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Use of chiral B(III) complexes in the cycloaddition of *C*,*N*-diphenylnitrone to *tert*-butyl vinyl ether

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Abstract

The 1,3-dipolar cycloaddition of *C*,*N*-diphenylnitrone to *tert*-butyl vinyl ether in the presence of several chiral B(III) complexes which incorporate different bidentate ligands has been investigated. The use of these B(III) species reverses the *endo*/*exo* diastereoselectivity in relation to the uncatalysed reaction, giving *trans* cycloadducts as major products. Some of the catalysts gave very fast and high yielding reactions, but the enantioselectivities were only low to moderate.

1. Introduction

The 1,3-dipolar cycloaddition of nitrones to olefins is a widely spread methodology for the preparation of isoxazolidines, which are valuable intermediates for the synthesis of bioactive molecules.[1] One of the main advantages of this reaction is that it enables the formation of up to three new stereogenic centres in a single step. The relative configuration of the cycloadducts depends on the *exo*/*endo* selectivity of the process. This diastereoselectivity is controlled by a combination of electronic and steric factors. According to Sustmann's classification,[2] the 1,3-dipolar cycloadditions of nitrones to olefins are type II processes. Therefore, for a given nitrone, the dominating frontier molecular orbital (FMO) interaction in the transition state (TS) depends on the olefin nature. It is experimentally observed that electron deficient olefins are more reactive towards nitrones than electron rich ones, while unactivated olefins are the less reactive. With the two latter olefin categories, it is usually necessary to work at high temperatures or pressures, or with large excesses of one of the reactants, in order to obtain reasonable conversions. An attractive way to increase the rate of these cycloadditions is the use of Lewis acids as promoters of the process. These species can interact with the nitrone and also with the dipolarophile if it contains functional groups able to coordinate to the acidic centre. The effect of this complexation will be a lowering of the FMO energy levels of the nitrone or the olefin

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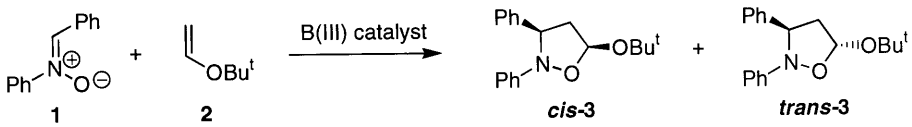
compared with those of the free reactant. In most successful examples of Lewis acid catalysed cycloadditions of nitrones, the dipolarophile is an olefin conjugated to a carbonyl group,[3–10] therefore the dominating TS interaction is $HOMO_{nitrone}$–$LUMO_{olefin}$ and the catalytic effect can be explained through the complexation of the acid with the olefin. Although less investigated, several examples have also been described of Lewis acid catalysed cycloadditions of nitrones to electron rich olefins.[11–16] In these reactions the predominant TS interaction is $HOMO_{olefin}$–$LUMO_{nitrone}$ and the catalytic effect has to be attributed to the complexation of the Lewis acid with the nitrone. Two kinds of electron rich olefins have been used for these studies: ketene acetals and vinyl ethers, but there is experimental evidence that the Lewis acid promoted addition of ketene acetals to nitrones may happen, at least in some cases, through a stepwise mechanism with the intermediacy of cationic species.[17] Recently, Jørgensen et al. have achieved excellent diastereo- and enantioselectivities in the cycloaddition of *C*,*N*-diarylnitrones to vinyl ethers catalysed by chiral aluminium complexes.[15a] In these reactions the major product is the *cis*-cycloadduct, which is also the predominant isomer of the uncatalysed cycloaddition. We[13] and the group of Bosnich[16] have found that this kind of reaction can also be accelerated with several Ti(IV) species, Meske[12] and the group of Scheeren[11] have investigated the use of chiral oxazaborolidines, and Furukawa and co-workers have described the catalysis by Pd(II) complexes.[14] All these catalysts gave variable diastereoselectivities, in some cases tuned by the metal ligands, and, when chiral auxiliaries have been incorporated into the complex, the enantioselectivities found were low to moderate.

We have now investigated the reaction of *C*,*N*-diphenylnitrone, **1**, with *tert*-butyl vinyl ether, **2**, in the presence of B(III) complexes (Scheme 1). The results are described herein.



Scheme 1.

