Homogeneous Catalysis. Metallocene Catalysts for [3+2] Nitrone−Olefin Cycloaddition Reactions

William W. Ellis,† Anna Gavrilova,† Louise Liable-Sands,‡ Arnold L. Rheingold,‡ and B. Bosnich*,†

Department of Chemistry, The University of Chicago, 5735 S. Ellis Avenue, Chicago, Illinois 60637, and Department of Biochemistry, University of Delaware, Newark, Delaware 19716

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The complex $[Cp_2Ti(OTf)_2]$ is a catalyst for the [3+2] cycloaddition of nitrones with electron-rich olefins. In the presence of small amounts of water, catalyst hydrolysis leads to the production of triflic acid, which is a powerful catalyst for these cycloaddition reactions. Acid catalysis can be suppressed by the use of Proton-Sponge. Metal catalysis appears to proceed via the bis(nitrone) adduct $[Cp_2Ti(nitrone)_2]^{2+}$. A crystal structure of one of these adducts is reported.

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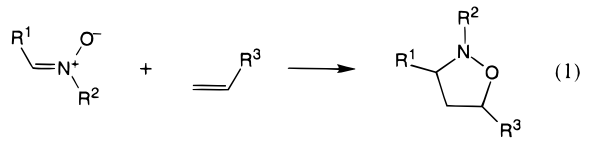
Introduction

The [3+2] nitrone−olefin cycloaddition reaction[1,2] (eq 1) is useful for the construction of complex molecules,



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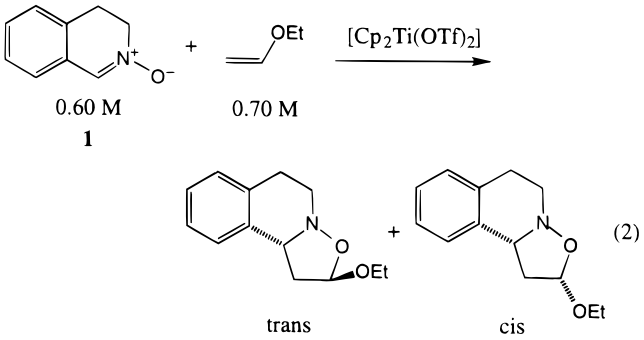
particularly alkaloids.[3] Traditionally, these additions are carried out thermally where it is found that the rate of reaction is accelerated by the use of electron-rich olefins such as enol ethers and ketene acetals. The regioselectivity is controlled by the stability of the carbenium ion of the olefin so that the carbon atom bearing the more stablilized carbenium ion forms a bond to the nitrone oxygen atom (eq 1). These 1,3-dipolar cycloadditions seem ideally suited for Lewis acid catalysis. Coordination of the nitrone oxygen atom to a Lewis acid is expected to activate this substrate to reaction with olefins, and after cyclization, the ether oxygen atom of the product is expected to bind less strongly to the Lewis acid. Consequently, the catalytic turnover frequency is unlikely to be strongly impeded by product inhibition. These circumstances are in contrast to Lewis acid catalysis of the Diels−Alder reaction for example, where the binding functionality of the dienophile substrate is preserved in the product.

It has been shown recently that nitrone−olefin cycloadditions can be catalyzed or promoted stoichiometrically by a variety of conventional Lewis acids, including derivatives of Al(III), Zn(II), B(III), and Ti(IV).[4,5] Given this, it seemed probable that structurally defined complexes of the type $[Cp_2Ti(OTf)_2]$,[6] $[Cp_2Zr(OTf)_2THF]$,[6] and $[Cp'_2Ti(H_2O)_2](OTf)_2$, where Cp is cyclopentadienyl, Cp′ is pentamethylcyclopentadienyl, OTf is CF_3SO_3, and THF is tetrahydrofuran, would act as catalysts for these 1,3-dipolar cycloadditions. We have shown previously that these complexes act as efficient catalysts for the Diels−Alder reaction and that the catalytic efficiency depends on the presence of good leaving ligands (OTf, H_2O) for substrate binding and hence activation of the dienophile.[6−8] We report here on a study of [3+2] nitrone−olefin cycloadditions catalyzed by $[Cp_2Ti(OTf)_2]$[9] and a chiral analogue.

Results and Discussion

Acid Catalysis. The reaction of the nitrone, **1**, and ethyl vinyl ether in CD_2Cl_2 solution at 25 °C in the presence of $[Cp_2Ti(OTf)_2]$ (0.04 M) was complete after 18 h (eq 2). The reaction is clean, as shown by ^1H NMR



(2)

spectroscopy, and the two isomers of the product can

† The University of Chicago.
‡ University of Delaware.

