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Catalytic Enantioselective 1,3-Dipolar Cycloaddition Reactions of Cyclic Nitrones: A Simple Approach for the Formation of Optically Active Isoquinoline Derivatives

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The first highly diastereo- and enantioselective catalytic 1,3-dipolar cycloaddition reaction of cyclic nitrones activated by chiral Lewis acids with electron-rich alkenes has been developed. The nitrones, mainly 3,4-dihydroisoquinoline *N*-oxides, are activated by chiral 3,3′-aryl BINOL−AlMe complexes and undergo a regio-, diastereo-, and enantioselective 1,3-dipolar cycloaddition reaction with especially alkyl vinyl ethers, giving the exo diastereomer of the cycloaddition products in high yield, >90% de and up to 85% ee. The reaction has been investigated under various conditions, and it is demonstrated that the reaction is an attractive synthetic procedure for the introduction of a chiral center in the 1-position of the isoquinoline skeleton. The mechanism of the reaction is discussed on the basis of the assignment of the absolute configuration of the cycloaddition product and theoretical calculations.

Introduction

The isoquinoline skeleton constitutes a fundamental part of numerous natural products and compounds with physiological activity.[1] As many naturally occurring isoquinoline alkaloids and their nonnatural derivatives have distinct properties of general interest, an intense synthetic effort has been devoted to the development of reactions leading to optically active isoquinoline derivatives. The asymmetric synthesis of, for example, optically active 1-substituted 1,2,3,4-tetrahydroisoquinolines has been of considerable interest, as these compounds are very useful compounds for the preparation of, for example, optically active alkaloids.[1,2] The synthesis of optically active 1-substituted 1,2,3,4-tetrahydroisoquinolines is normally based on diastereoselective reactions applying chiral starting material or reagents.[2] An attractive procedure for the preparation of optically active compounds is asymmetric catalysis, and it has been attempted to synthesize optically active 1-substituted 1,2,3,4-tetrahydroisoquinolines based on enantioselective reduction of, or addition to, the C═N bond in the 3,4-dihydroisoquinoline moiety.[2f,3]

A new approach for the formation of optically active 1-substituted 1,2,3,4-tetrahydroisoquinolines would be the 1,3-dipolar cycloaddition reaction of nitrones, derived from isoquinolines, and electron-rich alkenes in the presence of a chiral catalyst.[4] This paper presents the first highly diastereo- and enantioselective 1,3-dipolar cycloaddition reactions of cyclic nitrones with alkenes leading to optically active isoxazolidines which easily are converted to optically active isoquinoline derivatives. To understand the stereoselection, we will present theoretical calculations of the nitrone−chiral catalyst intermediate which can account for both the diastereo- and enantioselective outcome of the reaction.

The catalytic enantioselective 1,3-dipolar cycloaddition reaction has recently been developed to be a highly selective reaction of nitrones with electron-deficient alkenes activated by chiral Lewis acids.[5,6] However, few synthetic methods are available for the 1,3-dipolar cyclo-

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[1] See, e.g.: (a) Bentley, K. W. *Nat. Prod. Rep.* **1998**, 341. (b) Herbert, R. B. In *The Chemistry and Biology of Isoquinoline Alkaloids*; Philipson, J. D., Roberts, M. F., Zenk, M. H., Eds.; Springer-Verlag: Berlin, 1985; p 213. (c) Dyke, S. F.; Kinsman, R. G.; Kametami, T. G.; Fukumato, K.;. McDonald, E. Isoquinolines. In *Heterocyclic Compounds*; Grethe, G., Ed.; Wiley: New York, 1981; Vol. 38, p 1.

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[3] (a) Morimoto, T.; Suzuki, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1998**, *9*, 183. (b) Ukaji, Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 447. (c) Sigman, M. S.; Vechal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279.

[4] Numerous reviews describe the formation of isoxazolidine derivatives using a traditional 1,3-dipolar cycloaddition procedure, see, e.g.: (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, p 83. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988. (c) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 1.

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[6] See, e.g.: (a) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687. (b) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59. (c) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471. (d) Jensen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *Helv. Chem. Acta* **1997**, *80*, 2039. (e) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017. (f) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (g) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 3213. (h) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.*, **1998**, *120*, 5840. (i) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. *Tetrahedron Lett.* **1999**, *40*, 2001. (j) Crosignani, S.; Desimoni, G.; Faita, G.; Filippone, S.; Mortoni, A.; Righetti, P.; Zema, M. *Tetrahedron Lett.* **1999**, *40*, 7007. (k) Heckel, A.; Seebach, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 163.

