Catalytic Enantioselective Inverse-Electron Demand 1,3-Dipolar Cycloaddition Reactions of Nitrones with Alkenes

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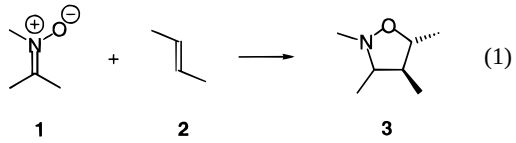
Abstract: A general reaction protocol for catalytic enantioselective 1,3-dipolar cycloaddition reaction of nitrones, activated by chiral Lewis acids, with electron-rich alkenes has been developed. The nitrones are activated by various chiral 2,2′-dihydroxy-1,1′-binaphthyl (BINOL)-AlMe complexes, and it has been found that 3,3′-diaryl-BINOL-AlMe complexes catalyze a highly regio-, diastereo-, and enantioselective 1,3-dipolar cycloaddition reaction of aromatic nitrones with vinyl ethers, giving the exo-diastereomer of the isoxazolidines with de's up to >90% and up to 97% ee. The reaction has been investigated under various conditions with different nitrones and vinyl ethers (and alkenes), and a general synthetic procedure is presented. The mechanism for the reaction is discussed on the basis of a linear stereochemical effect of the catalyst, the diastereoselectivity, and absolute stereochemistry of the isoxazolidines formed, and theoretical calculations of the 3,3′-diphenyl-BINOL-AlMe−nitrone intermediate.

Introduction

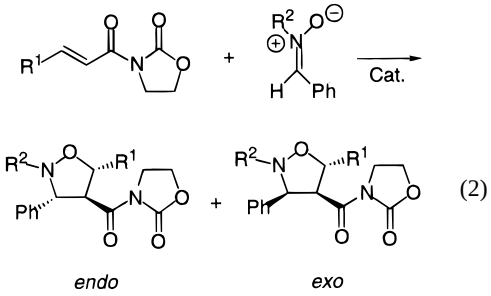
The 1,3-dipolar cycloaddition reaction is a very important reaction for the construction of five-membered heterocycles and has been used in numerous syntheses using 1,3-dipoles such as nitrones, nitrile oxides, azomethine ylides, and nitronates.[1] The 1,3-dipolar cycloaddition reaction between nitrone **1** and alkene **2** gives the isoxazolidine **3** (eq 1), which is of importance for the preparation of natural products such as β-amino alcohols and alkaloids.[1−3]



(1)

1 **2** **3**

The development of the 1,3-dipolar cycloaddition reaction of nitrones with alkenes has recently taken a new direction, as one of the major challenges now is to prepare optically active isoxazolidines.[3] The typical 1,3-dipolar cycloaddition reaction of nitrones with alkenes involves a dominant interaction of the $HOMO_{nitrone}$ and the $LUMO_{alkene}$, resulting in eight possible stereoisomers. These stereoisomers are two regioisomers, each as two diastereomers, and each of these two diastereomers as two enantiomers.[3a] To prepare enantiopure isoxazolidines, several types of chiral auxiliaries have been used, including chiral nitrones and chiral alkenes.[3a] However, this has several disadvantages, such as waste of optically active material and elevated temperatures. This can be circumvented using chiral Lewis acids for the activation of the alkene, resulting in a lowering of the energy of the $LUMO_{alkene}$ and enhancement of the regio-, diastereo-, and enantioselectivity of the reaction.[3a] The Lewis acid-catalyzed 1,3-dipolar cycloaddition reaction using this approach has mainly involved acryloyloxazolidinones as the alkene fragment reacting with various types of nitrones (eq 2).[4] By the use of this catalytic enantioselective approach, control of both regio-, diastereo-, and enantioselectivity has been achieved to a high degree.



(2)

endo *exo*

In 1982 DeShong et al. reported the first 1,3-dipolar cycloaddition reaction of electron-rich alkenes, such as vinyl acetate and vinyl ethers, with nitrones.[5] This work was extended to a stereoselective approach when chiral nitrones were used.[6] Application of chiral nitrones was investigated by Overton and colleagues for the preparation of optically pure β-lysine.[7] The cycloaddition of chiral vinyl ethers, derived from chiral alcohols, with nitrones has also been investigated.[8]

The inverse-electron demand 1,3-dipolar cycloaddition reaction of nitrones with alkenes requires a dominant interaction of the $LUMO_{nitrone}$ with the $HOMO_{alkene}$.[3a] Such a reaction requires an activation of the nitrone, and only very few examples are known in which the nitrone is activated by a Lewis acid followed by the reaction with an electron-rich alkene.[9] To our knowledge no general catalytic enantioselective inverse-electron demand 1,3-dipolar cycloaddition reactions of nitrones with alkenes showing high enantioselectivity have been reported. Seerden et al. have used vinyl ethers and ketene dialkyl acetals for the reaction with nitrones using oxazaborolidones as the catalysts, leading to control of the diastereoselectivity and up to 74% ee, but the product was formed in low yield.[9a] Herein we report

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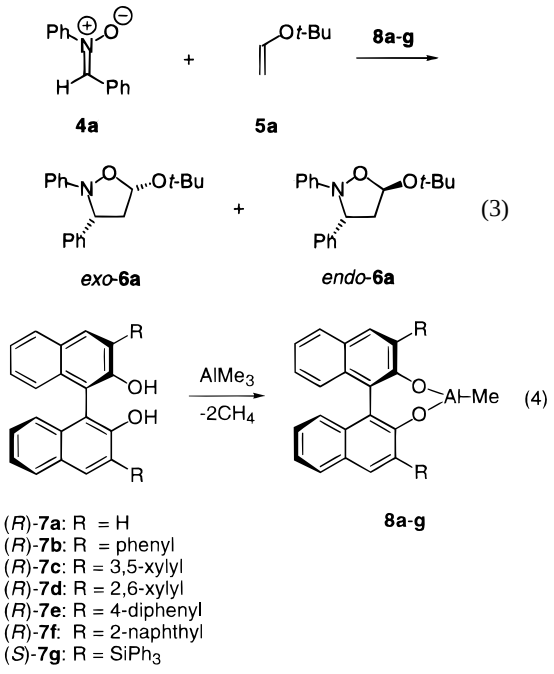
the first example of a catalytic 1,3-dipolar cycloaddition reaction with inverse-electron demand of aromatic nitrones with vinyl ethers catalyzed by chiral aluminum complexes giving isoxazolidines in high yield, with diastereo- and enantioselectivity.

Results and Discussion

To activate the nitrone by a Lewis acid for the 1,3-dipolar cycloaddition reaction with an electron-rich alkene, one has to consider the interaction of the nitrone with the Lewis acid. To activate simple nitrones such as benzylidenephenylamine *N*-oxide **4a**, the nitrone oxygen atom has to coordinate to the Lewis acid, and thus chiral Lewis acids that allow a monodentate coordination should be considered as the catalysts of choice.[3a] By screening several chiral Lewis acid complexes we have found that the combination of a chiral (*R*)-2,2′-dihydroxy-1,1′-binaphthyl (BINOL) derivative as the ligand with aluminum complexes leads to catalysts that are very useful for the inverse-electron demand 1,3-dipolar cycloaddition reaction of nitrones with alkenes.

The 1,3-dipolar cycloaddition reaction of nitrone **4a** with *tert*-butyl vinyl ether **5a** has been investigated as a model reaction (eq 3) using chiral catalysts **8a**−**g** obtained from the reaction of $AlMe_3$ with various (*R*)-BINOL derivatives **7a**−**f** and (*S*)-3,3′-bis(triphenylsilyl)BINOL **7g** (eq 4).



The reaction of nitrone **4a** with *tert*-butyl vinyl ether **5a** gives exclusively the 5-substituted isoxazolidine **6a**, both with and without catalyst (eq 3). This regioselectivity is normal for the 1,3-dipolar cycloaddition reaction of electron-rich alkenes, due to the attack of the nitrone oxygen atom to the oxygen-substituted alkene carbon atom.[3a,5] In the absence of a catalyst the reaction had to proceed at 50 °C in neat **5a** for 18 h to give complete conversion and gave the isoxazolidine *exo*-**6a** with high exo selectivity (Table 1, entry 1). However, in the presence of $AlMe_3$ as the catalyst (20 mol %) the reaction was complete within 4 h at ambient temperature, although with lower diastereoselectivity (entry 2).