(1) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633. (c) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403.
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(6) Hollis, T. K.; Robinson, N. P.; Bosnich, B. *Organometallics* **1992**, *11*, 2745
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(8) (a) Hollis, T. K.; Robinson, N. P.; Whelan, J.; Bosnich, B. *Tetrahedron Lett.* **1993**, *34*, 4309. (b) Hollis, T. K.; Odenkirk, W.; Robinson, N. P.; Whelan, J.; Bosnich, B. *Tetrahedron* **1993**, *49*, 5415.
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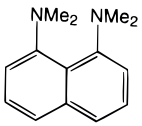
be isolated by liquid chromatography. A 45:55 trans/cis isomer ratio was observed. The majority of this catalysis, however, occurs by proton catalysis, as evidenced by the following experiments. With the same concentrations of substrates under the same conditions but in the presence of 0.04 M HOTf, the cycloaddition is complete in 1.5 h and the same (45:55) trans/cis isomer ratio of the products is observed. In the presence of pyridinium triflate (0.04 M) the reaction proceeds at a slower rate, taking 25 h for completion, but, again, the same isomer ratio is observed. That pyridinium triflate is capable of protonating the nitrone, **1**, in CD_2Cl_2 solution is evidenced by the downfield shift of the nitrone ^1H NMR resonances when pyridinium triflate is added to a CD_2Cl_2 solution of the nitrone. Such downfield shifts are not observed when Proton-Sponge, **2**, is added in 2-fold



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stoichiometric excess over HOTf. The reaction of nitrone, **1**, with ethyl vinyl ether (eq 2) in the presence of HOTf (0.04 M) and **2** (0.10 M) is very slow in CD_2Cl_2 at 25 °C, giving 15% of product after 64 h. The ratio of product isomers, however, is reversed from those previously observed; a 95:5 trans/cis ratio of isomers is observed. The purely thermal reaction of **1** (0.6 M) and ethyl vinyl ether (0.7 M) under the same conditions in the presence of **2** (0.10 M) proceeds at essentially the same rate and gives the same trans/cis ratio (95:5) of the product isomers. The fact that the proton-catalyzed reactions give the same isomer ratio as when $[Cp_2Ti(OTf)_2]$ is used as a catalyst implies that the complex is capable of generating acid in CD_2Cl_2 solution.

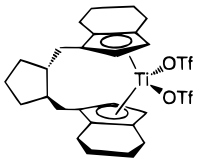
In a recent study we showed that the complex $[Cp_2Ti(OTf)_2]$ was readily hydrolyzed in CD_2Cl_2 solutions even if the normal precautions were taken to exclude water (CD_2Cl_2 distillation over CaH_2 under a dry atmosphere). It was demonstrated that the overall hydrolysis reaction illustrated in eq 3 occurred to

$$[Cp_2Ti(OTF)_2] + H_2O \rightarrow \text{“}[Cp_2TiO]\text{”} + 2HOTf \quad (3)$$

generate triflic acid. The species “$[Cp_2TiO]$” is probably oligomeric and is detected by ^1H NMR spectroscopy.[10] The titanium species “$[Cp_2TiO]$” was also observed in the present studies. Given the existence of the hydrolysis reaction and the potent HOTf catalysis, proton catalysis could be suppressed either by taking extreme measures to exclude water or by taking normal drying precautions and using Proton-Sponge to quench the acid. The former would reduce the practicability of the reaction, and consequently the latter approach was adopted. Although $[Cp_2Ti(OTf)_2]$ can be used as a catalyst, we found it more convenient to use the more robust bis(nitrone) adduct $[Cp_2Ti(\mathbf{1})_2](OTf)_2$, **3**. This adduct is readily prepared by addition of **1** to a solution of $[Cp_2Ti(OTf)_2]$ in THF, from which the adduct precipitates as a yellow solid. Recrystallization from acetone/ether gives the bisadduct as yellow crystals which are easy to handle. All nitrones were purified by sublimation.

Titanium-Catalyzed Reactions. Using the catalyst $[Cp_2Ti(\mathbf{1})_2](OTf)_2$ in the presence of Proton-Sponge, **2**, some of the results obtained are collected in Table 1 together with the results of the corresponding thermal reactions under similar conditions. It should be noted that for all of the catalyzed reactions some inactivation of the catalyst occurs because of the presence of adventitious water. The degree of catalyst inactivation tends to increase over time. Consequently, the times for completion of the catalytic reactions are lower limits, and in the case of the slower reactions, the completion times may be as much as twice those expected if no catalyst hydrolysis had occurred. Even so, the completion times are included for comparison with the rates of the corresponding thermal reactions. As will be noted, the thermal reactions do not compete with the catalytic reactions in most cases. The catalytic and the thermal reactions occur faster with cyclic substrates, and ketene acetals react faster than enol ethers. For the acylic nitrones,[9−12] the catalytic reactions are very slow with enol ethers at the low catalyst loading used here. Generally, the catalytic reactions give different ratios of isomers from those observed for the corresponding thermal reactions. Overall, these results indicate that reactions of cyclic nitrones are catalyzed efficiently by the titanium catalyst with both enol ethers and ketene acetals. Further, the more electron-rich ketene acetals undergo efficient catalysis with both cyclic and acylic nitrones.

Mechanism of Catalysis. Because the [3+2] cycloadditions are so prone to proton catalysis, it was important to confirm that, even in the presence of Proton-Sponge, the catalysis proceeded via the titanium complex. For this purpose, we employed the chiral catalyst [Ti(S,S-cyclacene)$(OTf)_2$], **4**,[12] for the reaction shown in eq 4. Under concentration conditions similar



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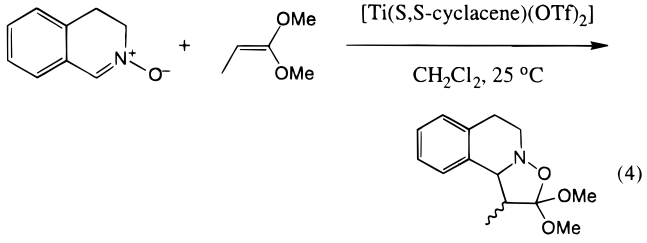

