Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9581–9584
Tetrahedron Letters

Evaluation of chiral bidentate ligand–metal complexes in asymmetric 1,3-dipolar cycloaddition reaction of nitrones with 3-alkenoyl-2-oxazolidinones

Takao Saito,* Takuya Yamada, Shingo Miyazaki and Takashi Otani

Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

Received 15 September 2004; revised 14 October 2004; accepted 22 October 2004

Abstract—For evaluation of a chiral C_2-symmetric bis(oxazoline) ligand, its Lewis acid complexes-catalyzed asymmetric 1,3-dipolar cycloaddition reactions of nitrones with electron-deficient dipolarophiles, 3-(2-alkenoyl)-1,3-oxazolidin-2-ones, have been investigated and it was found that the cycloadditions using a Cu(II)-bis(oxazoline) complex under optimized reaction conditions induced extremely high enantioselectivity.

The 1,3-dipolar cycloaddition (1,3-DC) reaction of nitrones with alkenes is an important reaction in organic synthesis.[1] It offers a straightforward and efficient synthesis of isoxazolidine derivatives with predictable and highly regio- and stereoselective construction of up to three stereogenic centers of the resulting isoxazolidine cycloadducts, which are readily converted to γ-amino alcohols as useful building blocks for compounds such as alkaloids, amino acids and β-lactam antibiotics.[2] Since the first pioneering catalytic enantioselective nitrone 1,3-DC reactions with different electron-demand types were reported by Scheeren and Jørgensen in 1994,[3] chiral Lewis acid-catalyzed nitrone 1,3-DC reactions have been developed by the groups of Jørgensen,[4–7] Kanemasa,[8] Kobayashi,[9,10] Furukawa,[11,12] Scheeren,[13] Iwasa,[14,15] Suga[16] and others.[17–20] Although a number of chiral catalysts have been developed so far, the reported catalysts for successful use in catalytic enantioselective nitrone 1,3-DC reactions are still limited. For example, in nitrone 1,3-DC reactions with 3-(2-alkenoyl)-1,3-oxazolidin-2-ones, DBFOX–Ni(II),[8a] XABOX–Mg(II)/Mn(II)[14] and trialkylsilyloxymethyl-substituted PYBOX–Ni(II)[15] complexes having tridentate or multi-points coordination sites were shown to give high *endo* and enantioselectivities (>90% ee's in most cases), while bidentate metal complexes, BINAP–Pd(II),[11] binaphtyldiamine-derived chiral bisimine–Ni(II) (BINIMs),[16] TADDOL–Ti(IV),[4a] and bis(oxazoline) [BOX]–Mg(II)[5,17] complexes, and even tri- and multi-dentate PYBOX–Yb(III)[6] and BINOL–BOX–Sc(III)[12] complexes were reported to induce enantioselectivity of 80–89% ee's or less with *endo* selectivity. The only exceptional cases of bidentate ligands–metal complexes showing high ee's were provided by BINOL–Yb(III)$(OTf)_3$[9] and TADDOL–Ti(IV)$(OTs)_2$ (50 mol%).[4b] However, in the former complex the combined use of chiral amine (*N*-methyl-bis[(*R*)-1-(1-naphthyl)ethyl]amine) was crucial and in the latter the use of 50 mol% of the catalyst and its tosylate as a counter anion were necessary.

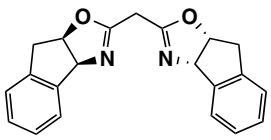
Recent reports on the 1,3-DC reactions seem to be directed towards development of new methods by designing essentially new and effective chiral ligands/catalysts and/or substrates to achieve high diastereo- and enantioselectivities. In this context, it is of value to find new combinations of chiral ligands–metal catalysts and substrates (reaction) wherein high efficiency is achieved, even if chiral catalysts and substrates are each known. On the other hand, it is true that even in similar reactions where the same substrates are used, resulting diastereoselectivity and enantioselectivity, in particular, are both dependent upon factors such as reaction conditions (solvent, temperature concentration, etc.) and additives (molecular sieves, amine, *N*-oxide, etc.) as well as the chiral ligands and Lewis acid metals employed.[1f,21,22] Therefore, it is of value to probe and tune

* Corresponding author. Fax: +81 03 3235 2214; e-mail: tsaito@ch.kagu.sut.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.149

such factors for gaining high efficiency and for exploitation of the catalysts.