Table 1. Diastero- and Enantioselectivity of the 1,3-Dipolar Cycloaddition Reaction of Nitrone **4a** with *tert*-Butyl Vinyl Ether **5a** Catalyzed by Different BINOL-AlMe Complexes **8a**−**g**[a]

entry	catalyst	reaction time	conversion[b]	*endo*-**6a**:*exo*-**6a**[b]	ee (*exo*-**6a**)[c] (%)
1		18 h[d]	>95	<5:>95	0
2	$AlMe_3$	4 h	>90	17:73	0
3	**8a**	3 h	>90	73:27	<5
4	**8b**	45 min	>95	<5:>95	89
5	**8c**	2 h	>95	<5:>95	87
6	**8d**	18 h	>90	21:79	79
7	**8e**	2.5 h	>90	12:88	78
8	**8f**	3 h	>95	10:90	80
9	**8g**	48 h	80	14:86	65[e]

[a] Reaction conditions: solvent: CH_2Cl_2; scale: **4** (0.1 mmol), **5a** (0.5 mmol), and 20 mol % **8a**−**g**. For further details see *Experimental Section*. [b] Determined by ^1H NMR spectroscopy of the crude product. [c] Ee of the exo isomer was determined by HPLC using a Daicel Chiralcel OD column. [d] Performed in neat *tert*-butyl vinyl ether (1 mL) at 50 °C. [e] Other enantiomer.

The results from the reaction of nitrone **4a** with **5a** in the presence of $AlMe_3$ as the catalyst stimulated the investigation of several chiral aluminum complexes as the asymmetric catalysts. Chiral aluminum catalysts, prepared by reacting $AlMe_3$ or $AlCl_3$ with chiral diols or bis(sulfonamides), have been used successfully in Diels−Alder[10] and hetero-Diels−Alder reactions.[11] The use of BINOL (**7a**) and a 3,3′-substituted BINOL such as 3,3′-diphenyl BINOL **7b** and 3,3′-bis(triphenylsilyl)-BINOL **7g** as ligands in combination with aluminum complexes

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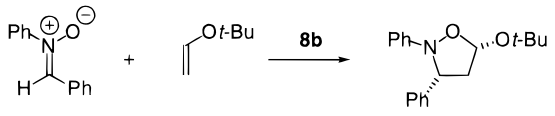
has resulted in reactions with very high enantioselectivities.[10−12] We have recently reported a simple and efficient route to the 3,3′-diaryl BINOLs (*R*)-**7b**−**f** by a Suzuki cross-coupling reaction, which makes this class of chiral ligands easily available in three steps from BINOL using standard reactions.[13]

The aluminum complexes **8a**−**g** of (*R*)-BINOL, (**7a**) 3,3′-diaryl substituted (*R*)-BINOLs **7b**−**f**, and (*S*)-3,3′-bis(triphenylsilyl) BINOL **7g**[14] were prepared in situ in dry CH_2Cl_2 by dropwise addition of a 2 M solution of $AlMe_3$ in heptane with evolution of CH_4 (eq 4). The mixture was agitated for 1 h and a solution of nitrone **4a** was added, followed by addition of freshly distilled *tert*-butyl vinyl ether **5a** (5 equiv). These reactions were carried out on a 0.1-mmol scale with 20 mol % catalyst, and the results are presented in Table 1. The diastereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy of the crude product using the following diagnostic signals:[5] *exo*-**6a** gives a doublet of doublets at $\delta = 4.42$ ppm with $J = 7.0$ and 9.0 Hz for the proton on C-3 and two doublets of doublets of doublets at $\delta = 2.34$ ppm ($J = 3.3$, 6.8, and 12.9 Hz) and 2.97 ppm ($J = 6.0$, 9.3, and 13.2 Hz) for the two protons on C-4, whereas *endo*-**6a** gives a doublet of doublets at $\delta = 4.81$ ppm ($J = 6.6$ and 9.3 Hz) and two doublets of doublets of doublets at $\delta = 2.51$ ppm ($J = 5.1$, 9.3, and 12.2 Hz) and 2.63 ppm ($J = 1.5$, 6.9, and 12.1 Hz). The diastereomers were separated by column chromatography and the enantiomeric excess (ee) of the major product (exo diastereomer) was determined by HPLC using a Daicel Chiralcel OD column. *It is important to note that the BINOL ligands can be recovered from the chromatography and can be reused without any decrease in reactivity and stereoselectivity, which makes this catalytic approach very attractive.*

The use of the simple (*R*)-BINOL-AlMe catalyst **8a** resulted in almost complete conversion after 3 h and in a diastereoselectivity of 73:27 in favor of *endo*-**6a**, but with <5% ee (Table 1, entry 3). The introduction of aryl or silyl substituents in the 3,3′-position of the ligand changed the diastereoselectivity dramatically compared with the unsubstituted BINOL-AlMe catalyst **8a**. The reaction now proceeds with high exo selectivity, as observed using the catalysts **8b**−**g** (entries 4−9). Furthermore, these complexes induce high enantioselectivity with ee's in the range 65−89%. The most effective catalyst is the (*R*)-BINOL-AlMe complex **8b**. In this case the reaction was completed within 45 min, giving *exo*-**6a** as the sole product (de >90%) with 89% ee (entry 4). The same diastereoselectivity was observed for the reaction catalyzed by **8c**, but with a slight decrease in enantioselectivity (entry 5). When two methyl substituents were attached to the phenyl group in the 2,6-position, as is the case for catalyst **8d** (instead of the 3,5- position as in catalyst **8c**), a decrease of both reactivity and selectivity was observed. Furthermore, the reaction has to proceed for 18 h to obtain high conversion, but at the expense of both exo selectivity and asymmetric induction, as only 79% ee was obtained (entry 6). Steric interactions of the methyl groups could explain the decrease in rate with **8d**. Similar chiral inductions were observed for the catalysts **8e** and **8f** (entries 7, 8). These reactions were also relatively fast and complete conversions were achieved after 2.5−3 h with good exo selectivities. The slowest reaction was observed when catalyst **8g** was applied (entry 9). Prolonged reaction time was required to get acceptable conversion, and still only 80% conversion resulted after 48 h. The endo:exo ratio of 14:86 is comparable to those obtained using the other ligands, but a substantial decrease in the enantioselectivity is observed, as only 65% ee is found. The very bulky triphenylsilyl substituents in catalyst **8g** probably retard the coordination of the nitrone to the catalyst, resulting in less facial discrimination.

Table 2. Influence of Solvent, Temperature, and Catalyst Amount on Diastereo- and Enantioselectivity of the 1,3-Dipolar Cycloaddition Reaction between Nitrone **4a** and *tert*-Butyl Vinyl Ether **5a** Catalyzed by BINOL-AlMe Complex **8b**[a]



4a **5a** *exo*-**6a**

entry	molar scale (mmol)	mol % **8b**	solvent	conversion[b]/ reaction time	isolated yield, %	endo:exo[b]	ee *exo*[c] (%)
1	0.1	20	CH_2Cl_2	>95/45 min	61	<5:>95	89
2	0.1	10	CH_2Cl_2	>95/45 min	70	<5:>95	87
3	1.0	10	CH_2Cl_2	>95/60 min	84	<5:>95	89
4	0.2	5	CH_2Cl_2	50/48 h	32	21:79	80
5	0.2	2.5	CH_2Cl_2	48/48 h	30	23:77	79
6	0.1	10	CH_2Cl_2[d]	>95/3 h	71	11:89	89
7	0.1	10	CH_2Cl_2[e]	>90/18 h	68	22:78	92
8	0.2	20	THF	>95/3 h	67	<5:>95	89
9	0.2	20	toluene	>95/2 h	57	<5:>95	92
10	0.2	20	toluene/ hexane	>95/45 min	74	<5:>95	93

[a] Reaction conditions: the molar scale is defined from **4** (1 equiv), **5a** (5 equiv). For further details see *Experimental Section*. [b] Determined by ^{1}H NMR spectroscopy of the crude product. [c] Ee of the exo isomer was determined by HPLC using a Daicel Chiralcel OD column. [d] Reaction temperature 0 °C. [e] Reaction temperature −25 °C.

Using a chiral (*R*)-BINOL-AlCl complex, prepared by reacting (*R*)-BINOL **7b** with Me_2AlCl as the Lewis acid instead of $AlMe_3$, as catalyst for the reaction between nitrone **4a** and *tert*-butyl vinyl ether **5a** resulted in an alteration of the selectivity. In this case the endo:exo ratio was 60:40, and, furthermore, the chiral induction decreased to 52% ee for *exo*-**6a** and to 27% ee for *endo*-**6a**. The reason for the change in selectivity might be due to dimerization of the catalyst, changing the reaction sphere of the Lewis acid site.

To optimize the enantioselectivity of the catalytic 1,3-dipolar cycloaddition reaction of nitrone **4a** with *tert*-butyl vinyl ether **5a** using **8b** as the catalyst (eq 3), the influence of catalyst amount, molar scale, temperature, and solvent was examined. These results are presented in Table 2.

