Catalytic Enantioselective 1,3-Dipolar Cycloadditions between Nitrones and Alkenes Using a Novel Heterochiral Ytterbium(III) Catalyst

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Asymmetric cycloadditions provide powerful methods for the synthesis of chiral complex molecules because multiple asymmetric centers can be constructed in one-step transformations. Among them, reactions using chiral catalysts are the most efficient and promising, and fruitful results have recently been reported in asymmetric Diels−Alder reactions.[1] On the other hand, 1,3-dipolar cycloadditions between nitrones and alkenes are most useful and convenient for the preparation of isoxazolidine derivatives, which are readily converted to 1,3-amino alcohol equivalents under mild reducing conditions.[2] Despite the importance of chiral amino alcohol units for the synthesis of biologically important alkaloids, amino acids, β-lactams, and amino sugars, etc.,[3] catalytic enantioselective 1,3-dipolar cycloadditions remain relatively unexplored.[3,4] In this paper, we describe highly diastereo- and enantioselective 1,3-dipolar cycloadditions using a novel heterochiral ytterbium(III) (Yb(III)) catalyst.

We have recently reported the unique characteristics of lanthanide triflates as Lewis acid catalysts[5] and have developed efficient chiral lanthanide catalysts in Diels−Alder reactions[6] and aza Diels−Alder reactions.[7] One of the features of the lanthanide catalysts is that catalytic processes are successfully completed even in reactions using nitrogen-containing compounds, while most Lewis acids are decomposed or deactivated in the presence of basic nitrogen atoms. In the course of our investigations to explore truly efficient asymmetric processes, we have focused on catalytic enantioselective 1,3-dipolar cycloadditions of nitrones with alkenes using a chiral lanthanide catalyst.[8,9] First, we chose *N*-benzylidenebenzylamine *N*-oxide (**1**) and 3-(2-butenoyl)-1,3-oxazolidin-2-one (**2**) as models, and the 1,3-dipolar cycloaddition reaction was performed in the presence of a chiral Yb(III) catalyst (20 mol %) prepared from $Yb(OTf)_3$, (*S*)-1,1′-binaphthol ((*S*)-BINOL), and triethylamine (Et_3N). The reaction proceeded smoothly at room temperature to afford the corresponding isoxazolidine derivative in a 65% yield with high *endo*/*exo* selectivity (99/1), and a moderate enantiomeric excess (ee) of the *endo* adduct was observed (Table 1). The enantiomeric excess was improved to 78% when *cis*-1,2,6-trimethylpiperidine (TMP) was used instead of Et_3N. Furthermore, it was found that *use of chiral amines influenced the selectivity dramatically and that combination of the chirality of BINOL and the amine was crucial for the selectivity*. Namely, 71% ee of the *endo* adduct was obtained in the model reaction using a catalyst prepared by the combination of (*S*)-BINOL and *N*-methyl-bis[(*R*)-1-phenylethyl]-amine ((*R*)-MPEA), while only 35% ee was observed by the combination of (*S*)-BINOL and (*S*)-MPEA. Moreover, it was exciting to find that 96% ee of the *endo* adduct was obtained with an excellent yield (92%) and diastereoselectivity (*endo*/*exo* = 99/1) by the combination of (*S*)-BINOL and a newly prepared chiral amine, *N*-methyl-bis[(*R*)-1-(1-naphthyl)ethyl]amine ((*R*)-MNEA).[10] The chiral Yb(III) catalyst thus prepared has two independent chiralities (heterochiral Yb(III) catalyst, *vide infra*), and it was found that the sense of the chiral induction in these reactions was mainly determined by BINOL and that the chiral amine increased or decreased the induction relatively.

