

## Copper(II)-Bisoxazoline Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrones with Electron-Rich Alkenes

Kim B. Jensen, Rita G. Hazell, and Karl Anker Jørgensen\*

Center for Metal Catalyzed Reactions, Department of Chemistry,  
Aarhus University, DK-8000 Aarhus C, Denmark

Received October 15, 1998

A transition-metal-catalyzed diastereo- and enantioselective 1,3-dipolar cycloaddition reaction between electrophilic nitrones and electron-rich alkenes has been developed employing chiral copper(II)- and zinc(II)-bisoxazolines as catalysts. In the presence of Cu(OTf)<sub>2</sub>-bisoxazoline as the catalyst, the nitrones, which coordinate to the chiral catalyst in a bidentate fashion, reacted smoothly with alkenes at room temperature to give isoxazolidines in good yields and diastereoselectivity and with high enantioselectivities of up to 94% ee. The influence of the metal salts, chiral ligands, and solvents on the reaction course has been investigated, and a general reaction protocol is developed. On the basis of the absolute stereochemistry of the 1,3-dipolar cycloaddition product, the coordination of the nitron to the catalyst is discussed and a mechanistic approach of the reaction is presented. It is proposed that the intermediate is one in which both the nitron and alkene are coordinated to the chiral copper(II)-bisoxazoline catalyst.

### Introduction

The 1,3-dipolar cycloaddition reaction provides a powerful method for the synthesis of five-membered heterocyclic rings. The isoxazolidine adducts obtained from the 1,3-dipolar cycloaddition reaction of nitrones with alkenes are very important compounds/intermediates in organic chemistry; these cycloadducts have found wide applications in synthesis and as synthons in total synthesis by their conversion into, for example, 3-amino alcohols and alkaloids.<sup>1–6</sup> During the past two decades numerous enantioselective total syntheses have been described using chiral isoxazolidines from asymmetric 1,3-dipolar cycloaddition reactions.<sup>7,8</sup> However, the chirality in the cycloadduct has mostly been achieved through incorporation of chiral center(s) in both the nitron and/or the alkene in the 1,3-dipolar cycloaddition reaction.<sup>8,9</sup>

Contrary to the Lewis acid catalyzed asymmetric carbo- and hetero-Diels–Alder reactions,<sup>10</sup> the use of chiral Lewis acids as catalyst in asymmetric 1,3-dipolar cycloaddition reactions is relatively unexplored. Recently, focus has been put on achiral Lewis acid catalyzed 1,3-dipolar cycloaddition reactions to influence the rate and regio- and stereoselectivity of the reaction,<sup>11–30</sup> and

advances in chiral Lewis acid catalyzed 1,3-dipolar cycloaddition reactions have been achieved.<sup>31–47</sup>

(1) Morrison, J. D. *Asymmetric Synthesis*, Academic Press: New York, 1983; Vol. 1, pp 1–11.

(2) Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissing, H.-U. *Organic Synthesis Highlights*; VCH: New York, 1991; pp 77–85.

(3) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988.

(4) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, pp 83–168.

(5) Padwa, A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 1069–1109.

(6) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396–403.

(7) Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425.

(8) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.

(9) Aggarwal, V. K.; Grainger, R. S.; Adams, H.; Spargo, P. L. *J. Org. Chem.* **1998**, *63*, 3481–3485.

(10) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007–1019.

(11) Kanemasa, S.; Uemura, T.; Wada, E. *Tetrahedron Lett.* **1992**, *33*, 7889–7892.

(12) Kanemasa, S.; Tsuruoka, T.; Wada, E. *Tetrahedron Lett.* **1993**, *34*, 87–90.

(13) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324–2339.

(14) Kanemasa, S.; Tsuruoka, T.; Yamamoto, H. *Tetrahedron Lett.* **1995**, *36*, 5019–5022.

(15) Kanemasa, S.; Tsuruoka, T. *Chem. Lett.* **1995**, 49–50.

(16) Murahashi, S.; Imada, Y.; Kohno, M.; Kawakami, T. *Synlett* **1993**, 395–396.

(17) Tamura, O.; Yamaguchi, T.; Noe, K.; Sakamoto, M. *Tetrahedron Lett.* **1993**, *34*, 4009–4010.

(18) Tamura, O.; Yamaguchi, T.; Okabe, T.; Sakamoto, M. *Synlett* **1994**, 620–622.

(19) Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Sakamoto, M. *J. Chem. Soc., Chem. Commun.* **1996**, 1861–1862.

(20) Tamura, O.; Mita, N.; Gotanda, K.; Yamada, K.-I.; Nakano, T.; Sakamoto, M. *Heterocycles* **1997**, *46*, 95–99.

(21) Katagiri, N.; Okada, M.; Morishita, Y.; Kaneko, C. *J. Chem. Soc., Chem. Commun.* **1996**, 2137–2138.

(22) Katagiri, N.; Okada, M.; Kaneko, C.; Furuya, T. *Tetrahedron Lett.* **1996**, *37*, 1801–1804.

(23) Camiletti, C.; Poletti, L.; Trombini, C. *J. Org. Chem.* **1994**, *59*, 6843–6846.

(24) Castellari, C.; Lombardo, M.; Pietropaolo, G.; Trombini, C. *Tetrahedron: Asymmetry* **1996**, *7*, 1059–1068.

(25) Degiorgis, F.; Lombardo, M.; Trombini, C. *Tetrahedron* **1997**, *53*, 11721–11730.

(26) Degiorgis, F.; Lombardo, M.; Trombini, C. *Synthesis* **1997**, 1243–1245.

(27) Tokunaga, Y.; Ihara, M.; Fukumoto, K. *Tetrahedron Lett.* **1996**, *37*, 6157–6160.

(28) Naito, T.; Shirikawa, M.; Ikai, M.; Ninomiya, I.; Kiguchi, T. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 13–19.

(29) Kashima, C.; Takahashi, K.; Fukuchi, I.; Fukusaka, K. *Heterocycles* **1997**, *44*, 289–304.

(30) Minakata, S.; Ezoe, T.; Nakamura, K.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 5205–5208.

(31) Gilbertson, S. R.; Dawson, D. P.; Lopez, O. D.; Marshall, K. L. *J. Am. Chem. Soc.* **1995**, *117*, 4431–4432.

(32) Seerden, J. P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett.* **1994**, *35*, 4419–4422.

(33) Seerden, J.-P. G.; Kuypers, M. M. M.; Scheeren, H. W. *Tetrahedron: Asymmetry* **1995**, *6*, 1441–1450.

(34) Seerden, J.-P. G.; Boeren, M. M. M.; Scheeren, H. W. *Tetrahedron* **1997**, *53*, 11843–11852.

(35) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710–1740.

(36) (a) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *Tetrahedron Lett.* **1996**, *37*, 5947–5950. (b) Hori, K.; Ito, J.; Ohta, T.; Furukawa, I. *Tetrahedron* **1998**, *54*, 12737–12744.

The focus in the chiral Lewis acid catalyzed 1,3-dipolar cycloaddition reaction has mainly been devoted to the activation of electron-deficient alkenes by the catalyst.<sup>31,35–47</sup> In previous papers, we have shown that chiral titanium(IV), magnesium(II), and ytterbium(III) complexes can act as chiral catalysts for reactions between different nitrones and various alkenes.<sup>40–46</sup> The electron-deficient alkenes are activated for the 1,3-dipolar cycloaddition reaction by a bidentate coordination to the metal catalyst. By this coordination, the LUMO<sub>alkene</sub> energy is significantly lowered compared to that of the uncoordinated alkene, giving rise to a more favorable HOMO<sub>nitron</sub>–LUMO<sub>alkene</sub> interaction leading to an increase of the reaction rate with the nitron. The introduction of a suitable chiral ligand on the metal can thus lead to induced chirality in 1,3-dipolar cycloaddition reactions.