In this context, we wish to report herein examples of catalytic enantioselective nitrone 1,3-dipolar cycloadditions with 3-alkenoyl-1,3-oxazolidin-2-ones by use of a readily available and simple, *bidentate* chiral bis(oxazoline) (**1**) ligand on a Cu(II) complex, enantioselectivity attained by which was extremely high.

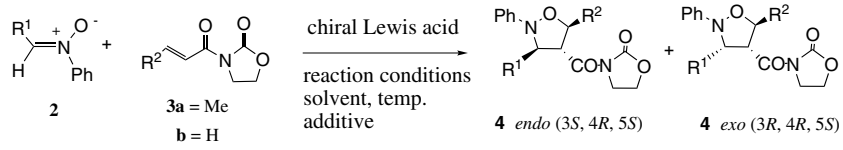


Bis(oxazoline) 1

We have previously reported highly enantioselective hetero Diels–Alder reactions of thiabutadienes to give optically active dihydrothiopyrans.[22f,g] In the reaction we selected bis(oxazoline)(**1**) [IndaBOX] as the homochiral catalyst ligand among a variety of chiral bis(oxazoline) derivatives with a great deal of structural diversity[23] and used bis(oxazoline)(**1**)–metal complexes [Cu(II)/Ni(II)$(OTf)_2$/$(ClO_4)_2$] as catalysts. Despite the possibility of deactivation of the catalysts and loss of stereochemical control caused by coordination of the thiocarbonyl compounds having relatively strong Lewis basicity, the reaction worked well.[22e,f] This fact prompted us to investigate enantiomeric 1,3-DC reactions of nitrones with the promising catalysts, bis(oxazoline)(**1**)–metal complexes, since a nitrone is a 1,3-dipole having relatively strong Lewis basicity which often causes a serious problem in Lewis acid-promoted reaction.[24]

Initially, screening of Lewis acids used in combination with bis(oxazoline)(**1**) ligand was made using 20 mol% of the catalyst in a model reaction of nitrone **2a** with *N*-crotonoyloxazolidinone **3a** at room temperature in dichloromethane in the presence of molecular sieves 4A. Some selected results are summarized in Table 1, entries 1–5.[25] $Yb(OTf)_3$ afforded cycloadduct **4a** in quantitative yield but enantiomeric excess's of *endo* and *exo* isomers were both as low as 12% and 21% ee, respectively (entry 1). Among the Lewis acids tested, the best results in enantioselectivities of both isomers were attained (>99% *endo* ee, >99% *exo* ee) when $Cu(OTf)_2$ was employed, whereas the *endo*/*exo* selectivity (70:30) was moderate (entry 5). It is clear that the presence of molecular sieves plays an important role and is crucial for the reaction (entries 5–8). When the reactions were performed in the absence of molecular sieves (entry 7)

Table 1. Catalytic enantioselective 1,3-DC reaction of nitrone **2a** with dipolarophile **3a** in the presence of Lewis acid–ligand **1** catalyst[a]



2 **3a** = Me, **b** = H **4** *endo* (3*S*, 4*R*, 5*S*) **4** *exo* (3*R*, 4*R*, 5*S*)

Entry	Lewis acid	Additive	Time (h)	Yield (%)[b]	*endo*/*exo*[c]	*endo* ee (%)[c]	*exo* ee (%)[c]
1	$Yb(OTf)_3$	MS4A	48	>99	84/16	12	21
2	$ZnBr_2$ + 2AgOTf	MS4A	216	90	47/53	41	73
3	$NiBr_2$ + $2AgClO_4$	MS4A	168	43[d]	66/34	2	16
4	$CuBr_2$ + $2AgClO_4$	MS4A	15	78	80/20	>99	>99
5	$Cu(OTf)_2$	MS4A	36	99	70/30	>99	>99
6	$Cu(OTf)_2$	MS5A	12	99	63/27	98	95
7	$Cu(OTf)_2$	None	36	0	—	—	—
8	$Cu(OTf)_2$	$MgSO_4$	3	0	—	—	—
9	$Cu(OTf)_2$[e]	MS4A	96	90	65/35	95	99
10	$Cu(OTf)_2$[f]	MS4A	240	74[d]	57/43	92	92
11[g]	$Cu(OTf)_2$	MS4A	168	99	70/30	>99	>99
12[h]	$Cu(OTf)_2$	MS4A	6	99	68/32	90	87
13[i]	$Cu(OTf)_2$	MS4A	48	99	75/25	89	87
14[j]	$Cu(OTf)_2$	MS4A	48	98	70/30	>99	>99
15[k]	$Cu(OTf)_2$	MS4A	48	99	70/30	>99	>99