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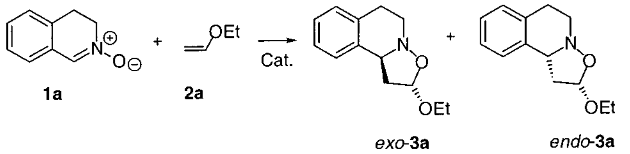
Table 1. Catalytic Diastereo- and Enantioselective 1,3-Dipolar Cycloaddition Reaction of 1a with 2a Catalyzed by Different Chiral Aluminum Complexes[a]



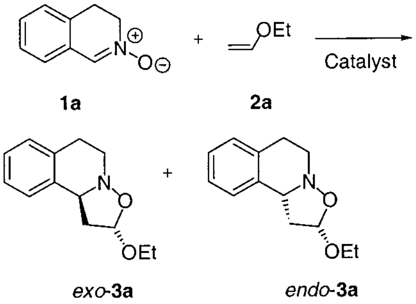
entry	catalyst	conv[b] [%]	rxn time [h]	*exo*-**3a**/*endo*-**3a**[b]	ee *exo*-**3a**[c] [%]
1		5	24	>95:<5	0
2	$AlMe_3$[d]	28	20	>95:<5	0
3	$AlCl_3$[e]	88	20	20:80	0
4	(*R*)-**4a**	11	42	85:15	24
5	(*R*)-**4b**	76	20	92:8	66
6	(*R*)-**4c**	96	46	89:11	58
7	(*R*)-**4d**	74	20	98:2	82
8	(*R*)-**4e**	78	20	87:13	67
9	(*S*)-**4f**	30	46	78:22	50[f]

[a] Reaction conditions: solvent, CH_2Cl_2; scale, **1a** (0.1 mmol), **2a** (0.4 mmol), and 20 mol % catalyst. [b] Determined by ^1H NMR spectroscopy of the crude product. [c] The ee of the *exo*-isomer was determined by HPLC using a Daicel Chiralcel OD column. [d] Performed with 10 mol % catalyst and 10 equiv of the alkene. [e] Performed with 10 mol % catalyst and 2 equiv of the alkene. [f] Opposite enantiomer.

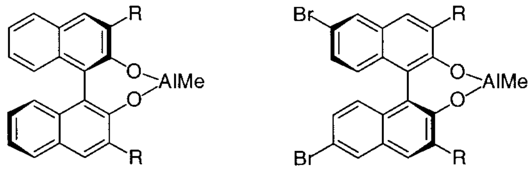
addition reaction of electron-rich alkenes with nitrones activated by chiral Lewis acids.[7] In the few reports on catalytic enantioselective 1,3-dipolar cycloaddition reaction of monodentate cyclic nitrones to electron-rich alkenes, racemic reactions or moderate enantioselectivity as high as 38% ee have been obtained so far.[7c,d,h] Furthermore, some of the reactions involving 3,4-dihydroisoquinoline *N*-oxide **1a** require up to 2000 bar in order to proceed.[7c]

Results and Discussion

Different chiral Lewis acid complexes have been tested for their ability to induce regio-, diastereo-, and enantioselectivity in the reaction of 3,4-dihydroisoquinoline *N*-oxide **1a** with ethyl vinyl ether **2a** (eq 1). It was found that chiral BINOL−AlX complexes gave the most promising results, and Table 1 shows some data for the reaction of **1a** with **2a** catalyzed by (*R*)-**4a**−(*S*)-**4f**.

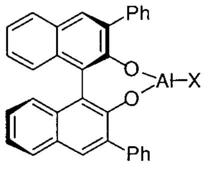


(1)



(*R*)-**4a**: R = H
(*R*)-**4b**: R = Ph
(*R*)-**4c**: R = (2,5-dihexyloxy)phenyl
(*R*)-**4d**: R = (2,5-dimethoxy)phenyl
(*R*)-**4e**: R = 2-naphthyl
(*S*)-**4f**: R = $SiPh_3$

(*S*)-**4g**: R = H
(*S*)-**4h**: R = Ph



(*R*)-**4i**: X = Cl
(*R*)-**4j**: X = I
(*R*)-**4k**: X = OTf

In the absence of a catalyst, only 5% conversion is found for the reaction of **1a** with **2a** after 24 h (Table 1, entry 1). The addition of $AlMe_3$ and $AlCl_3$ leads to a significant increase in the reaction rate and 28% conversion is observed with $AlMe_3$ (entry 2), while a much higher conversion of 88% is found for $AlCl_3$ (entry 3). It is notable that the diastereoselectivity depends on the aluminum compound used. In the case of $AlMe_3$, the reaction proceeds with an *exo*/*endo* ratio of >95:<5, whereas with $AlCl_3$ an *exo*/*endo* ratio of 20:80 is observed. A diastereoselective reaction is obtained when using (*R*)-**4a** as the catalyst; however, both the yield and ee of the major diastereomer *exo*-**3a** are low (entry 4). The 3,3′-aryl substituted BINOL−AlMe catalysts lead to a significant increase in both the conversion, diastereo-, and enantioselectivity (entries 5−9). The best results are obtained for BINOLs having phenyl or 2,5-dimethoxyphenyl substituents in the 3,3′-position (entries 5 and 7). The application of catalyst (*R*)-**4d** gave 74% conversion, an *exo*-**3a**/*endo*-**3a** ratio of 98:2, and 82% ee of *exo*-**3a** (entry 7). This is the first example of a highly diastereo- and enantioselective catalytic 1,3-dipolar cycloaddition reaction of a cyclic nitrone. The use of (*R*)-**4e** and (*S*)-**4f** gives good diastereo- and enantioselectivity but for the latter catalyst a somewhat lower yield (entries 8 and 9).