In this paper, we turn our interest to the Lewis acid catalyzed asymmetric 1,3-dipolar cycloaddition reaction between electron-rich alkenes and electron-deficient nitrones, thereby changing the interaction between the frontier molecular orbitals (FMOs) of the substrates to a HOMO<sub>alkene</sub>–LUMO<sub>nitron</sub> controlled reaction path. This type of reaction can in principle be considered as an inverse electron-demand 1,3-dipolar cycloaddition reaction. To our knowledge, only Scheeren et al. have reported a FMO interaction of this type in an asymmetric 1,3-dipolar cycloaddition reaction between an electron-neutral nitron and ketene acetals or vinyl ethers, catalyzed by a chiral oxazaborolidinone.<sup>32–34</sup> The catalysts used in these studies were of the oxazaborolidinone type, producing up to 62% ee at –78 °C and 31% ee at room temperature. In the case of cyclic vinyl ethers such as 2,3-dihydrofuran, a highly diastereoselective reaction takes place, but the ee of the adduct was only 38%.

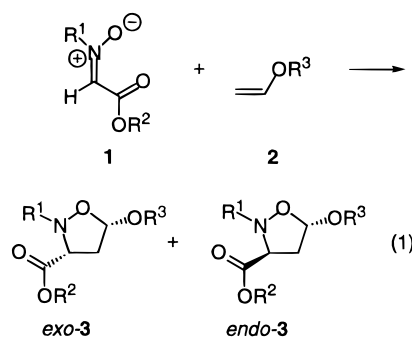
This paper presents a new metal-catalyzed 1,3-dipolar cycloaddition reaction of electrophilic nitrones with electron-rich alkenes in which the nitron is activated in a bidentate fashion by chiral Lewis acids.

## Results and Discussion

To accelerate the inverse electron-demand 1,3-dipolar cycloaddition reaction between a nitron and an electron-rich alkene, one can coordinate the nitron in a monodentate or bidentate fashion to a Lewis acid. In this paper, we will use the latter approach and present the development of catalytic enantioselective 1,3-dipolar cy-

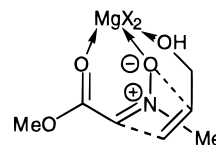
cloaddition reactions of nitrones with electron-rich alkenes leading to synthetically useful 1,3-dipolar cycloaddition adducts.

The nitron substrates for the inverse electron-demand 1,3-dipolar cycloaddition reaction presented here contain an ester substituent that allows for a bidentate coordination to the chiral Lewis acid. These nitrones, **1**, can react with electron-rich alkenes, **2**, in a regioselective reaction giving the isoxazolines *exo*-**3** or *endo*-**3** (eq 1).



By coordination to the Lewis acid, the HOMO and LUMO of **1** will be lowered compared with those of the free nitron, and the HOMO<sub>alkene</sub>–LUMO<sub>nitron</sub> interaction energy between the nitron–Lewis acid complex and an electron-rich alkene will be increased compared with that of the reaction in the absence of a Lewis acid.

Kanamasa et al. were probably the first who observed an acceleration in reaction rate of the 1,3-dipolar cycloaddition reaction between nitrones and allyl alcohol dipolarophiles by coordinating the nitron to a Lewis acid, such as MgX<sub>2</sub>, ZnBr<sub>2</sub>, TiCl<sub>2</sub>(*O*-Pr)<sub>2</sub>, or BF<sub>3</sub>·Et<sub>2</sub>O.<sup>12,14,15</sup> In the absence of 1 equiv of the Lewis acid, a slight decrease in reaction rate and a lack of diastereoselectivity were observed. The lack of selectivity is presumably caused by the *Z/E* isomerization of the nitron. In the presence of MgBr<sub>2</sub>, the selectivity of the reaction is explained by the favored chelation of the (*Z*)-nitron and concomitant coordination of the allyl alcohol to MgX<sub>2</sub>, as outlined in Figure 1.



**Figure 1.** The proposed coordination of the (*Z*)-nitron and allylic alcohol to MgX<sub>2</sub>, which accounts for the selectivity in the 1,3-dipolar cycloaddition reaction.<sup>15</sup>

Because the nitrones **1** exhibit *Z/E* isomerization in solution at room temperature when the carbon atom attached to the nitrogen atom has at least one hydrogen atom,<sup>48–51</sup> an investigation of the influence on the *Z/E* equilibrium by a bidentate coordination to a Lewis acid was undertaken in an attempt to obtain a more constrained intermediate. The *Z/E* equilibrium is also important for the diastereoselectivity of the reaction

(37) Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett.* **1997**, 1039–1040.

(38) Ukaji, Y.; Taniguchi, K.; Sada, K.; Inomata, K. *Chem. Lett.* **1997**, 547–548.

(39) Gillbertson, S. R.; Lopez, O. D. *J. Am. Chem. Soc.* **1997**, *119*, 3399–3400.

(40) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687–5691.

(41) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346–355.

(42) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59–64.

(43) Gothelf, K. V.; Jørgensen, K. A. *Acta Chem. Scand.* **1996**, *50*, 652–660.

(44) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471–2477.

(45) Jensen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *Helv. Chem. Acta* **1997**, *80*, 2039–2046.

(46) Sanchez-Blanco, A. I.; Gothelf, K. V.; Jørgensen, K. A. *Tetrahedron Lett.* **1997**, *38*, 7923–7926.

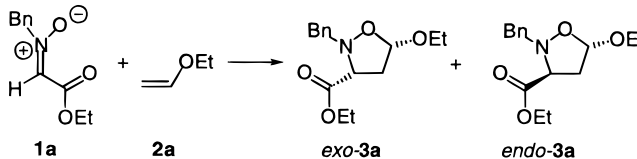
(47) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840–5841.

(48) Inouye, Y.; Takaya, K.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3541–3542.

(49) Aurich, H. G.; Franzke, M.; Kesselheim, H. P. *Tetrahedron Lett.* **1992**, *48*, 663–668.

(50) Inouye, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 244–247.

(51) (a) DeShong, P.; Dicken, M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4397–4403. (b) Burdisso, M.; Gandolfi, R.; Grünanger, P.; Rastelli, A. *J. Org. Chem.* **1990**, *55*, 3427–3429.

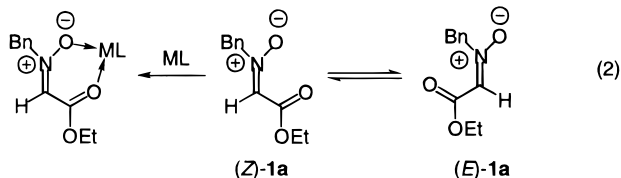
**Table 1.** 1,3-Dipolar Cycloaddition Reaction of *N*-Benzyl- $\alpha$ -ethoxycarbonylmethanimine *N*-Oxide **1a** with Ethyl Vinyl Ether **2a** under Various Reaction Conditions


entry <sup>a</sup>	solvent	catalyst	reactn time (h)	temp (°C)	conversion <sup>b</sup> (%)	<i>exo</i> - <b>3a</b> : <i>endo</i> - <b>3a</b>
1	CH <sub>2</sub> Cl <sub>2</sub>		66	rt	40	24:76
2	CH <sub>2</sub> Cl <sub>2</sub>		66	50	58	22:78
3	CH <sub>3</sub> CN		23	50	45	35:65
4	toluene		23	50	76	12:88
5	CH <sub>2</sub> Cl <sub>2</sub>	Cu(OTf) <sub>2</sub> <sup>c</sup>	8	rt	69	30:70

<sup>a</sup> The reactions were performed on a 0.1 mmol scale. <sup>b</sup> Conversion and *exo*-**3a**:*endo*-**3a** ratio were determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup> Catalyst loading, 25 mol %.

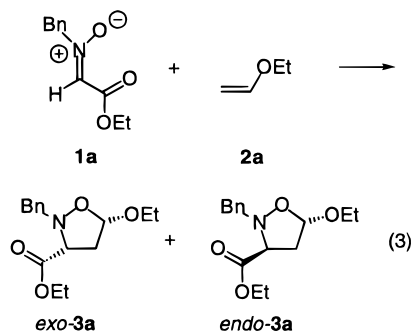
because, depending on the equilibrium, different ratios of the diastereomers are obtained.

The *Z/E*-equilibrium and the influence of Lewis acids have been studied for *N*-benzyl- $\alpha$ -ethoxycarbonylmethanimine *N*-oxide **1a** (eq 2) which is the class of nitrones used in the present investigations.



