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Ti(IV) Promoted 1,3-Dipolar Cycloaddition of Nitrones to Vinyl Ethers

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Abstract.- The 1,3-dipolar cycloaddition of nitrones to vinyl ethers is accelerated by Ti(IV) species. The efficiency of the catalyst parallels its complexation capacity. The use of $Ti(^iPrO)_2Cl_2$ favours the formation of trans cycloadducts, presumably through an endo bidentate complex , in which the metal atom is simultaneously coordinated to the vinyl ether and to the cyclic nitrone or the Z isomer of the acyclic nitrones.

Introduction

The utility of nitrones as precursors of complex organic molecules has been widely demonstrated.[1] When acting as 1,3-dipoles, nitrones are able to react with olefins to yield isoxazolidines which can behave as versatile synthetic intermediates. In these cycloaddition reactions two regioisomeric orientations can occur and the regioselectivity of the process results from a balance between electronic and steric effects. Moreover, up to three new chiral centers can be generated depending on the substitution pattern of the starting dipole and dipolarophile. For a given regioisomer, and provided that both the nitrone and the olefin were achiral, the approach of the reactants in the transition state may happen in an *endo* or *exo* mode, each one leading to a different diastereoisomer of the product. Therefore, the control of the stereoselectivity of the cycloaddition becomes extremely important and the use of Lewis acids emerges as an attractive possibility to achieve it.

During the last few years, several examples of nitrone cycloadditions promoted by a Lewis acid catalyst have been reported,[2-9] including some in which the introduction of chiral ligands has even allowed enantiodifferentiation.[5-9] In most of the reported examples the dipolarophile is an electron deficient olefin,[2a,3,5,7] and the acceleration of the reaction is explained by the formation of a highly electrophilic reactive complex between the catalyst and the olefin.[2] Some isolated metal complexes of this kind of dipolarophiles have shown enhanced reactivity and high stereoselectivity towards nitrones.[10]

In the cycloaddition of nitrones to allylic alcohols (non activated olefins)[2b-d,4,8] in the presence of various Lewis acids the regioselectivity of the reaction has shown to be dependent on the amount of metallic additive used.[2d] With these last dipolarophiles and α-methoxycarbonyl nitrones, a tandem transesterification-intramolecular cycloaddition process accounts for the achieved high level of stereocontrol.[4]

Since nitrones are able to coordinate Lewis acid species, one would expect acceleration in cycloadditions between the metallic nitrone complexes and electron rich olefins. Although it was reported that some calculations and preliminary experiments were in disagreement with these expectations,[5a] it has been recently published that chiral oxazaborolidines are efficient promoters of the cycloaddition of nitrones to

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ketene acetals and enol ethers, although the enantioselectivities were only moderate.[6,9] There are also examples in which the formation of stable metal complexes of a nitrone accelerates the cycloaddition and improves its regio- and stereoselectivity.[11]

In connection with this field, we have investigated the influence of different Lewis acids on the reaction between nitrones and enol ethers. We have found that several Ti(IV) species have a catalytic effect on the cycloaddition and also that the stereoselectivity of the process can be substantially modified. The results of our studies are described herein.

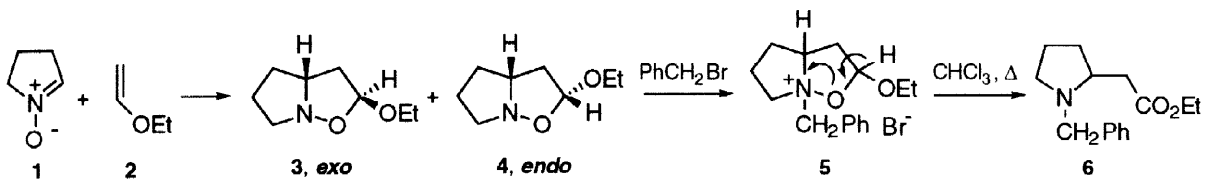
Results and Discussion

Cycloaddition of Cyclic Nitrone 1 to Ethyl Vinyl Ether

Contrary to their acyclic partners, cyclic nitrones are configurationally locked, therefore the *endo-exo* selectivity of their 1,3-dipolar cycloadditions to olefins can be directly deduced from the stereochemistry of the adducts formed. For this reason, we decided to initiate our study with the cycloaddition of 3,4-dihydro-2*H*-pyrrol 1-oxide, **1**, to ethyl vinyl ether, **2**, (Scheme 1). Dicken and DeShong reported that this reaction did not occur using the vinyl ether as solvent at 80 °C and performing it under high pressure conditions they isolated exclusively the *exo* adduct **3** in 83% yield.[12] Conversely, Ali and Wazeer subsequently described the isolation of a mixture of **3** and the *endo* isomer **4** in a 92:8 ratio and 70% overall yield from the reaction of **1** with a threefold excess of **2** in CH_2Cl_2 at 60 °C.[13] Similarly, in our hands the uncatalyzed reaction between **1** and **2** in $CHCl_3$ at 50 °C went to completion after 7 days with high regioselectivity to give a mixture of **3** and **4** in a 10:1 ratio. Column chromatography on alumina allowed the isolation of the major product **3** in 73% yield, the stereochemistry of which was unequivocally established through nOe experiments.