It appears from Table 2, entries 1 and 2, that no appreciable change is observed when going from 20 mol % catalyst to 10%, as both reactions are complete after 45 min and proceed with similar selectivities. However, when the amount of catalyst **8b** is reduced to 5 mol % and 2.5 mol %, the reaction is slow and only 50% of the nitrone is consumed after 2 days. Also, a slight decrease in diastereo- and enantioselectivity is observed (entries 4, 5). The reaction can be scaled up to 1.0 mmol by using 10 mol % catalyst without any decrease in reaction time and selectivity, and the isolated yield of *exo*-**6a** was 84% and the ee 89% (entry 3). When the reaction was carried out at low temperature (−78 °C), no reaction occurred within 3 days. However, at 0 °C a conversion of 95% was accomplished after 3 h with the same high asymmetric induction, but with a slight decrease in the exo selectivity (entry 6). At −25 °C the reaction was complete after 18 h with a very high ee of 92% of *exo*-**6a**,

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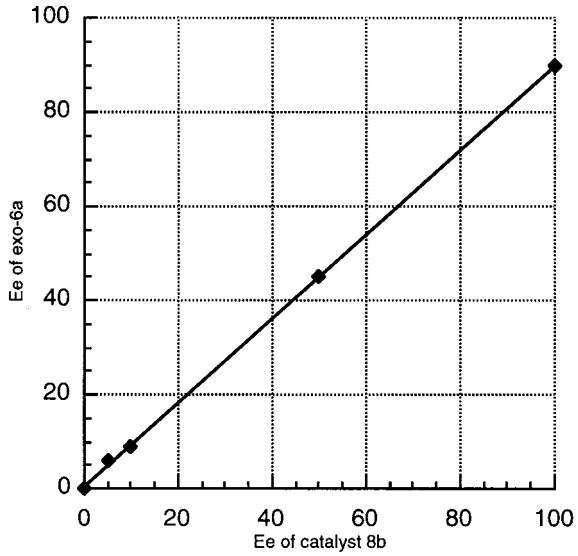
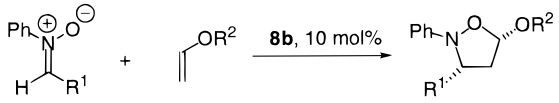


Figure 1. Linear relation between the optical purity of isoxazolidine *exo*-**6a** formed in the 1,3-dipolar cycloaddition reaction of nitrone **4a** and *tert*-butyl vinyl ether **5a** and the ee of the employed catalyst **8b**.

Table 3. 1,3-Dipolar Cycloaddition Reactions of Aromatic Nitrones **4a**−**d** with *tert*-Butyl Vinyl Ether **5a**, Ethyl Vinyl Ether **5b**, and Benzyl Vinyl Ether **5c** in the Presence of 10 mol % of BINOL-AlMe **8b** Catalyst[a]



4 **5** *exo*-**6**

entry	nitrone **4**, R^1	alkene **5**, R^2	product	yield/ reaction time	*endo*:*exo*[b]	ee *exo*[c]
1	Ph-**4a**	*t*-Bu-**5a**	**6a**	84/1 h	<5:>95	89
2	*p*-tolyl-**4b**	*t*-Bu-**5a**	**6b**	71/12 h	16:84	81
3	*p*-ClPh-**4c**	*t*-Bu-**5a**	**6c**	74/2 h	17:83	78
4	*p*-MeOPh-**4d**	*t*-Bu-**5a**	**6d**	65/18 h	10:90	77
5	Ph-**4a**	Et-**5b**	**6e**	79/1 h	<5:>95	91
6	*p*-tolyl-**4b**	Et-**5b**	**6f**	70/3 h	<5:>95	90
7	*p*-ClPh-**4c**	Et-**5b**	**6g**	78/2 h	<5:>95	94
8[d]	*p*-ClPh-**4c**	Et-**5b**	**6g**	66/6 h	<5:>95	97
9	*p*-MeOPh-**4d**	Et-**5b**	**6h**	50/18 h	<5:>95	88
10	*p*-ClPh-**4d**	Bn-**5c**	**6i**	68/18 h	<5:>95	85

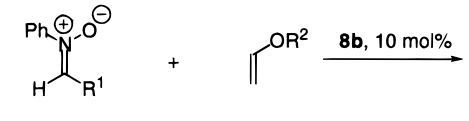
[a] The reactions were performed on a 0.5−2.0 mmol scale in CH_2Cl_2 at room temperature. For further details see *Experimental Section.* [b] The *endo:exo* ratio was determined by ^{1}H NMR spectroscopy of the crude product. [c] Ee of the exo isomer was determined by HPLC using a Daicel Chiralcel OD column. [d] Toluene as the solvent.

although at the expense of exo selectivity (entry 7). The effect of the solvent was also investigated (entries 8−10). When the 1,3-dipolar cycloaddition reaction of nitrone **4a** with **5a** was carried out in THF the reaction had to proceed for 3 h before **4a** was consumed, but the same diastereo- and enantioselectivity was observed (entry 8). In toluene the reaction was finished within 2 h and *exo*-**6a** was obtained with 92% ee and very high exo selectivity, but with a lower isolated yield (entry 9). To perform the reaction in a solvent with even lower polarity than toluene, the reaction was first carried out in hexane, but unfortunately the reaction did not proceed at all because of the insolubility of the nitrone in this solvent. When the 1,3-dipolar cycloaddition reaction of **4a** with **5a** in the presence of catalyst **8b** was carried out in a mixture of toluene and hexane, the same high diastereo- and enantioselectivity was found but with a significant increase in isolated yield (entry 10).

To get more information about the nature of the intermediate complex involved in this reaction, the reaction was also tested for nonlinear stereochemical effects of the catalyst.[15] A graphic representation of the ee of *exo*-**6a**, obtained by reaction of nitrone **4a** with *tert*-butyl vinyl ether **5a** using the (*R*)-BINOL-AlMe complex **8b** as the catalyst, as a function of the optical purity of **8b** is depicted in Figure 1.

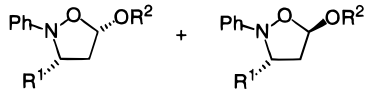
A linear relation between the ee of the catalyst and ee of the *exo*-**6a** is observed and it is therefore reasonable to believe that the catalytic intermediate consists of a discrete complex in which one (*R*)-BINOL-ALMe is involved (see the mechanistic discussion).

To illustrate a more general application of the BINOL-AlMe **8b**-catalyzed 1,3-dipolar cycloaddition reaction of nitrones with electron-rich alkenes, the reaction was investigated using various substrates. First, the variation of the substituents of the nitrone was investigated. The presence of an aromatic substituent on the nitrone nitrogen atom seems to be essential in the present reaction, as no reaction occurred when benzylidenebenzylamine *N*-oxide and benzylidene-*N*-propylamine *N*-oxide were used under the same reaction conditions. The reaction of various aromatic nitrones **4a**−**d** with *tert*-butyl vinyl ether **5a**, ethyl vinyl ether **5b** and benzyl vinyl ether **5c** catalyzed by the BINOL-AlMe complex **8b** (eq 5) has been studied and the results are given in Table 3.



4a: R^1 = Ph
4b: R^1 = *p*-tolyl
4c: R^1 = *p*-ClPh
4d: R^1 = *p*-MeOPh

5a: R^2 = *t*-Bu
5b: R^2 = Et
5c: R^2 = Bn



exo-**6** *endo*-**6** (5)

6a: R^1 = Ph, R^2 = *t*-Bu
6b: R^1 = *p*-tolyl, R^2 = *t*-Bu
6c: R^1 = *p*-ClPh, R^2 = *t*-Bu
6d: R^1 = *p*-MeOPh, R^2 = *t*-Bu
6e: R^1 = Ph, R^2 = Et
6f: R^1 = *p*-tolyl, R^2 = Et
6g: R^1 = *p*-ClPh, R^2 = Et
6h: R^1 = *p*-MeOPh, R^2 = Et
6i: R^1 = *p*-ClPh, R^2 = Bn

The 1,3-dipolar cycloaddition reaction of the various nitrones **4a**−**d** proceed well with the different aryl substituents on the nitrone carbon atom (eq 5). In general, high diastereo- and enantioselectivities are obtained as presented in Table 3. The addition of *tert*-butyl vinyl ether **5a** to the nitrones **4b** or **4c** in the presence of 10 mol % catalyst **8b** proceeds like the reaction involving **4a**, although with a slight decrease in diastereo- and enantioselectivity (entries 2, 3). Full conversion of **4b** and **4c** was obtained after 12 h and 2 h, respectively, and the isoxazolidines *exo*-**6b** and *exo*-**6c** were isolated in 71−74% yield. The same enantioselectivity was also found for nitrone

(15) See, e.g., (a) Girard, C.; Kagan, H. B. *Angew. Chem.* **1998**, *110*, 3088. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997.