2. Results and discussion

We had previously studied the uncatalysed reaction between **1** and **2** at 50°C in toluene (Table 1, entry 1).[13a] This cycloaddition proceeds very slowly to yield a mixture of the two diastereoisomeric isoxazolidines *cis*- and *trans*-**3** in 70% yield with a strong predominance of the *cis* isomer, presumably formed through an *exo*-TS from the more stable *Z* configuration of nitrone **1**.[18] The B(III) promoted reactions were performed in CH_2Cl_2 with a fourfold excess of olefin and 20% molar of catalyst (Fig. 1) referred to nitrone **1**. Prior to the introduction of chiral boranes into the reaction medium, we examined the influence of the presence of catecholborane, **4** (entry 2). This complex caused a remarkable acceleration of the cycloaddition and it also induced a complete inversion of the diastereoselectivity, yielding *trans*-**3** with 97% de in 86% yield. In a first set of experiments with chiral ligands, several boranes which incorporate bidentate C_2-symmetrical diolates, **5**–**8**, were assayed. It was expected that those complexes bearing aromatic residues, **5**–**7**, may benefit from a π-stacking interaction with the phenyl groups of nitrone **1**, shielding one of its faces to the approach of the olefin in the TS. On the other hand,

Table 1
Cycloaddition reaction of nitrone **1** to olefin **2** in the presence of B(III) complexes. $[\mathbf{1}]_0 = 0.1$ M, $[\mathbf{2}]_0 = 0.4$ M, $[\text{catalyst}]_0 = 0.02$ M

Entry	Catalyst	Solvent	Temp.	Time	Yield[a] (%)	*cis*-**3**/*trans*-**3**[b]	Ee *cis*-**3**[c] (%)	Ee *trans*-**3**[c] (%)
1	None	Toluene	50°C	14 days	70	33:1		
2	**4**	CH_2Cl_2	Rt	12 h	86	1:74		
3	**5**	CH_2Cl_2	Rt	40 h	44	1:2	14	–
4	**6**	CH_2Cl_2	Rt	40 h	31	1:2	–	–
5	**7**	CH_2Cl_2	Rt	40 h	66	1:4	12	28
6	**8**	CH_2Cl_2	Rt	40 h	54	1:4	9	26
7	**9**	CH_2Cl_2	Rt	<2 min	89	1:6	9	6
8	**9**	CH_2Cl_2	−20°C	45 min	67	1:9	8	40
9	**9**	Toluene	Rt	<2 min	89	1:9	–	8
10	**9**	Toluene	−20°C	45 min	70	1:8	13	29
11	**10**	CH_2Cl_2	Rt	<2 min	46	1:6	14	16
12	**11**	CH_2Cl_2	Rt	<2 min	69	1:7	–	–
13	**12**	CH_2Cl_2	Rt	40 min	82	1:7	8	16
14	**13**	CH_2Cl_2	Rt	40 min	54	1:6	–	29
15	**14**	CH_2Cl_2	Rt	<2 min	61	1:7	11	24
16	**14**	CH_2Cl_2	−40°C	15 min	78	1:8	13	28
17	**15**	CH_2Cl_2	Rt	<2 min	77	1:6	13	33
18	**15**	CH_2Cl_2	−40°C	15 min	78	1:8	13	28
19	**15**	THF	−20°C	15 min	78	1:3	16	31
20	**15**	DMF	−20°C	1 h	91	1:6	16	32
21	**16**	CH_2Cl_2	Rt	30 min	74	1:4	10	26
22	**17**	CH_2Cl_2	Rt	45 min	96	1:4	11	24
23	**18**	CH_2Cl_2	Rt	<2 min	44	1:8	57	–
24	**19**	CH_2Cl_2	Rt	30 min	61	1:8	–	8
25	**20**	CH_2Cl_2	Rt	30 min	67	1:9	–	19
26	**21** + $ZnEt_2$	CH_2Cl_2	Rt	40 h	32	2:1	–	20

[a] Yield of isolated **3** by column chromatography.
[b] *cis*-**3**/*trans*-**3** ratio determined by ^{1}H NMR on the crude reaction mixtures.
[c] Ee determined by HPLC (Daicel Chiracel OD), only values over 5% are indicated.