Then the same reaction was attempted in the presence of a Lewis acid catalyst. The cycloadditions were first run in deuterated solvents, in order to follow the conversion of the reactants by ^1H NMR spectroscopy. To estimate the reaction completion, we observed the relative intensity of the signal corresponding to the iminic proton of nitrone **1** ($\delta_H \approx 7$) with respect to those of the acetal proton of adducts **3** and **4** ($\delta_H \approx 5$). Both ZnI_2 and $ZnCl_2$ led to messy reaction mixtures in which no cycloadduct could be detected. Luckily, the reactions with Ti(IV) species gave better results and therefore they were also performed on a larger scale. These experiments (Table 1) were run with 0.1 M solutions of nitrone **1**, using 2 eq of olefin **2** and 0.2 eq of catalyst at 50 °C.

Among the catalysts tried, $Ti(^iPrO)_2Cl_2$ (entries 7 and 8) and $TiCl_4$ (entry 9) were the most efficient promoters of the reaction. Interestingly, while the use of $Ti(^iPrO)_4$ (entries 3 and 4) did not modify the stereoselectivity observed in the uncatalyzed reaction, with $TiCl_2(^iPrO)_2$ and $TiCl_4$ the relative amount of *endo* adduct increased notably, and with $TiCp_2Cl_2$ (entries 5 and 6) the selectivity was highly dependent on the solvent. The cycloadditions performed in benzene afforded cleaner reaction mixtures than those run in



1 2 3, *exo* 4, *endo* 5 6

Scheme 1

Table 1.

Reaction between nitrone **1** and olefin **2** at 50 °C. $[1]_0 = 0.1$ M, $[2]_0 = 0.2$ M, [Ti(IV)] = 0.02 M.

entry	Lewis acid	Solvent	Time	% Conversion	3(*exo*)/4(*endo*)[a]	Isolated yield of 6
1	none	$CHCl_3$	7 days	100	10:1	
2	none	benzene	7 days	100	10:1	57%
3	$Ti(^iPrO)_4$	$CHCl_3$	5 days	100	10:1	
4	$Ti(^iPrO)_4$	benzene	4 days	100	10:1	46%
5	$TiCp_2Cl_2$	$CHCl_3$	84 h	90	2:1	
6	$TiCp_2Cl_2$	benzene	35 h	100	10:1	25%
7	$Ti(^iPrO)_2Cl_2$	$CHCl_3$	21 h	75	1:1	
8	$Ti(^iPrO)_2Cl_2$	benzene	21 h	100	2:1	15%
9	$TiCl_4$	benzene	7.5 h	100	2:1	

[a]Ratio determined by ^1H NMR spectroscopy of the reaction mixtures.

chloroform. The kinetic control was conspicuous, since pure samples of isolated adducts **3** and **4** do not interconvert under the reaction conditions in the presence of $Ti(^iPrO)_2Cl_2$ and $Ti(^iPrO)_4$, respectively.

Reference experiments performed in $CDCl_3$ showed that nitrone **1** complexes efficiently to $TiCl_2(^iPrO)_2$ and $TiCl_4$, since 0.5 and 1.1 ppm downfield shifting of the iminic signal was respectively observed in the presence of 0.2 eq of the catalyst, but no evidence of complexation was found with $Ti(^iPrO)_4$ or $TiCp_2Cl_2$. These observations suggest that a more effective complexation of the starting nitrone favours the *endo* approach in the transition state, although other factors may be also relevant. Independent NMR experiments with olefin **2** showed a slight downfield shifting of its absorptions only in the presence of $TiCl_4$.

It is also significant that the NMR signal of the acetal proton of the *endo* adduct **4** suffers a considerably stronger downfield shifting than the corresponding signal of the *exo* adduct **3**, in the presence of the three Ti(IV) species that raise the *endo* percentage of the cycloaddition product, while with $Ti(^iPrO)_4$ no effect was detected for neither of the adducts. The preferential coordination of adduct **4** may be due to the better accomodation of the unshared electron pairs of both oxygen atoms to chelate the metal centre, and similar reasons may also stabilise the *endo* transition state leading to it (Figure 1). An analogous bidentate chelate of adduct **3** would be more sterically crowded and probably a monodentate complex is a better model for the *exo* transition state of the Ti (IV) catalyzed reactions.

Due to severe difficulties associated with the isolation of the adducts of the catalyzed reactions, we were unable to obtain reliable data to evaluate their preparative value. In an attempt to do it, all the

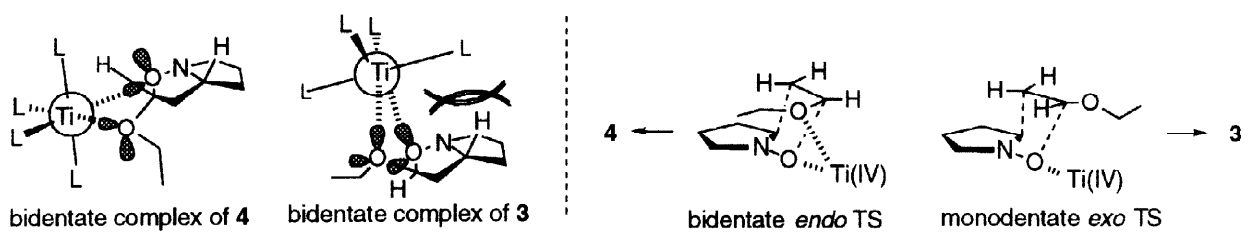


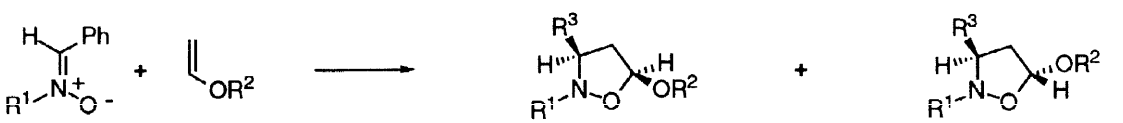
Figure 1

cycloadditions run in benzene were repeated and the reaction mixtures were treated *in situ* with an excess of benzyl bromide (Scheme 1). After exchanging the solvent with $CHCl_3$ and heating at 50 °C overnight, both isomers **3** and **4** led to the same β-aminoester **6**, which was fully characterized according to its spectrocopic data and correct elemental analysis. Similar transformations have been recently reported to take place with excellent yields.[9,14] Compound **6** was isolated from most reaction mixtures, but the yields were quite low, especially when the relative quantity of *endo* adduct **4** in the cycloaddition was higher (see Table 1).

