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Use of chiral Ti(IV) 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 Ti(IV) species which incorporate different bidentate C_2-symmetrical ligands has been investigated. Several complexes have shown very efficient catalytic activity. The *endo*/*exo* selectivity of the process can be dramatically reversed in relation to the uncatalysed reaction, but low enantioselectivities up to 41% ee are found.

1. Introduction

Cycloaddition processes are among the most attractive synthetic methodologies, because they allow the construction of new molecular skeletons with several stereogenic centres in a single step. The 1,3-dipolar cycloaddition of nitrones to olefins is a well-established procedure for the preparation of isoxazolidines.[1] These heterocycles are versatile intermediates for a variety of biologically important molecules, therefore the control of the stereochemical outcome of the dipolar cycloaddition of nitrones has been the object of intensive studies. To achieve asymmetric induction,[2] strategies based on the use of chiral nitrones or dipolarophiles have been mostly applied, although several groups have also employed asymmetric catalysis with different Lewis acids containing chiral ligands.

The reactivity of nitrones towards dipolarophiles and the regio- and stereoselectivity of their cycloadditions may be explained in terms of the FMO theory. The preferred approach of the reactants in the transition state results from a combination of electronic and steric factors. With electron deficient olefins, the main TS interaction is $HOMO_{nitrone}$–$LUMO_{olefin}$ and the catalytic effect of a Lewis acid can be explained through the complexation of the metal with the olefin, lowering the energy level of its LUMO. This has been the more widely studied case.[2b,3] On the contrary, when the dipolarophile is an electron rich olefin the predominant TS interaction is $HOMO_{olefin}$–$LUMO_{nitrone}$ and the catalytic effect has to be attributed to the complexation of the

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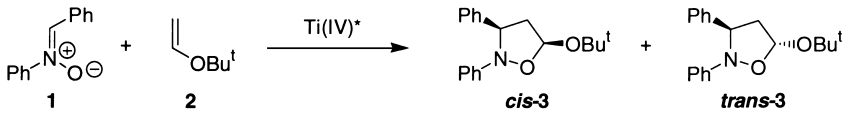
Lewis acid with the nitrone. Although less investigated, there are also some examples of this last class.[2b,4]

We recently demonstrated that several Ti(IV) species are capable of accelerating the cycloaddition of nitrones to enol ethers.[5] We also showed that some of these species produce notable changes in the *endo*/*exo* selectivity of the process. We have now investigated the reaction of *C*,*N*-diphenylnitrone, **1**, with *tert*-butyl vinyl ether, **2**, in the presence of chiral Ti(IV) complexes incorporating bidentate C_2-symmetrical ligands (Scheme 1). The results are described herein.



Scheme 1.

2. Results and discussion

We have already published the uncatalysed cycloaddition of **1** to **2** (Table 1, entry 1) which proceeds slowly to yield a mixture of isoxazolidines **3** with a strong predominance of the *cis* isomer. The *Z*-configuration of nitrone **1** in the solid phase and in solution has been firmly established, and it is generally accepted that this configuration is the one involved in the uncatalysed cycloadditions of **1**.[6] Therefore, the major *cis* isomer is supposed to be formed through an *exo* transition state. We also showed that the addition of $TiCl_2(^iPrO)_2$ to the reaction medium accelerated the cycloaddition of **1** to **2** and increased the proportion of *trans*-**3** (entries 2 and 3). Although the presence of a Lewis acid in the reaction medium could facilitate the *Z*/*E* isomerisation of acyclic nitrones,[1a] previous work performed with a rigid cyclic nitrone demonstrated that the presence of Ti(IV) species favours the *endo* TS in relation to the uncatalysed reaction.[5]

To introduce chirality into the titanium complex, we decided to substitute the isopropoxy ligands with a chiral C_2-symmetrical diolate (Fig. 1). According to preliminary NMR experiments,[5] we expected that the titanium complex would interact with the nitrone, but not with the vinyl ether. Typically, the chiral Ti(IV) complexes were freshly prepared by addition of $TiCl_2(^iPrO)_2$ to a toluene solution of the diol and the released ^{i}PrOH was removed. Then, the nitrone was added to the solution of the Ti(IV) catalyst and stirred for 1 h at room temperature before addition of the vinyl ether. The cycloadditions were performed in toluene, with a fourfold excess of dipolarophile, and the reactions were run until complete conversion of the nitrone, according to TLC and NMR analyses. The *cis*-**3**/*trans*-**3** ratio was determined on the crude reaction mixtures, through the relative area of the ^{1}H NMR signals corresponding to the acetal proton H_5 (δ 5.63 for *cis*-**3** and δ 5.55 for *trans*-**3**).