the dicyclohexyl derivative **8** may introduce more steric hindrance in the proximity of the boron atom. We found that the glycolate ligands (entries 3–6) were less effective than cathecolate, giving lower reaction rates, yields and diastereoselectivities. The best ee within this series was obtained with complex **7**, which contains an electron-releasing *p*-methoxy substituent in the aromatic rings, supporting the 'π-stacking hypothesis', but yet the enantioselectivity was quite low. Crucial improvements of the asymmetric induction are often produced by diminishing the reaction temperature, but the cycloaddition of **1** to **2** catalysed by the borane **7** was still too slow to work at lower temperatures. Therefore, we decided to increase the acidity of the boron complex, and hence its catalytic activity, by introduction of a triflate as the monodentate ligand. The reaction in the presence of the triflate complex **9** at room temperature (entry 7) was indeed very fast, and at −20°C (entry 8) both the diastereo- and the enantioselectivity of the process improved substantially (80% de and 40% ee for the major cycloadduct *trans*-**3**).

In an attempt to gain some insight into the geometry of the reacting complex, a solution containing equimolar amounts of nitrone **1** and the boron complex **9** in CD_2Cl_2 was analysed by

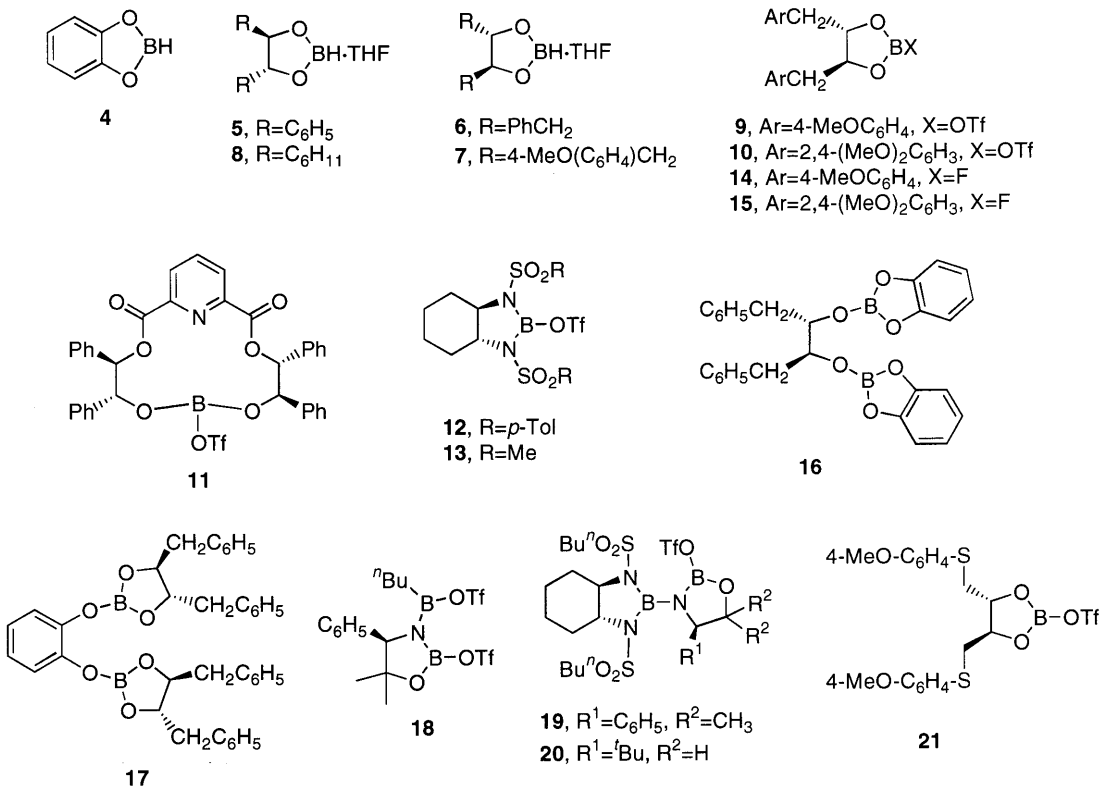


Figure 1.