Cycloaddition of Acyclic Nitrones 7 and 8 to Vinyl Ethers 2 and 9

We next decided to expand the study to acylic nitrones and the readily available *C,N*-diphenylnitrone, **7**, and *C*-phenyl-*N*-benzylnitrone, **8**, were chosen with this purpose. Our experiments centered on the use of $Ti(^iPrO)_2Cl_2$, one of the catalysts that has significantly modified the stereoselectivity of the reaction in the previous study with nitrone **1**. Table 2 shows the results of the cycloadditions of nitrones **7** and **8** to **2** and *tert*-butyl vinyl ether, **9** (Scheme 2). Except for some reference uncatalyzed cycloadditions (entries 1, 16 and 18), all the reactions were run in toluene, with a two- or fourfold excess of olefin, until complete conversion of the nitrone, according to tlc and ^1H NMR analyses.

The influence of the $Ti(^iPrO)_2Cl_2$ on the stereoselectivity of the studied cycloadditions is remarkable. From the uncatalyzed reaction between nitrone **7** and a large excess of ethyl vinyl ether[15] at 50 °C for 50 h we isolated the *cis* cycloadduct **10**, as major product, and its *trans* isomer, **11**, in 72% overall yield (entry 1). When the reaction was repeated with 2 eq of olefin **2** in the presence of 0.2 eq of catalyst at the same temperature, we obtained the same ratio of stereoisomers with lower yield (entry 2), but with 1 eq of $Ti(^iPrO)_2Cl_2$ and at room temperature (entry 3) a comparable yield of products was obtained with a similar conversion rate and the proportion of *trans* adduct **11** increased notably. It has been recently described that the addition of oxazaborolidines to this same reaction produces an analogous effect on the stereoselectivity.[6b,9] A decrease in the temperature (entries 4 and 5) still raises the amount of **11**, but also produces slow conversions and lower yields. The use of 2 eq of Ti(IV) additive was very detrimental to the yield (entry 6). If we assume that nitrone **7** reacts through its more stable *Z* configuration,[16] the effect in the stereoselectivity produced by the Lewis acid in favor of the *trans* cycloadduct must be interpreted as a decrease in the relative energy of the *endo* in relation to the *exo* transition state, in agreement with the above results obtained with the cyclic nitrone **1**.



7, R^1 = Ph **8**, R^1 = Bn

2, R^2 = Et **9**, R^2 = ^{t}Bu

10, R^1 = Ph, R^2 = Et, R^3 = Ph
12, R^1 = Ph, R^2 = Et, R^3 = Me
14, R^1 = Ph, R^2 = ^{t}Bu, R^3 = Ph
16, R^1 = Ph, R^2 = ^{t}Bu, R^3 = Me
18, R^1 = Bn, R^2 = Et, R^3 = Ph
20, R^1 = Bn, R^2 = Et, R^3 = Me
22, R^1 = Bn, R^2 = ^{t}Bu, R^3 = Ph

11, R^1 = Ph, R^2 = Et, R^3 = Ph
13, R^1 = Ph, R^2 = Et, R^3 = Me
15, R^1 = Ph, R^2 = ^{t}Bu, R^3 = Ph
17, R^1 = Ph, R^2 = ^{t}Bu, R^3 = Me
19, R^1 = Bn, R^2 = Et, R^3 = Ph
21, R^1 = Bn, R^2 = Et, R^3 = Me
23, R^1 = Bn, R^2 = ^{t}Bu, R^3 = Ph

Scheme 2

Table 2

Cycloaddition of nitrones **7** and **8** to olefins **2** and **9**.

entry	Nitrone	Olefin (eq)	Eq. catalyst	Temp.	Time	Yield[a]	*cis/trans*[b]
1	**7**	**2** (as solvent)	none	50 °C	50 h	72%	**10**:**11** (6:1)
2	**7**	**2** (2)	0.2	50 °C	30 h	47%	**10**:**11** (6:1)
3	**7**	**2** (4)	1	rt	48 h	64%	**10**:**11** (2.7:1)
4	**7**	**2** (4)	1	0 °C	5 days	42%	**10**:**11** (1.3:1)
5	**7**	**2** (4)	1	-20 °C	15 days	23%	**10**:**11** (1.1:1)
6	**7**	**2** (2)	2	0 °C	2 days	8%	**10**:**11** (1:1.8)
7	**7**	**9** (2)	none	50 °C	14 days	70%	**14**:**15** (33:1)
8	**7**	**9** (2)	0.2	50 °C	17 h	64%	**14**:**15** (8:1)
9	**7**	**9** (4)	1	50 °C	1.5 h	56%	**14**:**15** (6:1)
10	**7**	**9** (4)	1	rt	15 h	52%	**14**:**15** (5:1)
11	**7**	**9** (4)	1	0 °C	4 days	56%	**14**:**15** (1.4:1)
12	**7**	**9** (4)	1	-20 °C	15 days	59%	**14**:**15** (1:1.3)
13	**7**	**9** (2)	1	-20 °C	20 days	52%	**14**:**15** (1:2.7)
14	**7**	**9** (2)	none	-20 °C	20 days	—	—
15	**7**	**9** (2)	2	0 °C	11 days	28%	**14**:**15** (1:4.8)
16	**8**	**2** (as solvent)	none	50 °C	53 h	78%	**18**:**19** (2:1)
17	**8**	**2** (4)	0.5	50 °C	3 days	48%[c]	**18**:**19** (1:2)
18	**8**	**9** (as solvent)	none	50 °C	5 days	74%	**22**:**23** (4:1)
19	**8**	**9** (2)	0.5	50 °C	14 days	—	—