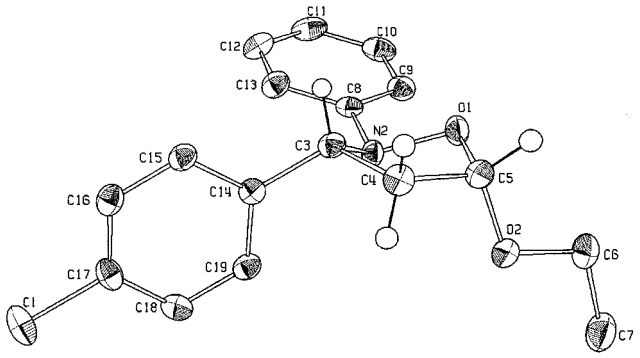


Figure 2. Crystal structure of *exo*-**6g**. Thermal ellipsoids are shown at 50% probability levels; selected hydrogen atoms are drawn as small circles of arbitrary radius.

4d, but the reaction required an increased reaction time of 18 h to achieve an acceptable yield (entry 4). When the same nitrones were reacted with ethyl vinyl ether **5b** in the presence of 10 mol % catalyst **8b**, the diastereo- and the enantioselectivities were very high and the isoxazolidines **6e**−**h** were isolated with endo:exo ratios of <5:>95 and with asymmetric inductions from 88% to 97% (entries 5−9). The reaction time needed for full conversion followed the same pattern as above and the reactivity of the nitrones toward vinyl ethers decreased in the following order: **4a**, **4c** > **4b** > **4d**, correlating with the electronic properties of the phenyl substituents. The enantioselectivity can be enhanced to 97% ee in the case of compound **6g** by using toluene as solvent, but at the expense of a slightly lower yield (66%) (entry 8). To incorporate a protected hydroxy group in the 5 position of the isoxazolidine ring, the 1,3-dipolar cycloaddition reaction was investigated with a substrate having a protected enol functionality. Nitrone **4c** was reacted with benzyl vinyl ether **5c** in the presence of 10 mol % catalyst **8b** and the isoxazolidine *exo*-**6i** was isolated in 68% yield after 18 h with high exo selectivity and 85% ee (eq 5) (Table 3, entry 10).

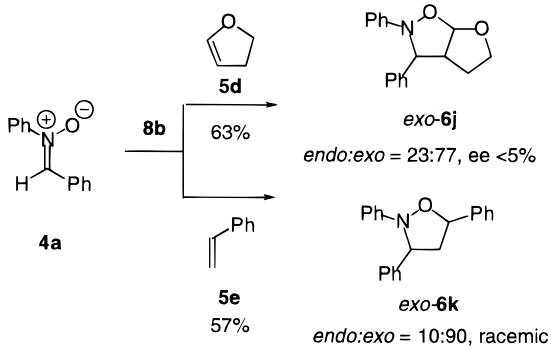
To get suitable crystals for X-ray crystallographic analysis and thereby to determine the absolute configuration of the isoxazolidines *exo*-**6a**−**i**, attempts to recrystallize *exo*-**6g** were performed. Slow cooling of a hot solution of *exo*-**6g** (ee = 94%) in hexane resulted in clear needles, which were suitable for crystallographic examination. Surprisingly, these crystals were racemic as determined by X-ray analysis. HPLC and optical rotation also confirmed the crystals of *exo*-**6g** to be racemic. The filtrate was therefore concentrated in vacuo to give *exo*-**6g** as the pure enantiomer (ee > 99.5%) as a clear pale yellow oil. The tendency for the racemic complexes to form crystals was also observed for the isoxazolidines **6e**−**f** and **6h**; thus, a simple procedure for obtaining the isoxazolidines as enantiomerically pure compounds is to filter the crystalline racemate from a hexane solution, followed by concentration of the filtrate.

The X-ray structure of *exo*-**6g** was determined and the crystals of **6g** were found to contain four molecules (two of each enantiomer) in the unit cell of space group $P2_1c$.[16] The crystal structure, presented in Figure 2, confirms the cis relation between the phenyl and ethoxy substituents in the 3 and 5 position of the isoxazolidine ring, in agreement with the ^{1}H NMR experiments. The structural data for the isoxazolidine ring is very similar to that of other characterized isoxazolidine[17] rings and will not be discussed further.

(16) The authors have deposited atomic coordinates for the structure at the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

(17) See, e.g., ref 4d and references therein for other characterized isoxazolidines.

The reaction has also been conducted with the electron-rich alkenes dihydrofuran **5d**, vinyl acetate, and the nonactivated alkene, styrene (**5e**) in the presence of 10 mol % catalyst **8b** (eq 6). However, only moderate results were obtained. The cyclic vinyl ether **5d** reacted quite slowly with nitrone **4a**, and the reaction was complete after 12 h but with low diastereoselectivity and very low ee (<5%). Prolonged reaction time was also necessary for good conversion in the case of styrene **5e**, and although high diastereoselectivity was obtained, the isoxazolidine *exo*-**6k** was isolated as a racemic compound. When the reaction was carried out with vinyl acetate, no reaction was observed after 3 days.

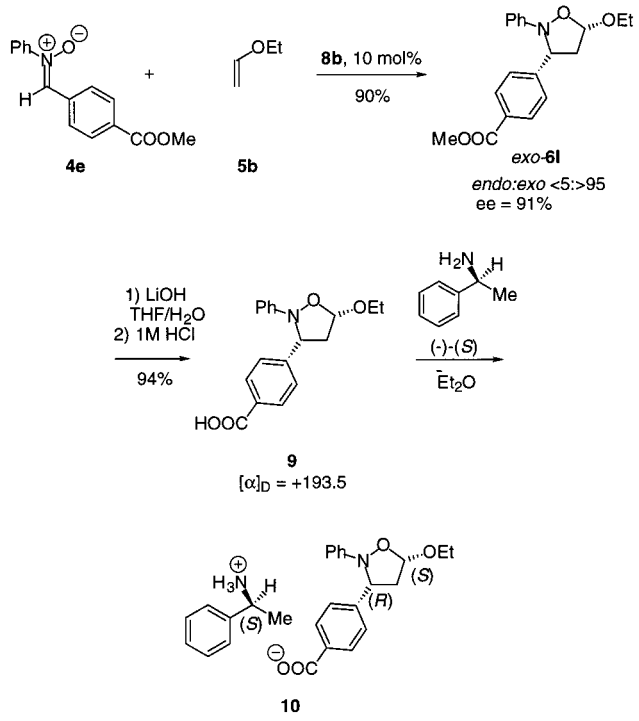


Absolute Assignment of the Stereochemistry. To assign the absolute stereochemistry of the two new chiral centers in the isoxazolidine ring (carbons 3 and 5) created in this 1,3-dipolar cycloaddition reaction, the isoxazolidines were converted into molecules containing a known configuration of another chiral carbon atom. First, we tried to transform the isoxazolidines **6** into β-amino aldehydes upon reduction, followed by hydrolysis of the generated hemiacetal, and then react the aldehyde with (*S*)-*N*-amino-2-methoxymethylpiperidine (SAMP) to obtain the corresponding hydrazone. Unfortunately, several attempts for the hydrogenolysis of the nitrogen−oxygen bond in the isoxazolidines by various catalysts such as Pd/C and $Pd(OH)_2$ proved very difficult, and no reproducible condition was found. Difficulties in reducing the N−O bond in isoxazolidines bearing an alkoxy substituent at the carbon atom next to the ring oxygen atom was also observed by DeShong et al.[6]

This problem was circumvented by the preparation of isoxazolidine *exo*-**6l** with an ester functionality in the para position of the C-3 phenyl substituent as depicted in Scheme 1. Nitrone **4e** was prepared by standard condensation between phenylhydroxylamine and 4-carbomethoxybenzaldehyde[18] and reacted with ethyl vinyl ether **5b** in the presence of 10 mol % **8b** as the catalyst. Complete conversion was achieved after 2 h, and the isoxazolidine *exo*-**6l** was isolated in very high yield, with good diastereo- and enantioselectivity (Scheme 1). The methyl ester was hydrolyzed by using LiOH in THF/H_2O to give dextrorotatory carboxylic acid **9** in almost quantitative yield after aqueous workup. The acid **9** formed diastereomeric salts with (−)-ephedrine, (−)-(*S*)-1-phenylethylamine, (+)-(*R*)-1-phenylethylamine, (−)-(*S*)-1-(1-naphthyl)ethylamine, (+)-(*R*)-1-(1-naphthyl)ethylamine, and brucine upon mixing equimolar amounts of the acid **9** and amine in Et_2O. Of these complexes, the salt **10** formed with (−)-(*S*)-1-phenylethylamine and **9** gave the best crystals for X-ray analysis. Crystals suitable for X-ray crystallography were prepared by slow evaporation of a solution of **10** in MeOH. The X-ray structure of **10** is presented in Figure 3.