Firstly we exchanged the isopropoxy groups by the diolate derived from (1*R*,2*R*)-hydrobenzoin (**hb**). We assumed the reactive Ti(IV)(diolate)(nitrone **1**)-complex to be a discrete unit, as is usually accepted for Ti(IV)(diolate)-complexes when interacting with other substrates.[7] Then, we expected that the nitrone would locate in an axial position when entering into the coordination sphere of the metal. Although this situation should be more sterically encumbered, it could benefit from a π-stacking interaction (Fig. 2). If so, the rotation of the nitrone around the Ti–O–C axis should be restricted, making one of its faces more easily accessible to the dipolarophile. Interestingly, the presence of (**hb**)$TiCl_2$ in the reaction medium (entry 4) increased the rate, the *trans* selectivity and

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

entry	Catalyst	Temp.	Time	Yield[a]	*cis*-3/*trans*-3	ee *cis*-3[b]	ee *trans*-3[b]
1[c]	none	50 °C	14 days	70%	33:1		
2[d]	$TiCl_2(^iPrO)_2$	50 °C	17 h	64%	8:1		
3[e]	$TiCl_2(^iPrO)_2$	rt	15 h	52%	5:1		
4	(hb)$TiCl_2$	rt	3 h	73%	1:4	27%	-
5	(pmb)$TiCl_2$	rt	3 h	83%	1:3	-	-
6	(taddol)$TiCl_2$	rt	24 h	47%	1:2	25%	-
7	(pybol)$TiCl_2$	rt	24 h	36%	1:5	-	6%
8	$TiCl(^iPrO)_2$(OTf)	rt	15 min	29%	1:9		
9	(taddol)TiCl(OTf)	rt	10 min	58%	1:5	-	6%
10	(pybol)TiCl(OTf)	rt	10 min	60%	1:6	19%	24%
11[f]	(pybol)TiCl(OTf)	rt	10 min	67%	1:6	-	-
12	(pmb)$Ti(OTf)_2$	rt	10 min	71%	1:4	-	-
13	(taddol)$Ti(OTf)_2$	rt	10 min	79%	1:6	-	9%
14	(pybol)$Ti(OTf)_2$	rt	10 min	39%	1:6	15%	-
15	$(hb)_2Ti$	50 °C	1 h	21%	5:1	16%	10%
16	$(pmb)_2Ti$	50 °C	1 h	12%	14:1	14%	-
17	$(taddol)_2Ti$	50 °C	1 h	19%	only ***cis*-3**	-	-
18	$(pybol)_2Ti$	50 °C	1 h	26%	11:1	14%	12%
19	(hb)$TiCl_2$ + ^iPrOH	rt	3 h	64%	1:11	-	-
20	(hb)TiCl(OTf) + ^iPrOH	rt	3 h	79%	1:9	-	-
21	(hb)$Ti(OTf)_2$ + ^iPrOH	rt	3 h	68%	1:7	-	-
22	(cydis)$TiCl_2$	rt	24 h	64%	1:5	-	41%
23[f]	(cydis)$TiCl_2$	rt	14 h	74%	1:4	-	-
24	(cydis)TiCl(OTf)	rt	10 min	60%	1:3	-	-
25	(cydis)$Ti(OTf)_2$	rt	10 min	63%	1:4	-	-

[a] Yield of isolated **3** by column chromatography.

[b] Ee determined by HPLC (Daicel Chiracel OD), only values over 5% are indicated.

[c] $[\mathbf{2}]_0 = 0.2$ M in toluene.

[d] $[\mathbf{1}]_0:[\mathbf{2}]_0:[\text{catalyst}]_0 = 1:2:0.2$.

[e] $[\mathbf{1}]_0:[\mathbf{2}]_0:[\text{catalyst}]_0 = 1:4:1$.

