Lanthanide(III)-Catalyzed Enantioselective Diels–Alder Reactions. Stereoselective Synthesis of Both Enantiomers by Using a Single Chiral Source and a Choice of Achiral Ligands

Shū Kobayashi* and Haruro Ishitani

Department of Applied Chemistry, Faculty of Science
Science University of Tokyo (SUT)
Kagurazaka, Shinjuku-ku, Tokyo 162

Received December 28, 1993

It is a very important task in the field of asymmetric synthesis to prepare both enantiomers stereoselectively.[1] In order to attain this goal, traditional methods have required both enantiomers of chiral sources; one enantiomer is prepared by using the (*R*)-chiral source, while the other enantiomer is synthesized by using the (*S*)-chiral source. However, for some chiral sources, the counterparts are of poor quality or are hard to obtain (for example, sugars, amino acids, alkaloids, etc.). In this paper, we disclose a conceptually different approach to obtaining both enantiomers: *choice of enantiofacial selectivity by use of the enantiomerically same chiral source and different achiral ligands.*[2]

Recently, we reported asymmetric Diels–Alder reactions catalyzed by a chiral ytterbium triflate, which was prepared from ytterbium triflate ($Yb(OTf)_3$), (*R*)-(+)-binaphthol, and a tertiary amine (Scheme 1).[3] In the presence of this catalyst, 3-acyl-1,3-oxazolidin-2-ones reacted with cyclopentadiene to afford the endo Diels–Alder adducts in high yields and with good to excellent enantiomeric excesses.[4] After this report, aging of the catalyst was found to take place. High selectivities (77% yield, endo/exo = 89/11, endo = 95% ee) were obtained when a diene and a dienophile were added just after $Yb(OTf)_3$, (*R*)-(+)-binaphthol, and a tertiary amine were stirred at 0 °C for 0.5 h in dichloromethane (the original catalyst system[5]). On the other hand, the selectivities lowered in accordance with the stirring time of the catalyst solution and temperature: at 0 °C for 5 h, 61% yield, endo/exo = 87/13, endo = 78% ee; at 23 °C for 5 h, 77% yield, endo/exo = 86/14, endo = 65% ee.

Although these results seemed to be ascribed to the aging of the catalyst, the best result (77% yield, endo/exo = 89/11, endo = 95% ee) was obtained when the mixture (the substrates and 20 mol % of the catalyst) was stirred at 0 °C for 20 h. It was suggested from this result that the substrates or the product stabilized the catalyst. The effect of the substrates or the product on the stabilization of the catalyst was then examined, and finally the dienophile was found to be effective in preventing the catalyst from aging. When 20 mol % of the original catalyst system and

Scheme 1. Preparation of "Chiral Yb Triflate"

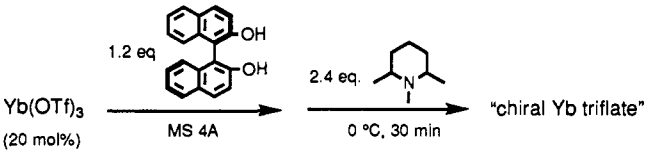
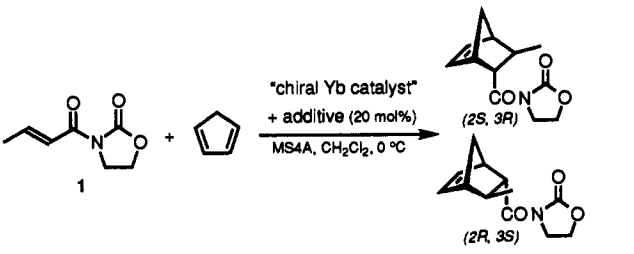


Table 1. Effect of Additives[a]



additive	yield (%)	endo/exo	2*S*,3*R*/2*R*,3*S* (ee (%))[b]
1	66	87/13	94.0/6.0 (88)
	77	89/11	96.5/3.5 (93)
	80	88/12	22.5/77.5 (55)
	69	88/12	15.5/84.5 (69)
	83	93/7	9.5/90.5 (81)[c]

[a] For preparation of the catalysts, see refs 6 and 7. [b] Enantiomer ratios of endo adducts. [c] 1,2,2,6,6-Pentamethylpiperidine was used instead of *cis*-1,2,6-trimethylpiperidine. $Yb(OTf)_3$, MS4A, and the additive were stirred in dichloromethane at 40 °C for 3 h.