The reaction of **1a** with **2a** catalyzed by (*R*)-**4b** or (*R*)-**4d** has been studied in different solvent compositions and catalyst loadings. The reaction of **1a** with **2a** in the presence of catalyst (*R*)-**4b** proceeds well in a variety of solvents, e.g., CH_2Cl_2, toluene, CH_2Cl_2−pet. ether, and CH_2Cl_2−*t*-BuOMe. In all four solvent compositions, 80−91% isolated yield of *exo*-**3a** is obtained. The highest selectivity for the reaction is achieved by using CH_2Cl_2−pet. ether giving *exo*-**3a** in >95% de and 78% ee. Even better enantioselectivity is found for the reaction catalyzed by (*R*)-**4d** in CH_2Cl_2−pet. ether where 85% ee of *exo*-**3a** is obtained. The reaction also proceeds well when the catalyst loading is reduced to 10 mol % for both catalyst (*R*)-**4b** and (*R*)-**4d** where similarly high diastereo- and enantioselectivities are obtained.

The 1,3-dipolar cycloaddition reaction of **1a** with **2a** has also been studied in the presence of various 3,3′-phenyl BINOL-derived ligands and different aluminum Lewis acids. Table 2 gives the results of these investigations.

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Table 2. Influence of Lewis Acid and Substition at the 6,6′-Position of the BINOL Ligand in the 1,3-Dipolar Cycloaddition Reaction of 1a with 2a at Room Temperature[a]

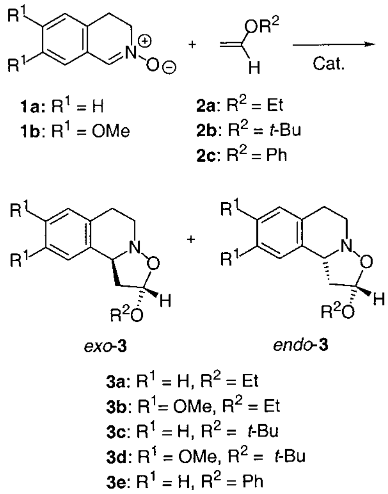
entry	cat/mol [%]	conv[b] [%]	rxn time [h]	*exo*-**3a**/*endo*-**3a**[b]	ee *exo*/*endo* [%][c]
1	(*R*)-**4b**/20	95	95/24	95:5	78/30
2	(*S*)-**4h**/20	98	98/20	98:2	68[d]/−
3	(*R*)-**4i**/20	98	98/25	87:13	48/0
4	(*R*)-**4j**/20	100	100/19	27:73	66/6
5	(*R*)-**4k**/10	100	100/20	42:58	13/3

[a] Reaction conditions: solvent, CH_2Cl_2 or CH_2Cl_2−pet. ether; scale, 0.1−0.2 mmol. The molar scale is defined from **1a** (1 equiv), **2a** (4 equiv). [b] Determined by ^1H NMR spectroscopy of the crude product. [c] The ee was determined by HPLC using a Daicel Chiralcel OD column. [d] Opposite enantiomer.

An introduction of bromine in the 6,6′-position of the catalyst [(*S*)-**4h**] gives no significant change in conversion and diastereoselectivity; however, a small decrease in enantioselectivity is found compared with catalyst (*R*)-**4b** (Table 2, entries 1 and 2). An interesting change of diastereoselectivity takes place by changing the third substituent of the aluminum Lewis acid. An exchange of the methyl substituent [(*R*)-**4b**] to chloride [(*R*)-**4i**] reduces the *exo*-**3a**/*endo*-**3a** ratio from 95:5 to 87:13, while the ee of *exo*-**3a** is reduced from 78% to 48% (entries 1 and 3). Catalyst (*R*)-**4j** which contains the Al−I functionality changes the diastereoselectivity of the reaction, and *endo*-**3a** is now formed as the major product (entry 4). Unfortunately, the ee of *endo*-**3a** is low. The use of a chiral aluminum catalyst substituted with triflate gives poor diastereo- and enantioselective in the reaction (entry 5). The diastereoselectivity of the 1,3-dipolar cycloaddition of **1a** with **2a** is thus dependent on the X-substituent of the BINOL−AlX catalyst. Although the ee of *endo*-**3a** is low when using (*R*)-**4j** as the catalyst, it might be a useful approach for controlling an *endo*-selective reaction of this class of substrates. It should be noted that anions at the Lewis acid center have previously been shown to control the diastereoselectivity in 1,3-dipolar cycloaddition of electron-deficient alkenes with nitrones catalyzed by TADDOL−TiX_2 complexes.[6b]