[f] $[\mathbf{1}]_0:[\mathbf{2}]_0:[\text{catalyst}]_0 = 1:4:0.5$.

the yield of the cycloaddition, but only the minor diastereoisomer, *cis*-**3**, showed a significant ee. This result indicates that a reactive complex between the nitrone and the Ti(IV) catalyst is actually formed, but differentiation between the diastereotopic faces of the coordinated dipole is insufficient.

Looking for a more effective interaction between the phenyl groups of the nitrone and the aromatic residues of the diolate, the (1*S*,2*S*)-1,2-bis(*p*-methoxybenzyl)ethyleneglycolate (**pmb**) was tested as the bidentate ligand (entry 5), but essentially the same results were obtained. We next decided to modify the distance between the coordination sites of the diolate. Taddolate ligands, with 1,4 relative chelating positions, are among the most sterically demanding auxiliaries. They

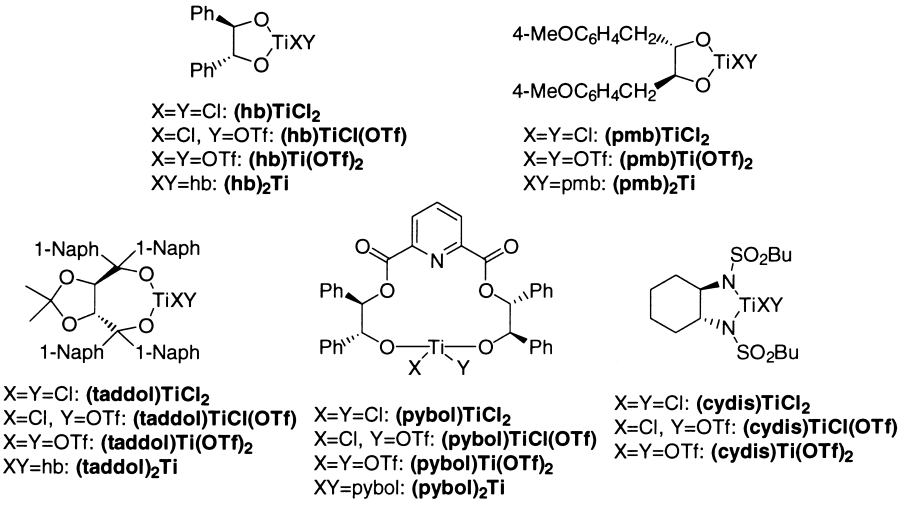


Figure 1.

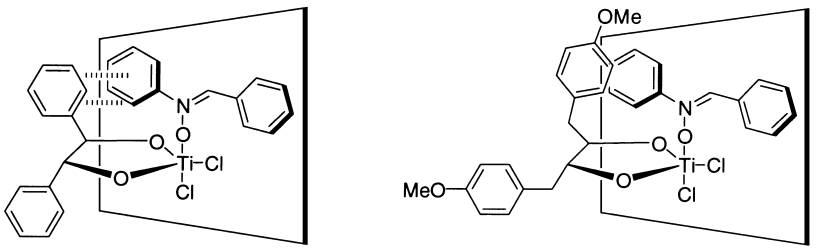


Figure 2.

have been effectively used as Ti(IV) ligands in cycloadditions of nitrones to electron-deficient olefins.[2b] Conversely, in this case the incorporation of taddolate (entry 6) produced a decrease of the reaction rate, yield and diastereoselectivity.

The new diol bis-[(1*R*,2*R*)-2-hydroxy-1,2-diphenyl]ethyl pyridine-2,6-dicarboxylate (**pybol**) was prepared from pyridine-2,6-dicarboxylic acid and (*1R*,2*R*)-hydrobenzoin in 75% yield, by a similar procedure to that described for the synthesis of pybox ligands.[8] This 1,11-diol incorporates additional nucleophilic sites, which may participate in the coordination sphere of the metal, increasing the rigidity of the reactive complex. In practice, the only benefit produced by the use of the complex (**pybol**)$TiCl_2$ (entry 7) was the improvement of the *trans* selectivity of the process.