Several examples of the 1,3-dipolar cycloadditions between nitrones and 3-(2-alkenoyl)-1,3-oxazolidin-2-ones using the novel heterochiral Yb(III) catalyst are shown in Table 2. In most cases, the desired isoxazolidine derivatives were obtained in excellent yields with excellent diastereo- and enantioselectivities.[11] It is noted that high levels of selectivities were attained at room temperature. Nitrones derived from aromatic and heterocyclic aldehydes gave satisfactory results, and even in the reaction using the nitrone derived from an aliphatic aldehyde, the cycloaddition proceeded smoothly to give the *endo* adduct in an excellent enantiomeric excess, although low *endo*/*exo* selectivity was observed. Moreover, it was found that alkenes which could be employed in the present 1,3-dipolar cycloaddition were not limited to 3-(2-alkenoyl)-1,3-oxazolidin-2-one derivatives. When *N*-phenylmaleimide was used as a dipolarophile, the desired isoxazolidine derivative was obtained in a 70% yield with *endo*/

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(3) For a review, see: Frederickson, M. *Tetrahedron* **1997**, *53*, 403.

(4) For pioneering works in this field, see: (a) Seerden, J.-P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett.* **1994**, *35*, 4419. (b) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687. (c) Seerden, J.-P. G.; Kuypers, M. M. M.; Scheeren, H. W. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1441. (d) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59. (e) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710. (f) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *Tetrahedron Lett.* **1996**, *37*, 5947. (g) Ukaji, Y.; Taniguchi, K.; Sada, K.; Inomata, K. *Chem. Lett.* **1997**, 547. (h) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471 and references therein.

(5) For example, see: (a) Kobayashi, S.; Busujima, T.; Nagayama, S. *J. Chem. Soc., Chem. Commun.* **1998**, 19. (b) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049. (c) Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett.* **1997**, 1039. (d) Kobayashi, S.; Ishitani, H.; Ueno, M. *Synlett* **1997**, 115. (e) Kobayashi, S. *Synlett* **1994**, 689 and references therein.

(6) (a) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Tetrahedron Lett.* **1993**, *34*, 4535. (b) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083. (c) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758. (d) Kobayashi, S.; Ishitani, H.; Araki, M.; Hachiya, I. *Tetrahedron Lett.* **1994**, *35*, 6325. (e) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623.

(7) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357.

(8) We have recently found that lanthanide triflates are excellent catalysts in achiral 1,3-dipolar cycloadditions between nitrones and alkenes and also in three-component coupling reactions of aldehydes, hydroxylamines, and alkenes. Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett.* **1997**, 1039. Cf. Minakata, S.; Ezoe, T.; Ilhyong, R.; Komatsu, M.; Ohshiro, Y. The 72nd Annual Meeting of the Chemical Society of Japan, Tokyo, 1997, 2F3 37. See also ref 9.

(9) Quite recently, Jørgensen et al. reported similar asymmetric 1,3-dipolar cycloadditions using $Yb(OTf)_3$−PyBOX; however, enantiomeric excesses obtained were up to 73%. Sanchez-Blanco, A. I.; Gothelf, K. V.; Jøgensen, K. A. *Tetrahedron Lett.* **1997**, *38*, 7923.

(10) (*R*)-MNEA was prepared from (*R*)-1-(1-naphthyl)ethylamine. Details are described in the Supporting Information.

(11) A typical experimental procedure is described for the reaction of *N*-benzylidenebenzylamine *N*-oxide (**1**) with 3-(2-butenoyl)-1,3-oxazolidin-2-one (**2**): To a mixture of $Yb(OTf)_3$ (0.10 mmol), (*S*)-BINOL (0.10 mmol), and MS 4A (125 mg) was added (*R*)-MNEA (0.20 mmol) in dichloromethane (1 mL) at 0 °C, and the mixture was stirred for 30 min at the same temperature. Compounds **1** (0.50 mmol) in dichloromethane (0.25 mL) and **2** (0.50 mmol) in dichloromethane (0.25 mL) were successively added, and the mixture was stirred for 20 h at room temperature. Saturated sodium hydrogen carbonate was then added to quench the reaction, and the insoluble materials were filtered. After a usual work up, the crude product was purified by column chromatography on silica gel to afford the desired isoxazolidine derivative (92% yield, *endo*/*exo* = 99/1). The diastereomeric ratio was determined by ^{1}H NMR analysis, and the enantiomeric excess of the *endo* adduct was determined to be 96% ee by HPLC analysis (Daicel Chiralpak OD). The absolute configuration was assigned to be 3′*R*, 4′*S*, 5′*R* by comparison of the optical rotation with that of the literature.[4b]