A valuable cyclic nitrone for the 1,3-dipolar cycloaddition reaction is 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide **1b**. The cycloadducts obtained in the reactions of this nitrone with electron-rich alkenes are potential precursors for important natural products and compounds with physiological activity.[1,8] The results of the catalytic diastereo- and enantioselective reaction of the nitrones **1a**,**b** with different vinyl ethers **2a**-**c** are presented in Table 3.

Table 3. Diastereo- and Enantioselective 1,3-Dipolar Cycloaddition Reaction of 1a and 1b with the Vinyl Ethers 2a−c Catalyzed by the Chiral Aluminum Complexes



entry	cat./mol [%]	1	2	3	yield [%][a]	*exo*/*endo*[b]	ee *exo*/*endo* [%][c]
1	**4d**/20	**1a**	**2a**	**3a**	85	96:4	85/12
2	**4b**/20	**1b**	**2a**	**3b**	76	97:3	70/0
3	**4b**/10	**1a**	**2b**	**3c**	86	95:5	70/26
4	**4b**/20	**1b**	**2b**	**3d**	92	100:0	65/−
5	**4b**/20	**1a**	**2c**	**3e**	24	>95:<5	10/−

[a] Isolated yield of *exo*-diastereomer. [b] Determined by ^1H NMR spectroscopy of the crude product. [c] The ee was determined by HPLC using a Daicel Chiralcel OD or OJ column.

The results in Table 3 show that the catalytic 1,3-dipolar cycloaddition reaction of **1a** and **1b** proceeds well for ethyl vinyl ether **2a** and *tert*-butyl vinyl ether **2b**. The products, *exo*-**3a**−**d**, are obtained in good to high isolated yield, diastereo- and enantioselectivity (entries 1−4). It is notable that for the reaction between **1b** and **2b**, the reaction gives exclusively *exo*-**3d** in high yield and with 65% ee (entry 4). Increasing the size of the vinyl ether to that of phenyl vinyl ether **2e** leads also to a highly diastereoselective reaction; unfortunately, both the yield and ee of *exo*-**3e** are low (entry 5).

We have also performed the 1,3-dipolar cycloaddition reaction of pyrroline-*N*-oxide with **2a** in the presence of the chiral BINOL−ALMe catalysts (*R*)-**4b** and (*R*)-**4d**. The reaction proceeds with high *exo*-selectivity and moderate ee (40%); however, the isolated yield of the cycloaddition adduct was low (<40% yield).

The catalytic diastereo- and enantioselective reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide **1b** with ethyl vinyl ether **2a** leads to the formation of optically active *exo*-**3b**. This reaction allows for a simple and attractive approach to the introduction of a chiral center, e.g., an ester functionality, in the 1-position of the isoquinoline skeleton (Scheme 1). Reaction of *exo*-**3b** with benzyl bromide followed by reduction with $H_2/Pd(OAc)_2$ gives the (−)-(1*S*)-amino ester **5** in high yield. This reaction shows the potential of the present reaction and gives a simple procedure for assignment of the absolute configuration of the chiral center formed in the reaction. A comparison of the optical rotation of **5** with the literature value[9] shows that catalyst (*R*)-**4b** introduces a (1*S*)-configuration at the chiral center formed in the cycloaddition step.

The absolute configuration of the new chiral center in the 1,3-dipolar cycloaddition reaction of the cyclic nitrones with electron-rich alkenes was not predicted by us because the opposite enantiomer was obtained in the analogous reactions of acyclic nitrones with electron-rich alkenes catalyzed by chiral BINOL−AlMe complexes.[7f] The origin of this change in the absolute configuration