We anticipated that the substitution of chloride by triflate ligands could increase the catalyst activity, due to the formation of more acidic titanium species. In fact, a cationic complex of bis-(η^5-Cp)Ti(IV) with two nitrone molecules as ligands, prepared from the corresponding bis-triflate, has recently been isolated.[9] As a reference, the effect of triflate was first tried with an achiral complex (entry 8) and then it was used in combination with the chiral taddolate and pybolate ligands (entries 9 and 10). In all these cases, a strong acceleration of the reaction was indeed observed and also a remarkably high *trans* diastereoselectivity, but the enantiomeric induction was again quite low. An attempt to improve the ee by increasing the molar ratio of the catalyst (entry 11) was unsuccessful. The substitution of both chloride ligands by triflate (entries 12–14) did not cause additional substantial changes.

Titanium complexes with two identical bidentate ligands (entries 15–18) showed lower catalytic activity and the reactions were run at 50°C. With this series of complexes, the reaction yields decreased substantially and the diastereoselectivity was completely inverted in favour of the *cis* cycloadduct. Enantioselectivities were low in all the cases.

In another set of experiments, the residual ^{i}PrOH was not removed from the reaction medium after preparing the chiral complexes (entries 19–21). In these runs the cycloadditions proceeded with high yield and the highest observed *trans* selectivities.

In search for more sterically demanding coordination centres in the titanium complex, we decided to prove a cyclohexyldisulfonamide derived ligand (entry 22). The **cydis** complex showed a similar acceleration effect compared to its diolate analogues; the yield and *trans* diastereoselectivity were good and a considerable improvement in the enantioselectivity of the major *trans* product was observed. An increase in the catalyst proportion (entry 23) or the substitution of the chloride ligands by triflate (entries 24–25) enhanced the catalytic effect, as in the diolate series, but did not improve the stereoselectivity.

The remarkable inversion of the *cis*/*trans* selectivity of the cycloaddition produced by the chiral titanium complexes is in contrast with the results found using aluminium complexes.[10] A plausible explanation to account for the intriguing change in the stereoselectivity produced by the Ti(IV) catalysts is shown in Fig. 3, where two competitive *exo* and *endo* transition states, both of them involving the *Z*-nitrone, are represented. According to this model, steric reasons may account for the clear predominance of *cis*-**3** in the absence of a Lewis acid. For the uncatalysed reaction, the *exo* TS is less sterically congested, since the ^{t}BuO group of the olefin is pointing away from the nitrone. The increase of the ratio of *trans*-**3** in the presence of $TiCl_2(^{i}PrO)_2$ can be attributed mainly to electronic factors. The stabilisation of the *endo* TS may be due to a better accommodation of the unshared electron pairs of both oxygen atoms to chelate the metal centre. However, the less sterically crowded *exo* TS is still preferred, although to a less extent. With the chiral (diolate)-$TiCl_2$ and (diolate)TiCl(OTf) complexes, a complete inversion of the diastereoselectivity occurs, favouring the *trans* adduct. In these complexes, the size of the coordination sphere of the metal has increased considerably and its interaction with the ^{t}BuO group in the *exo* TS may be even more destabilising than the interaction of the ^{t}BuO group with the nitrone substituents in the *endo* TS. In agreement with that is the enhancement of the *endo* selectivity in the presence of ^{i}PrOH (compare entries 4 and 19), which probably increases further the bulkiness of the metal surroundings.

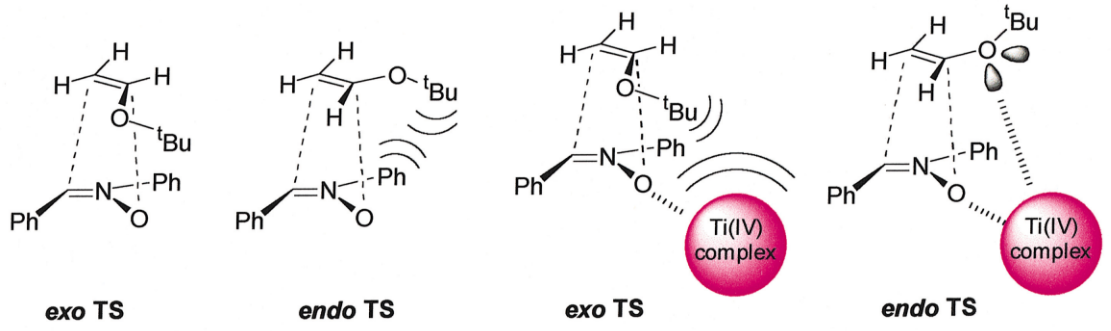


Figure 3.

