why **C1**, derived from **L1**, affords the highest ee. However, **L5** gave the highest ee, in comparison with **L1**, **L3** and **L4**, in the Rh(III)-catalyzed asymmetric hydrosilyation aforementioned [17].

Having established the ligand electronic preference for the ADA reaction with Sc(III)-Pybox catalysis, we then examined the ligand steric effects using the ligands **L6**–**L8**, with each containing the electron-withdrawing 4-Cl substituent. It is found that the reactions effected by the catalysts **C6**–**C8** can also be completed within 5 min and importantly, substituents near the catalytic center exert considerable effects on the enantioselectivity, with the bulky *t*Bu-substituted **C7** affording a high ee of 96%. Although the *i*Pr- and Ph-substituted Pybox ligands have been reported [10–14], it is the combination of a sterically bulkier substituent and the electron-withdrawing effect of chloride, leading to **L7**/**C7**, that afforded a surprising high enantioselectivity of 96% ee (Entry 7) under mild reaction conditions (0 °C). Our results can be compared with the best results in the literature (−50 °C, 99% ee, 16 h) in similar ADA reactions with Pybox catalysts reported by Desimoni et al. [15]. Interestingly, Fukuzawa showed that when using *t*Bu-substituted

Table 1
Effect of ligands on the ADA reaction of **1** with **2**[a]

Entry	Catalyst	Substrate	Time	*endo*/*exo*[b]	ee	Configuration[c]
1	**C1**	**1**	<5 min	94/6	84	*S*
2	**C2**	**1**	<5 min	93/7	83	*S*
3	**C3**	**1**	<5 min	93/7	81	*S*
4	**C4**	**1**	<5 min	94/6	79	*S*
5	**C5**	**1**	<5 min	93/7	72	*S*
6	**C6**	**1**	<5 min	89/11	18	*R*
7	**C7**	**1**	<5 min	86/14	96	*S*
8	**C8**	**1**	<5 min	93/7	74	*S*
9	**C7**	**2**	2 h	77/23	92	*(2S,3R)*
10	**C1**	**2**	5 h	91/9	84	*(2S,3R)*

[a] Reactions were performed at 0 °C in dichloromethane with the ratio of catalyst/substrate = 1/20; the conversion determined by ^1H NMR was 100% for all.

[b] The *endo*/*exo* ratio and ee value of the *endo* isomer were analyzed by HPLC equipped with a Chiralcel-OD column.

[c] The configuration of product was confirmed by comparing with the literature [10].

bis(oxazoline) and Sc(III) as catalyst, the same reaction led to an almost racemic product [10], although a similar Cu(II) catalyst gave rise to an excellent ee [23]. However, the phenyl-substituted **C6**, which contains the same chloro substituent as **C7**, resulted in a low ee of 18% (Entry 6), with the configuration of product reversed.

We also examined the ADA reaction of another substrate, 3-((*E*)-2-butenoyl)-1,3-oxazolin-2-one **2** (Scheme 2). Again, the catalyst **C7** was highly efficient; the reaction was completed within 2 h with a 92% ee (Entry 9, Table 1). This also represents a fast ADA reaction and can be compared with the best results reported in the literature (17 °C, 93% ee, 24 h) [15]. Interestingly, although **L7** is bulkier than **L1**, **C7** is not only more enantioselective but also more active than **C1** in catalyzing the reaction of **2** (Entry 10, Table 1). However, the same catalyst afforded only 70% ee and 41% yield in the same reaction in supercritical CO_2 [11].

The high enantioselectivity observed with the *t*Bu-substituted **C7** and the reversal in enantioselectivity on going to the phenyl-substituted **C6** is intriguing (Entries 6 and 7, Table 1). The reversal in enantioselectivity has previously been observed by Desimoni et al. in the ADA reaction of **1** with cyclopentadiene catalyzed by Sc(III) complexes containing (*R*,*R*)-R-Pybox (R = *i*-Pr, Ph) ligands [13]. This reversal in product configuration was also noted by Jacobsen's group in asymmetric ring opening of *meso* epoxides catalyzed by Yb(III)-(*S*,*S*)-R-Pybox (R = *t*-Bu, Ph) [7] and by Evans et al. in the aldol reaction of ethyl glyoxylate with enolsilanes catalyzed by analogous Sc(III) complexes [24]. Similar observations have been made with closely related bis(oxazoline) ligands [25]. The sense of enantioselection is also shown to vary with the size of metal cations even when the ligand is kept unchanged. In general, the reversal is believed to stem from the Lewis acid center adopting different geometries [13,26,27]. In the current case, our preliminary study appears to suggest that the reversal in enantioselection is due to weak C–H–π interactions between the π orbital of a phenyl ring on **L6** and a hydrogen atom of the attacking diene at the transition state. However, the detailed mechanism remains to be investigated.

4. Conclusions

A series of bis(oxazolinyl)pyridine ligands with different electronic and steric properties have been evaluated for the Diels–Alder reactions between alkenoyl-1,3-oxazolidin-2-ones and cyclopentadiene. Our results demonstrate that electron-deficient ligands improve the enantioselectivity of ADA reactions, and substituents at the 4′ position near the metal center can impact dramatically on the enantioselectivity. In the case of ADA reaction of **1** and **2**, integrating the bulky *t*Bu substituent and electron-withdrawing effect of chloride led to a fast reaction and a high ee of up to 96% under mild reaction conditions.

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