[a]Yields are referred to isolated products. [b]Ratio determined by ^{1}H NMR spectroscopy of the reaction crudes. [c]An additional 25% of cycloadducts derived from *C*-methyl-*N*-benzylnitrone, **20** and **21**, were also isolated.

As byproducts of the reaction between **7** and **2**, variable amounts of the isoxazolidines **12** and **13** were also detected by the presence of additional acetal protons in the ^{1}H NMR spectra of the reaction crudes. Their formation can be explained by the cycloaddition of olefin **2** to *C*-methyl-*N*-phenylnitrone, which must be generated in the reaction medium through a transoximination process, due to the presence of acetaldehyde coming from the vinyl ether. This transoximination process could not be reproduced in the absence of $Ti(^iPrO)_2Cl_2$. *C*-Methyl-*N*-phenylnitrone is so reactive that the reaction between phenylhydroxylamine and acetaldehyde gives its dimeric derivatives,[17] but compound **12** could be independently prepared in 36% yield by heating a 1:1 mixture of phenylhydroxylamine and acetaldehyde in ethyl vinyl ether at 50 °C for 24 h. The minor *trans* isomer **13** could not be isolated.

The uncatalyzed reaction of nitrone **7** with 2 eq of olefin **9** (entry 7) went to completion after 14 days at 50 °C, affording **14** and **15** with a high *exo* selectivity and 70% total yield. The stereochemistry of the major isomer was elucidated as *cis* by nOe experiments, that showed proximity between the acetal (H_5, δ_H 5.63) and the benzylic (H_3, δ_H 4.39) hydrogen atoms. This cycloaddition was strongly accelerated by the presence of $Ti(^iPrO)_2Cl_2$, that also influenced the stereoselectivity (entries 8 and 9). Performing the reaction at lower temperatures (entries 10-15) the percentage of *trans* adduct was spectacularly increased. Thus, the *cis/trans*

ratio can be shifted from 33:1 (entry 7) to 1:2.7 (entry 13) and the yields are still quite good. The results of two parallel runs at -20 °C with and without $Ti(^iPrO)_2Cl_2$ (entries 13 and 14) demonstrate that the *cis* cycloadduct also arises from a transition state with a complexed nitrone and not as a consequence of a competitive uncatalyzed thermal process. With 2 eq of Lewis acid (entry 15) the stereoselectivity is even more strongly influenced but the yield decreases notably.

In the experiments of entries 8 and 11 we also detected two cycloadducts, **16** and **17**, derived from *C*-methyl-*N*-phenylnitrone. As above, these new compounds were independently prepared from hydroxylamine, acetaldehyde and *tert*-butyl vinyl ether in 73% yield with a *cis/trans* ratio of 48:1. Only the major isomer **16** could be isolated and fully characterized.

Heating nitrone **8** in ethyl vinyl ether at 50 °C (entry 16) we obtained adducts *cis* **18** and *trans* **19**[6b] in a 2:1 ratio and 78% yield. The addition of $Ti(^iPrO)_2Cl_2$ (entry 17) again inverted the stereoselectivity and also led to the formation of the methyl derivatives **20** and **21** (1:1.5), isolated in 25% yield. The reaction between **8** and a large excess of olefin **9** without any additive (entry 18) yielded 74% of **22** and **23** in a 4:1 ratio. These compounds were fully characterized and the stereochemistry of the major *cis* adduct **22** was determined by nOe experiments. The use of catalysis conditions (entry 19) gave only unidentified products, probably due to the weak stability of nitrone **8** in the presence of the Lewis acid, already evidenced in the former experiment of entry 17, and also to the lower dipolarophilic activity of *tert*-butyl ether **9** compared to ethyl ether **2**.

In summary, we have demonstrated that several Ti(IV) species are able to promote the cycloaddition reaction of nitrones with electron rich dipolarophiles, such as vinyl ethers. The efficiency of the catalyst parallels its complexation capacity. The titanium ligands have an influence on the *endo/exo* selectivity of the process. With the cyclic nitrone **1** the addition of $Ti(^iPrO)_2Cl_2$ favors the formation of the *endo* cycloadduct, presumably through a bidentate complex of the metal with the nitrone and the vinyl ether. For the acyclic nitrones **7** and **8**, a similar transition state with the participation of the *Z* isomer of the nitrone would explain the increase in the percentage of *trans* cycloadducts when the Ti(IV) promoter is present in the reaction medium. We are working to exploit these promising findings in an enantioselective version of this process.