In the solid phase, nitron **1a** exists in the *Z* form, and an <sup>1</sup>H NMR spectrum in CD<sub>3</sub>CN recorded immediately after dissolving **1a** shows a (*Z*-**1a**)/(*E*-**1a**) ratio of 16:1. After 1 h at room temperature, the (*Z*-**1a**)/(*E*-**1a**) ratio has changed to 4.3:1. Addition of a Lewis acid changes the (*Z*-**1a**)/(*E*-**1a**) equilibrium toward an increase (>90%) in the *Z* form, and both Lewis acids, such as titanium(IV) and zinc(II), the latter also in the presence of chiral ligands, have the properties to coordinate to **1a**, bringing it into the *Z* form.

The preliminary experiments focused on the 1,3-dipolar cycloaddition reaction of *N*-benzyl- $\alpha$ -ethoxycarbonylmethanimine *N*-oxide **1a** to ethyl vinyl ether **2a** (eq 3).



The reaction proceeds in a regioselective manner with or without catalyst to give the isoxazolidines *exo*-**3a** and *endo*-**3a**, which are useful substrates for further transformation, i.e., to amino acids. The results for the reaction of **1a** with **2a** under various reaction conditions are presented in Table 1.

In the absence of a catalyst, the reaction between **1a** and **2a** proceeds very slowly at room temperature, giving only 40% conversion after 66 h (Table 1, entry 1), whereas

elevated temperatures in various solvents accelerate the reaction to different extents (entries 2–4). The *exo*-**3a**/*endo*-**3a** ratio is dependent on the solvent, and a preference for *endo*-**3a** is obtained especially in toluene (entry 4). It is considered that *exo*-**3a** is predominantly formed from (*Z*-**1a**), through an *exo*-transition state, and *endo*-**3a** is produced mainly from (*E*-**1a**), by an *exo*-transition state.<sup>51</sup> Because the (*Z*-**1a**)/(*E*-**1a**) ratio is solvent-dependent with a decreased ratio when less polar solvents are used,<sup>48–50,52</sup> it can be seen that the reactivity of (*E*-**1a**) is higher than that of (*Z*-**1a**) (entries 2–4).<sup>27,53</sup> In the presence of 25 mol % of Cu(OTf)<sub>2</sub> as the catalyst, the reaction of **1a** proceeds at room temperature to give **3a** with 69% conversion after only 8 h (entry 5). No appreciable difference is seen in the (*Z*-**1a**)/(*E*-**1a**) ratio of the Cu(OTf)<sub>2</sub>-catalyzed reaction compared to that of the uncatalyzed reaction. Tamura et al. have investigated the same reaction in the presence of equimolar amounts of Eu(fod)<sub>3</sub> as the catalyst and found that *endo*-**3a** is the major diastereomer formed; the stereoselectivity was explained by an *endo* attack of the alkene to (*Z*-**1a**).<sup>20</sup>

The C<sub>2</sub>-symmetric cationic MX<sub>2</sub>-bisoxazoline complexes<sup>54</sup> such as (*S*)-**4a–c**, (*R*)-**4d,e**, (*S*)-**5a**, and (*R*)-**5b** can act as Lewis acid catalysts for a variety of different addition reactions such as carbo-<sup>55–58</sup> and hetero-Diels–Alder<sup>59–62</sup> reactions. These catalysts can also be applied for the 1,3-dipolar cycloaddition reaction of electron-deficient alkene with nitrones.<sup>41</sup>

The results for the 1,3-dipolar cycloaddition reaction of *N*-benzyl- $\alpha$ -ethoxycarbonylmethanimine *N*-oxide **1a**

(52) Inouye, Y.; Hara, J.; Kakisawa, H. *Chem. Lett.* **1980**, 1407–1410.

(53) Hara, J.; Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3871–3872.

(54) (a) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339–345. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45.

(55) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460–6461.

(56) (a) Evans, D. A.; Murry, J. A.; Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798–800. (b) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481–7484.

(57) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027–7030.

(58) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786–787.

(59) Yao, S.; Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2345–2349.

(60) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757–5762.

(61) Johannsen, M.; Jørgensen, K. A. *Tetrahedron* **1996**, *52*, 7321–7328.

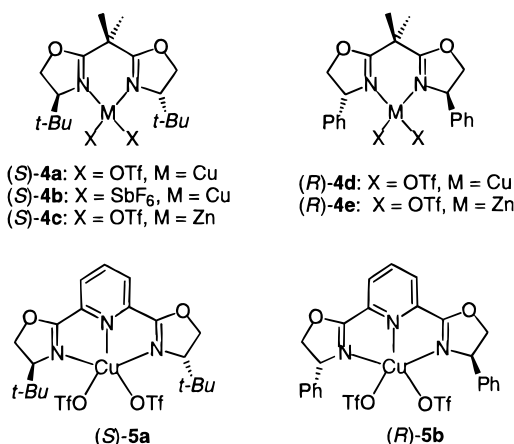
(62) Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; K., K. *Tetrahedron: Asymmetry* **1996**, *8*, 2165–2168.

**Table 2.** 1,3-Dipolar Cycloaddition between *N*-Benzyl- $\alpha$ -ethoxycarbonylmethanimine *N*-Oxide **1a** with Ethyl Vinyl Ether **2a** in the Presence of Various Copper(II) and Zinc(II) Salts Coordinated to the Chiral Bisoxazoline Ligands (*S*)-**4a**–**c**, (*R*)-**4d,e**, (*S*)-**5a**, and (*R*)-**5b** at Room Temperature

entry <sup>a</sup>	catalyst <sup>b</sup>	reactn time (h)	conversion <sup>c</sup> (%)	<i>exo</i> - <b>3a</b> : <i>endo</i> - <b>3a</b> <sup>c</sup>	ee <sup>d</sup> ( <i>exo</i> - <b>3a</b> / <i>endo</i> - <b>3a</b> , %)
1 <sup>e</sup>	<b>4a</b>	8	93	84:16	89/35
2 <sup>e,g</sup>	<b>4b</b>	24	81	44:56	0/0
3 <sup>e</sup>	<b>4c</b>	24	73	66:34	62/0
4 <sup>e</sup>	<b>4d</b>	7	86	43:57	44/0
5 <sup>e</sup>	<b>4e</b>	24	79	46:54	62 <sup>h</sup> /0
6 <sup>f</sup>	<b>5a</b>	2.5	75	58:42	0/0
7 <sup>f</sup>	<b>5b</b>	2.5	69	47:53	0/0

<sup>a</sup> The reactions were performed on a 0.1 mmol scale. <sup>b</sup> Catalyst load, 25 mol %. <sup>c</sup> Conversion and *exo*-**3a**:*endo*-**3a** ratio were determined by <sup>1</sup>H NMR spectroscopy. <sup>d</sup> Determined by HPLC (Daicel Chiralcel OD using hexane/*i*-PrOH 99.5:0.5, flow 0.7 mL/min). <sup>e</sup> CH<sub>2</sub>Cl<sub>2</sub> as the solvent. <sup>f</sup> Toluene as the solvent. <sup>g</sup> Catalyst load, 1 mol %. <sup>h</sup> Opposite enantiomer compared with entry 3.

with ethyl vinyl ether **2a** (eq 3) in the presence of various copper(II) and zinc(II) salts coordinated to the chiral



bisoxazoline ligands (*S*)-**4a**–**c**, (*R*)-**4d,e**, (*S*)-**5a**, and (*R*)-**5b** are presented in Table 2.