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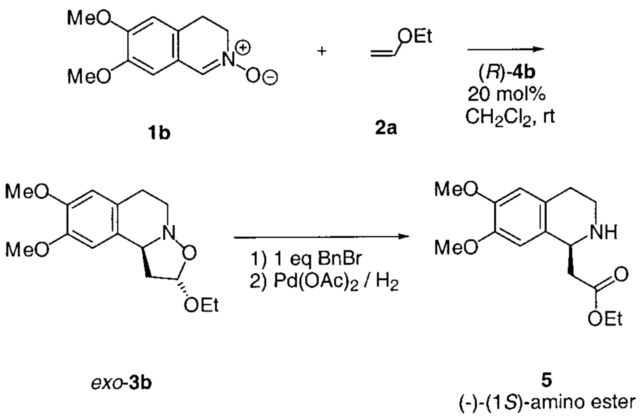
(8) See, e.g.: (a) Pelletier, J. C.; Cava, M. P. *Synthesis* **1987**, 474. (b) Fülöp, F.; Semega, E.; Bernáth, G. *J. Heterocycl. Chem.* **1990**, *27*, 957. (c) Takeuchi, Y.; Kamada, Y.; Nishimura, K.; Nishioka, H.; Nishikawa, M.; Hashigaki, K.; Yamato, M.; Harayama, T. *Chem. Pharm. Bull.* **1994**, *42*, 796. (d) Fülöp, F.; Wamhoff, H.; Sohár, P. *Synthesis* **1995**, 863. (e) Ukaji, Y.; Yoshida, Y.; Inomata, K. *Tetrahedron: Asymmetry* **2000**, *11*, 733.

(9) Battersby, A. R.; Bink, R.; Edwards, T. P. *J. Chem. Soc.* **1960**, 3474.

Scheme 1



upon changing the nitrone from an acyclic to a cyclic nitrone has been the subject of theoretical calculations. The calculations have been performed for catalyst (*R*)-**4b** using the AM1 semiempirical method.[10] Several intermediate structures of the complex formed by coordination of nitrone **1a** to (*R*)-**4b** were investigated. It has been found that the most stable intermediate **6** (Figure 1a), by theoretical calculations, is the one where the nitrone coordinates to the chiral catalyst in a fashion that maximizes $\pi-\pi$ interaction between the aromatic part of the nitrone and the naphthyl ring of the BINOL ligand. This intermediate (**6**) has the *re*-face of the nitrone shielded by the chiral ligand and is 3 kcal/mol more stable than the intermediate having the *re*-face unshielded. The approach of ethyl vinyl ether **2a** to the *si*-face of the nitrone in **6** in a diastereo- and enantioselective fashion shown in Figure 1b is consistent with the stereochemical outcome of the reaction.

In summary, cyclic nitrones of the 3,4-dihydroisoquinoline *N*-oxide type undergo a highly diastereo- and enantioselective 1,3-dipolar cycloaddition reaction with electron-rich alkenes in the presence of chiral BINOL−AlMe complexes as catalysts. It is shown that this reaction can be used for the introduction of a chiral center in the 1-position of the isoquinoline skeleton. The nitrone coordinates to the chiral BINOL−AlMe catalyst to maximize $\pi-\pi$ interaction between the aromatic part of the nitrone and the naphthyl ring of the BINOL ligand leading to an *exo*-selective approach of the alkene to the *si*-face of the activated nitrone.

Experimental Section

General Methods. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise stated, at 300 and 75 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^1H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. Solvents were dried using standard conditions and stored over molecular sieves (4 Å). CH_2Cl_2 was distilled from CaH_2 prior to use. Purification of reactions products was carried out by flash chromatography (FC) using Merck silica gel 60 (230−400 mesh). TLC was performed on Merck analytical silica gel 60 F_{254} plates and visualized with blue stain. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. HPLC was performed using 4.6 mm × 25 cm Daicel Chiracel OD or OJ columns employing hexane/*i*-PrOH ratios between 98:2 and 92:8 with UV-detection at 225 nm. All glass equipment was flame-dried under vacuum before used.