Experimental

Previously described methods were used to prepare nitrones **1**,[18] **7**,[19] and **8**.[20] Vinyl ethers **2** and **9** are commercially available. All reagents and solvents were dried just before use. The solutions of nitrone **1** were stirred with 4 Å molecular sieves and filtered just before use. Nitrones **7** and **8** were rendered anhydrous by melting them under vacuum and refilling with nitrogen (three consecutive times). The vinyl ethers were distilled over sodium. $Ti(^iPrO)_2Cl_2$ solutions were freshly prepared.[5a] Reaction mixtures were stirred magnetically. Solutions were concentrated using a rotary evaporator at 15-20 Torr. The organic extracts were dried over anhydrous sodium sulfate. Column chromatography was performed using Merck silica gel (230-400 mesh). Tlc was performed using 0.25 mm Alugram Sil plates, Macherey-Nägel. Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^1H 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. Elemental analyses were performed by *Servei d'Anàlisi Química de la UAB* or by *Institut de Química Bio-Orgànica de Barcelona*. HRMS were performed by *Servei de Masses, Departament d'Ecotecnologies, CSIC.*

Cycloaddition of nitrone* 1 *to vinyl ether* 2 *in* $CHCl_3$ *in the presence of Ti(IV). General procedure.

A solution of nitrone **1** in $CHCl_3$ was placed in a Schlenk flask under nitrogen. While magnetically stirring, the Ti(IV) catalyst was added at rt and the mixture was heated at 50 °C for 30 min. After cooling to rt, vinyl ether **2** was added, the mixture was heated at 50 °C and the reaction evolution was followed by ^1H NMR analysis of aliquot samples. Saturated solution of $NaHCO_3$ was added to the cooled reaction mixture, the organic layer was separated and the aqueous phase extracted with $CHCl_3$. The organic extracts were dried, the solvent removed and the residue was purified by flash chromatography (hexane/Et_2O/$CHCl_3$, 6/1/1) to give the known[13] isoxazolidines **3** and **4** with identical spectroscopic data to those previously reported.

***Cycloaddition of nitrone* 1 *to ethyl vinyl ether* 2 *in benzene. General procedure. Preparation of* 6**

A solution of nitrone **1** in benzene was placed in a Schlenk flask under nitrogen. While magnetically stirring, the Ti(IV) catalyst was added at rt (except for the reference reaction) and the mixture was heated at 50 °C for 30 min. After cooling to rt, vinyl ether **2** was added and the mixture was again heated at 50 °C for the appropriate time. To the cooled reaction mixture, 1 eq of benzyl bromide was added and the mixture stirred at rt for 2 h. Removal of the solvent gave the *N*-benzyl bromide **5**, as a solid residue, that was redissolved in $CHCl_3$ and heated at 50 °C for 10 h. The cooled solution was washed twice with saturated $NaHCO_3$ solution, the organic extracts were dried, the solvent removed and the oily residue was purified by flash chromatography (hexane/EtOAc, 9/1) to give pure ethyl (*N*-benzyl-2-pyrrolidyl)acetate, **6**, as a colourless oil. **5**: mp 123-4 °C; IR (KBr): 2966, 2931, 1454, 1159 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.52 (d, J=7.7 Hz, 2H: $2H_{Ar}$), 7.22 (m, 3H: $3H_{Ar}$), 5.91 (d, J=13.1 Hz, 1H: C*H*$_2$Ph), 5.62 (m, 1H: H_2), 5.25 (m, 1H: H_{3a}), 4.76 (d, J=13.1 Hz, 1H: C*H*$_2$Ph), 4.23 (td, J_{gem}=$J_{6,5}$=12.1 Hz, $J_{6,5}$=6.9 Hz, 1H: H_6), 3.82 (dq, J_{gem}=9.5 Hz, J=6.9 Hz, 1H: OCH_2), 3.56 (dq, J_{gem}=9.5 Hz, J=6.9 Hz, 1H: OCH_2), 3.10 (m, 2H: H_3 and H_6), 2.57 (m, 2H: H_3 and H_4/H_5), 1.89 (m, 3H: 1/2H_4 and 2/1H_5), 1.13 (t, J=7.3 Hz, 3H: CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 132.1 (C_{Ar}), 130.4 (C_{Ar}), 128.9 (C_{Ar}), 128.3 (C_{Ar}), 108.7 (C_2), 77.7 (C_{3a}), 69.4 (*C*H_2Ph), 66.7 (OCH_2), 65.4 (C_6), 41.0 (C_3), 31.3 (C_4), 22.0 (C_5), 14.7 (CH_3). **6**: bp 100 °C (oven)/0.08 Torr; IR (film): 1265, 1026 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.26 (m, 5H: $5H_{Ar}$), 4.07 (q, J=7.3 Hz, 2H: OCH_2), 3.94 (d, J=13.1 Hz, 1H: C*H*$_2$Ph), 3.26 (d, J=13.1 Hz, 1H: C*H*$_2$Ph), 2.87 (m, 2H: H_2 and H_5), 2.63 (dd, J_{gem}=15.0 Hz, $J_{1',2}$=4.4 Hz, 1H: $H_{1'}$), 2.32 (dd, J_{gem}=15.0 Hz, $J_{1',2}$=8.4 Hz, 1H: $H_{1'}$), 2.16 (q, J_{gem}≈$J_{5,4}$≈8.1 Hz, 1H: H_5), 1.99 (m, 1H: H_3), 1.63 (m, 3H: H_3 and 2H_4), 1.18 (t, J=7.3 Hz, 3H: CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 172.1 ($C_{2'}$), 138.3 (C_{Ar}), 128.8 (C_{Ar}), 128.1 (C_{Ar}), 126.9 (C_{Ar}), 60.8 (C_2), 60.2 (OCH_2), 58.5 (*C*H_2Ph), 53.8 (C_5), 39.5 ($C_{1'}$), 30.8 (C_3), 22.0 (C_4), 14.1 (CH_3); MS (*m/z*) 247 (M^+, 5), 160 (100), 91 (99). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.83; H, 8.55; N, 5.71.