3-(2-butenoyl)-1,3-oxazolidin-2-one (**1**) (additive) was stirred at 0 °C for 5 h in dichloromethane, the product was obtained in 66% yield, endo/exo = 87/13, and the enantiomeric excess of the endo adduct was 88%.

Moreover, after screening several additives other than **1**, it was found that some additives were effective not only in stabilizing the catalyst but also in controlling the enantiofacial selectivities in the Diels–Alder reaction. Selected examples are shown in Table 1. When 3-acetyl-1,3-oxazolidin-2-one was combined with the original catalyst system (to form catalyst A[6]), the endo adduct was obtained in 93% ee and the absolute configuration of the product was 2*S*, 3*R*. On the other hand, when acetylacetone derivatives were mixed with the catalyst, reverse enantiofacial selectivities were observed. The endo adduct with the absolute configuration 2*R*, 3*S* was obtained in 81% ee when 3-phenylacetylacetone (PAA) was used as an additive (catalyst B[7]). In these cases, the chiral source was the same (*R*)-(+)-binaphthol. Therefore, *the enantioselectivities were controlled by the achiral ligands 3-acetyl-1,3-oxazolidin-2-one and PAA.*

In the reactions of other 3-acyl-1,3-oxazolidin-2-ones, the same selectivities were observed (Table 2).[8]

Although the precise structures of the catalysts are not yet clear, these exciting selectivities are believed to be strongly dependent on the specific coordination number of ytterbium-

(1) (a) Stinson, S. C. *Chem. Eng. News* **1993**, Sept. 27, 38. (b) Narasaka, K. *Synthesis* **1991**, 1.

(2) Although selectivities were not high enough, both enantiomers were prepared by use of a single chiral source in the Mn(III)-catalyzed asymmetric oxidation of an olefin. Yamada, T.; Imagawa, K.; Nagata, T.; Mukaiyama, T. *Chem. Lett.* **1992**, 2231.

(3) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Tetrahedron Lett.* **1993**, *34*, 4535. For achiral Diels–Alder reactions using $Yb(OTf)_3$, see: Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Ibid.* **1992**, *33*, 6815.

(4) Narasaka et al. reported an excellent chiral titanium catalyst for this reaction. (a) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340 and references cited therein. See also: (b) Chaouis, C.; Jurczak, J. *Helv. Chim. Acta* **1987**, *70*, 436. (c) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (d) Evans, D. A.; Miller, S. J.; Lectka, T. *Ibid.* **1993**, *115*, 6460. (e) Ishihara, K.; Gao, Q.; Yamamoto, H. *Ibid.* **1993**, *115*, 10412. (f) Maruoka, K.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938. (g) Seerden, J. G.; Scheeren, H. W. *Tetrahedron Lett.* **1993**, *34*, 2669. (h) Kaufmann, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545. (i) Hashimoto, S.; Komeshita, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437.

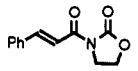
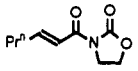
(5) While $Yb(OTf)_3$ or (*R*)-(+)-binaphthol dissolved only sluggishly in dichloromethane, the mixture of $Yb(OTf)_3$, (*R*)-(+)-binaphthol, and an amine became an almost clear solution.

(6) Catalyst A: To a mixture of $Yb(OTf)_3$[12] (0.10 mmol), (*R*)-(+)-binaphthol (0.12 mmol), and MS4A (125 mg) was added *cis*-1,2,6-trimethylpiperidine[13] (0.24 mmol) in dichloromethane (0.75 mL) at 0 °C. The mixture was stirred for 30 min at this temperature, and then 3-acetyl-1,3-oxazolidin-2-one (0.10 mmol) in dichloromethane (0.25 mL) was added.

(7) Catalyst B: 3-Phenylacetylacetone (PAA, 0.10 mmol) in dichloromethane (0.5 mL) was added to $Yb(OTf)_3$ (0.10 mmol) and MS4A (125 mg), and the mixture was stirred at 40 °C for 1 h. After cooling to room temperature, (*R*)-(+)-binaphthol (0.12 mmol) was added. The mixture was cooled to 0 °C, *cis*-1,2,6-trimethylpiperidine (or 1,2,2,6,6-pentamethylpiperidine,[14] see tables) (0.24 mmol) in dichloromethane (0.5 mL) was added, and the mixture was stirred for an additional 30 min at the same temperature.