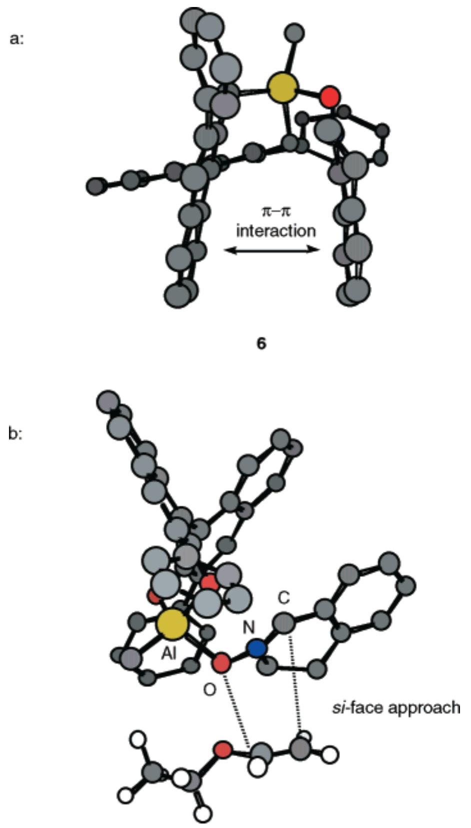


Figure 1. (a) The most stable intermediate (**6**) of the nitrone **1a** coordinated to (*R*)-**4b** in a fashion that maximizes the $\pi-\pi$ interaction between the aromatic part of the nitrone and the naphthyl ring of the (*R*)-BINOL ligand. Color code: carbon, gray; nitrogen, blue; oxygen, red; aluminum, yellow. (b) Approach of ethyl vinyl ether **2a** to the *si*-face of 3,4-dihydroisoquinoline *N*-oxide **1a** coordinated to the chiral (*R*)-BINOL−ALMe catalyst (*R*)-**4b**. Color code: carbon, gray; hydrogen, white; nitrogen, blue; oxygen, red; aluminum, yellow.

Materials. The chiral ligands in the catalysts **4a**,[11] **4b**,**e**,[12] **4c**,**d**,[13] **4f**,[14] **4h**,[15] and the nitrones 3,4-dihydroisoquinoline *N*-oxide **1a** and 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide **1b**[16] were synthesized according to the literature. *tert*-Butyl vinyl ether and ethyl vinyl ether and $AlMe_3$ (2 M in hexan) were received from Aldrich. The vinyl ethers were distilled from sodium immediately prior to use. Millex filter units, 45 μm pore size, were received from Millipore.

General Procedure for the Stereoselective 1,3-Dipolar Cycloaddition Reactions. The appropriate ligand (0.04 mmol) was placed in a 5 mL Schlenk flask. The flask was evaporated 1 h and flushed three times with N_2. A solution of CH_2Cl_2 (1 mL) was added with a syringe. To this solution was added a 2

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M solution of $AlMe_3$ in hexane (20 μL, 0.04 mmol) whereupon the solution turned yellow under the evolution of CH_4.[7f] The solution was stirred for 1 h, and nitrone **1** (0.2 mmol) was added together with 4 equiv of the vinyl ethers **2** (1.6 mmol) and pet. ether (0.5 mL). After the appropriate reaction time, the reaction was quenched with MeOH (0.2 mL) and filtered through a 20 mm plug of silica. The silica was washed with 5% MeOH in CH_2Cl_2 (5 mL), and the combined fractions were evaporated. The crude product from 1,3-dipolar cycloaddition reactions of 3,4-dihydroisoquinoline *N*-oxide **1a** with vinyl ethers **2a**−**c** was purified by FC (silica gel, pet. ether/Et_2O, 70:30) to give the single diasteromer of **3**. Generally, the *endo*-isomers appeared with lower R_f values than the *exo*-isomers ($\Delta R_f = 0.1$). The crude product from the 1,3-dipolar cycloaddition reactions of 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide **1b** with vinyl ethers **2a**,**b** was purified by FC. The ligand was eluated out first (silica gel, pet. ether/Et_2O 70:30), changing the eluent to CH_2Cl_2/MeOH, 98:2. The *exo*-isomer was eluated out as the first of the two diastereomers ($\Delta R_f = 0.28$).

(−)-(2*S*,10b*S*)-2-Ethoxy-1,5,6,10b-tetrahydro-2*H*-isoxazolo[3,2,-*a*]isoquinoline (*exo*-3a). Synthesized according to the general procedure on a 0.4 mmol scale with catalyst (*R*)-**4b** (10 mol %): yield 91%; ee = 77%; yellow oil; $[\alpha]_D = 98.7$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR δ 1.25 (t, $J = 7.1$ Hz, 3H), 2.44 (ddd, $J = 5.5, 8.8, 12.9$ Hz, 1H), 2.65 (ddd, $J = 1.1, 6.9, 12.9$ Hz, 1H), 2.88 (m, 2H), 3.20 (ddd, $J = 4.6, 7.4, 11.9$ Hz, 1H), 3.31 (ddd, $J = 5.5, 5.7, 11.7$ Hz, 1H), 3.50 (dq, $J = 7.1, 9.5$ Hz, 1H), 3.88 (dq, $J = 7.1, 9.5$ Hz, 1H), 4.77 (t, $J = 7.9$ Hz, 1H), 5.26 (d, $J = 5.3$ Hz, 1H), 7.08−7.23 (m, 4H); ^{13}C NMR δ 15.0, 26.7, 43.4, 49.6, 60.0, 63.1, 101.5, 126.4, 127.3, 128.1, 133.7, 135.6; HPLC (Daicel Chiralcel OD, hexane/*i*−PrOH = 98:2, flow rate = 1.0 mL/min) $t_R = 10.5$ min (minor), $t_R = 28.7$ min (major); MS m/z 219 (M^+). All structural assignments were in agreement with the MS, ^{1}H, and ^{13}C NMR data available from the literature.[7c,d]