Ti(*^{i}*PrO)*$_2$*Cl*$_2$ *catalyzed cycloaddition of nitrones* 7 *and* 8 *to vinyl ethers* 2 *and* 9. *General procedure.

To a solution of nitrone (1.0 mmol) in toluene (5 ml), a 0.2 M solution of $Ti(^iPrO)_2Cl_2$ (5 ml, 1.0 mmol) was added and the mixture was stirred for 30 min at the reaction temperature. Then the necessary amount of olefin was added and the reaction evolution was followed by tlc (hexane/Et_2O, 3/1) and ^1H NMR analysis of aliquot samples. When the nitrone had fully converted, 5 ml of toluene and 5 ml of 10% Na_2CO_3 solution were added. The organic phase was separated, washed with brine, dried and the solvent removed. The crude material was purified by flash chromatography (hexane/Et_2O, 3/1), giving a mixture of isoxazolidines. A second flash chromatography (hexane/Et_2O, 29/1) allowed the separation of pure products.

For experiments in entries 6, 13 and 15 of Table 2, a 1.0 M solution of $Ti(^iPrO)_2Cl_2$ was used.

***cis*-2,3-Diphenyl-5-*tert*-butoxyisoxazolidine, 14**: colourless needles; mp 74-75 °C (MeOH); IR (film): 2973, 1602, 1490 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.55 (d, J=7.0 Hz, 2H: $2H_{Ar}$), 7.37 (t, J=7.0 Hz, 2H: $2H_{Ar}$), 7.28 (t, J=7.0 Hz, 1H: $1H_{Ar}$), 7.15 (m, 2H: $2H_{Ar}$), 6.91 (m, 3H: $3H_{Ar}$), 5.63 (dd, $^{cis}J_{5,4}$=5.9 Hz, $^{trans}J_{5,4}$=3.7 Hz, 1H: H_5), 4.39 (dd, $^{cis}J_{3,4}$= 9.5 Hz, $^{trans}J_{3,4}$=6.6 Hz, 1H: H_3), 2.96 (ddd, J_{gem}=13.2 Hz, $^{cis}J_{4,3}$=9.5 Hz, $^{cis}J_{4,5}$=5.9 Hz, 1H: H_4), 2.32 (ddd, J_{gem}=13.2 Hz, $^{trans}J_{4,3}$=6.6 Hz, $^{trans}J_{4,5}$=3.7 Hz, 1H: H_4), 1.35 (s, 9H: ^{t}Bu); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 150.9 (C_{Ar}), 141.9 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 127.4 (C_{Ar}), 127.2 (C_{Ar}), 121.7 (C_{Ar}), 115.6 (C_{Ar}), 96.2 (C_5), 75.0 (CMe_3), 68.9 (C_3), 47.2 (C_4), 28.9 (CH_3); MS (*m/z*) 297 (M^+, 6), 241 (37), 133 (72), 105 (100). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.78; H, 7.81; N, 4.69.

***trans*-2,3-Diphenyl-5-*tert*-butoxyisoxazolidine, 15**: colourless needles; mp 115-117 °C (MeOH); IR (film): 2985, 1588, 1490 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.42 (d, J=6.8 Hz, 2H: $2H_{Ar}$), 7.28 (t, J≈7.3 Hz, 2H: $2H_{Ar}$), 7.19 (t, J=7.7 Hz, 1H: $1H_{Ar}$), 6.89 (t, J=7.7 Hz, 2H: $2H_{Ar}$), 6.85 (d, J=7.7 Hz, 2H: $2H_{Ar}$), 6.79 (t, J=7.7 Hz, 1H: $1H_{Ar}$), 5.55 (br d, $J_{5,4}$=5.1 Hz, 1H: H_5), 4.72 (dd, $^{trans}J_{3,4}$=9.5 Hz, $^{cis}J_{3,4}$=7.3 Hz, 1H: H_3), 2.55 (ddd, J_{gem}=12.4 Hz, $^{cis}J_{4,3}$=7.3 Hz, $^{trans}J_{4,5}$=1.5 Hz, 1H: H_4), 2.40 (ddd, J_{gem}=12.4 Hz, $^{trans}J_{4,3}$=9.5 Hz, $^{cis}J_{4,5}$=5.1 Hz, 1H: H_4), 1.17 (s, 9H: ^{t}Bu); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 152.4 (C_{Ar}), 141.6 (C_{Ar}), 128.8 (C_{Ar}), 128.2 (C_{Ar}), 127.3 (C_{Ar}), 126.5 (C_{Ar}), 121.1 (C_{Ar}), 115.4 (C_{Ar}), 97.0 (C_5), 74.9 (CMe_3), 67.4 (C_3), 47.5 (C_4), 28.8 (CH_3); MS (*m/z*) 297 (M^+, 12), 241 (45), 133 (76), 105 (100). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.68; H, 7.86; N, 4.68.