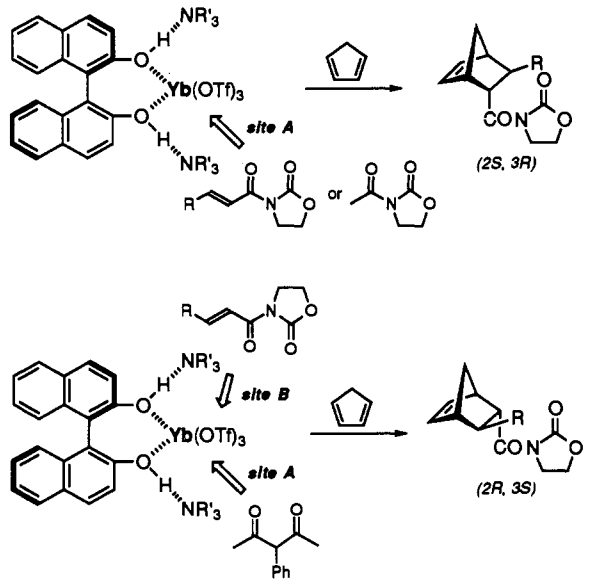
0002-7863/94/1516-4083$04.50/0

Table 2. Synthesis of Both Enantiomers of the Diels–Alder Adducts between Cyclopentadiene and Dienophiles by Use of Catalysts A and B

dienophile	catalyst A[a] yield (%)	endo/exo	2S,3R/2R,3S (ee (%))[c]	catalyst B[b] yield (%)	endo/exo	2S,3R/2R,3S (ee (%))[c]
1	77	89/11	96.5/3.5 (93)	83	93/7	9.5/90.5 (81)[d]
	77	89/11	97.5/2.5 (95)[e]			
	40	81/19	91.5/8.5[f] (83)	60	89/11	10.5/89.5[f] (79)
				51	89/11	8.5/91.5[f] (83)[d]
				51	89/11	5.5/94.5[f] (89)[g]
	34	80/20	93.0/7.0 (86)	81	91/9	10.0/90.0 (80)
	81	80/20	91.5/8.5 (83)[e]	85	91/9	9.0/91.0 (82)[g]
				60	91/9	7.5/92.5 (85)[h]

[a] See ref 4. [b] See ref 5. 1,2,2,6,6-Pentamethylpiperidine was used instead of 1,2,6-trimethylpiperidine. [c] Enantiomer ratios of endo adducts. [d] $Yb(OTf)_3$, MS4A, and the additive were stirred in dichloromethane at 40 °C for 3 h. [e] Without additve. [f] 2R,3R/2S,3S. [g] $Tm(OTf)_3$ was used instead of $Yb(OTf)_3$. $Tm(OTf)_3$, MS4A, and the additive were stirred in dichloromethane at 40 °C for 3 h. [h] $Er(OTf)_3$ was used instead of $Yb(OTf)_3$. $Er(OTf)_3$, MS4A, and the additive were stirred in dichloromethane at 40 °C for 3 h.

Scheme 2. Synthesis of Both Enantiomers Using the Same Chiral Source



(III)[9] (Scheme 2). Two binding sites for the ligands are now postulated in the Yb catalysts. 3-(2-Butenoyl)-1,3-oxazolidin-2-one (**1**) or 3-acetyl-1,3-oxazolidin-2-one coordinates in site A under equilibrium conditions to stabilize the original catalyst system, and when **1** coordinates Yb(III), cyclopentadiene attacks from the *si* face of **1** (site A favors *si* face attack). On the other hand, in catalyst B (the original catalyst system and PAA), site A is occupied by PAA.[10] Since another coordination site still remains in the Yb(III) catalyst owing to the specific coordination numbers, **1** coordinates at site B and cyclopentadiene attacks from the *re* face (site B favors *re* face attack).