(4)

to those used for the catalytic reactions in Table 1 (catalyst, 0.02 M; nitrone, 0.5 M; ketene acetal, 1.0 M) and in the presence of Proton-Sponge (0.05 M), the catalytic reaction shown in eq 4 proceeded slowly (72 h

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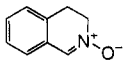
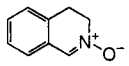
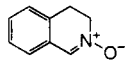
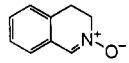
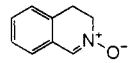
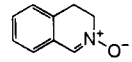
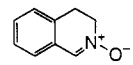
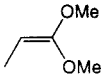
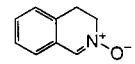
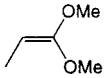
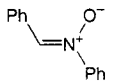
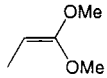
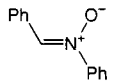
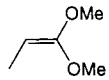
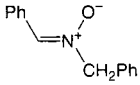
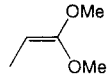
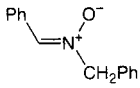
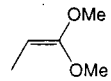
Table 1. Nitrone−Olefin [3+2] Cycloadditions in Dichloromethane-(d_2) Solutions at 25 °C

Entry	Nitrone (conc M)	Olefin (conc M)	Catalyst (conc M)	Proton-Sponge (conc M)	Time (h)	%Nitrone Conversion	Isomer Ratio	Isolated Yield
1	 (0.60)	 (0.70)	**3** (0.04)	0.10	60	>95	75:25 trans:cis	70% trans 17% cis
2	 (0.60)	 (0.70)	—	0.10	213	37	94:6 trans:cis	—
3	 (0.50)	 (0.60)	**3** (0.03)	0.08	20	>95	39:61 trans:cis	29% trans 45% cis
4	 (0.50)	 (0.60)	—	0.08	150	17	>98% trans	—
5	 (0.50)	 (0.60)	**3** (0.03)	0.08	40	>95	88:12 trans:cis	81% trans 10% cis
6	 (0.50)	 (0.60)	—	0.08	500	29	>98% trans	—
7	 (0.50)	 (0.60)	**3** (0.02)	0.05	0.3	>95	65:35 trans:cis	56% trans 32% cis
8	 (0.50)	 (0.60)	—	0.05	95	<1	—	—
9	 (0.50)	 (0.65)	**3** (0.03)	0.08	0.5	>95	32:68 trans:cis	84%
10	 (0.50)	 (0.65)	—	0.08	20	<1	—	—
11	 (0.50)	 (1.0)	**3** (0.03)	0.08	31	>95	17:83 trans:cis	93%
12	 (0.50)	 (1.0)	—	0.08	20	<1	—	—

for 25% reaction). The ratio of isomers was different from that observed with the $[Cp_2Ti(\mathbf{1})_2]^{2+}$ catalyst (Table 1, entry 7); the ratio was 92:8 versus 65:35 (trans/cis). The isomers were separated, and the major isomer was found by a chiral shift reagent to have an ee of 14%. The observation of ee indicates that the catalysis involves the titanium Lewis acid.

The thermal [3+2] nitrone−olefin cycoladditions are believed to be concerted.[13] Inspection of Table 1 shows that the isomer ratios are generally different for the catalyzed and for the corresponding thermal reactions. For all of the titanium-catalyzed reactions the isomers are formed in constant proportions throughout the reaction, and prolonged exposure of the product isomers to the catalyst does not lead to a change in isomer ratios. The observation that the isomer ratios found with the achiral catalyst, **3**, and those found for the chiral

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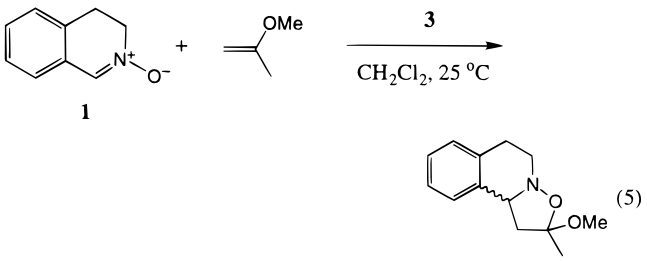
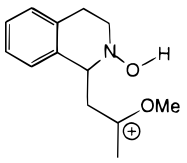
catalyst, **4**, are different for the reaction shown in entry 7 (Table 1) suggests that the isomer ratios are controlled to some extent by the structure of the catalyst. The results listed in Table 1 indicate that the isomeric ratios are also controlled by the substrate structures. For example, the isomer ratios are reversed for the catalyzed reactions of ethyl vinyl ether and *tert*-butyl vinyl ether with substrate **1**. Presumably, this isomer ratio reversal is connected with the different steric effects that operate in the transition states. The variations in the isomer ratios shown by entries 1, 3, 5, and 7 (Table 1), for example, are presumably governed to some extent by the substrate and catalyst steric interactions present in the transition states. At most, these isomer variations correspond to a few kcal mol^{-1}, and it does not seem prudent to speculate on the precise origins of the isomer ratio variations.