The use of (*S*)-**4a** as the catalyst for the 1,3-dipolar cycloaddition reaction of nitron **1a** with ethyl vinyl ether **2a** (eq 3) leads to a conversion of 93% (Table 2, entry 1). The diastereoselectivity has now changed to *exo*-selectivity in the reaction, as *exo*-**3a** and *endo*-**3a** were obtained in a ratio of 84:16 with 89% and 35% ee, respectively. Application of catalyst (*R*)-**4d** leads to a lack of diastereoselectivity, and a moderate ee of only 44% for *exo*-**3a** was obtained (entry 4). The major enantiomer of *exo*-**3a** produced using (*R*)-**4d** as the catalyst has the same absolute stereochemistry as that produced by the use of (*S*)-**4a**, even though the absolute stereochemistry of the ligand has changed. This effect has also been observed in copper(II)-bisoxazoline catalyzed hetero-Diels–Alder reactions.<sup>60–62</sup> The change of the counterion of the catalyst from triflate (in (*S*)-**4a**) to antimonate (in (*S*)-**4b**) leads, to our surprise, to a nonselective reaction (entry 2). Compared to the Diels–Alder reaction,<sup>56,63</sup> the Lewis acidity of the two zinc(II)-bisoxazoline catalysts (*S*)-**4c** and (*R*)-**4e** was weaker than that of the corresponding copper(II) catalyst, as seen from the 73% and 79% conversions, respectively, for the former (entries 3 and

5) compared with 93% and 86% conversions after 7–8 h (entries 1 and 4) for the latter. The ee of *exo*-**3a** was 62% in both cases using (*S*)-**4c** and (*R*)-**4e** as the catalyst in the zinc(II)-bisoxazoline catalyzed reaction. The absolute stereochemistry of the major enantiomer changed when moving from (*S*)-**4c** to (*R*)-**4e**. Hence, there is reason to believe that the two zinc(II)-bisoxazoline catalyst–substrate intermediates have the same geometry. Investigations of the copper(II)(pybox) complexes (*S*)-**5a** and (*R*)-**5b**, which were anticipated to possess a preferred square-planar coordination or square-pyramidal geometry with one or two accessible coordination sites<sup>56</sup> indicated that the bidentate coordination of the nitron **1a** to the copper(II)(pybox) complex is not feasible because of missing selectivities in the reaction between nitron **1a** and alkene **2a** (entries 6 and 7).

The diastereo- and enantioselectivity in the 1,3-dipolar cycloaddition reaction of nitron **1a** with ethyl vinyl ether **2a** in the presence of the copper(II)-bisoxazoline catalysts is very solvent dependent. The results for the reaction of **1a** with **2a** in the presence of (*S*)-**4a** as the catalyst in different solvents are presented in Table 3. In relation to the results, it should also be mentioned that in the copper(II)-bisoxazoline catalyzed carbo- and hetero-Diels–Alder reaction solvent effects have shown considerable changes in reaction rate, yield and enantioselectivity.<sup>61,63</sup>

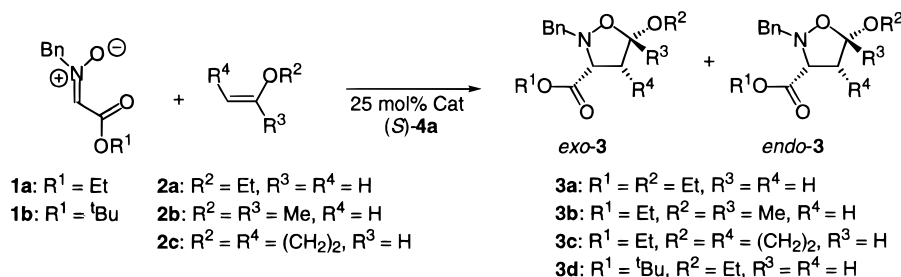
The catalytic reaction in toluene between *N*-benzyl- $\alpha$ -ethoxycarbonylmethanimine *N*-oxide **1a** and ethyl vinyl ether **2a** gives a higher ee but a lower diastereoselectivity compared to results of the reaction performed in CH<sub>2</sub>Cl<sub>2</sub> (Table 3, entries 1 and 2). In toluene and CH<sub>2</sub>Cl<sub>2</sub>, 93% and 89% ee, respectively, of *exo*-**3a** were obtained. However, a moderate ee of *endo*-**3a** is found in CH<sub>2</sub>Cl<sub>2</sub>, whereas a racemic mixture is formed in toluene. Application of a mixture of petroleum ether and CH<sub>2</sub>Cl<sub>2</sub> as the solvent (entry 3) leads to an ee of 92% of *exo*-**3a** and an improvement of the *exo*-**3a**/*endo*-**3a** ratio compared with that for the reaction in toluene. More polar solvents proved to be less effective for the reaction, and considerable amounts of byproduct and regioisomers were obtained (entries 4–6).

The reaction course is dependent on the temperature and amount of both the alkene and the catalyst in the standard reaction of nitron **1a** with ethyl vinyl ether

**Table 3. Solvent Effects in the 1,3-Dipolar Cycloaddition Reaction of *N*-Benzyl- $\alpha$ -ethoxycarbonylmethanimine *N*-Oxide **1a** with Ethyl Vinyl Ether **2a** in the Presence of the Copper(II)-bisoxazoline (*S*)-**4a** at Room Temperature**

entry <sup>a</sup>	solvent	reactn time (h)	conversion <sup>b</sup> (%)	<i>exo</i> - <b>3a</b> : <i>endo</i> - <b>3a</b> <sup>b</sup>	ee <sup>c</sup> ( <i>exo</i> - <b>3a</b> / <i>endo</i> - <b>3a</b> , %)
1	toluene	24	98	70:30	93/0
2	CH <sub>2</sub> Cl <sub>2</sub>	8.5	93	84:16	89/35
3	petroleum ether/CH <sub>2</sub> Cl <sub>2</sub>	24	84	77:23	92/37
4	CH <sub>3</sub> CN	23	65 <sup>d</sup>	68:32	9 <sup>e</sup> /2
5	THF	23	80 <sup>d</sup>	57:43	51/0
6	CH <sub>3</sub> NO <sub>2</sub>	96	99 <sup>d</sup>	37:63 <sup>f</sup>	14/2

<sup>a</sup> The reactions were performed on a 0.1 mmol scale. <sup>b</sup> Conversion and *exo*-**3a**:*endo*-**3a** ratio were determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup> HPLC (Daicel Chiralcel OD using hexane/*i*-PrOH 99.5:0.5, flow 0.7 mL/min). <sup>d</sup> Byproducts formed. <sup>e</sup> Opposite enantiomer. <sup>f</sup> The regioselectivity was 65:35 in favor of the 5-isomer relative to the 4-isomer.

**Table 4. Asymmetric 1,3-Dipolar Cycloaddition Reactions between the Nitrones **1a,b** and Alkenes **2a,c** Catalyzed by 25 mol % of Copper(II)-bisoxazoline Catalyst (*S*)-**4a****

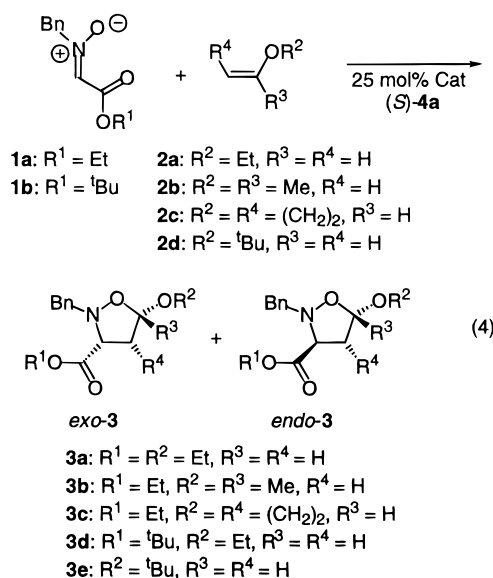
entry <sup>a</sup>	nitrone	alkene	product	reactn time (h)	yield <sup>b</sup> (%)	<i>exo</i> - <b>3</b> : <i>endo</i> - <b>3</b> <sup>c</sup>	ee ( <i>exo</i> - <b>3</b> / <i>endo</i> - <b>3</b> %) <sup>d</sup>
1	<b>1a</b>	<b>2a</b>	<b>3a</b>	20	83	77:23	89/16
2	<b>1a</b>	<b>2b</b>	<b>3b</b>	20	83	31:69	90/94
3	<b>1a</b>	<b>2c</b>	<b>3c</b>	20	43	50:50	12/0
4	<b>1b</b>	<b>2a</b>	<b>3d</b>	38	52	50:50	0/0

<sup>a</sup> The reactions were performed on a 0.25 mmol scale. For details, see Experimental Section. <sup>b</sup> Isolated yields. <sup>c</sup> The *endo*:*exo* ratio was determined by <sup>1</sup>H NMR spectroscopy. <sup>d</sup> The ee was determined by HPLC (Daicel Chiralcel OD or OJ using hexane/*i*-PrOH).