(+)-(2*S*,10b*S*)-2-Ethoxy-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-isoxazolo[3,2,-*a*]isoquinoline (*exo*-3b). Synthesized according to the general procedure on a 0.4 mmol scale employing catalyst (*R*)-**4b** (20 mol %): yield 76%; ee = 70%; yellow oil; $[\alpha]_D = +47.4$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR δ 1.21 (t, $J = 7.2$ Hz, 3H), 2.40 (ddd, $J = 5.4, 8.7, 12.9$ Hz, 1H), 2.58 (ddd, $J = 1.2, 7.8, 13.2$ Hz, 1H), 2.77 (m, 2H), 3.15 (ddd, $J = 5.4, 6.3, 11.7$ Hz, 1H), 3.26 (ddd, $J = 5.4, 6.3, 11.7$ Hz, 1H), 3.45 (dq, $J = 6.9, 9.3$ Hz, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 3.84 (dq, $J = 7.2, 9.5$ Hz, 1H), 4.66 (t, $J = 7.2$ Hz, 1H), 5.23 (d, $J = 4.8$ Hz, 1H), 6.56 (s, 1H), 6.57 (s, 1H); ^{13}C NMR δ 15.1, 26.4, 43.4, 49.7, 55.8, 55.9, 59.8, 63.2, 101.7, 109.9, 110.8, 125.7, 127.1, 147.6, 147.8; HPLC (Daicel Chiralcel OJ, hexane/*i*−PrOH = 96:4, flow rate = 1.0 mL/min) $t_R = 27.7$ min (major), $t_R = 44.2$ min (minor); TOF ES$^+$ m/z 302 (M + Na)$^+$; HRMS calcd for $C_{15}H_{21}NaNO_4$ 302.1368, found 302.1360.

(+)-(2*S*,10b*S*)-2-*tert*-Butoxy-1,5,6,10b-tetrahydro-2*H* isoxazolo[3,2,-*a*]isoquinoline (*exo*-3c). Synthesized according to the general procedure on a 0.4 mmol scale with catalyst (*R*)-**4b** (10 mol %): yield 86%; ee = 70%; yellow oil; $[\alpha]_D = 81.7$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR δ 1.28 (s, 9H), 2.43 (ddd, $J = 5.5, 8.8, 12.7$ Hz, 1H), 2.53 (ddd, $J = 0.9, 6.6, 12.6$ Hz, 1H), 2.87 (m, 2H), 3.13 (ddd, $J = 5.1, 6.5, 11.5$ Hz, 1H), 3.28 (ddd, $J = 4.9, 5.4, 10.4$ Hz, 1H), 4.75 (t, $J = 8.2$ Hz, 1H), 5.57 (d, $J = 4.4$ Hz, 1H), 7.08−7.19 (m, 4H); ^{13}C NMR δ 27.1, 28.9, 44.1, 49.5, 60.4, 74.5, 96.9, 126.3, 126.4, 127.4, 128.2, 133.8, 135.9; HPLC (Daicel Chiralcel OD, hexane/*i*−PrOH = 98:2, flow rate = 1.0 mL/min) $t_R = 7.4$ min (minor), $t_R = 10.2$ min (major); MS m/z 247 (M^+). All structural assignments were in agreement with the ^{1}H NMR data available from the literature.[7d]

(+)-(2*S*,10b*S*)-2-*tert*-Butoxy-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-isoxazolo[3,2,-*a*]isoquinoline (*exo*-3d). Synthesized according to the general procedure on a 0.4 mmol scale employing catalyst (*R*)-**4b** (20 mol %): yield 92%; ee = 65%; yellow oil; $[\alpha]_D = +52.1$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR δ 1.27 (s, 9H), 2.41 (ddd, $J = 6.0, 8.8, 12.8$ Hz, 1H), 2.49 (ddd, $J = 1.2, 6.8, 12.4$ Hz, 1H), 2.79 (m, 2H), 3.11 (ddd, $J = 4.4, 8.4, 11.2$ Hz, 1H), 3.26 (ddd, $J = 4.8, 5.6, 10.4$ Hz, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 4.68 (t, $J = 8.4$ Hz, 1H), 5.56 (d, $J = 4.8$ Hz, 1H), 6.57 (s, 1H), 6.59 (s, 1H); ^{13}C NMR δ 25.7, 27.9, 42.9, 48.5, 54.8, 54.9, 59.1, 73.5, 95.9, 108.9, 109.7, 124.7, 126.3, 146.5, 146.7; HPLC (Daicel Chiralcel OJ, hexane/*i*−PrOH = 96:4, flow rate = 0.3 mL/min) $t_R = 14.1$ min (major), $t_R = 16.0$ min (minor); TOF ES$^+$ m/z 330 (M + Na)$^+$; HRMS calcd for $C_{17}H_{25}NaNO_4$ 330.1681, found 330.1700.