(18) Yimina, C.; Tsujimoto, T.; Suda, K.; Yamuchi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2165.

Scheme 1



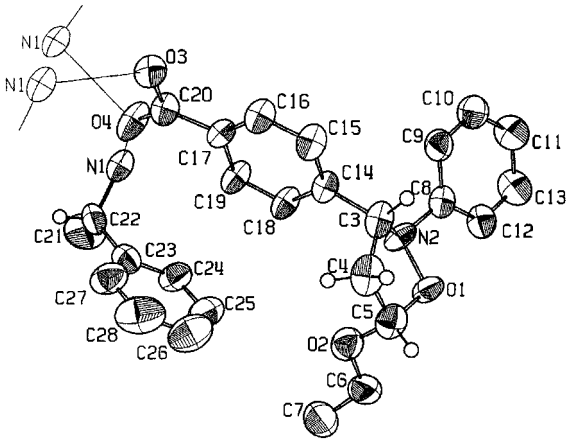


Figure 3. Crystal structure of the diasteromeric salt **10** (Scheme 1) used for the assignment of the absolute stereochemistry of the chiral centers in the isoxazolidine ring formed by reaction of nitrone **4e** with ethyl vinyl ether **5b** catalyzed by (*R*)-BINOL-AlMe **8b**. Only the major component is shown. Thermal ellipsoids are shown at 50% probability levels; selected hydrogen atoms are drawn as small circles of arbitrary radius. The hydrogen bonds between the carboxyl group and the $-NH_3$ groups of three different cations are indicated by the thin lines.

On the basis of the absolute stereochemistry of (−)-(*S*)-1-phenylethylamine in the X-ray structure **10**, Figure 3, the absolute stereochemistry of the chiral centers formed in the isoxazolidine ring of the major enantiomer by the 1,3-dipolar cycloaddition reaction of nitrone **4e** with ethyl vinyl ether catalyzed by **8b** is assigned to be 3*R*,5*S*. The absolute stereochemistry of the isoxazolidine indicates that the alkene approaches the re face (on the basis of assignment relative to the nitrone carbon atom) of the nitrone when coordinated to the catalyst.

Mechanistic Aspects of the (*R*)-BINOL-AlMe-catalyzed 1,3-Dipolar Cycloaddition Reaction. The observation of a linear relation between the ee of the catalyst and the ee of *exo*-**6a** (Figure 1) indicates that the catalytic intermediate in the reaction is one in which only a monomeric (*R*)-BINOL-AlMe catalyst is involved.

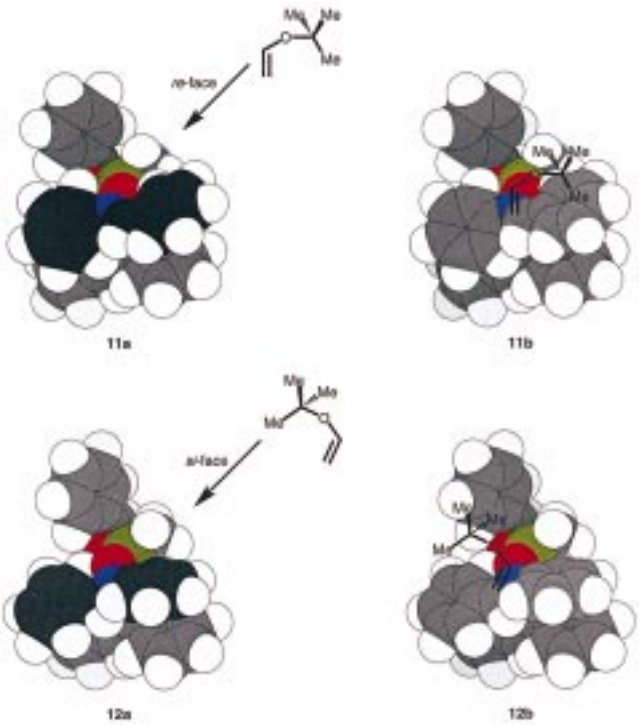


Figure 4. Intermediates **11a** and **12a** show the optimized structures of the nitrone **4a** coordinated to the (*R*)-BINOL-AlMe catalyst **8b**. In **11a** the re face of the nitrone is available for approach of the alkene, whereas in **12a** the si face is accessible. Color code: carbon atoms of the nitrone in intermediates **11a** and **12a** are shown in black to distinguish these atoms from carbon atoms of the BINOL and Me fragments of the (*R*)-BINOL-AlMe catalyst, which are grey; aluminum, green; oxygen, red; nitrogen, blue, hydrogen, white. In **11b** and **12b** an overlay of a ChemDraw representation of the approach of the alkene (*tert*-butyl vinyl ether) to the two different faces, re and si, respectively, of the coordinated nitrone and a Chem3D representation of the nitrone−catalyst intermediate are outlined. Color code: carbon, grey; aluminum, green; oxygen, red; nitrogen, blue, hydrogen, white.

The coordination of the nitrone to the (*R*)-BINOL-AlMe catalyst leads to the active intermediate, and the highly regio-, diastereo-, and enantioselective catalytic properties of the reaction indicate that the BINOL fragment provides a "nearly sterically perfect environment".

In an attempt to understand the coordination of the nitrone to the (*R*)-BINOL-AlMe catalyst and the approach of the alkene to the various possible intermediates, theoretical calculations of different intermediates have been performed. The size of the intermediate, the BINOL-AlMe **8b** catalyst and nitrone **4a**, precludes the use of ab initio DFT calculations. However, semiempirical calculations of the intermediates, although probably less reliable than the DFT calculations, might give important information about the structure of the intermediate. We have thus applied AM-1 calculations[19] to the different coordination modes of **4a** with the catalyst **8b**. The results, which account for both the diastereo- and enantioselectivity in the reaction, are presented below.

The geometry of various intermediates consisting of nitrone **4a** coordinated in two different ways to the (*R*)-BINOL-AlMe **8b** catalyst has been optimized. The coordination of **4a** to **8a**

(19) The structures of intermediates **11a** and **12a** have been optimized using AM1 calculations: (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107* 3902. (b) Dewar, M. J. S.; Holder, A. J. *Organometallics* **1990**, *9*, 508.

can take place in two different ways, one which allows approach of the alkene to the re face of the nitrone and the other approach to the si face. The coordination of the nitrone to catalyst **8b** leads to a change of geometry of the aluminum center from planar to tetrahedral, and the structures of these two intermediates, **11a** and **12a**, are shown in Figure 4. The carbon atoms of the nitrone in intermediates **11a** and **12a** are shown in black to distinguish the carbon atoms of the nitrone from the carbon atoms of the BINOL and Me fragments of the (*R*)-BINOL-AlMe catalyst.

In intermediate **11a**, Figure 4, nitrone **4a** is coordinated to the BINOL-AlMe **8b** catalyst in such a way that the re face of **4a** is available for attack by the alkene, whereas in intermediate **12a**, the si face is accessible. The total energy of **11a** is calculated to be −7571.38 eV, whereas the total energy of **12a** is 6 kcal mol^{-1} higher, indicating that the former is slightly more stable than the latter. However, we are fully aware that the level of the present calculations does not allow one to distinguish between the two intermediates from an energetic point of view. The major structural difference between the two intermediates is, besides the orientation of the nitrone, the Al−O (nitrone) bond length. In **12a** it has been calculated to be 2.36 Å, which is significantly longer than the same bond in **11a** (1.81 Å).

The two intermediates, **11a** and **12a** (Figure 4), give important information about the mechanism for the highly diastereo- and enantioselective 1,3-dipolar cycloaddition reaction of aromatic nitrones with vinyl ethers catalyzed by the (*R*)-BINOL-AlMe complexes. For **11a**, the vinyl ether, exemplified with *tert*-butyl vinyl ether, can approach the re face of nitrone, whereas in **12a** the si face is available.

Structures **11b** and **12b** (Figure 4) show the exo approach of the vinyl ether to the nitrone when coordinated to the catalyst, **11a** and **12a**, respectively [please observe that the carbon atoms of the nitrone now have the same gray color as the carbon atoms of the BINOL and Me fragments of the (*R*)-BINOL-AlMe catalyst], as an overlay of a ChemDraw representation of *tert*-butyl vinyl ether and a Chem3D representation of the nitrone−catalyst intermediate. For intermediate **11b** the vinyl ether fits into "the pocket" formed by the arrangement of the 3-phenyl substituent of the BINOL ligand and the coordinated nitrone. The exo approach of the vinyl ether to the re face of the nitrone as outlined in **11b** is in good accordance with the experimental results. If the vinyl ether approaches, in an endo selective fashion, the re face of the nitrone when coordinated to the (*R*)-BINOL-AlMe catalyst (**11a**), the ether substituent (ethyl, *tert*-butyl, or benzyl) will suffer an unfavorable steric repulsion with the 3-phenyl substituent of the BINOL fragment, which reduces the possibility for the reaction path. In **12b** the exo approach of the vinyl ether to the si face of the nitrone coordinated to the (*R*)-BINOL-AlMe catalyst is outlined. For this reaction path it appears that a more severe steric repulsion between the *tert*-butyl substituent of the vinyl ether and the 3-phenyl substituent of the BINOL ligand takes place, thus eliminating this reaction path compared with the former.