**2a** in CH<sub>2</sub>Cl<sub>2</sub> as the solvent (eq 3). In the presence of 50 mol % of catalyst (*S*)-**4a**, a quantitative conversion was obtained and the selectivities were similar to the reaction using 25 mol % of the catalyst. Reduction of the catalyst loading to 10 mol % reduces the diastereo- and enantioselectivity, and an *exo*-**3a**/*endo*-**3a** ratio of approximately 50:50, with only moderate ee of the *exo*-**3a** (<20% ee), was obtained. The addition of twice as much alkene increased the reaction rate but decreased the selectivity of the reaction slightly. The ee of the 1,3-dipolar cycloaddition reaction in the presence of 25 mol % loading of the catalyst changes slightly as the reaction proceeds. In the beginning of the reaction course, a very high enantioselectivity of 97% ee of *exo*-**3a** was obtained; however, the ee of *exo*-**3a** went to a level of 89% when the reaction had gone to nearly completion.

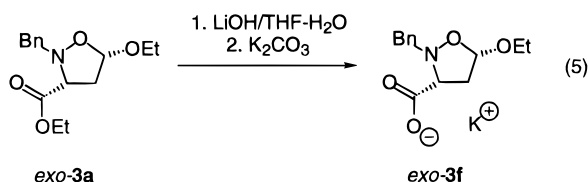
The more general application of this new *exo*-selective catalytic approach to the 1,3-dipolar cycloaddition reaction is demonstrated by performing the reaction of the different nitrones **1a,b** with the alkenes **2a–d** in the presence of (*S*)-**4a** as the catalyst (eq 4). The reactions were allowed to continue until <sup>1</sup>H NMR spectroscopy of the reaction mixtures reveal that >90% conversion has taken place at room temperature, and the results are presented in Table 4.

The nitrone **1a** reacts with ethyl vinyl ether **2a** in the presence of (*S*)-**4a** as the catalyst to give *exo*-**3a** as the major diastereomer formed in 89% ee under these reaction conditions (Table 4, entry 1). The 1,3-dipolar cycloaddition of nitrone **1a** with 2-methoxy propene **2b** leads to a change in diastereoselectivity, as *endo*-**3b** now is the major diastereomer formed in an *exo*-**3b**/*endo*-**3b** ratio of 31:69 (entry 2). Both diastereomers are formed in very high ee as 90% and 94% ee of *exo*-**3b** and *endo*-

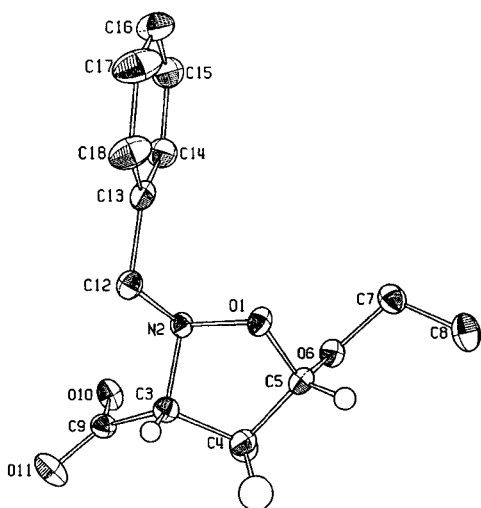


**3b** are formed, respectively. Cyclic alkenes, such as 2,3-dihydrofuran **2c**, react with nitrone **1a** in a nondiastereoselective reaction, giving 50% of each of the two diastereomers with only 12% ee of *exo*-**3c** (entry 3). It is also notable that an exchange of the ethyl ester in **1a** with a *tert*-butyl ester, *N*-benzyl- $\alpha$ -*tert*-butoxycarbonylmethanimine *N*-oxide **1b**, leads to a nonselective diastereo- and enantioselective 1,3-dipolar cycloaddition reaction. The catalytic 1,3-dipolar cycloaddition reaction of nitrone **1a** proceeds also with *tert*-butyl vinyl ether **2d**. However, adducts *exo*-**3e** and *endo*-**3e** are formed in only 35% yield in an *exo*-**3e**/*endo*-**3e** ratio of 26:74, and both diastereomers are formed in 50% ee.

To determine the absolute stereochemistry of the major enantiomer of *exo-3a* formed by reaction of nitrone **1a** with **2a** in the presence of catalyst (*S*)-**4a**, the chiral 1,3-dipolar cycloaddition adduct *exo-3f* was synthesized (eq 5). The *exo-3a* adduct was separated from the *endo-3a* adduct and hydrolyzed with LiOH in a THF/H<sub>2</sub>O solution giving the corresponding carboxylic acid which was converted to the crystalline potassium salt *exo-3f* by addition of 0.5 equiv K<sub>2</sub>CO<sub>3</sub>.



The absolute stereochemistry of the isoxazolidine *exo-3f* as determined by X-ray analysis is presented in Figure 2. The chiral centers formed in the 1,3-dipolar cycloaddition reaction are assigned as (3*R*,5*S*). The absolute stereochemistry of *exo-3f* indicates that the alkene approaches the *re*-face (relative to the nitrone carbon atom) of nitrone **1a** when (*S*)-**4a** is applied as the catalyst.



**Figure 2.** The X-ray structure of *exo-3f*. The hydrogen atoms are shown only for the isoxazolidine ring.

The results presented in Table 2 for the use of copper(II)-bisoxazoline catalyst (*S*)-**4a**, which has the possibility for a bidentate coordination, compared with the results for the application of the copper(II)(pybox) (*S*)-**5a** and (*R*)-**5b** catalysts, indicate that nitrone **1a** coordinates to the catalyst in a bidentate fashion. In relation to this observation, it should be mentioned that the copper(II)-bisoxazolines generally give the best enantiomeric results for substrates which can coordinate in a bidentate fashion and that coordination of substrates, such as  $\alpha$ -dicarbonyl compounds, leads to a square-planar complex.<sup>54b,60,64–66</sup> Coordination of nitrone **1a** to (*S*)-**4a** in this fashion leads to intermediate **6** (Figure 3, top).

The square-planer copper(II)-bisoxazoline–nitron intermediate **6** has the *si*-face of the nitrone available for approach of the alkene. However, this approach is *not* in accordance with the absolute stereochemistry of the isoxazolidine adduct, determined by X-ray analysis in Figure 2, as approach to the *si*-face will lead to the (3*S*,5*R*)-isoxazolidine of *exo-3a*. This absolute stereochemistry of the 1,3-dipolar cycloaddition adduct is not in accordance with what should be “expected” on the basis of previous assignments of the absolute stereochemistry of products obtained using (*S*)-**4a** as the catalyst for addition reactions.<sup>54b,60,64–66</sup>

To account for the absolute stereochemistry of the 1,3-dipolar cycloaddition adduct obtained by reaction of nitrone **1a** with the electron-rich alkenes catalyzed by (*S*)-**4a**, different models for the intermediate have been investigated. On the basis of these studies and the experimental observation that addition of ethyl vinyl ether **2a** to the copper(II)-bisoxazoline–nitron intermediate gives a significant color change from yellow-green to green, it is postulated that both **1a** and **2a** can be coordinated to the chiral catalyst during the reaction, leading to a pentacoordinated intermediate.

For a pentacoordinated intermediate containing the chiral bisoxazoline ligand, the nitrone, and ethyl vinyl ether, the requirement is that both the bisoxazoline ligand and the nitrone have to be in a *cis* fashion at the metal. This leads to an intermediate, **7** (Figure 3, bottom), in which the nitrone is coordinated in the equatorial plane and the bisoxazoline in the equatorial and axial positions, leaving the remaining axial position available for the coordination of ethyl vinyl ether. The coordination of ethyl vinyl ether in this axial position allows the alkene fragment to approach the *re*-face of the nitrone in an *exo*-selective fashion, leading to the formation of the isoxazolidine with the same absolute (3*R*,5*S*) stereochemistry as observed experimentally.

The absolute stereochemistry of the 1,3-dipolar cycloaddition adduct can also be accounted for by a tetrahedral copper(II)-bisoxazoline–nitron intermediate, **8** (Figure 3, top). This intermediate has the *re*-face of nitrone **1a** available for approach of ethyl vinyl ether and is also in accordance with the experimental results. However, such a tetrahedral intermediate (**8**) is not in accordance with what should be “expected” on the basis of previous assignments of the absolute stereochemistry of products obtained using the same catalyst addition reactions.<sup>54b,60,64–66</sup> Nevertheless, we leave both intermediates **7** and **8** in Figure 3 as possible candidates for the intermediate in these reactions.