Although the best enantioselectivity found (41%, entry 22) is still quite low for enantioselective synthetic applications, it is the best so far obtained for the *trans* cycloadduct in cycloadditions of this kind with acyclic nitrones. The complete reversion of diastereoselectivity and the high yields are encouraging findings for further studies.

3. Experimental

Previously described methods were used to prepare nitrone **1**,[11] (1*R*,2*R*)-hydrobenzoin,[12] (1*S*,2*S*)-1,2-bis(*p*-methoxybenzyl)ethyleneglycol,[13] (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetra(naph-1-yl)-1,3-dioxolane-4,5-dimethanol,[14] and *N*-(1*R*,2*R*)-2-{[(4-*n*-butylsulfonyl)amino]cyclohexyl}*n*-butanesulfonamide.[15] 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). $TiCl_2(^iPrO)_2$[16] and $Ti(^iPrO)_2(OTf)_2$[17] solutions were freshly prepared. Anhydrous toluene was used in all the reactions. Reaction mixtures were stirred magnetically. TLC was performed using 0.25 mm Alugram Sil plates, Machery-Nägel. 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) and hexane-2-propanol 98:2 as mobile phase and 350–300 psi pressure and 1 mL/min flow. Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona on Bruker AC-250-WB or AM-400-WB instruments. Mass spectra were performed on a Hewlett–Packard 5985B instrument. HRMS was performed by Servei de Masses, Departament d'Ecotecnologies, CSIC, Barcelona.

3.1. Preparation of bis[(1R,2R)-2-hydroxy-1,2-diphenylethyl]pyridine-2,6-dicarboxylate (*pybol*)

To a stirred solution of (1*R*,2*R*)-hydrobenzoin (570 mg, 2.7 mmol) and triethylamine (1 mL, 7.0 mmol) in chloroform (5 mL) was added dropwise a solution of 2,6-pyridinecarbonyl dichloride (210 mg, 1.2 mmol) in chloroform (2.5 mL) at 0°C. The mixture was stirred at room temperature for 1.5 h. Then it was washed with 10% HCl (15 mL) and with brine until neutral. The organic layer was dried over anhydrous sodium sulfate. Removal of the solvent under vacuum at room temperature furnished 740 mg of a brown solid. This crude material was purified by flash chromatography on alumina (chloroform:methanol 9:1 as eluent) giving 503 mg (75% yield) of 2,6-bis[(1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl]pyridine-2,6-dicarboxylate as a white solid: mp 176–179°C (EtOAc/hexane); IR (KBr): 3564, 3501, 3374 (br), 1736, 1244 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.29 (d, J = 8.0 Hz, 2H), 7.95 (t, J = 8.0 Hz, 1H), 7.25–7.12 (m, 20H), 6.24 (d, J = 8.0 Hz, 2H), 4.85 (d, J = 8.0 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.9, 148.1, 139.5, 138.5, 137.0, 128.5, 128.2, 128.1, 127.8, 127.5, 127.4, 82.7, 76.9; MS (*m*/*z*) 559 (M^+, 2), 214 (18), 197 (16), 168 (100). Anal. calcd for $C_{35}H_{27}NO_6$+$CH_3CO_2CH_2CH_3$: C, 72.32, H, 5.76, N, 2.16. Found: C, 72.54, H, 5.46, N, 2.31. $[\alpha]_D^{20}$ +190 (*c* 1.0, $CHCl_3$).

3.2. Preparation of TiCl(iPrO)2(OTf)

A Schlenk flask containing Ag(OTf) (64 mg, 0.25 mmol) under nitrogen was connected to a vacuum pump (0.1 torr) for 1 h while stirring. Then toluene (2 mL) and a 0.25 M solution of $TiCl_2(^iPrO)_2$ in toluene (1 mL, 0.25 mmol) were consecutively added. The mixture was stirred

preserved of light at room temperature for 12 h. Then it was filtered, the solution was transferred to another Schlenk flask and used as such in consecutive operations.

3.3. Preparation of the chiral complexes (**hb**)$TiCl_2$, (**pmb**)$TiCl_2$, (**taddol**)$TiCl_2$, (**pybol**)$TiCl_2$ and (**cydis**)$TiCl_2$

A Schlenk flask containing the bidentate ligand (0.05 mmol) under nitrogen was connected to a vacuum pump (0.1 torr) for 1 h while stirring. Toluene (1 mL) was added and then, dropwise, a 0.1 M solution of $TiCl_2(^iPrO)_2$ in toluene (0.5 mL, 0.05 mmol). The resulting solution was stirred preserved of light at room temperature for 12 h.