On the basis of the calculated structure of the nitrone coordinated to the (*R*)-BINOL-AlMe catalyst, we are thus able to account for both how the nitrone coordinates to the catalyst and how the alkene approaches the activated nitrone, giving the high regio-, diastereo-, and enantioselectivity obtained in this new 1,3-dipolar cycloaddition reaction.

Conclusion

A new highly selective catalytic inverse-electron demand 1,3-dipolar cycloaddition reaction of nitrones with electron-rich alkenes is developed. It is shown that 3,3′-diaryl-BINOL-AlMe complexes are highly regio-, diastereo-, and enantioselective catalysts for the 1,3-dipolar cycloaddition reaction of nitrones, which can coordinate in a monodentate fashion to the catalyst, with vinyl ethers. The reaction leads to *exo*-isoxazolidines in good yield with endo:exo ratios <5:>95 and with ees up to 97%. A preferred coordination of the nitrone to the 3,3′-diaryl-BINOL-AlMe catalyst leads to a shielding of the si face of the nitrone, and a preferred exo-selective and enantioselective approach of the vinyl ether to the re face of the nitrone accounts for the absolute stereochemical outcome of the 1,3-dipolar cycloaddition reaction.

Experimental Section

General Methods. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise stated, at 300 MHz and 75 MHz, respectively. The chemical shifts are reported in ppm downfield to tetramethylsilane (TMS). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Solvents were dried using standard conditions and stored over molecular sieves (4 Å). THF and Et_2O were distilled from sodium benzophenone before use. All glass equipment was flame-dried under vacuum before use. HPLC were performed using a Daicel Chiracel OD column with hexane/*i*-PrOH 98:2 to 99.5:0.5 with UV detection at 247 nm.

Materials. The ligands **7a**,[20] **7b**−**f**,[13] and **7g**[14] were prepared as described in the literature. Benzylidenephenylamine *N*-oxide **4a**,[21] (4-methylbenzylidene)phenylamine *N*-oxide **4b**,[22] (4-chlorobenzylidene)-phenylamine *N*-oxide **4c**,[23] (4-methoxybenzylidene)phenylamine *N*-oxide **4d**,[24] and (4-carbomethoxybenzylidene)phenylamine *N*-oxide **4d**[18] were synthesized according to the literature. *tert*-Butyl vinyl ether, ethyl vinyl ether, dihydrofuran, vinyl acetate, and styrene were received from Aldrich and distilled from sodium immediately before use. Benzyl vinyl ether was prepared as described in the literature from benzyl alcohol using butyl vinyl ether and $Hg(OAc)_2$ and distilled from sodium before use.[25] Millex filter units, 45-μm pore size, were received from Millipore.

General Procedure for the Stereoselective 1,3-Dipolar Cycloaddition Reactions. The appropriate ligand **7** (0.02 mmol) was placed in a 5-mL Schlenk flask flushed three times with N_2, and CH_2Cl_2 (1 mL) was added with a syringe. To this solution was added a 2 M solution of $AlMe_3$ in heptane (10 μL, 0.02 mmol), whereupon the solution turned yellow under the evolution of CH_4. The solution was stirred for 1 h and a solution of nitrone **4** (0.1 mmol) in CH_2Cl_2 (1 mL) was added together with the vinyl ethers **5** (0.5 mmol). After the appropriate reaction time, the reaction was quenched with MeOH (1 mL) and filtered through a 20-mm plug of silica. The silica was washed with Et_2O (3 mL) and the combined fractions were evaporated. The crude material was purified by column chromatography (silica gel, petroleum ether/Et_2O 9:1) to give the single diastereomer of **6**. Generally, the endo isomers appeared with lower R_f values than the exo isomers ($\Delta R_f = 0.1$).

The reactions with 10 mol % catalyst were performed in the same manner, whereas the reactions using 2.5 mol % and 5 mol % catalyst were performed on a 0.2-mmol scale using the same amount of solvent. The reactions on 1.0-mmol scale are performed in the same manner by scaling everything up 10 times. Racemic mixtures of the isoxazolidines *exo*-**6a-l** for HPLC analysis were prepared by stirring a mixture of the nitrone **4** (0.1 mmol) and the vinyl ether **5** (1.0 mmol) in CH_2Cl_2 overnight in the presence of $AlMe_3$ (25 mol %).

(20) Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7991.
(21) (a) Kamm, O. *Organic Synthesis*; Wiley: New York, 1941; Collect. Vol. 1, p 445. (b) Wheeler, O. H.; Gore, P. H. *J. Am. Chem. Soc.* **1956**, *78*, 3363.
(22) Beckett, A. H.; Coutts, R. T.; Ogunbona, F. A. *Tetrahedron* **1973**, *29*, 4189.
(23) Boyland, E.; Nery, R. *J. Chem. Soc.* **1963**, 3141.
(24) Nunno, L.; Scilimati, A. *Tetrahedron* **1991**, *47*, 4121.
(25) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

(+)-(3*R*,5*S*)-5-*tert*-Butoxy-2,3-diphenylisoxazolidine (*exo*-6a) was synthesized according to the general procedure on a 1.0-mmol scale with catalyst **8b** (10 mol %): yield 84%; ee = 89%; semicrystalline solid; $[\alpha]_D$ = +160.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.39 (s, 9H), 2.34 (ddd, *J* = 3.3, 6.8, and 12.9 Hz, 1H), 2.97 (ddd, *J* = 6.0, 9.3, and 13.2 Hz, 1H), 4.42 (dd, *J* = 7.0 and 9.0 Hz, 1H), 5.65 (dd, *J* = 3.3 and 6.1 Hz, 1H), 6.93 (m, 2H), 7.15−7.38 (m, 6H), 7.56 (m, 2H). ^{13}C NMR δ 28.9, 47.0, 68.9, 75.1, 96.4, 115.7, 121.9, 127.3, 127.4, 128.5, 128.7, 142.0, 150.9. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 0.7 mL/min) t_r = 12.2 min (minor), t_r =23.6 min (major). HRMS (EI) calcd for $C_{19}H_{23}NO_2$ (M^+) 297.1723, found 297.1732.

(+)-(3*R*,5*R*)-5-*tert*-Butoxy-2,3-diphenylisoxazolidine (*endo*-6a) was synthesized according to the general procedure on a 0.5-mmol scale using BINOL **7b** and $AlMe_2Cl$ (10 mol %) as the catalyst: yield 40%; ee = 26.6%; semicrystalline solid; $[\alpha]_D$ = +4.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.26 (s, 9H), 2.50 (ddd, *J* = 5.1, 9.3, and 12.2 Hz, 1H), 2.63 (ddd, *J* = 1.5, 6.9, and 12.1 Hz, 1H), 4.81 (dd, *J* = 6.6 and 9.3 Hz, 1H), 5.65 (br. d, *J* = 4.2 Hz, 1H), 6.88 (t, *J* = 7.0 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 2H), 7.14−7.40 (m, 5H), 7.49 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR δ 28.8, 47.5, 67.5, 74.9, 97.1, 115.5, 121.1, 126.5, 127.4, 128.2, 128.8, 141.6, 152.4. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99.5:0.5, flow rate = 0.7 mL/min) t_r = 31.0 min (minor), t_r = 33.5 min (major). HRMS (EI) calcd for $C_{19}H_{23}NO_2$ (M^+) 297.1723, found 297.1738.

(+)-(3*R*,5*S*)-5-*tert*-Butoxy-3-(4-methylphenyl)-2-phenylisoxazolidine (*exo*-6b) was synthesized according to the general procedure on a 1.0-mmol scale with catalyst **8b** (10 mol %): yield 71%; ee = 81%; clear oil; $[\alpha]_D$ = +145.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.42 (s, 9H), 2.36 (ddd, *J* = 3.3, 7.2, and 13.2 Hz, 1H), 2.40 (s, 3H), 2.99 (ddd, *J* = 6.0, 9.3, and 12.9 Hz, 1H), 4.40 (dd, *J* = 7.2 and 8.7 Hz, 1H), 5.67 (dd, *J* = 3.3 and 6.0 Hz, 1H), 6.90−7.05 (m, 3H), 7.16−7.25 (m, 4H), 7.49 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR δ 21.2, 29.0, 47.4, 68.8, 75.0, 96.2, 115.8, 121.8, 127.2, 128.5, 129.4, 137.0, 138.9, 151.0. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min) t_r = 7.0 min (minor), t_r = 11.6 min (major). HRMS (EI) calcd for $C_{20}H_{25}NO_2$ (M^+) 311.1885, found 311.1899.