This structural dependence and kinetic control of isomer ratios suggest that the titanium-catalyzed reactions may proceed by a concerted path. Acid-catalyzed isomeric equilibration, however, has been observed for the reaction of methoxypropene and the substrate **1**. The catalytic reaction gives a 36:64 (cis/trans) ratio of isomers (eq 5). This same reaction catalyzed (CH_2Cl_2, 25 °C) by pyridinium triflate gives the reverse ratio of isomers, namely 62:38 (cis/trans).



36:64 (cis:trans) (5)

When the pure minor isomer from the proton-catalyzed reaction was isolated and then exposed to pyridium triflate (CD_2Cl_2, 25 °C), slow equilibration occurred to give an isomer ratio that was the same as that observed for the proton-catalyzed reaction. This implies that for this proton-catalyzed reaction the reaction proceeds by a nonconcerted path involving a carbenium ion intermediate of the type **5**.



5

For the titanium-catalyzed reactions the catalytic species could be either the bisadduct $[Cp_2Ti(\mathbf{1})_2](OTf)_2$, **3**, or the monoadduct $[Cp_2Ti(\mathbf{1})(OTf)](OTf)$. Saturated CD_2Cl_2 solutions of **3** are used for catalysis. Under these circumstances, ^1H NMR spectroscopy indicates that only the bisadduct, **3**, exists in solution. The fact that for most of the catalysis a large excess of the nitrone, **1**, is present implies that the amount of monoadduct present must be exceedingly small during catalysis. Because there appears to be no persuasive reason to suppose that the monoadduct is vastly more reactive than the bisadduct, it is reasonable to conclude that the majority of catalysis proceeds by way of the bisadduct. We note that equilibration between the mono- and bisadducts is very rapid because we have found that the addition of 1 equiv of $[Cp_2Ti(OTf)_2]$ to a CD_2Cl_2 solution of the bisadduct, **3**, gives the monoadduct in essentially quantitative yield upon mixing. During catalysis, therefore, there will be no buildup of monospecies arising from kinetic impediments to bisadduct formation.

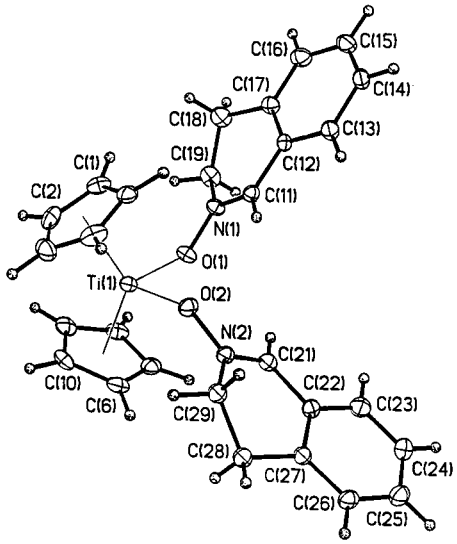


Figure 1. Crystal structure of $[Cp_2Ti(\mathbf{1})_2]^{2+}$. There are two independent molecules. Average Ti−centroid(Cp) distance is 2.06 Å and centroid(Cp)−Ti−centroid(Cp) angle is 132°. The average Ti−O distance is 1.99 Å. These and the other values are unexceptional (see Supporting Information).

Table 2. Crystallographic Data for $C_{30}H_{28}F_6N_2O_8S_2Ti$

formula	$C_{30}H_{28}F_6N_2O_8S_2Ti$
fw	770.50
cryst syst	monoclinic
space group	$P2_1/n$
a, *b*, *c*, Å	16.4732(3), 19.3198(1), 21.7754(1)
β, deg	106.918(1)
volume, Å^3	6630.2(2)
Z	8
D_x, g cm^{-3}	1.544
μ(Mo Kα), cm^{-1}	4.61
T, K	2223
diffractometer	Siemens P4/CCD
2*θ* range, deg	4−56 (hemisphere)
no. of rflns (collctd, indpdnt)	26 061, 13 014
$R(F)$, $R(wF^2)$,[a] %	5.76, 13.57
GOF	1.05
N_o/N_v	13 004/928

[a] $R(F) = \Sigma\Delta/\Sigma(F_o)$; $R(wF) = \Sigma[\Delta w^{1/2}]/[F_o w^{1/2}]$; $\Delta = |F_o - F_c|$; $w^{-1} = \sigma^2(F_o) + gF_o^2$.

Crystal Structure. A crystal structure of the bisadduct, **3**, was determined. It is shown in Figure 1 together with a selection of bond lengths and bond angles. Crystallographic information is provided in Table 2. There do not appear to be other crystal structures of nitrone−titanium(IV) complexes reported, although crystal structures of other nitrone−metal complexes have been reported recently.[14] These structures are not directly comparable to the present one because in the

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other systems the nitrone is part of a bidentate chelate. The structure appears unexceptional. The structure indicates that if similar substrate binding obtains in complexes bearing highly substituted Cp rings, the approach of the olefin to the coordinated nitrone may be impeded. This could be the reason that catalysis using the more hindered chiral catalyst, **4**, proceeds more slowly. The difference in isomer ratios observed for catalyst **4** compared to catalyst **3** could arise from different steric interactions in the two transition states.