3.4. Preparation of the chiral complexes (**hb**)TiCl(OTf), (**taddol**)TiCl(OTf), (**pybol**)TiCl(OTf) and (**cydis**)TiCl(OTf)

A Schlenk flask containing the bidentate ligand (0.05 mmol) under nitrogen was connected to a vacuum pump (0.1 torr) for 1 h while stirring. Toluene (1 mL) was added and then, dropwise, a 0.12 M solution of $Ti(^iPrO)_2Cl(OTf)$ in toluene (0.5 mL, 0.05 mmol). The resulting solution was stirred preserved of light at room temperature for 12 h.

3.5. Preparation of the chiral complexes (**hb**)$Ti(OTf)_2$, (**pmb**)$Ti(OTf)_2$, (**taddol**)$Ti(OTf)_2$, (**pybol**)$Ti(OTf)_2$ and (**cydis**)$Ti(OTf)_2$

A Schlenk flask containing the bidentate ligand (0.05 mmol) under nitrogen was connected to a vacuum pump (0.1 torr) for 1 h while stirring. Toluene (1 mL) was added and then, dropwise, a 0.08 M solution of $Ti(^iPrO)_2(OTf)_2$ in toluene (0.6 mL, 0.05 mmol). The resulting solution was stirred preserved of light at room temperature for 12 h.

3.6. Preparation of the chiral complexes (**hb**)$_2$Ti, (**pmb**)$_2$Ti, (**taddol**)$_2$Ti and (**pybol**)$_2$Ti

A Schlenk flask containing the bidentate ligand (0.1 mmol) under nitrogen was connected to a vacuum pump (0.1 torr) for 1 h while stirring. Toluene (200 μL) was added and then, dropwise, a 0.24 M solution of $Ti(^iPrO)_4$ in toluene (200 μL, 0.05 mmol). The resulting solution was stirred preserved of light at room temperature for 12 h.

3.7. Cycloaddition of nitrone **1** to vinyl ether **2** promoted by $Ti(^iPrO)_2Cl(OTf)$

A 0.05 M solution of $Ti(^iPrO)_2Cl(OTf)$ in toluene (800 μL, 0.04 mmol) was placed in a Schlenk flask under nitrogen. A solution of nitrone **1** (50 mg, 0.25 mmol) in toluene (1.1 mL) was added dropwise and the mixture was stirred at room temperature for 30 min. The vinyl ether **2** (100 μL, 0.8 mmol) was added and stirring was prolonged for 15 min. 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 purification of the residue by flash chromatography on silica gel (hexane:ether, 3:1) yielded a 1:9 mixture of *cis*- and *trans*-**3**[5] (20 mg, 29%).

3.8. Cycloaddition of nitrone **1** to vinyl ether **2** promoted by chiral Ti(IV) complexes. General procedure

In order to remove the ^{i}PrOH from the solutions containing the chiral complexes (prepared as described above), they were evaporated to dryness in the following manner: first the flow of nitrogen was increased until a thick mash was obtained (2–3 h) and then the system was connected to a vacuum pump for 1 h. The resulting coloured powder was solved in toluene (1 mL), a solution of nitrone **1** (50 mg, 0.25 mmol) in toluene (1 mL) was introduced into the same flask, and the mixture was stirred at room temperature for 1 h. Then the vinyl ether **2** (130 μL, 1.0 mmol) was added and the reaction evolution was followed by TLC and ^{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 ees were determined by HPLC.

3.9. Cycloaddition of nitrone **1** to vinyl ether **2** promoted by (***hb***)TiXY in the presence of ^{i}PrOH

To a solution containing the chiral complex prepared as above, a solution of nitrone **1** (50 mg, 0.25 mmol) in toluene (1 mL) was added dropwise and the mixture was stirred at room temperature for 1 h. Then the vinyl ether **2** (130 μL, 1.0 mmol) was added and the reaction evolution was followed by TLC and ^{1}H NMR analyses of aliquot samples. The reaction work-up was identical to that described above for the general procedure.

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