***cis*-2-Benzyl-5-ethoxy-3-methylisoxazolidine, 20**: colourless oil; IR (film): 2973, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.41 (d, J=6.6 Hz, 2H: $2H_{Ar}$), 7.31 (m, 3H: $3H_{Ar}$), 5.07 (dd, $^{cis}J_{5,4}$=6.6 Hz, $^{trans}J_{5,4}$=2.9 Hz, 1H: H_5), 4.12 (d, J=13.9 Hz, 1H: CH_2Ph), 3.77 (d, J=13.9 Hz, 1H: CH_2Ph), 3.71 (dq, J_{gem}=9.5 Hz, J=7.1 Hz, 1H: OCH_2), 3.41 (dq, J_{gem}=9.5 Hz, J=7.1 Hz, 1H: OCH_2), 2.80 (m, 1H: H_3), 2.64 (dt, J_{gem}=13.2 Hz, $^{cis}J_{4,3}$≈$^{cis}J_{4,5}$≈6.3 Hz, 1H: H_4), 1.94 (dt, J_{gem}=13.2 Hz, $^{trans}J_{4,3}$=8.7 Hz, $^{trans}J_{4,5}$=2.9 Hz, 1H: H_4), 1.22 (d, J=5.8 Hz, 3H: CH_3CH), 1.17 (t, J=7.1 Hz, 3H: CH_3CH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 137.5 (C_{Ar}), 128.5 (C_{Ar}), 128.0 (C_{Ar}), 127.5 (C_{Ar}), 100.5 (C_5), 63.5 (CH_2O), 61.0 (C_3), 59.9 (CH_2Ph), 4.6 (C_4), 16.7 (CH_3CH), 15.1 (CH_3CH_2); MS (*m/z*) 221 (M^+, 21), 134 (17), 99 (86), 91 (100). HRMS (EI) (M^+) calcd for $C_{13}H_{19}NO_2$ 221.1416, found 221.1418.

***trans*-2-Benzyl-5-ethoxy-3-methylisoxazolidine, 21**: colourless oil; IR (film): 2975, 2938, 1103, 1074 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.42-7.26 (m, 5H: $5H_{Ar}$), 5.12 (br d, $J_{5,4}$=5.1 Hz, 1H: H_5), 4.14 (d, J=13.2 Hz, 1H: CH_2Ph), 4.05 (d, J=13.2 Hz, 1H: CH_2Ph), 3.81 (dq, J_{gem}=9.5 Hz, J=7.1 Hz, 1H: OCH_2), 3.41 (m, 2H: H_3, OCH_2), 2.41 (ddd, J_{gem}=12.4 Hz, $^{cis}J_{4,3}$=6.6 Hz, $^{trans}J_{4,5}$=1.5 Hz, 1H: H_4), 2.10 (ddd, J_{gem}=12.4 Hz, $^{trans}J_{4,3}$= 8.5 Hz, $^{cis}J_{4,5}$=5.1 Hz, 1H: H_4), 1.22 (t, J=7.3 Hz, 3H: CH_3CH_2), 1.13 (d, J=5.8 Hz, 3H: CH_3CH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.1 (C_{Ar}), 129.0 (C_{Ar}), 128.3 (C_{Ar}), 127.2 (C_{Ar}), 102.8 (C_5), 64.1 (CH_2Ph), 62.9, (CH_2O), 59.4 (C_3), 44.1 (C_4), 19.2 (CH_3CH), 15.2 (CH_3CH_2); MS (*m/z*) 221 (M^+, 8), 134 (8), 99 (85), 91 (100). HRMS (EI) (M^+) calcd for $C_{13}H_{19}NO_2$ 221.1416, found 221.1414.

***cis*-2-Benzyl-3-phenyl-5-*tert*-butoxyisoxazolidine, 22**: colourless oil; bp 150 °C (oven)/0.2 Torr; IR (film): 2973, 1370 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.50-7.20 (m, 10H: $10H_{Ar}$), 5.46 (dd, $^{cis}J_{5,4}$=6.3 Hz, $^{trans}J_{5,4}$=3.8 Hz, 1H: H_5), 3.98 (d, J=14.6 Hz, 1H: CH_2Ph), 3.65 (m, 1H: H_3), 3.62 (d, J=14.6 Hz, 1H: CH_2Ph), 2.83 (dt, J_{gem}=13.8 Hz, $^{cis}J_{4,3}$≈$^{cis}J_{4,5}$≈6.9 Hz, 1H: H_4), 2.29 (ddd, J_{gem}=13.8 Hz, $^{trans}J_{4,3}$=10.2 Hz,

trans$J_{4,5}$=3.8 Hz, 1H: H_4), 1.19 (s, 9H: ^{t}Bu); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.7 (C_{Ar}), 137.8 (C_{Ar}), 128.5 (C_{Ar}), 128.8 (C_{Ar}), 128.1 (C_{Ar}), 127.8 (C_{Ar}), 126.7 (C_{Ar}), 95.7 (C_5), 74.3 (*C*Me$_3$), 70.6 (C_3), 59.3 (*C*H$_2$Ph), 47.4 (C_4), 28.8 (CH_3); MS (*m/z*) 312 (M^++1, 2), 255 (34), 133 (66), 91 (100). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.12; H, 8.10; N, 4.50. Found: C, 77.09; H, 8.10; N, 4.48.

***trans*-2-Benzyl-3-phenyl-5-*tert*-butoxyisoxazolidine, 23**: colourless oil; bp 205 °C (oven)/0.2 Torr; IR (film): 2973, 2931, 2875 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.45-7.20 (m, 10H: 10H_{Ar}), 5.49 (br d, $J_{5,4}$=4.4 Hz, 1H: H_5), 4.29 (dd, *trans*$J_{4,3}$=8.8 Hz, *cis*$J_{4,3}$=6.6 Hz, 1H: H_3), 4.13 (d, J=13.5 Hz, 1H: C*H*$_2$Ph), 4.06 (d, J=13.5 Hz, 1H: C*H*$_2$Ph), 2.49 (m, 2H: 2H_4), 1.27 (s, 9H: ^{t}Bu); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.3 (C_{Ar}), 128.9 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 127.8 (C_{Ar}), 127.4 (C_{Ar}), 126.9 (C_{Ar}), 97.5 (C_5), 74.5 (*C*Me$_3$), 68.2 (C_3), 63.2 (*C*H$_2$Ph), 46.6 (C_4), 29.1 (CH_3); MS (*m/z*) 312 (M^++1, 4), 255 (29), 133 (58), 105 (54), 91 (100). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.12; H, 8.10; N, 4.50. Found: C, 77.06; H, 8.16; N, 4.54.