400 MHz ^{1}H NMR. In the presence of **9**, the signals of all protons of the nitrone resolved clearly and could be completely assigned. The iminic proton experienced a considerable downfield shifting (from δ 7.96 to 8.54), while the *ortho* protons of the *C*-phenyl and *N*-phenyl groups (δ 8.35 and 7.77, respectively) showed chemical shifts very similar to those observed for the free nitrone.[19] Presaturation of the signal corresponding to the iminic proton induced positive NOE on both the *C*-phenyl and the *N*-phenyl H_{ortho}, indicating the *Z* configuration of the nitrone in the reactive complex. This observation strongly supports the hypothesis that the major *trans* cycloadduct formed in the catalysed reaction is produced through an *endo* TS from the complexed *Z*-nitrone.

The use of toluene as solvent (entries 9 and 10) did not produce beneficial changes. The introduction of a second methoxy substituent in the aromatic residues of the diolate (entry 11) and the increase in the size and rigidity of the diolate (entry 12) were ineffective. Complexes **12** and **13** having a C_2-symmetrical cyclohexyldisulfonamide as the bidentate ligand were also tested (entries 13 and 14). This kind of ligand showed the best enantioselectivity in the previous studies with chiral Ti(IV) catalysts,[13b] but the performance of their boron complexes was not superior to that of the diolate derivatives.

Comparison of the results of entries 5 and 7 (where all the other variables remained unchanged) seemed to indicate that the inclusion of hydride as the monodentate ligand of the catalyst was beneficial to the enantioselectivity in relation to the triflate. In an attempt to understand the reasons for that, theoretical calculations of the reactive intermediates derived

from nitrone **1** and complexes **7** or **9** were performed.† Molecular mechanics (MMFF94) were used to obtain the energy global minimum and then the geometry of the intermediate complexes were optimised applying semiempirical (AM-1) calculations. Depicted in Fig. 2 are the two possible approaches, *exo* or *endo*, of the vinyl ether **2** to each face of nitrone **1** coordinated to catalyst **7** with the optimised geometry; the *re* and *si* descriptors refer to the carbon atom of the nitrone and the hydride ligand is shown in yellow. According to this model, the *re*-face of the nitrone seems more available to the dipolarophile, and the *endo* approach to this face looks less sterically encumbered than the *exo* approach. For the complex nitrone **1**–catalyst **9**, the calculations gave an optimised trigonal geometry around the boron atom, as expected, with similar accessibility to both faces of the complexed nitrone.

