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Asymmetric hetero-Diels–Alder reaction of glyoxylate esters and Danishefsky's diene catalyzed by chiral bis(oxazoline)–lanthanide complexes

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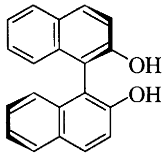
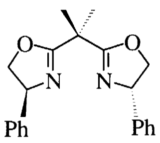
Abstract

Asymmetric hetero-Diels–Alder reactions of glyoxylate esters and Danishefsky's diene catalyzed by various chiral bis(oxazoline)–lanthanide complexes afforded the corresponding aldol adducts, which upon treatment with trifluoroacetic acid, furnished the hetero-Diels–Alder product in up to 77% enantiomeric excess and 73% isolated yield. © 2000 Elsevier Science Ltd. All rights reserved.

In recent years, C_2-symmetric chiral bis(oxazoline) ligand–metal complexes have received a great deal of attention due to their successful use in various asymmetric catalytic processes,[1] but there are few reports of the use of these ligands in lanthanide catalysis.[2] Here we wish to report the development of chiral bis(oxazoline)–lanthanide complexes as a new type of asymmetric catalyst for hetero-Diels–Alder reactions of glyoxylate esters and Danishefsky's diene, wherein a significant effect of slow addition of Danishefsky's diene is observed in increasing not only the enantioselectivity, but also the chemical yield.



(*R*)-**1**



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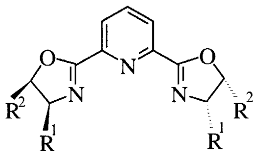
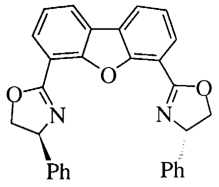


3a $R^1 = {}^iPr$, $R^2 = H$
3b $R^1 = Ph$, $R^2 = H$
3c $R^1 = R^2 = Ph$



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Ligands **2** and **3** were synthesized in two steps by coupling the corresponding acyl chloride and amino alcohol followed by intramolecular ring closure by stirring these intermediates with aqueous methanolic NaOH.[1a] Ligand **4** was prepared according to the literature method.[1a] Ligand **5** was synthesized from

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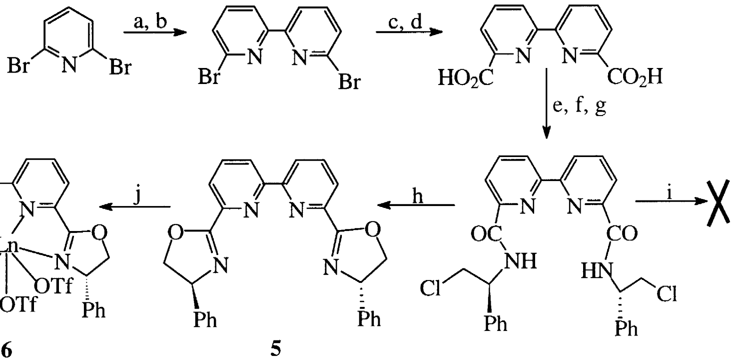
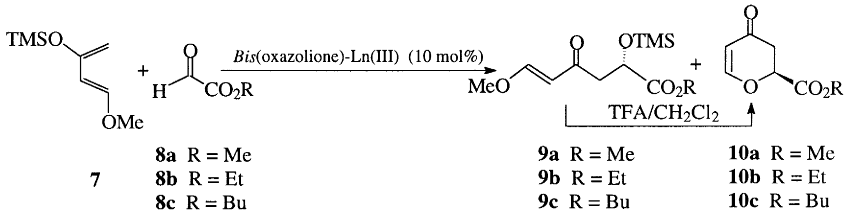
2,6-dibromopyridine with a small modification of the intramolecular condensation process[1a] (Scheme 1). The chiral catalysts were prepared by the reaction of an equimolar amount of lanthanide triflate and the ligand in the presence of MS 4 Å in 1:3 CH_2Cl_2:Et_2O at room temperature under a nitrogen atmosphere. Though these Ln(III) complexes were not isolated, we assume the structures of complexes derived from **3**, **4** and **5** are similar to **6**. However, the structure of the complex obtained from ligand **2** is different from the above.[3] The lanthanide complexes thus prepared were examined as asymmetric catalysts for the hetero-Diels–Alder reaction (Scheme 2).



Scheme 1. (a) BuLi, Et_2O, −78°C, 2 h; (b) $CuCl_2$, O_2, 40% yield; (c) BuLi, THF; (d) CO_2, 25% yield; (e) $SOCl_2$; (f) (*S*)-phenylglycinol; (g) $SOCl_2$, 74% yield; (h) $NaHCO_3$, CH_2Cl_2, 95% yield; (i) NaOH, MeOH; (j) $Ln(OTf)_3$, CH_2Cl_2:Et_2O=1:3, MS 4 Å, rt



Scheme 2.