(+)-(3*R*,5*S*)-5-*tert*-Butoxy-3-(4-chlorophenyl)-2-phenylisoxazolidine (*exo*-6c) was synthesized according to the general procedure on a 1.0-mmol scale with catalyst **8b** (10 mol %): yield 74%; ee = 78%; clear oil; $[\alpha]_D$ = +145.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.37 (s, 9H), 2.27 (ddd, *J* = 3.0, 6.1, and 13.2 Hz, 1H), 2.95 (ddd, *J* = 6.0, 9.3, and 12.6 Hz, 1H), 4.40 (dd, *J* = 6.0 and 9.3 Hz, 1H), 5.66 (dd, *J* = 3.3 and 6.0 Hz, 1H), 6.90−7.00 (m, 3H), 7.16−7.25 (m, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR δ 28.9, 46.8, 68.1, 75.1, 96.3, 115.5, 122.0, 128.6, 128.7, 128.8, 133.1, 140.7, 150.6. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min) t_r = 5.7 min (minor), t_r = 7.0 min (major). HRMS (EI) calcd for $C_{19}H_{22}ClNO_2$ (M^+) 331.1339, found 331.1325.

***endo*-6c:** Yield 10%; ee = 0%; clear oil; ^{1}H NMR δ 1.25 (s, 9H), 2.44 (ddd, *J* = 5.1, 9.3, and 12.5 Hz, 1H), 2.61 (ddd, *J* = 1.8, 7.2, and 12.2 Hz, 1H), 4.78 (dd, *J* = 6.6 and 9.3 Hz, 1H), 5.62 (br. d, *J* = 4.5 Hz, 1H), 6.85−6.98 (m, 3H), 7.14−7.22 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR δ 28.8, 47.4, 66.9, 75.0, 97.0, 115.5, 121.4, 127.9, 128.3, 128.9, 133.1, 140.1, 152.1. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min) t_r = 11.7 min, t_r = 13.8 min (major). HRMS (EI) calcd for $C_{19}H_{22}ClNO_2$ (M^+) 331.1339, found 331.1321.

(+)-(3*R*,5*S*)-5-*tert*-Butoxy-3-(4-methoxyphenyl)-2-phenylisoxazolidine (*exo*-6d) was synthesized according to the general procedure on a 1.0-mmol scale with catalyst **8b** (10 mol %): yield 65%; ee = 77%; clear oil; $[\alpha]_D$ = +141.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.38 (s, 9H), 2.32 (ddd, *J* = 3.3, 7.2, and 12.6 Hz, 1H), 2.95 (ddd, *J* = 6.0, 9.0, and 13.0 Hz, 1H), 3.81 (s, 3H), 4.35 (dd, *J* = 7.2 and 8.7 Hz, 1H), 5.64 (dd, *J* = 3.3 and 6.0 Hz, 1H), 6.88−7.0 (m, 5H), 7.19 (t, *J* = 7.9 Hz, 2H), 7.46 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR δ 29.0, 47.3, 55.3, 68.6, 75.0, 96.2, 114.1, 115.9, 121.8, 128.5, 133.8, 150.9, 159.0. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min) t_r = 10.1 min (minor), t_r = 13.3 min (major). HRMS (EI) calcd for $C_{20}H_{25}NO_3$ (M^+) 327.1834, found 327.1851.

(+)-(3*R*,5*S*)-5-Ethoxy-2,3-diphenylisoxazolidine (*exo*-6e) was synthesized according to the general procedure on a 0.5-mmol scale with catalyst **8b** (10 mol %): yield 79%; ee = 91%; clear oil; $[\alpha]_D$ = +217.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR[9c] ^{13}C NMR δ 15.2, 46.8, 63.6, 69.2, 100.6, 116.6, 122.5, 127.4, 127.6, 128.5, 128.8, 141.4, 150.3. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min) t_r = 11.2 min (minor), t_r = 25.3 min (major). HRMS (EI) calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1415, found 269.1402.

(+)-(3*R*,5*S*)-5-Ethoxy-3-(4-methylphenyl)-2-phenylisoxazolidine (*exo*-6f) was synthesized according to the general procedure on a 2-mmol scale with catalyst **8b** (10 mol %): yield 70%; ee = 90%; $[\alpha]_D$ = +171.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.34 (t, *J* = 7.2 Hz, 3H), 2.37 (s, 3H), 2.40 (ddd, *J* = 2.4, 7.2, and 13.2 Hz, 1H), 3.04 (ddd, *J* = 6.0, 9.3, and 13.2 Hz, 1H), 3.65 (dq, *J* = 7.2 and 9.8 Hz, 1H), 4.04 (dq, *J* = 7.2 and 9.3 Hz, 1H), 4.30 (dd, *J* = 6.6 and 9.3 Hz, 1H), 5.38 (dd, *J* = 2.4 and 6.0 Hz, 1H), 6.92−7.02 (m, 3H), 7.14−7.25 (m, 4H), 7.44 (d, *J* = 8.1 Hz, 2h). ^{13}C NMR δ 15.2, 21.4, 47.0, 63.6, 69.1, 100.6, 116.7, 122.5, 127.4, 128.5, 129.5, 137.2, 138.2, 150.3. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min) t_r = 5.3 min (minor), t_r = 12.2 min (major). HRMS (EI) calcd for $C_{18}H_{21}NO_2$ (M^+) 283.1572, found 283.1752.

(+)-(3*R*,5*S*)-3-(4-Chlorophenyl)-5-ethoxy-2-phenylisoxazolidine (*exo*-6 g) was synthesized according to the general procedure on a 1-mmol scale with catalyst **8b** (10 mol %): yield 78%; ee = 94%; $[\alpha]_D$ = +210.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.34 (ddd, *J* = 2.1, 6.6, and 13.2 Hz, 1H), 3.02 (ddd, *J* = 6.0, 9.9, and 13.2 Hz, 1H), 3.64 (dq, *J* = 7.2 and 9.6 Hz, 1H), 4.01 (dq, *J* = 7.2 and 9.9 Hz, 1H), 4.33 (dd, *J* = 6.6 and 9.6 Hz, 1H), 5.39 (dd, *J* = 2.1 and 6.0 Hz, 1H), 6.90−7.02 (m, 3H), 7.18−7.25 (m, 2H), 7.35 (d, *J* = 8.1 Hz, 2h), 7.49 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR δ 15.2, 46.5, 63.6, 68.4, 100.6, 116.4, 122.6, 128.6, 128.8, 128.9, 133.3, 140.2, 150.1. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99.5:0.5, flow rate = 0.7 mL/min) t_r = 13.1 min (minor), t_r = 14.1 min (major). HRMS (EI) calcd for $C_{17}H_{18}ClNO_2$ (M^+) 303.1026, found 303.1042.

(+)-(3*R*,5*S*)-5-Ethoxy-3-(4-methoxyphenyl)-2-phenylisoxazolidine (*exo*-6h) was synthesized according to the general procedure on a 0.5-mmol scale with catalyst **8b** (10 mol %): yield 50%; ee = 88%; $[\alpha]_D$ = +145.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.32 (t, *J* = 7.2 Hz, 3H), 2.37 (ddd, *J* = 2.1, 7.2, and 13.2 Hz, 1H), 3.01 (ddd, *J* = 6.0, 9.3, and 13.2 Hz, 1H), 3.63 (dq, *J* = 7.2 and 9.9 Hz, 1H), 3.82 (s, 3H), 4.01 (dq, *J* = 7.2 and 9.3 Hz, 1H), 4.25 (dd, *J* = 7.2 and 9.3 Hz, 1H), 5.37 (dd, *J* = 2.1 and 6.0 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 7.16−7.22 (m, 3H), 7.44 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR δ 15.2, 46.9, 55.3, 63.6, 69.0, 100.6, 114.1, 116.8, 122.6, 124.3, 128.5, 128.7, 150.3, 160.1. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min) t_r = 7.4 min (minor), t_r = 13.5 min (major). HRMS (EI) calcd for $C_{18}H_{21}NO_3$ (M^+) 299.1521, found 299.1536.