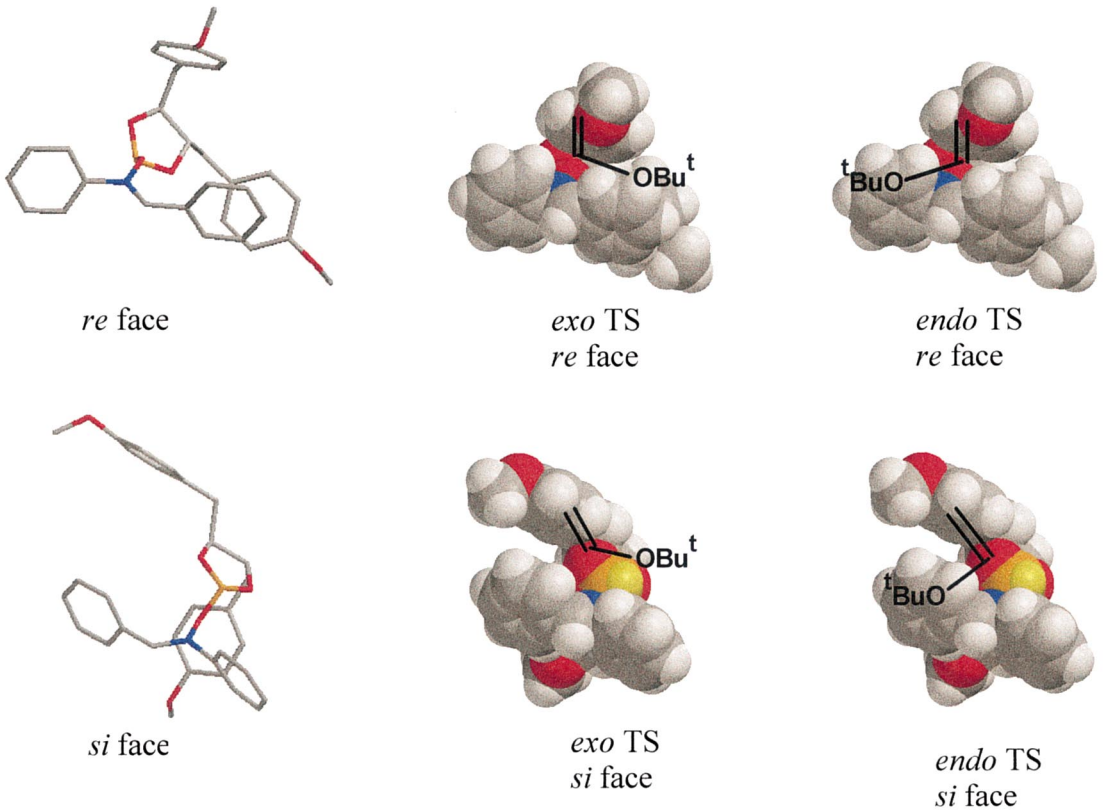


Figure 2.

Considering the above results, it was thought that B(III) complexes containing a fluoride anion as the monodentate ligand could have higher catalytic activity than the hydride complexes while preserving the tetragonal geometry, leading to a better asymmetric induction. This idea was tested with complexes **14** and **15**, prepared in situ by reaction of the corresponding triflates **9** and **10** with n-Bu_4NF. In the presence of these fluoride complexes (entries 15–20) the cycloaddition was indeed very fast, the yields were good and the enantioselectivities were similar to that observed for the corresponding hydride complex, with higher diastereoselectivity

† The calculations were performed using the PC SPARTAN plus program of Wavefunction, Inc.

(compare entries 5, 15 and 17). Unfortunately, lowering the reaction temperature or changing the solvent did not produce significant improvements in the asymmetric induction.

It has been described that a nucleophilic oxygen atom may interact with two acidic metal centres simultaneously, with the consequent loss of flexibility of the reacting system.[20] To propitiate this kind of interaction with nitrone **1**, the bicentric complexes **16**–**20** were prepared, and their influence in the studied cycloaddition was examined (entries 21–25). All these complexes were efficient promoters of the reaction. Interestingly, the addition of **16** and **17**, with reversed proportion of the diolate ligands, gave almost identical results, while **18**–**20**, which include amino-alcohol moieties, gave better diastereoselectivities, but the enantiodifferentiation was poor in all the cases. A last experiment was performed in the presence of complex **21**, in combination with $ZnEt_2$ (entry 26). The purpose was to bring about the simultaneous coordination of the zinc nucleus with a sulphur atom of the diolate residue and the oxygen atom of the nitrone, which at the same time should also be coordinated to the boron nucleus. This catalytic system was not so effective in terms of reactivity and yield as all the former B(III) complexes, giving poor asymmetric induction and with opposite diastereoselectivity.

In summary, the cycloaddition of nitrone **1** to vinyl ether **2** is efficiently promoted by B(III) complexes giving fast reactions in high yields and with good diastereoselectivity in favour of the *trans*-cycloadduct, contrary to the uncatalysed reaction, where the *cis*-cycloadduct predominates. Although the enantioselectivities are still quite low, the only efficient enantioselective version previously described for this reaction, catalysed by (BINOL)–AlMe complexes,[15a] yields almost exclusively *cis*-cycloadducts. Therefore, the improvement of the use of chiral B(III) complexes emerges as a promising complement to the Al(III) promoted reactions.

3. Experimental

Previously described methods were used to prepare nitrone **1**,[21] (1*R*,2*R*)-hydrobenzoin,[22] (1*S*,2*S*)-1,2-dibenzylethyleneglycol,[23] (1*S*,2*S*)-1,2-bis(*p*-methoxybenzyl)ethyleneglycol,[24] (1*R*,2*R*)-dicyclohexylethyleneglycol,[24] [(1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl]pyridine-2,6-dicarboxylate,[13b] *N*-{(1*R*,2*R*)-2-[(methylsulfonyl)amino]cyclohexyl}metanesulfonamide,[25] *N*-{(1*R*,2*R*)-2-[(*p*-toluenesulfonyl)amino]cyclohexyl}-*p*-toluenesulfonamide,[25] *N*-{(1*R*,2*R*)-2-[(*n*-butylsulfonyl)amino]cyclohexyl}butanesulfonamide,[26] 1,1-dimethyl-(*S*)-phenylglycinol,[27] and L-*tert*-leucinol.[28] Commercially available vinyl ether **2** was distilled from sodium. Nitrone **1** was dried by melting it under vacuum and refilling with nitrogen (three consecutive times). Reaction mixtures were stirred magnetically. A commercial 1.0 M solution of cathecolborane in CH_2Cl_2 was used. TLC was performed using 0.25 mm Alugram Sil plates, Machery–Nagel. HPLC was performed with a Daicel Chiracel OD 4.6×250 mm column connected to a Waters 600 pump, under the following conditions: samples of 20 μL (8 mg/mL), hexane/2-propanol (98/2) as the mobil phase, 350–300 psi pressure and 1 mL/min flow. Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in the *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona* on a Bruker AC-250-WB or AM-400-WB instrument. Mass spectra were obtained on a Hewlett–Packard 5985B instrument. HRMS was performed in the *Departamento de Química Orgánica de la Universidad de Zaragoza*.

