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 tBu substituent and electron-withdrawing chloride.

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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′-iPr-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 CO2, affording 88% ee; however, using Sc(III)-(4′-tBu-Pybox) as catalyst, a much lower enantioselectivity and yield were obtained [11]. Extensive studies by Desimoni’s group have established that both the diastereoselectivity and enantioselectivities 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 cyanylation 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 hydrosilylation and shown indeed that the reaction rates and enantioselectivities 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 1H NMR and 13C NMR spectra were recorded at 400 and 100 MHz, respectively, with CDCl3 as solvent on a Bruker...
2.2. Synthesis of Pybox ligands L1–L8

2.2.1. Ligands L1–L5

2,6-Bis-[4′S-isopropyl oxazolin-2′-yl]-4-chloropyridine (L1), 2,6-bis-[4′S-isopropyl oxazolin-2′-yl]-4-bromopyridine (L2), 2,6-bis-[4′S-isopropyl oxazolin-2′-yl]-4-methoxypyridine (L4) and 2,6-bis-[4′S-isopropyl oxazolin-2′-yl]-4-dimethylaminopyridine (L5) were synthesized according to the literature methods [17-19]. 2,6-Bis-[4′S-isopropyl oxazolin-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-isopropyl oxazolin-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 the addition of CHCl3 (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. Powdered molecular sieves (4 Å) were heated at 350 °C for 8 h and kept in sealed vials in a dryer before use.

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

Chelidamic acid (422 mg, 2.1 mmol) was treated with SOCl2 (11 mL) and a drop of DMF at reflux for 2 days. The excess SOCl2 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 CHCl3 (9 mL) was slowly added a solution of the acid chloride in CHCl3 (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 CH2Cl2 (3 × 20 mL) and then dried over MgSO4. 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 CH2Cl2 (5 mL) and Et3N (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 Na2SO4. After evaporation, the crude product was purified by crystallization from ethanol to yield L6 as white solid (137 mg, 50%). The 1H NMR and 13C 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. [α]D31 = −133.3 (c = 0.5 in CHCl3); 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) δ 161.7, 148.3, 145.5, 126.3, 76.3, 70.1, 34.3, 26.2; HRMS Calcd. for C19H26N3O2Cl (M) 363.1714; found 363.1714.

2.2.5. Synthesis of 2,6-bis-[4′S-benzyl oxazolin-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. [α]D32 = 0.5 in CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.28 (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); 13C NMR (100 MHz, CDCl3) 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 C25H22N3O2Cl (M) 431.1401; found 431.1404.

2.3. General procedure for the ADA reaction

Anhydrous CH2Cl2 (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 1H 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].
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 hydroisilylation 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 Et3N, 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 –NMe2 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 (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, 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 higher 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 hydroisilylation 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 tBu-substituted C7 affording a high ee of 96%. Although the iPr- 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 tBu-substituted

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\text{Table 1} \\
\text{Effect of ligands on the ADA reaction of 1 with 2}^a
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<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Substrate</th>
<th>Time</th>
<th>endo/exo$^b$</th>
<th>ee</th>
<th>Configuration$^c$</th>
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<td>1</td>
<td>C1</td>
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<td>&lt;5 min</td>
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<td>$S$</td>
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<td>C2</td>
<td>1</td>
<td>&lt;5 min</td>
<td>93/7</td>
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<td>1</td>
<td>&lt;5 min</td>
<td>93/7</td>
<td>81</td>
<td>$S$</td>
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<tr>
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<td>&lt;5 min</td>
<td>94/6</td>
<td>79</td>
<td>$S$</td>
</tr>
<tr>
<td>5</td>
<td>C5</td>
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<td>&lt;5 min</td>
<td>93/7</td>
<td>72</td>
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<td>86/14</td>
<td>96</td>
<td>$S$</td>
</tr>
<tr>
<td>8</td>
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<td>&lt;5 min</td>
<td>93/7</td>
<td>74</td>
<td>$S$</td>
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<tr>
<td>9</td>
<td>C7</td>
<td>2</td>
<td>2 h</td>
<td>77/23</td>
<td>92</td>
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<tr>
<td>10</td>
<td>C1</td>
<td>2</td>
<td>5 h</td>
<td>91/9</td>
<td>84</td>
<td>(2S,3R)</td>
</tr>
</tbody>
</table>

$^a$ Reactions were performed at 0 °C in dichloromethane with the ratio of catalyst/substrate = 1/20; the conversion determined by $^1$H 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-butenyl)-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 CO2 [11].

The high enantioselectivity observed with the 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)-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)-Pybox (R = t-Bu, Ph) [7] and by Evans et al. in the aldol reaction of ethyl glyoxylate with enol silanes 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(oxazolyl)pyridine ligands with different electronic and steric properties have been evaluated for the Diels–Alder reactions between alkenyl-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 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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References