(+)-(3*R*,5*S*)-5-Benzyloxy-3-(4-chlorophenyl)-2-phenylisoxazolidine (*exo*-6i) was synthesized according to the general procedure on a 0.2-mmol scale with catalyst **8b** (10 mol %): yield 68%; ee = 85%. ^{1}H NMR δ 2.41 (ddd, *J* = 1.5, 6.0, and 13.2 Hz, 1H), 3.03 (ddd, *J* = 5.8, 9.4, and 13.2 Hz, 1H), 4.33 (dd, *J* = 6.0 and 9.9 Hz, 1H), 4.68 (d, *J* = 12 Hz, 1H), 4.98 (d, *J* = 12 Hz, 1H), 5.44 (dd, *J* = 1.5 and 6.0 Hz, 1H), 6.90−7.02 (m, 3H), 7.18−7.45 (m, 9H), 7.48 (d, *J* = 9.0 Hz, 2H). HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 0.7 mL/min) t_r = 12.9 min (minor), t_r = 15.3 min (major). HRMS (EI) calcd for $C_{22}H_{20}ClNO_2$ (M^+) 365.1182, found 365.1211.

(*rac*)-2,3,3a,4,5,6a-Hexahydro-2,3-diphenylfuro[3,2-*d*]isoxazolidine (*exo*-6j) was synthesized according to the general procedure on a 0.5-mmol scale with catalyst **8b** (10 mol %): yield 51%; ee = <5%; clear oil; ^{1}H NMR.[26] ^{13}C NMR δ 28.3, 53.5, 69.3, 71.0, 105.3, 119.2, 123.7, 127.4, 127.7, 128.4, 128.8, 137.8, 148.8. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_r = 12.5 min (minor), t_r = 18.6 min (major). HRMS (EI) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1259, found 267.1281.

***endo*-6j):** Yield 12%; ee = 0%; clear oil; ^{1}H NMR.[26] HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_r = 10.1 min (minor), t_r = 13.3 min (major). HRMS (EI) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1259, found 267.1278.

(*rac*)-2,3,5-Triphenylisoxazolidine (*exo*-6k) was synthesized according to the general procedure on a 0.5-mmol scale with catalyst **8b**

(26) Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1967**, 4179.

(10 mol %): yield 57%; ee = 0%; semicrystalline solid; ^{1}H NMR.[27] ^{13}C NMR δ 48.7, 71.6, 80.6, 114.0, 121.4, 126.3, 126.9, 127.4, 128.4, 128.6, 128.9, 129.0, 137.9, 142.9, 152.5. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min) t_r = 12.5 min, t_r = 14.6 min. HRMS (EI) calcd for $C_{21}H_{19}NO$ (M^+) 301.1460, found 301.1444.

(+)-(3*R*,5*S*)-3-(4-Carbomethoxyphenyl)-5-ethoxy-2-phenylisoxazolidine (*exo*-6l) was synthesized according to the general procedure on a 2.0-mmol scale with catalyst **8b** (10 mol %). The reaction was finished after 2 h: yield 90%; ee = 91%; $[\alpha]_D = +173.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.28 (t, J = 7.2 Hz, 3H), 2.36 (ddd, J = 2.1, 6.0, and 13.2 Hz, 1H), 3.03 (ddd, J = 5.7, 9.6, and 13.2 Hz, 1H), 3.62 (dq, J = 6.9 and 9.9 Hz, 1H), 3.92 (s, 3H), 3.98 (dq, J = 6.9 and 9.6 Hz, 1H), 4.41 (dd, J = 6.0 and 9.9 Hz, 1H), 5.39 (dd, J = 1.8 and 6.0 Hz, 1H), 6.85−6.95 (m, 3H), 7.18 (t, J = 8.1 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 8.03 (d, J = 8.1 Hz, 2H). ^{13}C NMR δ 15.2, 46.3, 52.1, 63.6, 68.6, 100.6, 116.3, 122.6, 127.3, 128.6, 129.4, 130.1, 146.9, 150.1, 166.9. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min) t_r = 14.3 min (major), t_r = 18.9 min (minor). HRMS (EI) calcd for $C_{19}H_{21}NO_4$ (M^+) 327.1470, found 327.1492.

(+)-(3*R*,5*S*)-3-(4-Carboxyphenyl)-5-ethoxy-2-phenylisoxazolidine (*exo*-9). The methyl ester *exo*-**6l** (0.63 g, 2 mmol) was dissolved in 50 mL of THF/H_2O (3:1), and LiOH (0.165 g, 4 mmol) was added. The reaction mixture was stirred overnight, diluted with H_2O (50 mL), and the THF was removed in vacuo. The aqueous phase was extracted with EtOAc (2 × 40 mL) to remove unreacted starting material, and neutralized with 1 M HCl, whereupon a white solid starts to precipitate. The mixture was extracted with EtOAc (3 × 50 mL), and the organic phase was dried (Na_2SO_4) and evaporated to give the free acid *exo*-**9** as a pale yellow glass; yield 0.59 g (94%); $[\alpha]_D = +193.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.32 (t, J = 7.2 Hz, 3H), 2.38 (ddd, J = 1.5, 6.0, and 12.9 Hz, 1H), 3.05 (ddd, J = 6.3, 9.9, and 12.9 Hz, 1H), 3.62 (dq, J = 7.2 and 9.9 Hz, 1H), 3.99 (dq, J = 7.2 and 9.9 Hz, 1H), 4.45 (dd, J = 6.0 and 9.9 Hz, 1H), 5.41 (dd, J = 1.8 and 6.0 Hz, 1H), 6.90−7.00 (m, 3H), 7.18 (t, J = 8.1 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H), 8.10 (d, J = 9.0 Hz, 2H), 10.5 (s br., 1H). ^{13}C NMR δ 15.2, 46.2, 63.6, 68.6, 100.7, 116.3, 122.7, 127.5, 128.6, 128.7, 130.8, 148.0, 150.0, 172.0. HRMS (EI) calcd for $C_{18}H_{19}NO_4$ (M^+) 313.1313, found 313.1328.

Formation of the Diastereomeric Salt 10. To a solution of **9** (0.022 mg, 0.07 mmol) in Et_2O (2 mL) in a 10-mL round-bottomed flask was added a solution of (−)-(*S*)-1-phenylethylamine (10 μL, 0.08 mmol) in Et_2O (1 mL); the flask was capped and left overnight. After 1/2 h the formation of a white crystalline compound starts. The resulting white crystals were filtered, washed with ether, and dried in vacuo: yield: 29 mg (95%).

X-ray Analysis of *exo*-6 g and Complex 10. Exo-6g, $C_{17}H_{18}NO_2Cl$, is monoclinic, $P2_1/c$, with a = 10.1400(5), b = 16.8233(8), c = 9.6098(5) Å, β = 114.163(1), V = 1495.7(1), Z = 4. Reflections (14 675) were measured on a SMART diffractometer[28] at 120 K using graphite-monochromated MoKα radiation collecting a hemisphere of data out to θ = 27.7°. The structure was solved by direct methods (SIR97[29]) and refined by full matrix least squares on Fsq.[30] Of 3306 unique reflections, the 2643 with $I > 3\sigma(I)$ were used in the refinement of 263 parameters, giving R = 0.033, R_w = 0.032.

Complex 10. This family of compounds seem to be very difficult to crystallize in the optically active form and gave, with different cations, either no crystals or tiny crystals with unit cell volumes of 5000−8000 Å^3, and with far too few significant reflections. The phenethylammonium salt, however, gave usable, though tiny and poorly diffracting, crystals.

X-ray Analysis of 10, $C_{18}H_{18}NO_4^-$, $C_8H_{12}N^+$, is orthorhombic, $P2_12_12_1$, with a = 6.1488(4), b = 17.506(1), c = 22.638(2) Å, V = 2436.8 Å^3, Z = 4. Same procedure as for *exo*-**6g** gave 31 422 reflections measured, 5396 unique, 2042 significant [$I > 3\sigma(I)$]. The structure was solved without difficulty, but anisotropic displacement parameters for the central part of the molecule showed disorder. Each atom was split into two isotropic atoms, and geometric considerations showed unambiguously a superposition of two anions of identical conformation except for rotation about the single bonds outside the rings. To stabilize refinement and save parameters, constraints were introduced according to Pawley:[31] all phenyl rings identical with mm2 symmetry; the 5-ring with its attached oxygen identical for the two disordered anions; thermal motion described by the TLS model for three sections: phenyl group(s) attached to N2, phenyl group(s) at C3, 5-rings with ethoxy group; one common occupation parameter for disordered part; hydrogen atoms in calculated positions, methyl and $-NH_3^+$ refined with a parameter for rotation from the staggered position; carboxyl group and phenylethylammonium ion ordered, refined anisotropically. Parameters (232) were refined, final R = 0.059, R_w = 0.070. Atomic coordinates, bond lengths and angles, and thermal parameters for *exo*-**6g** and **10** have been deposited at the Cambridge Crystallographic Data Center (CCDC).

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Supporting Information Available: Copies of NMR spectra, MS spectra and X-ray data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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