Preparation of cis-5-ethoxy-3-methyl-2-phenylisoxazolidine, 12

A mixture of phenylhydroxylamine (200 mg, 1.8 mmol), acetaldehyde (100 µl, 1.8 mmol) and ethyl vinyl ether (2 ml) was heated in a sealed flask at 50 °C for 20 h. Concentration under vacuum gave a yellow oil, which was purified by flash chromatography (hexane/Et_2O, 3/1) giving 135 mg (36%) of **12** as a colourless oil: bp 110 °C (oven)/0.2 Torr; IR (film): 2980, 1595, 1490 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.28 (t, J=7.7 Hz, 2H: 2H_{Ar}), 7.15 (d, J=8.0 Hz, 2H: 2H_{Ar}), 7.03 (t, J=7.3 Hz, 1H: 1H_{Ar}), 5.33 (dd, *cis*$J_{5,4}$=6.6 Hz, *trans*$J_{5,4}$=2.2 Hz, 1H: H_5), 3.90 (dq, J_{gem}=9.5 Hz, J=7.3 Hz, 1H: OCH_2), 3.53 (dq J_{gem}=9.5 Hz, J=7.3 Hz, 1H: OCH_2), 3.43 (m, 1H: H_3), 2.60 (ddd, J_{gem}=13.1 Hz, *cis*$J_{4,3}$=8.0 Hz, *cis*$J_{4,5}$=6.6 Hz, 1H: H_4), 2.01 (ddd, J_{gem}=13.1 Hz, *trans*$J_{4,3}$=5.8 Hz, *trans*$J_{4,5}$=2.2 Hz, 1H: H_4), 1.39 (d, J=6.6 Hz, 3H: C*H*$_3$CH), 1.26 (t, J=7.3 Hz, 3H: C*H*$_3$CH$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 150.4 (C_{Ar}), 128.5 (C_{Ar}), 123.4 (C_{Ar}), 117.8 (C_{Ar}), 101.3, (C_5), 64.0 (C_3), 61.9 (CH_2O), 43.0 (C_4), 19.3 (*C*H$_3$CH), 15.1 (*C*H$_3$CH$_2$); MS (*m/z*) 208 (M^++1, 58), 207 (M^+, 79), 162 (37), 118 (33), 99 (100). HRMS (EI) (M^+) calcd for $C_{12}H_{17}NO_2$ 207.1259, found 207.1266.

Preparation of cis-, 16, and *trans*-3-methyl-2-phenyl-5-*tert*-butoxyisoxazolidine, 17

A mixture of phenylhydroxylamine (200 mg, 1.8 mmol), acetaldehyde (100 µl, 1.8 mmol) and *tert*-butyl vinyl ether (2 ml) was heated in a sealed flask at 50 °C for 20 h. Concentration under vacuum gave a yellow oil, which was purified by flash chromatography (hexane/Et_2O, 3/1) giving 298 mg (70%) of **16** and 12 mg (3%) of a 1/1 mixture of **16** and **17**. **16** + **17**: Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.45; H, 8.94; N, 6.12. **16**: colourless oil; IR (film): 2973, 1595, 1490 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.25 (t, J=8.0 Hz, 2H: 2H_{Ar}), 7.09 (d, J=8.0 Hz, 2H: 2H_{Ar}), 6.95 (t, J=8.0 Hz, 1H: 1H_{Ar}), 5.61 (dd, *cis*$J_{5,4}$=6.6 Hz, *trans*$J_{5,4}$=2.9 Hz, 1H: H_5), 3.59 (m, 1H: H_3), 2.50 (ddd, J_{gem}=12.4 Hz, *cis*$J_{4,3}$=8.0 Hz, *cis*$J_{4,5}$=6.6 Hz, 1H: H_4), 1.91 (ddd, J_{gem}=12.4 Hz, *trans*$J_{4,3}$=5.1 Hz, *trans*$J_{4,5}$=2.9 Hz, 1H: H_4), 1.43 (d, J=6.6 Hz, 3H: C*H*$_3$CH), 1.31 (s, 9H: ^{t}Bu); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 151.1 (C_{Ar}), 128.6 (C_{Ar}), 122.4 (C_{Ar}), 116.5 (C_{Ar}), 97.0 (C_5), 74.9 (*C*Me$_3$), 61.5 (C_3), 43.2 (C_4), 28.8 (*C*H$_3$CH), 20.0 (*C*H$_3$C). **17**: ^{1}H NMR (250 MHz, $CDCl_3$, observable signals from a mixture of **16** and **17**): δ 3.90 (q, J≈6.0 Hz, H_3), 2.35 (ddd, J_{gem}=12.4 Hz, $J_{4,3}$=6.6 Hz, $J_{4,5}$=2.9 Hz, H_4), 2.20 (m, H_4), 1.26 (s, ^{t}Bu), 1.25 (d, J≈6.0 Hz, C*H*$_3$CH); ^{13}C NMR (62.5 MHz, $CDCl_3$, significant signals from a mixture of **16** and **17**): δ 151.2 (C_{Ar}), 128.5 (C_{Ar}), 121.8 (C_{Ar}), 116.6 (C_{Ar}), 97.2 (C_5), 74.7 (*C*Me$_3$), 59.4 (C_3), 44.4 (C_4), 28.9 (*C*H$_3$CH), 18.7 (*C*H$_3$C).

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