3.1. Preparation of (2S,3S)-1,4-bis(2,4-dimethoxyphenyl)-2,3-butanediol

To a stirred suspension of CuI (190 mg, 1.0 mmol) in anhydrous THF (16 mL) at −40°C under a nitrogen atmosphere, a solution of 10.8 mmol of 2,4-dimethoxyphenylmagnesium bromide (prepared from 16 mL, 10.8 mmol of 1-bromo-2,4-dimethoxybenzene and 294 mg, 12.1 mmol of Mg in 5 mL of anhydrous THF) was added dropwise. The mixture was stirred for 5 min and a solution of (2*S*,3*S*)-1,2:3,4-diepoxybutane[29] (prepared from 3.3 mmol of 2,3-*O*-isopropylidene-L-threitol 1,4-bismethanesulphonate) in ether (3 mL) was added. The mixture was allowed to warm up to 0°C and stirred for 2 h. Cold water was added, the organic phase was separated and the aqueous layer extracted with ether (2×10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent evaporated under vacuum. The crude material was purified by silica gel flash chromatography (hexane/EtOAc, 5/2), followed by recrystallisation in toluene to give 775 mg (2.1 mmol, 64%) of the diol: mp 82–83°C (toluene); IR (KBr): 3459, 3352 (br), 2935, 2838, 1616, 1509, 1457, 1260, 1211, 1157, 1122, 1041 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.05 (d, $J=8.4$ Hz, 1H), 6.43 (s, 1H), 6.41 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.65 (m, 1H), 2.90–2.70 (complex absorption, 2H), 2.64 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 159.5, 158.3, 131.5, 119.1, 104.2, 98.5, 73.3, 55.3, 34.1; MS (m/z): 362 (M^+, 2), 181 (10), 152 (31), 151 (100), 121 (29); HRMS (EI) (M^+) calcd for $C_{20}H_{26}O_6$ 362.1729, found 362.1719. $[\alpha]_D^{20}$ +7.2 (*c* 1.9, $CHCl_3$).

3.2. Preparation of (2S,3S)-1,4-bis(4-methoxybenzylthio)-2,3-butanediol

Triethylamine (1.6 mL, 11.5 mmol) and $LiOH{\cdot}H_2O$ (510 mg, 12.1 mmol) were added to a solution of 4-methoxybenzylmercaptane (1.8 mL, 12.9 mmol) in 4 mL of $CHCl_3$ placed in a pressure resisting flask. The mixture was stirred at 50°C for 30 min, then it was cooled to room temperature and a solution of (2*S*,3*S*)-1,2:3,4-diepoxybutane[28] (prepared from 3.6 mmol of 2,3-*O*-isopropylidene-L-threitol 1,4-bismethanesulphonate) in ether (3 mL) was added. The mixture was heated at 80°C for 20 h, then cooled, acidified with 3% HCl (pH 3) and extracted with CH_2Cl_2 (2×5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent evaporated under vacuum. The crude material was purified by silica gel flash chromatography (CH_2Cl_2), followed by recrystallisation in EtOAc/pentane to give 1.22 g (3.1 mmol, 86%) of the diol: mp 90–91°C (EtOAc/pentane); IR (KBr): 3423 (br), 2917, 2847, 1616, 1511, 1244, 1180, 1110, 1026 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.20 (d, $J=8.7$ Hz, 2H), 6.82 (d, $J=8.7$ Hz, 2H), 3.77 (s, 3H), 3.66 (s, 2H), 3.57 (m, 1H), 2.65–2.45 (complex absorption, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 158.6, 129.9, 129.8, 113.9, 70.6, 55.1, 35.6, 35.0; MS (CI, NH_3): 412 (M^++18, 2), 395 (M^++1, 26), 121 (100). Anal. calcd for $C_{20}H_{26}O_4S$: C, 60.89; H, 6.64; S, 16.25. Found: C, 60.68; H, 6.38; S, 16.06. $[\alpha]_D^{20}$ −62.7 (*c* 3.0, $CHCl_3$).