Typically, cyclocondensation was effected by stirring an equiv. of the glyoxylate ester with the chiral catalyst (10 mol%) at rt overnight, followed by slow addition of 1.1 equiv. of Danishefsky's diene. The resulting mixture was stirred at −78°C, and the progress of the reaction was monitored by TLC. The reaction was quenched with aqueous saturated $NaHCO_3$ to provide the mixture (1:1 determined by 300 MHz NMR) of the corresponding Mukaiyama aldol products **9** as well as the pyranone products **10** (Scheme 2) after standard work-up. The crude mixture, upon treatment with an excess of trifluoroacetic acid in CH_2Cl_2 at rt for 1 h, furnished the cyclocondensation product **10**. The level of enantioselection associated with various hetero-Diels–Alder cycloadducts was analyzed by chiral HPLC analysis (Daicel Chiralpack AD column). The representative results are summarized in Table 1.

Significantly, all lanthanide catalysts complete the hetero-Diels–Alder reaction within 16 h except for entry 4 in which the lanthanide complex catalyzes diene decomposition into 4-methoxy-3-butene-2-one. Ytterbium catalysts provide the higher enantioselectivity. After screening of a variety of bis(oxazoline) ligands, 2,6-bis[4′-(s)-isopropyloxazoli-2-yl] pyridine (**3a**) is proved to give the most satisfactory results. It should be noted here that the geometry and coordination number of the ligand are both important. The presence of MS 4 Å is found to be essential. In the absence of MS 4 Å, both the chemical yield and enantioselectivity for pyranone formation are lowered. Furthermore, the mixed solvent of ether and

Table 1
Asymmetric catalytic hetero-Diels–Alder reaction

Entry	R	Ligand	Metal	Solvent	Time(h)	Yield[a] (%)	*ee*[b](%)
1	Et	**1**	Yb	CH_2Cl_2	8	56	14
2	Et	**3a**	Yb	CH_2Cl_2	12	38	29
3	Et	**3a**	Yb	$C_6H_5CH_3$	16	19	21
4	Et	**3a**	Yb	n-C_6H_{14}	10	/	/
5	Et	**3a**	Yb	THF	10	42	29
6	Et	**3a**	Yb	CH_2Cl_2	12	41	59
7	Et	**3a**	Yb	Et_2O	12	44	56
8	Et	**3a**	Yb	Et_2O:CH_2Cl_2[c]	12	50	60
9	Et	**3a**	Sc	Et_2O:CH_2Cl_2	10	46	18
10	Et	**3a**	La	Et_2O:CH_2Cl_2	10	46	6
11	Et	**3a**	Sm	Et_2O:CH_2Cl_2	10	46	29
12	Et	**3a**	Dy	Et_2O:CH_2Cl_2	10	48	58
13	Et	**3a**	Yb	Et_2O:CH_2Cl_2	12	35	19[d]
14	Et	**2**	Yb	Et_2O:CH_2Cl_2	10	37	17
15	Et	**3b**	Yb	Et_2O:CH_2Cl_2	10	52	4
16	Et	**3c**	Yb	Et_2O:CH_2Cl_2	10	49	34
17	Et	**4**	Yb	Et_2O:CH_2Cl_2	10	46	<1
18	Et	**5**	Yb	Et_2O:CH_2Cl_2	10	46	9
19	Me	**3a**	Yb	Et_2O:CH_2Cl_2	10	80	63
20	Bu	**3a**	Yb	Et_2O:CH_2Cl_2	10	74	39
21	Me	**3a**	Yb	Et_2O:CH_2Cl_2	8	73[e]	77
22	Et	**3a**	Yb	Et_2O:CH_2Cl_2	8	41[e]	72
23	Bu	**3a**	Yb	Et_2O:CH_2Cl_2	8	73[e]	71

a)Isolated yield of pyranone b)Determined by chiral HPLC (AD Column) analysis c) CH_2Cl_2:Et_2O=1:3 d)In the absence of MS 4Å e)Slow addition of the Danishefsky's diene within 2-3 h

dichloromethane is the best. Interestingly, higher enantioselectivity was obtained by using the sterically less demanding methyl glyoxylate and slow addition of Danishefsky's diene by syringe pump. It should be pointed out that the glyoxylate ester should be stirred vigorously with the lanthanide catalyst for at least eight hours so the substrate can be fully coordinated by the lanthanide complex.

The combination of the best conditions Ln(Yb), ligand (^{i}Pr-pybox, **3a**), mixed solvent of ether and dichloromethane and slow addition of the Daneshefsky's diene achieved an enantioselectivity of 77% for the hetero-Diels–Alder reaction of methyl glyoxylate, a better enantioselectivity than obtained with cationic bis(oxazolines)–Cu,[4] other lanthanide complexes[5] and the (±)-BINOL–Ti-activator system,[6] and is even comparable to the (*R*)-BINOL–Ti-activator system.[7] The chiral ligand can be recovered in 80–90% isolated yield. Further investigations of this novel catalytic system are underway.

Acknowledgements

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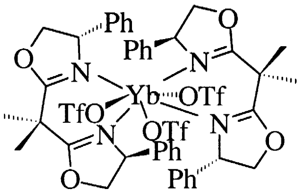
3. When the molecular ratio of bidentate ligand **2**: Yb(OTf)$_3$=2:1 was used, the hetero-Diels–Alder reaction product was obtained in 46% ee and 40% yield which is better than that of 1:1 (Table 1, entry 14). Therefore we speculate the structure of the complex derived from **2** to be as the following:



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