Conclusion

The present work shows that structurally defined transition metal catalysts can be used to induce the [3+2] nitrone−olefin cycloaddition reactions. Rapid proton catalysis, however, can be suppressed by the use of effective bases. The metal-catalyzed reaction appears to be a concerted process. Asymmetric induction has been observed suggesting that the present systems may eventually be developed into chiral catalysts.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker Avance DMX 500 MHz spectrometer. All ^{1}H NMR chemical shifts are reported relative to TMS when $CDCl_3$ is used as solvent and relative to residual $CDHCl_2$ (δ 5.32) when CD_2Cl_2 is used as solvent. Elemental analysis was performed by Desert Analytics, Tucson, AZ.

Solvents and reagents were obtained from Aldrich except the following: acetone, Et_2O, hexane, CH_2Cl_2, and $CDCl_3$ (Fisher); *C,N*-diphenylnitrone (Lancaster). When necessary, CH_2Cl_2 (CaH_2) and Et_2O (Na/benzophenone) were dried and distilled before use. THF (Na/benzophenone), CD_2Cl_2 (CaH_2), and acetone (4 Å molecular sieves) were always dried and distilled before use. $CDCl_3$ was filtered through basic Al_2O_3 before use. Chromatography was performed on 230−400 mesh, 60 Å silica gel (Aldrich).

The enol ethers (Aldrich) were distilled from CaH_2 before use. The ketene acetals were prepared according to the literature procedures and were distilled from CaH_2 and stored in resealable ampules at −25 °C in a desiccator.[15,16] Nitrone **1** and *C*-phenyl-*N*-benzyl nitrone were prepared according to the literature methods.[17] All of the nitrones were sublimed prior to use and stored in an argon-filled glovebox. The catalysts $Cp_2Ti(OTf)_2$ and pyridinium triflate were purchased from Aldrich. The Proton-Sponge was obtained from Aldrich and sublimed before use.

Crystallographic Structure Determination. Crystallographic data are collected in Table 1. Yellow block crystals were determined to belong to the monoclinic crystal system. Systematic absences in the diffraction data uniquely determined the space group as $P2_1/n$. Corrections for absorption were not required. The structure was solved by direct methods, completed from difference Fourier maps, and refined with anisotropic thermal parameters for all nonhydrogen atoms. The asymmetric unit consists of two formula units. Two of the four unique triflate counterions were disordered: one showed rotational disorder in the CF_3 group; the other was located in two positions rotated by about 30° about an axis at the midpoint of the S−C bond. Additionally, one of the Cp rings is rotationally disordered. Hydrogen atom contributions were mostly idealized but were ignored on the disordered Cp ring. All computations used SHELXTL 4.2 software (G. Sheldrick, Siemens XRD, Madison, WI).

Preparation of Complex $[Cp_2Ti(1)_2](OTf)_2$, 3. In the glovebox, titanocene bis(triflate) (235.6 mg, 0.4947 mmol) and the nitrone **1** (154.6 mg, 1.050 mmol) were added to a 5 mL Schlenck tube containing a Teflon-coated stir bar. After sealing the tube with a rubber septum, it was removed from the glovebox and attached to a Schlenck line. The mixture was stirred and heated to 50 °C with an oil bath. Next, 2 mL of THF was added via cannula, giving a red solution, which quickly became cloudy, producing a thick yellow precipitate. The mixture was stirred for 30 min at 50 °C. After cooling to 25 °C, the mixture was transferred via cannula onto a medium-porosity filter stick. The solid thus obtained was washed with THF (2 × 5 mL) and dried in vacuo; 299.0 mg (78.4%) of complex **3** was obtained as a yellow powder. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 8.98 (s, 2 H), 7.93 (d, J = 7.7 Hz, 2 H), 7.66 (t, J = 7.8 Hz, 2 H), 7.48 (t, J = 7.9 Hz, 2 H), 7.41 (d, J = 7.6 Hz, 2 H), 6.79 (s, 10 H), 4.46 (t, J = 8.2 Hz, 4 H), 3.51 (t, J = 8.2 Hz, 4 H). Crystals of the complex for elemental analysis and X-ray diffraction were obtained as follows: 72.9 mg of the powder was dissolved in a minimal amount of warm (50 °C) dry acetone in a Schlenck tube. After filtering through a medium porosity frit, dry Et_2O was slowly added until clouding persisted. After the mixture stood for 1 day, the supernatant liquid was poured off, and the crystals were washed with Et_2O (3 ×). After drying under a stream of argon, crystals were chosen for X-ray diffraction. Upon drying in vacuo for 24 h, 49.0 mg (67% yield) was obtained from the remainder. Anal. Calcd for $C_{30}H_{28}N_2F_6O_8S_2Ti$: C, 46.76; H, 3.66; N, 3.64. Found: C, 46.79; H, 3.75; N, 3.73.