(2,10b)-2-Phenyloxy-1,5,6,10b-tetrahydro-2*H*-isoxazolo-[3,2,-*a*]isoquinoline (*exo*-3e). Synthesized according to the general procedure on a 0.4 mmol scale employing catalyst (*R*)-**4b** (20 mol %): yield 24%; ee = 10%; colorless oil; ^{1}H NMR δ 2.60 (ddd, $J = 5.8, 8.4, 13.6$ Hz, 1H), 2.78 (ddd, $J = 5.2, 7.6, 12.8$ Hz, 1H), 2.89 (m, 2H), 3.27 (m,32H), 4.83 (t, $J = 6.4$ Hz, 1H), 5.82 (d, $J = 4.8$ Hz, 1H), 6.90−7.23 (m, 9H); ^{13}C NMR δ 26.3, 43.9, 49.6, 60.1, 100.1, 116.8, 122.0, 126.6, 127.4, 128.3, 129.4, 133.8, 135.3, 156.8; HPLC (Daicel Chiralcel OJ, hexane/*i*−PrOH = 92:8, flow rate = 0.3 mL/min) $t_R = 44.6$ min (major), $t_R = 90.3$ min (minor). TOF ES$^+$ m/z: 330 (M + Na)$^+$; HRMS calcd for $C_{18}H_{19}NaNO_2$ 290.1157, found 290.1174.

Formation of (1*S*)-2-Benzyl-1-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. To a solution of *exo*-**3b** (58% ee, 73.8 mg, 0.264 mmol) in toluene (1 mL) was added 1.05 equiv of BnBr (33 μL, 0.277 mmol); the flask was capped and stirred overnight. The reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O (3 × 2 mL). The organic layer was dried and the solvent evaporated. The crude product was purified by FC (silica gel, pet. ether/Et_2O, 40:60): yield 61%; yellow oil; ^{1}H NMR δ 1.18 (t, $J = 7.2$ Hz, 3H), 2.36 (dd, $J = 3.3, 14.7$ Hz, 1H), 2.55 (dd, $J = 5.4, 14.4$ Hz, 1H), 2.73−2.9 (m, 3H), 3.10 (ddd, $J = 1.8, 4.8, 13.2$ Hz, 1H), 3.65 (d, $J = 13.2$ Hz, 1H), 3.72 (d, $J = 13.0$, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 4.03 (dq, $J = 7.2, 11.1$ Hz, 1H), 4.14 (dq, $J = 7.2, 10.5$ Hz, 1H), 6.53 (s, 1H), 6.54 (s, 1H), 7.18−7.29 (m, 5H); ^{13}C NMR δ 14.1, 23.1, 41.7, 42.0, 55.7, 55.8, 57.4, 58.3, 60.3, 110.1, 111.5, 126.0, 126,9, 128.0, 128.7, 128.8, 139.2, 147.3, 147.6, 171.9; MS m/z 369 (M^+).

Formation of (−)-(1*S*)-1-Ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5). (1*S*)-2-Benzyl-1-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (59.5 mg, 0.161 mmol) obtained in the previous reaction was dissolved in EtOH (3 mL). The reaction vessel was set under vacuum and flushed with N_2. This procedure was repeated (3×), and 0.75 equiv of $Pd(OAc)_2$ (27 mg, 0.122 mmol) was added. Vacuum was applied, and subsequently the reaction vessel was flushed with H_2 and the mixture was sonicated for 3 h and filtered through a glass fiber filter and the residual $Pd(OAc)_2$ washed with EtOH and pyridine. The combined fractions were concentrated in vacuo and coevaporated with toluene (3×). The residue was purified by FC (deactivated silica gel, CH_2Cl_2/MeOH, 90:10): yield 90%; ee = 58%; oil $[\alpha]_D = -10.2$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR δ 1.24 (t, $J = 6.9$ Hz, 3H), 2.96−3.20 (m, 2H), 3.33 (ddd, $J = 6.3, 6.3, 12.6$ Hz, 1H), 3.45 (ddd, $J = 5.4, 6.0, 11.4$ Hz, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 4.19 (q, $J = 7.2$ Hz, 2H), 4.80 (t, $J = 6.6$ Hz, 1H), 6.60 (s, 2H); ^{13}C NMR δ 14.1, 26.5, 39.3, 40.1, 51.6, 55.9, 56.0, 61.4, 108.6, 111.6, 124.7, 125.1, 148.0, 148.6, 171.1; HPLC (Daicel Chiralcel OD, hexane/*i*−PrOH = 95:5, flow rate = 1.0 mL/min) $t_R = 30.2$ min (major), $t_R = 44.1$ min (minor); MS m/z 279 (M^+).

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Supporting Information Available: ^{1}H and ^{13}C NMR and MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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