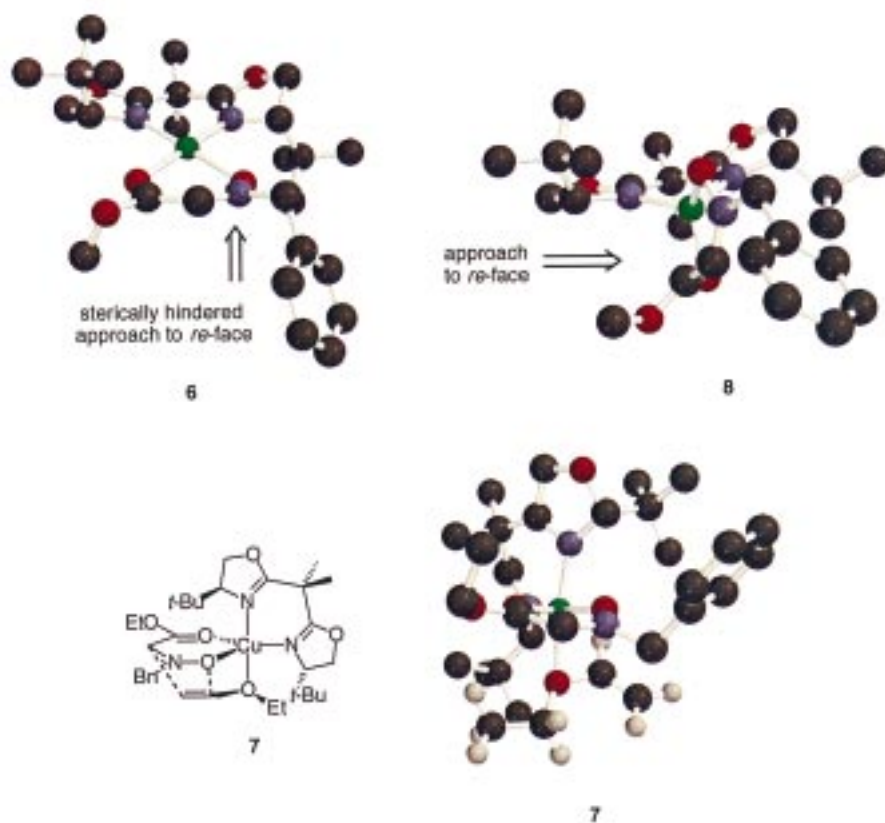
## Conclusion

A new copper(II)-bisoxazoline catalyzed diastereo- and enantioselective 1,3-dipolar cycloaddition reaction between electron-poor nitrones that can coordinate to the chiral Lewis acid in a bidentate fashion and electron-rich alkenes has been developed. In the presence of Cu(OTf)<sub>2</sub>-bisoxazoline as the catalyst, the nitrones react smoothly with vinyl ethers at room temperature, giving isoxazolidines in good yields and diastereoselectivity and with enantioselectivities up to 94% ee, especially for ethyl vinyl ether and 2-methoxy propene. The reaction leads to an approach of the alkene fragment of the vinyl ether to the *re*-face of the nitrone. On the basis of the absolute stereochemistry of the isoxazolidine formed, a penta-

(64) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojlovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824–5825.

(65) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599–8605.

(66) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *39*, 2404–2406.



**Figure 3.** Top: a square-planar copper(II)-bisoxazoline–nitron intermediate (**6**) in which the *re*-face of the nitron is shielded by the *tert*-butyl substituent of the bisoxazoline ligand, and a tetrahedral copper(II)-bisoxazoline–nitron intermediate (**8**) showing the possible approach to the *re*-face of the nitron. Bottom: a pentacoordinated intermediate (**7**). To the left is a representation of the coordination of both the nitron and ethyl vinyl ether to the copper(II)-bisoxazoline catalyst. To the right is a model for the intermediate in which only the hydrogen atoms of the vinyl ether are shown. The latter model is viewed from the same site as intermediates **6** and **8** above.

coordinated or a tetrahedral intermediate are proposed to account for the absolute stereochemistry. In the former intermediate, the chiral bisoxazoline ligand and the nitron occupy four of the five available coordination sites at the copper(II) center, and the vinyl ether is coordinated to the last coordination site.

### Experimental Section

**General Methods.** The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts for  $^1\text{H}$  and  $^{13}\text{C}$  NMR are reported in  $\text{CDCl}_3$  as the solvent and in ppm downfield from tetramethylsilane (TMS). HPLC was performed using a 4.6 mm  $\times$  25 cm Daicel Chiracel OD or OJ columns. Mass spectra were recorded at 70 eV with a direct inlet. Optical rotation was measured on a Perkin-Elmer 241 polarimeter. TLC was performed on Merck analytical silica gel 60 F<sub>254</sub> plates and visualized with blue stain. Solvents were dried using standard procedures. All glass equipment was dried in an oven at 150 °C before use.

**Materials.** The starting materials ethyl glyoxalate and *tert*-butyl glyoxalate were prepared as described in the literature,<sup>67–69</sup> stored at –18 °C, and distilled under water vacuum prior to use. *N*-Benzyl- $\alpha$ -ethoxycarbonylmethanimine *N*-oxide **1a** and *N*-benzyl- $\alpha$ -*tert*-butoxycarbonylmethanimine *N*-oxide **1b** were synthesized from addition of benzylhydroxylamine

hydrochloride to the corresponding glyoxylates according to the literature.<sup>69</sup>  $\text{Cu}(\text{OTf})_2$ ,  $\text{Zn}(\text{OTf})_2$ ,  $\text{CuBr}_2$ ,  $\text{AgSbF}_6$ ,  $\text{AgPF}_6$ , 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-4,5-dihydrooxazole], 2,2'-isopropylidenebis[(4*R*)-4-phenyl-4,5-dihydrooxazole], 2,6-bis-[(4*S*)-*tert*-butyl-4,5-dihydrooxazole-2-yl]pyridine, 2,6-bis-[(4*R*)-phenyl-4,5-dihydrooxazole-2-yl]pyridine, benzylhydroxylamine hydrochloride, ethyl vinyl ether, 2,3-dihydrofuran, and 2-methoxy propene were purchased from Aldrich and distilled over solid sodium prior to use.  $\text{Cu}(\text{OTf})_2$ ,  $\text{Zn}(\text{OTf})_2$ ,  $\text{CuBr}_2$ , and  $\text{AgSbF}_6$  were stored under  $\text{N}_2$ .

**Asymmetric 1,3-Dipolar Cycloaddition Reactions; General Procedure for the Reaction Using 25 mol % of Catalyst (S)-4a.** A flame-dried Schlenk tube was charged with  $\text{Cu}(\text{OTf})_2$  (22.6 mg, 0.0625 mmol) and the ligand 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-4,5-dihydrooxazole] (21.5 mg, 0.073 mmol) under a stream of  $\text{N}_2$ . Dry  $\text{CH}_2\text{Cl}_2$  (5 mL) was added, and the mixture was then stirred at room temperature for 1–2 h. To the green solution nitron **1** (0.25 mmol) and alkene **2** (0.50 mmol) were added. The solution was then stirred at room temperature for the time given in the tables. The reaction mixture was then filtered through a 30 mm layer of silica gel. The silica gel layer was washed with 25–50 mL of 0.3–0.6%  $\text{Et}_3\text{N}$  in  $\text{CH}_2\text{Cl}_2$ , and the solvent was evaporated. The crude product was purified by FC (silica gel, hexane/ $\text{Et}_2\text{O}$  95:5 containing 0.3% of  $\text{Et}_3\text{N}$ ). The less polar isomer was the *exo*-isomer, and the more polar compound was the *endo*-isomer. In most of the cases, the diastereomers could not be fully separated. The ratio and assignment of the diastereomers were possible by both  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data, except in one case. *Exo*-**3b** and *endo*-**3b** are given as combinations of the  $^{13}\text{C}$  NMR spectra below.

(+)-(3*R*,5*S*)-2-*N*-Benzyl-5-ethoxy-isoxazolidine-3-carboxylic Acid Ethyl Ester. Total yield: 83%. *Exo*-**3a**:  $[\alpha]_{\text{D}}$

(67) Jung, M. E.; Shishido, K.; Davis, L. H. *J. Org. Chem.* **1982**, *47*, 891–892.