Catalysis of the [3+2] Reaction. Reaction of Ethyl Vinyl Ether with Nitrone 1.[4c] In a typical procedure, the catalyst complex **3** (18.8 mg, 0.0244 mmol), nitrone **1** (45.8 mg, 0.311 mmol), and Proton-Sponge (12.8 mg, 0.0597 mmol) were added to a screw-capped NMR tube in the glovebox. This was sealed with a Teflon-lined plastic cap. CD_2Cl_2 (490 μL) followed by ethyl vinyl ether (40 μL, 0.42 mmol) were added via syringe in a nitrogen-flushed glovebag. An orange solution was obtained. The progress of the reaction was followed by ^{1}H NMR spectroscopy. The percent conversion was determined by integration of the product peaks against the nitrone peaks (complexed and uncomplexed). The trans/cis ratio of products was 75:25. Upon completion of the reaction (60 h), the sample was washed with aqueous $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (4 ×). After filtration through a small amount of Celite, the combined extracts were concentrated to give a dark oil (92.0 mg). The oil was flash chromatographed through silica gel (20 g) using hexane/Et_2O (2:1) as eluant. *trans*-1,5,6,10b-Tetrahydro-2*H*-isoxazol[3,2-*a*]isoquinolin-2-yl ethyl ether (54.8 mg, 70% yield) eluted first, followed by the cis isomer (13.2 mg, 17% yield). ^{1}H NMR (500 MHz, $CDCl_3$): trans isomer δ 7.23−7.08 (m, 4 H), 5.26 (d, J = 5.3 Hz, 1 H), 4.77 (t, J = 7.9 Hz, 1 H), 3.88 (dq, J = 9.5, 7.1 Hz, 1 H), 3.50 (dq, J = 9.5, 7.1 Hz, 1 H), 3.31 (ddd, J = 11.7, 5.7, 5.5 Hz, 1 H), 3.20 (ddd, J = 11.9, 7.4, 4.6 Hz, 1 H), 2.88 (m, 2 H), 2.65 (ddd, J = 12.9, 6.9, 1.1 Hz, 1 H), 2.44 (ddd, J = 12.9, 8.8, 5.5 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H); cis isomer δ 7.20−7.05 (m, 4 H), 5.37 (dd, J = 6.5, 3.9 Hz, 1 H), 4.59 (t, J = 9.3 Hz, 1 H), 3.85 (dq, J = 9.6, 7.2 Hz, 1 H), 3.54 (m, 1 H), 3.51 (dq, J = 9.6, 7.1 Hz, 1 H), 3.40 (ddd, J = 10.3, 4.7, 3.0 Hz, 1 H), 3.07 (ddd, J = 16.3, 11.7, 4.7 Hz, 1 H), 2.96 (ddd, J = 13.3, 8.5, 6.6 Hz, 1 H), 2.79 (dt, J = 16.3, 3.1 Hz, 1 H), 2.35 (ddd, J = 13.5, 10.0, 3.7 Hz, 1 H), 1.19 (t, J = 7.1 Hz, 3 H). All structural assignments were made by comparison with ^{1}H NMR data available from the literature.[4c]

Reaction of *tert*-Butyl Vinyl Ether with Nitrone 1. Using the above procedure, *tert*-butyl vinyl ether (47 μL, 0.36 mmol) and **1** (39.4 mg, 0.268 mmol) were reacted in the presence of the catalyst complex **3** (13.9 mg, 0.0180 mmol) and Proton-Sponge (10.5 mg, 0.0490 mmol) in CD_2Cl_2 (490 μL). The

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products were separated on 15 g of silica gel using 2:1 hexane/Et_2O. *trans*-1,5,6,10b-Tetrahydro-2*H*-isoxazol[3,2-a]isoquinolin-2-yl *tert*-butyl ether (21.8 mg, 29% yield) eluted before the cis isomer (34.1 mg, 45% yield). ^{1}H NMR (500 MHz,$CDCl_3$): trans isomer δ 7.21−7.04 (m, 4 H), 5.57 (dd, J = 5.7, 1.3 Hz, 1 H), 4.76 (t, J = 7.9 Hz, 1 H), 3.29 (ddd, J = 11.1, 5.4, 5.4 Hz, 1 H), 3.14 (ddd, J = 11.3, 7.7, 5.1 Hz, 1 H), 2.88 (m, 2 H), 2.53 (ddd, J = 12.7, 6.9, 1.5 Hz, 1 H), 2.45 (ddd, J = 12.6, 9.0, 5.7 Hz, 1 H), 1.29 (s, 9 H); cis isomer δ 7.18−7.03 (m, 4H), 5.66 (dd, J = 6.7, 4.4 Hz, 1 H), 4.54 (dd, J = 10.4, 8.5 Hz, 1 H), 3.55 (ddd, J = 12.5, 10.4, 3.3 Hz, 1 H), 3.39 (ddd, J = 10.4, 4.8, 2.7 Hz, 1 H), 3.08 (ddd, J = 16.4, 12.2, 4.5 Hz, 1 H), 2.90 (ddd, J = 13.3, 8.2, 6.7 Hz, 1 H), 2.79 (dt, J = 16.3, 3.0 Hz, 1 H), 2.31 (ddd, J = 13.3, 10.7, 4.4 Hz, 1 H), 1.25 (s, 9 H).