[a] Reaction of **2a** (0.22 mmol) with **3a** (0.20 mmol) was carried out in CH_2Cl_2 (2 mL) at room temperature in the presence of 20 mol% catalyst (Lewis acid/**1** = 1.0:1.1) and an additive (200 mg), unless otherwise noted.
[b] Isolated yield.
[c] Determined by ^1H NMR spectroscopy and/or chiral HPLC analysis.
[d] Incomplete.
[e] 15 mol% of catalyst was used.
[f] 10 mol% of catalyst was used.
[g] At 0 °C.
[h] At 40 °C.
[i] In toluene.
[j] In THF.
[k] In THF–CH_2Cl_2 (1:4).

Table 2. Catalytic enantioselective 1,3-DC reaction of nitrones **2a**–**k** with dipolarophiles **3a**,**b** in the presence of $Cu(OTf)_2$–ligand **1** catalyst[a]

Entry	R^1	R^2	Time (h)	Cycloadduct	Yield (%)[b]	*endo*/*exo*[c]	*endo* ee (%)[c]	*exo* ee (%)[c]
1	Ph	Me	36	**4a**	99	70/30	>99	>99
2	4-$CH_3OC_6H_4$	Me	36	**4b**	71	50/50	>99	>99
3	4-$CH_3C_6H_4$	Me	36	**4c**	97	70/30	>99	>99
4	4-FC_6H_4	Me	36	**4d**	89	80/20	95	96
5	4-ClC_6H_4	Me	36	**4e**	94	70/30	>99	>99
6	4-BrC_6H_4	Me	15	**4f**	99	74/26	93	97
7	4-$CF_3C_6H_4$	Me	36	**4g**	99	86/14	95	94
8	4-NCC_6H_4	Me	48	**4h**	86	83/17	99	95
9	4-$NO_2C_6H_4$	Me	240	**4i**	29[d]	86/14	>99	>99
10	2-Naphthyl	Me	36	**4j**	94	60/40	95	98
11	2-Furyl	Me	24	**4k**	90	91/9	96	99
12	Ph	H	12	**4l**	93	22/78	52	96

[a] Reaction of **2a**–**k** (0.22 mmol) with **3a**,**b** (0.20 mmol) was carried out in CH_2Cl_2 (2 mL) at room temperature in the presence of 20 mol% catalyst ($Cu(OTf)_2$/**1** = 1.0:1.1) and an additive (200 mg), unless otherwise noted.
[b] Isolated yield.
[c] Determined by ^1H NMR spectroscopy and/or chiral HPLC analysis.
[d] Incomplete.

or in the presence of a dehydrating agent such as $MgSO_4$ (entry 8), the nitrone decomposed and almost no cycloadduct was obtained. Molecular sieves 5A was somewhat less effective than molecular sieves 4A for enantioselectivities of both *endo* and *exo* isomers (entry 6 vs entry 5). Even when 15 or 10 mol% of the catalyst was used (entries 9 and 10), high enantioselectivities were still maintained for both *endo* isomer (95% ee, 92% ee) and *exo* isomer (99% ee, 92% ee), though the reaction became slow. At 0 °C the reaction proceeded slowly and the cycloadduct **4a** was obtained in 99% yield in an *endo*/*exo* ratio of 70:30 with *endo* >99% ee and *exo* >99% ee (entry 11). The reaction at 40 °C proceeded smoothly for 6 h to afford **4a** in 99% yield in an *endo*/*exo* ratio of 68:32 with *endo* 90% ee and with *exo* 87% ee (entry 12). The reaction in toluene improved the *endo*/*exo* selectivity (75:25), whereas the *endo* ee and *exo* ee both were lowered by 10–12% to 89% ee and 87% ee, respectively (entry 13). In THF or in a mixed solvent of 25 vol% of THF–CH_2Cl_2, the *endo*/*exo* selectivity and enantioselectivity were both maintained in a ratio of 70:30 with *endo* and *exo* ee's of >99% (entries 14 and 15).