3.3. Preparation of the chiral complexes **5**–**13**

A Schlenk flask containing the bidentate ligand (0.05 mmol) under nitrogen was connected to a vacuum pump (0.1 Torr) at room temperature for 1 h. Anhydrous CH_2Cl_2 (1 mL) was added, followed by 1 M solution of $BH_3{\cdot}THF$ or $(^nBu)_2B(OTf)$ (50 μL, 0.05 mmol) in CH_2Cl_2. The mixture was stirred at room temperature for 1 h. With the only exception of **11**, which precipitated, all complexes gave yellow or pink solutions, depending on the ligands.

3.4. Preparation of the chiral complexes **14** and **15**

A Schlenk flask containing the diol (0.05 mmol) under nitrogen was connected to a vacuum pump (0.1 Torr) at room temperature for 1 h. Anhydrous CH_2Cl_2 (1 mL) and a 1 M solution of (^{n}Bu)$_2$B(OTf) (50 μL, 0.05 mmol) in CH_2Cl_2 were consecutively added, and the mixture stirred at room temperature for 30 min. Then a 1 M solution of Bu_4NF in THF (50 μL, 0.05 mmol) was added and the mixture was stirred at room temperature for 14 h. After the addition of Bu_4NF, the colour of the solutions of complexes **9** and **10** shifted from pale-yellow and pink, respectively, to strong violet.

3.5. Cycloaddition of nitrone **1** to vinyl ether **2** promoted by complexes **4**–**15**. General procedure

A solution of nitrone **1** (50 mg, 0.25 mmol) in CH_2Cl_2 (1.5 mL) was placed in a Schlenk flask under nitrogen. While stirring at the reaction temperature (see Table 1), a freshly prepared solution of the catalyst (0.05 mmol) was added dropwise through a syringe. After stirring for 1 h at the reaction temperature, the vinyl ether **2** (130 μL, 1.0 mmol) was added and the evolution of the reaction mixture was monitored by TLC or ^{1}H NMR analyses of aliquot samples.

The reaction mixture was filtered through a pad of silica gel, which was then washed with MeOH/$CHCl_3$, 1/9. The overall solution was concentrated and the residue was purified by flash chromatography on silica gel (hexane/ether, 3/1) to yield a mixture of *cis*- and *trans*-**3**. The diastereoisomers were separated by a second flash chromatography on silica gel (hexane/ether, 29/1) and their ee's were determined by HPLC.

3.6. Preparation of **16**

A Schlenk flask containing (1*S*,2*S*)-1,2-dibenzylethyleneglycol (13 mg, 0.05 mmol) under nitrogen was connected to a vacuum pump (0.1 Torr) at room temperature for 1 h. Anhydrous CH_2Cl_2 (0.9 mL) was added, followed by a 1 M solution of cathecolborane (100 μL, 0.10 mmol) in CH_2Cl_2. The solution was stirred at room temperature for 1 h.

3.7. Preparation of **17**

A Schlenk flask containing cathecolborane (5 mg, 0.05 mmol) under nitrogen was connected to a vacuum pump (0.1 Torr) at room temperature for 1 h. Another Schlenk flask containing 2,3-butanediol (24 mg, 0.10 mmol) under nitrogen was also connected to a vacuum pump (0.1 Torr) at room temperature for 1 h. Anhydrous CH_2Cl_2 (0.5 and 0.4 mL) was added, respectively, to each flask. Then, 1 M BH_3·THF (100 μL, 0.1 mmol) was added to the suspension of (1*S*,2*S*)-1,2-dibenzylethyleneglycol, which dissolved completely. This solution was stirred for 1 h and then added dropwise via a syringe to the first flask containing the cathecolborane.

Anhydrous CH_2Cl_2 (0.9 mL) was added, followed by a 1 M solution of cathecolborane (100 μL, 0.10 mmol) in CH_2Cl_2. The solution was stirred at room temperature for 1 h.

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