Reaction of 2,3-Dihydrofuran with Nitrone 1.[4c] Using the above procedure, 2,3-dihydrofuran (27 μL, 0.357 mmol) and **1** (39.1 mg, 0.266 mmol) were reacted in the presence of the catalyst complex **3** (14.2 mg, 0.0184 mmol) and Proton-Sponge (10.6 mg, 0.0494 mmol) in CD_2Cl_2 (510 μL). The products were separated on 20 g of silica gel using 2:1 hexane/Et_2O. *cis*-5,-8a,10,11,11a,11b-Hexahydro-6*H*-furo[3′,2′:4,5]isoxazolo[3,2-*a*]-isoquinoline (6.3 mg, 10% yield) eluted before the trans isomer (53.1 mg, 81% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): cis isomer δ 7.21 (m, 2 H), 7.16 (t, J = 4.5 Hz, 1 H), 7.06 (t, J = 4.5 Hz, 1 H), 5.88 (d, J = 3.5 Hz, 1 H), 4.09 (q, J = 7.8 Hz, 1 H), 3.90 (m, 1 H), 3.70 (m, 2 H), 3.50 (m, 1 H), 3.29 (m, 1 H), 2.99 (dd, J = 16.5, 3.5 Hz, 1 H), 2.82 (m 1 H), 1.92 (m, 2 H); trans isomer δ 7.20 (m, 3 H), 7.09 (d, J = 7.5 Hz, 1 H), 5.73 (d, J = 5.5 Hz, 1 H), 4.35 (br s, 1 H), 4.22 (ddd, J = 10.5, 8.5, 6.0 Hz, 1 H), 4.04 (td, J = 8.1, 2.2 Hz, 1 H), 3.59 (dt, J = 12.8, 4.1 Hz, 1 H), 3.29 (m, 1 H), 3.15 (m, 2 H), 2.54 (dt, J = 15.8, 4.0 Hz, 1 H), 2.28 (m, 1 H), 2.20 (m, 1 H).

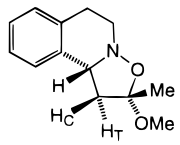
Reaction of 1,1-Dimethoxy-1-propene with Nitrone 1.[4a] Using the above procedure, the ketene acetal (45 μL, 0.39 mmol) was reacted with nitrone **1** (43.9 mg, 0.298 mmol) in the presence of the catalyst complex **3** (9.1 mg, 0.012 mmol) and Proton-Sponge (6.5 mg, 0.030 mmol) in CD_2Cl_2 (500 μL). The products were separated on 15 g of silica gel using 2:1 hexane/Et_2O. The trans product (45.2 mg, 56% yield) eluted before the cis product (26.0 mg, 32% yield). ^{1}H NMR (500 MHz, $CDCl_3$): trans product δ 7.22−7.10 (m, 4 H), 4.36 (d, J = 9.9 Hz, 1 H), 3.49 (dt, J = 10.5, 4.1 Hz, 1 H), 3.45 (s, 3 H), 3.36 (dt, 11.0, 4.8 Hz, 1 H), 3.31 (s, 3 H), 3.00 (ddd, J = 15.9, 10.4, 5.2 Hz, 1 H), 2.90 (dt, J = 16.4, 4.1 Hz, 1 H), 2.67 (dq, J = 9.9, 6.9 Hz, 1 H), 1.30 (d, J = 6.9 Hz, 3 H); cis product δ 7.22−7.12 (m, 3 H), 7.01 (d, J = 7.8 Hz, 1 H), 5.00 (d, J = 7.7 Hz, 1 H), 3.51 (m, 1 H), 3.41 (s, 3 H), 3.37 (s, 3 H), 3.34 (m, 1 H), 2.97 (quintet, J = 7.7 Hz, 1 H), 2.96−2.82 (m, 2 H), 0.88 (d, J = 7.2 Hz, 3 H). The isomers were identified by NOE experiments involving the irradiation of the aliphatic methyl protons observed at δ 1.3 for the major isomer and at δ 0.88 for the minor isomer. The proton (at δ 4.36 for the major isomer and at δ 5.00 for the minor isomer) of the tertiary carbon atom adjacent to the carbon bearing the methyl group was enhanced by 5.7% for the major (trans) isomer and was enhanced by 0.8% for the minor (cis) isomer.

Reaction of 1,1-Dimethoxy-1-propene with Nitrone 1 Catalyzed by Chiral Complex 4. Using the above procedure, the ketene acetal (70 μL, 0.60 mmol) was reacted with nitrone **1** (44.3 mg, 0.30 mmol) in the presence of the chiral complex **4** (8.1 mg, 0.012 mmol) and Proton-Sponge (7.0 mg, 0.030 mmol) in CD_2Cl_2 (470 μL). After 3 days, 25% conversion had occurred, and the catalyst had completely hydrolyzed. The products were formed in a 92:8 ratio (trans/cis). The trans product (11.7 mg, 16% yield) was isolated after chromatography on 30 g of silica gel using 2:1 hexane/ether as eluant. An enantiomeric excess of 14% was measured using the chiral shift reagent Eu(hfc)$_3$ in C_6D_6.

Reaction of the 1,1-Dimethoxy-1-propene with *C*-Phenyl-*N*-benzyl Nitrone.[4b] Using the above procedure, the ketene acetal (70 μL, 0.60 mmol) and nitrone (62.7 mg, 0.297 mmol) were reacted in the presence of the catalyst complex **3** (14.0 mg, 0.0182 mmol) and Proton-Sponge (11.8 mg, 0.0551 mmol) in CD_2Cl_2 (440 μL). The products were flash chromatographed through 20 g of silica gel using 8:1 hexane/Et_2O. *trans*-5,5-Dimethoxy-4-methyl-3-phenyl-*N*-benzyl isoxazolidine eluted first. Only partial separation of isomers was obtained. The combined fractions (86.3 mg, 93% yield) had a 17:83 ratio of products (trans/cis). The ^{1}H NMR data came from samples of the pure products which eluted at the beginning and end of the product-containing fractions.^{1}H NMR (500 MHz, $CDCl_3$): trans isomer δ 7.44 (m, 2 H), 7.37−7.19 (m, 8 H), 3.97 (d, J = 14.0 Hz, 1 H), 3.82 (d, J = 14.0 Hz, 1 H), 3.64 (d, J = 10.5 Hz, 1 H), 3.40 (s, 3 H), 3.36 (s, 3 H), 2.65 (dq, J = 10.5, 7.0 Hz, 1 H), 0.98 (d, J = 7.0 Hz, 3 H); cis isomer δ 7.39 (m, 4 H), 7.35−7.20 (m, 6 H), 4.46 (d, J = 7.0 Hz, 1 H), 4.02 (d, J = 14.5 Hz, 1 H), 3.89 (d, J = 14.5 Hz, 1 H), 3.36 (s, 3 H), 3.29 (s, 3 H), 2.74 (quintet, J = 7.0 Hz, 1 H), 0.78 (d, J = 7.0 Hz, 3 H).