Finally, the 1,3-DC reactions of nitrones **2b**–**k** bearing a variety of *C*-substituents (R^1) with dipolarophile **3a** were performed in the presence of 20 mol% of $Cu(OTf)_2$–**1** complex in CH_2Cl_2 at room temperature (Table 2). Although *endo*/*exo* selectivities were moderate to good, extremely high enantioselectivities were achieved in all cases. It is noteworthy that as the substituents (R^1) on the nitrones **2** become more electron withdrawing, the *endo* selectivity increases. Acryloyl dienophile **3b** also reacted with nitrone **2a** to afford cycloadduct **4l** in good yield (93%); however, in this case *exo* selectivity was observed in a 22:78 *endo*/*exo* ratio along with high *exo* ee of 96%.

In summary, we have developed an asymmetric 1,3-DC reaction of nitrones to give isoxazolidine cycloadducts in good yields with extremely high enantioselectivity, which is catalyzed by a readily available *bidentate* chiral bis(oxazoline)–$Cu(OTf)_2$ complex.

Acknowledgements

This work was supported in part by Grant-in-Aid for Scientific Research from the Ministry of Education, Sports and Culture, Japan.

References and notes

1. (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 2, Chapter 9, p 83; (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863; (c) Gothelf, K. V.; Jørgensen, K. A. *Acta Chem. Scand.* **1996**, *50*, 652; (d) Kanemasa, S. *Synlett* **2002**, 1371; (e) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH, 2002; p 211; (f) Kanemasa, S. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH, 2002; p 249.
2. Frederickson, M. *Tetrahedron* **1997**, *53*, 403.
3. (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.
4. (a) Jensen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *Helv. Chim. Acta* **1997**, *80*, 2039; (b) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59.
5. (a) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483; (b) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346.
6. Sanches-Blanco, A. I.; Gothelf, K. V.; Jørgensen, K. A. *Tetrahedron Lett.* **1997**, *38*, 7923.
7. Inverse electron-demand 1,3-DC using BINOL–AlMe: (a) Simonsen, K. B.; Bayon, P.; Hazell, R. G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845; (b) Simonsen, K. B.; Jørgensen, K. A.; Hu, Q.-S.; Pu, L. *Chem. Commun.* **1999**, 811, BOX-$Cu(OTf)_2$: (c) Jensen, K. B.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353.
8. (a) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355; (b) Shirahase, M.; Kanemasa, S.; Oderaotoshi, Y. *Org. Lett.* **2004**, 675; Non-chiral TPH-Al: (c) Kanemasa, S.; Ueno, N.; Shirahase, M. *Tetrahedron Lett.* **2002**, *43*, 675.
9. Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840.

10. Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 3213.
11. Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017.
12. Kodama, H.; Hori, K.; Ohta, T.; Furukawa, I. *J. Organomet. Chem.* **2000**, *603*, 6.
13. Seerden, J.-P. G.; Kuypers, M. M. M.; Scheeren, H. W. *Tetrahedron: Asymmetry* **1995**, *6*, 1441.
14. Iwasa, S.; Ishima, Y.; Widaglo, H. S.; Aoki, K.; Nishiyama, H. *Tetrahedron Lett.* **2004**, *45*, 2121.
15. (a) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227; (b) Iwasa, S.; Maeda, H.; Nishiyama, K.; Tsushima, S.; Tsukamoto, Y.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 8281; (c) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715.
16. Suga, H.; Kakehi, A.; Ito, S.; Sugimoto, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 327.
17. (a) Crosignani, S.; Desimoni, G.; Faita, G.; Filippone, S.; Mortoni, A.; Righetti, P. P.; Zema, M. *Tetrahedron Lett.* **1999**, *40*, 7007; (b) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. P. *Tetrahedron Lett.* **1999**, *40*, 2001.
18. Inverse electron-demand 1,3-DC: (a) Ding, X.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett.* **2002**, 302; (b) Ding, X.; Taniguchi, K.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2001**, 468; (c) Ukaji, Y.; Taniguchi, K.; Sada, K.; Inomata, K. *Chem. Lett.* **1997**, 547.
19. Quite recently, highly *exo* and enantioselective nitrone 1,3-DC using bidentate chiral BOX–Cu(II) complexes has been reported, in which 1,5,5-tri-substituted 2-alkenoylpyrazolidin-3-one dipolarophiles were employed. Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718.
20. 1,3-DC with mono-coordinating dipolarophiles (enals): (a) Kezuka, S.; Ohtsuki, N.; Mita, T.; Kogami, Y.; Ashizawa, T.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2197; (b) Viton, F.; Bernardinelli, G.; Kündig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968; (c) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874; (d) Karlson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2002**, *13*, 923, See also Refs. 8b,c.
21. In 1,3-DC reactions: (a) Huang, Z.-Z.; Kang, Y.-B.; Zhou, J.; Ye, M.-C.; Tang, Y. *Org. Lett.* **2004**, 1677; (b) Minakata, S.; Ezoe, T.; Nakamura, K.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 5205, See also Refs. 5a,b; 6; 10; 17a,b.
22. In other reactions: (a) Kobayashi, S. *Synlett* **1994**, 689; (b) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Chem. Comun.* **1997**, 281; (c) Posner, G. H.; Dai, H. Y.; Bull, D. S.; Lee, J. K.; Eydoux, F.; Ishihara, Y.; Welsh, W.; Pryor, N. *J. Org. Chem.* **1996**, *61*, 671; (d) Sibi, M. P.; Gorikunti, U.; Liu, M. *Tetrahedron* **2002**, *58*, 8357; (e) Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309, see also our earlier reports; (f) Saito, T.; Takekawa, K.; Takahashi, T. *Chem. Commun.* **1999**, 1001; (g) Saito, T.; Takekawa, K.; Nishimura, J.; Kawamura, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2957; (h) Saito, T.; Suda, H.; Kawamura, M.; Nishimura, J.; Yamaya, A. *Tetrahedron Lett.* **1997**, *38*, 6035; (i) Saito, T.; Kawamura, M.; Nishimura, J. *Tetrahedron Lett.* **1997**, *38*, 3231.
23. Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.
24. Tanaka, J.; Kanemasa, S. *Tetrahedron* **2001**, *57*, 899.
25. A typical procedure: A mixture of $Cu(OTf)_2$ (0.04 mmol) and powdered molecular sieves 4A (200 mg) was dried at 180 °C under reduced pressure for 2 h in a flask. After cooling to room temperature, bis(oxazoline) (**1**, 0.044 mmol) and dichloromethane (1.0 mL) was added to the flask and the mixture was stirred for 1 h. A solution of dipolarophile **3a** (0.20 mmol) in CH_2Cl_2 (0.5 mL) and CH_2Cl_2 (0.5 mL) were successively added with stirring for 1 h. Nitrone **2a** (0.22 mmol) was added and stirred for 36 h at room temperature. The mixture was filtered and the filtrate was quenched with satd aq $NaHCO_3$, extracted with CH_2Cl_2 and dried ($MgSO_4$). Evaporation of the solvent and column chromatography of the residue (EtOAc/hexane, 1:2) afforded pure product **4a** quantitatively. Physical data of (3*S*,*R*,*S*)-*endo*-**4a**: $[\alpha]_D^{27}$ −17.5 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 1.54 (3H, d, $J = 6.25$ Hz), 4.00 (2H, ddd, $J = 8.54$, 14.0, 18.6), 4.35 (2H, ddd, $J = 8.54$, 14.0, 16.2), 4.44 (1H, dq, $J = 6.25$, 7.35), 4.79 (1H, dd, $J = 6.98$, 7.35), 5.17 (1H, d, $J = 6.98$), 6.89–6.98 (3H, m, Ar), 7.19–7.37 (5H, m, Ar), 7.46 (2H, m, Ar), which are identical with those in the literature.[3b,8a,11,15a,b] HRMS Found: M 352.1429, calcd for $C_{20}H_{20}N_2O_4$M 352.1423. HPLC (Chiralpak AD, *i*-PrOH/hexane 1:9, 1.0 mL/min, 25 °C) $t = 11.6$ min for (3*S*,4*S*,5*R*)-*exo*, $t = 12.1$ min for (3*R*,4*R*,5*S*)-*exo*, $t = 20.7$ min for (3*S*,4*R*,5*S*)-*endo*, $t = 32.1$ min for (3*R*,4*S*,5*R*)-*endo* isomer.