(68) Subasinghe, N.; Schulte, M.; Chan, M. Y.-M.; Roon, R. J.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1990**, *33*, 2734–2744.

(69) Inouye, Y.; Watanabe, Y.; Takahashi, S.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3763–3764.

+96° ( $c = 1.0$ , CHCl<sub>3</sub>).  $R_f = 0.35$  (Et<sub>2</sub>O/petroleum ether 40:60). HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99.5:0.5, flow rate = 0.7 mL/min)  $t_R = 34.0$  min (major),  $t_R = 38.8$  min (minor). Ee = 89%. <sup>1</sup>H NMR  $\delta$  1.15 (t,  $J = 7.1$  Hz, 3H), 1.24 (t,  $J = 7.1$  Hz, 3H), 2.54 (ddd,  $J = 13.2, 7.1, 2.2$  Hz, 1H), 2.64 (ddd,  $J = 13.2, 8.8, 5.5$  Hz, 1H), 3.39 (dq,  $J = 9.4, 7.1$  Hz, 1H), 3.48 (dd,  $J = 8.8, 7.7$  Hz, 1H), 3.73 (dq,  $J = 9.9, 7.1$  Hz, 1H), 4.02 (d,  $J = 14.3$  Hz, 1H), 4.14 (q,  $J = 7.1$  Hz, 1H), 4.15 (q,  $J = 7.1$  Hz, 1H), 4.22 (d,  $J = 14.3$  Hz, 1H), 5.14 (dd,  $J = 5.5, 2.2$  Hz, 1H), 7.27–7.33 (m, 3H), 7.40 (dd,  $J = 8.2, 1.6$  Hz, 2H). <sup>13</sup>C NMR  $\delta$  14.0, 14.9, 39.8, 61.3, 61.5, 63.3, 65.5, 100.5, 127.3, 128.1, 129.2, 136.0, 169.7. MS  $m/z = 279$  (M<sup>+</sup>).

**Endo-3a:** (mixture of *endo-3a/exo-3a*)  $R_f = 0.32$  (Et<sub>2</sub>O/petroleum ether 40:60). HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99.5:0.5, flow rate = 0.7 mL/min)  $t_R = 55.9$  min (major),  $t_R = 60.8$  min (minor). Ee = 16%. <sup>1</sup>H NMR  $\delta$  1.20 (t,  $J = 7.1$  Hz, 3H), 1.22 (t,  $J = 7.1$  Hz, 3H), 2.56 (ddd,  $J = 12.6, 7.2, 1.1$  Hz, 1H), 2.74 (ddd,  $J = 13.2, 8.2, 5.5$  Hz, 1H), 3.47 (dq,  $J = 9.9, 7.1$  Hz, 1H), 3.80 (dq,  $J = 9.4, 7.2$  Hz, 1H), 3.91 (t,  $J = 7.7$  Hz, 1H), 4.11 (q,  $J = 7.1$  Hz, 2H), 4.18 (d,  $J = 12.6$  Hz, 1H), 4.34 (d,  $J = 13.2$  Hz, 1H), 5.24 (d,  $J = 5.0$  Hz, 1H), 7.26–7.35 (m, 3H), 7.40 (dd,  $J = 8.2, 1.7$  Hz, 2H). <sup>13</sup>C NMR  $\delta$  14.0, 15.0, 39.7, 61.3, 63.2, 65.0, 65.3, 103.4, 127.5, 128.3, 129.1, 136.8, 170.7. MS  $m/z = 279$  (M<sup>+</sup>).

**2-N-Benzyl-5-methoxy-5-methyl-isoxazolidine-3-carboxylic Acid Ethyl Ester.** Total yield: 83%. **Exo-3b:** (mixture of *endo-3b/exo-3b*)  $R_f = 0.22$  (Et<sub>2</sub>O/petroleum ether 40:60). HPLC (Daicel Chiralcel OJ, hexane/*i*-PrOH = 99.5:0.5, flow rate = 0.5 mL/min)  $t_R = 32.3$  min (major),  $t_R = 48.3$  min (minor). Ee = 90%. <sup>1</sup>H NMR  $\delta$  1.25 (t,  $J = 7.1$  Hz, 1H), 1.42 (s, 3H), 2.34 (dd,  $J = 13.2, 9.3$  Hz, 1H), 2.70 (dd,  $J = 13.2, 7.1$  Hz, 1H), 3.23 (s, 3H), 3.58 (dd,  $J = 9.3, 7.1$  Hz, 1H), 4.02 (d,  $J = 13.8$  Hz, 1H), 4.14 (q,  $J = 7.1$  Hz, 1H), 4.15 (q,  $J = 7.1$  Hz, 1H), 4.25 (d,  $J = 13.7$  Hz, 1H), 7.28–7.42 (m, 5H). <sup>13</sup>C NMR  $\delta$  14.0, 14.1, 19.3, 21.0, 45.0, 45.5, 49.2, 49.3, 61.3, 61.7, 65.0, 66.3, 66.9, 104.9, 107.7, 127.5, 127.5, 128.2, 128.3, 129.2, 129.3, 136.1, 136.7, 169.8, 170.8. MS  $m/z = 279$  (M<sup>+</sup>).

**Endo-3b:**  $R_f = 0.22$  (Et<sub>2</sub>O/petroleum ether 40:60). HPLC (Daicel Chiralcel OJ, hexane/*i*-PrOH = 99.5:0.5, flow rate = 0.5 mL/min)  $t_R = 35.4$  min (major),  $t_R = 42.1$  min (minor). Ee = 94%. <sup>1</sup>H NMR  $\delta$  1.18 (t,  $J = 7.1$  Hz, 3H), 1.46 (s, 3H), 2.56 (dd,  $J = 12.1, 9.3$  Hz, 1H), 2.65 (dd,  $J = 12.0, 7.1$  Hz, 1H), 3.32 (s, 3H), 3.96 (dd,  $J = 9.4, 7.2$  Hz, 1H), 4.09 (q,  $J = 7.1$  Hz, 2H), 4.15 (d,  $J = 13.2$  Hz, 1H), 4.33 (d,  $J = 13.2$  Hz, 1H), 7.28–7.42 (m, 5H). <sup>13</sup>C NMR  $\delta$  14.0, 14.1, 19.3, 21.0, 45.0, 45.5, 49.2, 49.3, 61.3, 61.7, 65.0, 66.3, 66.9, 104.9, 107.7, 127.5, 127.5, 128.2, 128.3, 129.2, 129.3, 136.1, 136.7, 169.8, 170.8. MS  $m/z = 279$  (M<sup>+</sup>).

**2-N-Benzyl-hexahydro-furo[3,2-d]isoxazole-3-carboxylic Acid Ethyl Ester.** Total yield: 43%. **Exo-3c:** (mixture of *endo-3c/exo-3c*)  $R_f = 0.31$  (Et<sub>2</sub>O/petroleum ether 40:60). HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 98:2, flow rate = 1.0 mL/min)  $t_R = 17.6$  min (major),  $t_R = 20.4$  min (minor). Ee = 12%. <sup>1</sup>H NMR  $\delta$  1.28 (t,  $J = 7.1$  Hz, 3H), 1.83–2.10 (m, 3H), 3.51 (d,  $J = 7.1$  Hz, 1H), 3.81 (d,  $J = 13.7$  Hz, 1H), 3.93–4.04 (m, 2H), 4.17 (d,  $J = 13.7$  Hz, 1H), 4.19 (q,  $J = 7.1$  Hz, 2H), 5.69 (d,  $J = 5.5$  Hz, 1H), 7.25–7.39 (m, 5H). <sup>13</sup>C NMR  $\delta$  14.2, 28.6, 49.9, 60.8, 61.2, 69.6, 70.9, 104.8, 127.5, 128.3, 129.1, 136.0, 168.7. MS  $m/z = 277$  (M<sup>+</sup>).