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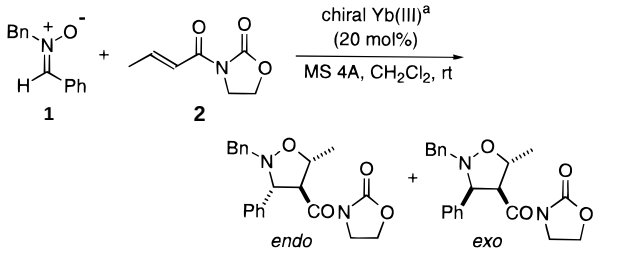
Table 1. Effect of Amines



amine	yield (%)	*endo*/*exo*	ee (%)[b]
Et_3N	65	99/1	63
$^iPr_2NEt$	73	>99/1	62
cis-1,2,6-TMP[c]	73	99/1	78
(*R*)-MPEA[d]	92	>99/1	71
(*S*)-MPEA	80	97/3	35
(*R*)-MNEA[e]	92	99/1	96
(*S*)-MNEA	87	99/1	62

[a] Chiral Yb(III) = $Yb(OTf)_3$ + (*S*)-BINOL + amine. [b] ee of the *endo* adducts. [c] *cis*-1,2,6-Trimethylpiperidine.

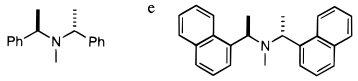
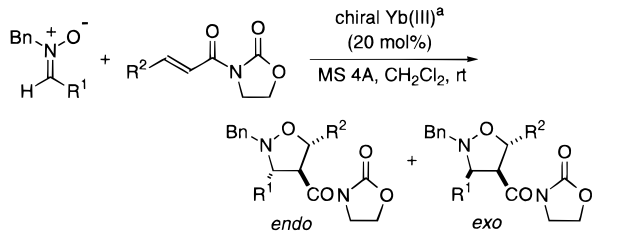


Table 2. Catalytic Enantioselective 1,3-Dipolar Cycloadditions



R^1	R^2	yield (%)	*endo*/*exo*	ee (%)[b]
Ph	CH_3	92	99/1	96
p-Cl-Ph	CH_3	93	99/1	92
p-MeO-Ph	CH_3	82	95/5	90
2-furyl	CH_3	89	95/5	89
1-naphthyl	CH_3	88	98/2	85
Ph	H	91	>99/1	79
Ph	C_3H_7	89	98/2	93
C_2H_5	CH_3	88	53/47	96

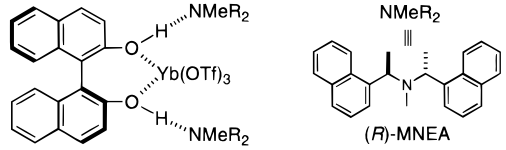
[a] Chiral Yb(III) = $Yb(OTf)_3$ + (*S*)-BINOL + (*R*)-MNEA. [b] ee of the *endo* adducts.

exo = >99/1, and the enantiomeric excess of the *endo* adduct was 70% ee under the standard reaction conditions.[12,13]

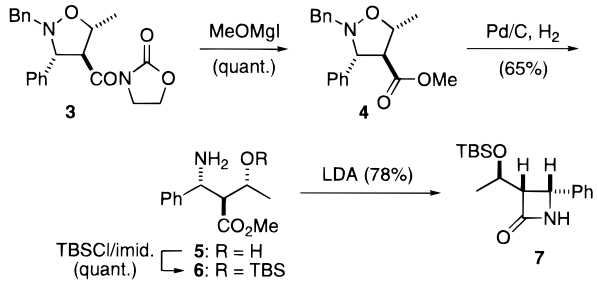
As for the structure of the heterochiral Yb(III) catalyst, the following structure was supported from our previous work (Scheme 1).[6c−e] Actually, the existence of hydrogen bonds between the phenolic hydrogens of (*S*)-BINOL and the nitrogens of (*R*)-MNEA was confirmed by the IR spectra of the catalyst.[14,15]