Reaction of 1,1-Dimethoxy-1-propene with *C,N*-Diphenyl Nitrone.[4b] Using the above procedure, the ketene acetal (46 μL, 0.40 mmol) and nitrone (59.9 mg, 0.304 mmol) were reacted in the presence of the complex **3** (14.1 mg, 0.0183 mmol) and Proton-Sponge (10.7 mg, 0.0499 mmol) in CD_2Cl_2 (470 μL). On completion of the reaction, a 32:68 ratio of products (trans/cis) was obtained. The products were flash chromatographed on 20 g of silica gel using 4:1 hexane/Et_2O. *trans*-2,3-Diphenyl-4-methyl-5,5-dimethoxyisoxazolidine eluted first. Only partial separation of isomers was obtained, which enabled the preparation of pure ^{1}H NMR samples for each isomer. The combined fractions (76.7 mg, 84% yield) had a 31:69 ratio of products (trans/cis). ^{1}H NMR (500 MHz, $CDCl_3$): trans isomer δ 7.52 (d, J = 7.0 Hz, 2 H), 7.39 (t, J = 7.5 Hz, 2 H), 7.33 (tt, J = 7.5, 1.5 Hz, 1 H), 7.17 (t, J = 8.0 Hz, 2 H), 6.89 (m, 3 H), 4.21 (d, J = 10.4 Hz, 1 H), 3.54 (s, 3 H), 3.36 (s, 3 H), 2.71 (dq, J = 10.4, 6.8 Hz, 1 H), 1.05 (d, J = 6.8 Hz, 3 H); cis isomer δ 7.40 (d, J = 7.0 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 2 H), 7.28 (m, 1 H), 7.17 (dd, J = 8.8, 7.3 Hz, 2 H), 6.89 (m, 3 H), 4.97 (d, J = 7.1 Hz, 1 H), 3.41 (s, 3 H), 3.21 (s, 3 H), 2.85 (quintet, J = 7.1 Hz, 1 H), 0.79 (d, J = 7.1 Hz, 3 H).

Reaction of Methoxypropene with Nitrone 1.[4a] The nitrone **1** (207.0 mg, 1.406 mmol) and pyridinium triflate (25.8 mg, 0.113 mmol) were dissolved in CH_2Cl_2 (2.2 mL). Methoxypropene (260 μL, 2.7 mmol) was then added. After 24 h, the mixture was worked up as described above. The products were flash chromatographed on 50 g of silica gel using 2:1 hexane/Et_2O. The cis product (84.5 mg, 28% yield) eluted before the trans product (141.9 mg, 48% yield). ^{1}H NMR (500 MHz, $CDCl_3$): cis product δ 7.18−7.00 (m, 4 H), 4.71 (t, J = 9.2 Hz, 1 H), 3.62 (td, J = 11.1, 3.3 Hz, 1 H), 3.38 (td, J = 11.3, 4.1 Hz, 1 H), 3.31 (s, 3H), 3.03 (ddd, J = 16.2, 11.2, 4.9 Hz, 1 H), 2.79 (d, J = 14.7 Hz, 1 H), 2.71 (dd, J = 12.9, 8.1, 1 H), 2.57 (t, J = 11.5 Hz, 1 H), 1.55 (s, 3 H); trans product δ 7.22−7.13 (m, 2 H), 7.10 (t, J = 8.8 Hz, 2 H), 4.87 (t, J = 7.9 Hz, 1 H), 3.38 (s, 3 H), 3.30 (t, J = 5.8 Hz, 2 H), 2.91 (dt, J = 16.2, 5.2 Hz, 1 H), 2.84 (dt, J = 16.2, 6.1 Hz, 1 H), 2.79 (dd, J = 12.6, 7.0 Hz, 1 H), 2.30 (dd, J = 12.6, 8.8 Hz, 1 H), 1.46 (s, 3 H). The stereochemistry of the cis product was determined by difference NOE ^{1}H NMR spectroscopy. The $-CH_3$ group at 1.55 ppm was irradiated, establishing that the resonance at 2.71 ppm (H_C; 5.7% enhancement) has a cis relationship to the methyl group, whereas the resonance at 2.57 ppm (H_T; 0.8% enhancement) has a trans relationship. Irradiation of the benzylic resonance at 4.71 ppm showed that the benzylic proton was also cis to H_C (5.4% enhancement) and trans to H_T (1.5% enhancement).



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Supporting Information Available: Tables of atomic coordinates, bond distances and angles, thermal parameters, and diagrams of the two independent molecules (15 pages). Ordering information is given on any current masthead page.

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