**Endo-3c:**  $R_f = 0.26$  (Et<sub>2</sub>O/petroleum ether 40:60). HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 98:2, flow rate = 1.0 mL/min)  $t_R = 23.3$  min,  $t_R = 30.1$  min. Ee = 0%. <sup>1</sup>H NMR  $\delta$  1.29 (t,  $J = 7.1$  Hz, 3H), 1.90–2.10 (m, 3H), 3.34–3.40 (m, 2H), 4.03 (d,  $J = 13.7$  Hz, 1H), 4.03 (m, 1H), 4.12 (d,  $J = 13.7$  Hz, 1H), 4.17 (q,  $J = 7.2$  Hz, 2H), 5.78 (d,  $J = 4.9$  Hz, 1H), 7.26–7.40 (m, 5H). <sup>13</sup>C NMR  $\delta$  14.1, 30.7, 51.1, 59.1, 61.1, 67.9, 71.2, 106.0, 127.3, 128.1, 128.8, 136.1, 169.4. MS  $m/z = 277$  (M<sup>+</sup>).

**2-N-Benzyl-5-ethoxy-isoxazolidine-3-carboxylic Acid tert-Butyl Ester.** Total yield: 52%. **Exo-3d:** (mixture of *endo-3d/exo-3d*)  $R_f = 0.50$  (Et<sub>2</sub>O/petroleum ether 40:60). HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99.5:0.5, flow rate = 0.5 mL/min)  $t_R = 26.0$  min,  $t_R = 28$  min. Ee = 0%. <sup>1</sup>H NMR  $\delta$  1.14 (t,  $J = 7.1$  Hz, 3H), 1.44 (s, 9H), 2.51 (ddd,  $J = 13.1, 7.7, 2.2$  Hz, 1H), 2.57–2.68 (m, 1H), 3.34–3.44 (m, 2H), 3.73 (dq,  $J = 9.9, 7.1$  Hz, 1H), 3.98 (d,  $J = 14.4$  Hz, 1H), 4.30 (d,  $J =$

14.3 Hz, 1H), 5.11 (dd,  $J = 6.0, 2.2$  Hz, 1H), 7.27–7.42 (m, 5H). <sup>13</sup>C NMR  $\delta$  15.0, 28.0, 39.9, 61.3, 63.5, 66.1, 82.1, 100.7, 127.4, 128.2, 129.4, 135.0, 211.3. MS  $m/z = 307$  (M<sup>+</sup>). **Endo-3d:** (mixture of *endo-3d/exo-3d*)  $R_f = 0.45$  (Et<sub>2</sub>O/petroleum ether 40:60). HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99.5:0.5, flow rate = 0.5 mL/min)  $t_R = 37.5$  min,  $t_R = 53.3$  min. Ee = 0%. <sup>1</sup>H NMR  $\delta$  1.21 (t,  $J = 7.1$  Hz, 3H), 1.39 (s, 9H), 2.49 (ddd,  $J = 12.6, 7.1, 1.0$  Hz, 1H), 2.69 (ddd,  $J = 13.1, 8.2, 4.9$  Hz, 1H), 3.46 (dq,  $J = 9.3, 7.1$  Hz, 1H), 3.76–3.84 (m, 2H), 4.20 (d,  $J = 13.2$  Hz, 1H), 4.30 (d,  $J = 12.6$  Hz, 1H), 5.21 (d,  $J = 4.9$  Hz, 1H), 7.26–7.42 (m, 5H). <sup>13</sup>C NMR  $\delta$  15.1, 27.9, 39.5, 63.2, 65.1, 66.0, 81.8, 103.3, 127.5, 128.3, 129.3, 137.4, 169.9. MS  $m/z = 307$  (M<sup>+</sup>).

**Procedure for the Conversion of *exo-3a* into (+)-(3*R*,5*S*)-2-N-Benzyl-5-ethoxy-isoxazolidine-3-carboxylic Acid.** To the ester *exo-3a* (45.7 mg, 0.164 mmol) dissolved in THF/H<sub>2</sub>O (1:1, 4.0 mL) at room temperature was added LiOH (14.0 mg, 0.58 mmol). The solution was stirred at room temperature for 1 h. The solution was acidified to pH 1 with 4 M HCl and extracted twice with EtOAc. The combined organic phase was washed with brine, and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude compound was used without further purification in the next step (40.0 mg, 97%).  $[\alpha]_D = +78^\circ$  ( $c = 1.0$ , CH<sub>3</sub>OH).  $R_f = 0.10$ –0.26 (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 5:95). <sup>1</sup>H NMR  $\delta$  1.15 (t,  $J = 7.1$  Hz, 3H), 2.32 (ddd,  $J = 13.2, 10.4, 4.9$  Hz, 1H), 2.60 (dd,  $J = 13.1, 1.6$  Hz, 1H), 3.42 (dq,  $J = 9.4, 7.1$  Hz, 1H), 3.72 (dq,  $J = 9.3, 7.1$  Hz, 1H), 3.73 (dd,  $J = 9.9, 1.1$  Hz, 1H), 4.00 (d,  $J = 14.2$  Hz, 1H), 4.22 (d,  $J = 13.3$  Hz, 1H), 5.25 (d,  $J = 4.4$  Hz, 1H), 7.35 (s, 5H). <sup>13</sup>C NMR  $\delta$  14.9, 38.4, 62.0, 62.8, 63.2, 100.3, 128.4, 128.9, 129.4, 134.5, 171.7. MS  $m/z = 251$ .

**Procedure for the Conversion of Carboxylic Acid of *exo-3a* into (+)-(3*R*,5*S*)-2-N-Benzyl-5-ethoxy-isoxazolidine-3-carboxylic Acid Potassium Salt (*exo-3f*).** To the carboxylic acid (40.0 mg, 0.16 mmol) dissolved in MeOH (1.0 mL) was added K<sub>2</sub>CO<sub>3</sub> (11.0 mg, 0.08 mmol). After the mixture stirred at 40 °C overnight, half of the mixture was evaporated to dryness. Recrystallation of the white powder in CH<sub>3</sub>CN provided *exo-3f* as colorless crystals (5.0 mg).  $[\alpha]_D = +166^\circ$  ( $c = 1.0$ , CH<sub>3</sub>OH). <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  1.06 (t,  $J = 7.2$  Hz, 3H), 2.28 (ddd,  $J = 13.2, 9.9, 2.7$  Hz, 1H), 2.71 (ddd,  $J = 13.2, 8.3, 6.6$  Hz, 1H), 3.18 (m, 1H), 3.31 (dq,  $J = 9.3, 7.1$  Hz, 1H), 3.57 (dq,  $J = 9.8, 7.2$  Hz, 1H), 3.70 (d,  $J = 14.2$  Hz, 1H), 4.27 (d,  $J = 14.3$  Hz, 1H), 5.02 (dd,  $J = 6.6, 3.3$  Hz, 1H), 7.15–7.25 (m, 3H), 7.35 (d,  $J = 7.1$  Hz, 2H). <sup>13</sup>C NMR (CD<sub>3</sub>OD)  $\delta$  15.4, 42.5, 62.3, 64.5, 71.3, 102.3, 128.0, 129.0, 130.6, 138.8, 177.0.

**X-ray Determinations.** Data were collected from a needle-shaped crystal of *exo-3f* on a SMART diffractometer using Mo K $\alpha$  radiation ( $\lambda = 0.71073$  Å). *Exo-3f* is tetragonal, space group *I*4<sub>1</sub>,  $a = b = 17.8839(6)$  Å,  $c = 17.7409(8)$  Å. A total of 41591 reflections were measured, 6376 unique, internal agreement 0.041. The structure was solved by direct methods (SIR97)<sup>70</sup> and refined by least squares to  $R = 0.024$ ,  $R_w = 0.025$  for 472 parameters. The absolute configuration was determined from the anomalous scattering contribution of potassium by least-squares refinement of the Rogers parameter,<sup>71</sup> giving a value of 0.96(3). In all, 2916 Friedel pairs were included in the refinement.

**Acknowledgment.** We are indebted to The Danish National Research Foundation and Statens Teknisk Videnskabelige Forskningsråd for financial support.

**Supporting Information Available:** <sup>1</sup>H and <sup>13</sup>C NMR and MS data for products and X-ray data for *exo-3f*. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO982081B

(70) Altomare, A.; Cascarano, G.; Giacivazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camilli, M. *J. Appl. Chem.* **1994**, *27*, 435.  
(71) Rogers, D. *Acta Crystallogr.* **1981**, *A37*, 734–741.