Finally, to demonstrate the synthetic utility of the present reactions, we synthesized a 6-hydroxyethyl β-lactam derivative

Scheme 1. A Novel Heterochiral Yb(III) Catalyst



Scheme 2. Conversion to β-Lactam



(Scheme 2). Isoxazolidine derivative **3** (96% ee), prepared via the catalytic enantioselective 1,3-dipolar cycloaddition, was treated with methoxymagnesium iodide[16] to give methy ester **4**. Reductive N−O bond cleavage and deprotection of the *N*-benzyl part of **4** was performed in the same pot using Pd/C under hydrogen atmosphere (10 kg/cm^2)[17] to afford amino ester **5**. After the resulting alcohol moiety was protected as its *tert*-butyldimethylsilyl (TBS) ether, cyclization of **6** proceeded smoothly using lithium diisopropylamide (LDA)[18] to afford the corresponding β-lactam (**7**)[19,20] in a good yield. The enantiomeric excess of **7** was 96% (determined by HPLC analysis), which means no racemization occurred during the transformation.

In summary, catalytic enantioselective 1,3-dipolar cycloadditions using a novel heterochiral Yb(III) catalyst have been developed. Wide substrate generality and high levels of stereoselectivities have been achieved in these reactions. Further investigations into the synthesis of biologically important natural products using these asymmetric cycloadditions are now in progress.

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Supporting Information Available: Experimental procedures and physical data of the products (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(12) It is believed that bidentate coordination (for example, Yb(III)−3-(2-alkenoyl)-1,3-oxazolidin-2-one) is necessary to obtain high selectivities in many chiral lanthanide-catalyzed reactions.[13] These results are very interesting and promising because it has been shown that even monodentate coordination can achieve good selectivities by using the heterochiral Yb(III) catalyst.

(13) See refs 6 and 7. See also: (a) Marko, I. E.; Evans, G. R. *Tetrahedron Lett.* **1994**, *35*, 2771. (b) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 220. Quite recently, asymmetric hetero Diels−Alder reactions of aldehydes with Danishefsky's diene using a chiral Yb(III) phosphate were reported. (c) Hanamoto, T.; Sugimoto, Y.; Inanaga, J. *Synlett* **1997**, 79.

(14) A bond pair (953 and 987 cm^{-1}), which indicated hydrogen bonds (the OH···N and O$^-$···H$^+$N equilibrium), was observed in the area from 930 to 1000 cm^{-1} in the IR spectra of the heterochiral Yb(III) catalyst.[15] Direct coordination of the amine to Yb(III) is doubtful in light of the fact that the 1,3-dipolar cycloaddition proceeded very slowly when $Yb(OTf)_3$ and (*R*)-MNEA were first combined and then (*S*)-BINOL was added.

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(16) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.

(17) Kametani, T.; Huang, S. P.; Nakayama, A.; Honda, T. *J. Org. Chem.* **1982**, *47*, 2328.

(18) Sekiya, M.; Ikeda, K.; Terao, Y. *Chem. Pharm. Bull.* **1981**, *29*, 1747.

(19) For **7**: ^{1}H NMR ($CDCl_3$) δ 0.35 (s, 6H), 0.97 (s, 9H), 1.17 (d, 3H, J = 6.2 Hz), 2.69 (d, 1H, d, J = 9.4, 10.5 Hz), 3.85 (d, 1H, J = 10.5 Hz), 4.25 (dq, 1H, J = 9.4, 6.2 Hz), 7.19−7.36 (m, 6H); ^{13}C NMR ($CDCl_3$) δ −1.6, 19.1, 21.9, 25.3, 58.8, 68.0, 70.9, 127.2, 128.1, 128.7, 151.5, 171.8; HRMS calcd for $C_{17}H_{27}NO_2Si$ (M^+) 305.1811, found 305.1764.

(20) For carbapenems and penems, see: (a) Palomo, C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Heidelberg, 1990; p 565. (b) Perrone, E.; Franceschi, G. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Heidelberg, 1990; p 613.