Table 3. Effect of $Ln(OTf)_3$

Ln	catalyst A[a] yield (%)	endo/exo	2S,3R,3S (ee (%))[c]	catalyst B[b] yield (%)	endo/exo	2S,3R/2R,3S (ee (%))[c]
Lu	60	89/11	96.5/3.5 (93)	30	89/11	24.5/75.5 (51)
Yb	77	89/11	96.5/3.5 (93)	88	92/8	15.0/85.0 (70)
Tm	46	86/14	87.5/12.5 (75)	72	91/9	13.0/87.0 (74)
Er	24	83/17	84.5/15.5 (69)	59	90/10	13.0/87.0 (74)
Ho	12	73/27	62.5/37.5 (25)	70	84/16	21.0/79.0 (58)
Y	6	70/30	60.0/40.0 (20)	85	91/9	19.5/80.5 (61)
Gd	0			61	85/15	28.5/71.5 (43)

[a] See ref 6. [b] See ref 7. [c] Enantiomer ratios of endo adducts.

The effect of other lanthanide triflates was also examined.[11] As shown in Table 3, lanthanide elements strongly influenced the yields and selectivities. The slight difference between the two catalyst systems (catalysts A and B) on the effect of the lanthanide elements was observed. In catalyst A, lutetium triflate ($Lu(OTf)_3$) was also effective in generating the endo Diels–Alder adduct in 93% ee. The yields and selectivities diminished rapidly in accordance with the enlargement of the ionic radii. On the other hand, in catalyst B the best results were obtained when thulium triflate ($Tm(OTf)_3$) or erbium triflate ($Er(OTf)_3$) was employed. Deviations to either larger or smaller ionic radii resulted in decreased selectivities; however, the Diels–Alder adduct was obtained in 85% yield with good selectivity (endo/exo = 92/8, endo isomer = 61% ee) even when holmium triflate ($Ho(OTf)_3$) was used.

In summary, both enantiomers of the Diels–Alder adducts between 3-acyl-1,3-oxazolidin-2-ones and cyclopentadiene were prepared by chiral lanthanide(III)-catalyzed reactions using the same chiral source, (*R*)-(+)-binaphthol. *It is noted that the chiral catalysts with reverse enantiofacial selectivities could be prepared by using the same chiral source and a choice of achiral ligands.*

Further investigations to clarify the precise structures of the catalysts and the reaction mechanism as well as to develop other asymmetric reactions using the chiral lanthanide catalysts are now actively in progress.

Acknowledgment. The authors are greatful to Mr. Iwao Hachiya in our laboratory for his helpful discussion. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

Supplementary Material Available: Experimental procedures and NMR and HPLC spectra (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) A typical experimental procedure is described for the reaction of **1** with cyclopentadiene: To catalyst A or B were added successively at 0 °C **1** (0.50 mmol) in dichloromethane (0.25 mL) and cyclopentadiene (1.5 mmol, freshly distilled before use) in dichloromethane (0.25 mL), and the mixture was stirred for 20 h at 0 °C (catalyst A) or at room temperature (catalyst B). Water was then added to quench the reaction, and the insoluble materials were filtered off. After a usual workup, the crude product was purified by silica gel column chromatography on silica gel to afford the desired Diels–Alder adduct. The diastereomer ratio was determined by ^1H NMR analysis, and the enantiomeric excess of the endo adduct was determined by HPLC analysis (DAICEL CHIRALPAK AD). The absolute configuration was assigned by comparison of the optical rotation with that reported in the literature.[4a]

(9) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; John Wiley & Sons: New York, 1988, p 955.

(10) 3-Acyl-1,3-oxazolidin-2-ones are weakly coordinating ligands, whereas PAA is stronger coordinating. From the experiments, site A seems to be more easily available for coordination than site B.

(11) Danishefsky et al. reported $Eu(hfc)_3$-catalyzed hetero-Diels–Alder reactions of aldehydes with siloxy dienes. Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451. Quite recently, Shibasaki et al. reported a catalytic asymmetric nitro aldol reaction using a chiral lanthanum complex *as a base*. Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okumura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372.

(12) (a) Thom, K. F. U.S. Patent 3615169 (1971); *Chem. Abst.* **1972**, *76*, 5436a. (b) Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017.

(13) Deno, N.; Fruit, R. E., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 3502.

(14) Kurumada, T.; Ohsawa, H.; Oda, O.; Fujita, T.; Toda, T.; Yoshioka, T. *J. Polym. Sci., Polym. Chem. Ed.* **1985**, *23*, 1477.