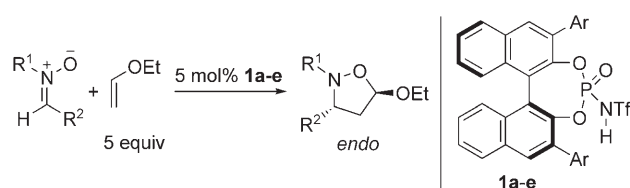


Enantioselective 1,3-Dipolar Cycloaddition of Nitrones with Ethyl Vinyl Ether: The Difference between Brønsted and Lewis Acid Catalysis**

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Chiral Brønsted acid catalysis has recently become attractive because of its wide application in various asymmetric syntheses.^[1] Among these catalysts, chiral phosphoric acids represent an outstanding example.^[2] Whereas phosphoric acids are used to activate imine type compounds, we reported the first preparation of chiral *N*-triflyl phosphoramidate **1a** (Scheme 1, Table 1) and its utility in activating a carbonyl



Scheme 1. Chiral phosphoramidate-catalyzed 1,3-dipolar cycloaddition of diaryl nitrones with ethyl vinyl ether. Tf = trifluoromethanesulfonyl.

group in the asymmetric Diels–Alder reaction of ethyl vinyl ketone with silyloxydienes.^[3] In these reactions, ethyl vinyl ketone was activated by **1a** to give the *endo* products in up to 92 % *ee*, whereas chiral phosphoric acids failed to give the Diels–Alder product under the same reaction conditions. Another example of a chiral *N*-triflyl phosphoramidate serving as a catalyst for carbonyl group activation is the asymmetric Nazarov cyclization reported by Rueping et al.^[4] Reported herein is a new application of our chiral phosphoramidate in the asymmetric 1,3-dipolar cycloaddition of diaryl nitrones with ethyl vinyl ether (Scheme 1). This is the first example of an asymmetric 1,3-dipolar cycloaddition of nitrones catalyzed by a chiral Brønsted acid. Wittkopp and Schreiner reported some pioneering work on 1,3-dipolar cycloadditions between an *N*, α -diphenyl nitrone and isopropyl vinyl ether at high temperature with one equivalent of an achiral thiourea derivative as a catalyst, and modest acceleration was reported.^[5] Our phosphoramidate can effectively catalyze the

reaction at lower temperatures (–40 to –55 °C). In sharp contrast to the *exo* selectivity of the AlMe–binol catalyzed cycloaddition of diaryl nitrones with alkyl vinyl ether reported by Jørgensen and co-workers,^[6] our reactions give the *endo* products as the major diastereomers.^[7]

First, we tested commercially available *N*, α -diphenyl nitrone as a substrate for 1,3-dipolar cycloadditions. When the reaction was carried out between –78 and –20 °C in CH₂Cl₂, the *ee* value was increased to 64 % from 51 % at room temperature. When electron-withdrawing groups were introduced to the nitrone similar results were observed, but the reaction rate was accelerated significantly. Then, the cycloaddition of *N*-(4-chlorophenyl)- α -phenyl nitrone was conducted in different solvents and at various temperatures with **1a** as the catalyst.^[8] CHCl₃ gave the best results with respect to both the diastereo- and enantioselectivities of the products (Table 1, entry 1).

Next, we compared chiral phosphoramidates bearing different aryl groups at the 3,3'-positions of the binol backbone under the optimized reaction conditions (Table 1). On the

Table 1: Catalyst screening for the 1,3-dipolar cycloaddition of nitrone (see Scheme 1).^[a,b]

Entry	Ar		Yield [%] ^[c]	<i>endo:exo</i> ^[d]	<i>ee</i> [%] ^[e]
1		1a	70	79:21	77
2		1b	53	57:43	17
3		1c	86	81:19	7
4		1d	92	90:10	76
5		1e	92	96:4	84

[a] Nitrone substituents: R¹ = 4-ClPh and R² = Ph. Ad = adamantyl. [b] CHCl₃ was used as the solvent and reactions were run at –55 °C for 1 h. [c] Yield of isolated cycloadduct. [d] Determined by ¹H NMR spectroscopy. [e] Determined for the *endo* product by chiral HPLC methods.

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basis of the diastereo- and enantioselectivities of the reaction, catalysts having 2,6-isopropyl groups on the phenyl ring attached to the binol backbone (**1a**, **1d**, and **1e**) are superior to those lacking the isopropyl groups (**1b** and **1c**). Gratifyingly, the catalyst with the 1-adamantyl group at the *para* position of Ar ring (**1e**) gave a higher *ee* value than **1a** or **1d** (Table 1, entry 5 versus entries 1 and 4). In fact, X-ray crystallographic analysis of **1e** revealed that the adamantyl groups in the molecule are positioned to create a suitable chiral environment for the reaction (Figure 1). The crystal

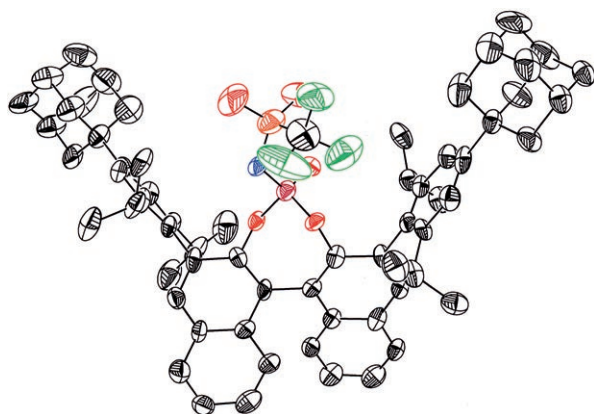


Figure 1. ORTEP view (50% probability level) of catalyst **1e** in anion form (O red, S yellow, F green, N blue, P purple, C gray).

structure of **1e** reveals that one P–O bond (1.45 Å) is shorter than the other two bonds (1.60 Å), which implies the existence of P=O bond.^[9] The observed P–N bond (1.61 Å) is longer than P=N bond (1.52 Å).^[9] Thus, as suggested in the molecular structures of the phosphoramides (Scheme 1), the proton is located on the N atom, instead of the O atom bonded to the P center.

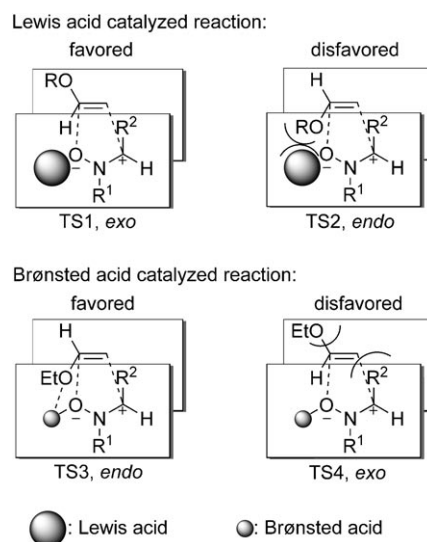
The scope of the nitrones in 1,3-dipolar cycloaddition was examined by using catalyst **1e** (Table 2). In most cases (the exceptions are Table 2, entries 12 and 16) the reaction was complete within 1 hour and gave the *endo* products predominantly and with high enantioselectivities. For diphenyl nitrones an electron-withdrawing group (R^2) is necessary to ensure good enantioselectivity.

The diastereoselectivity difference between the above [3+2] cycloaddition catalyzed by Brønsted acid **1e** (up to 96% *endo* selective) and the reaction catalyzed by a AlMe₃-binol complex (up to > 95% *exo* selective) can be rationalized by transition-state (TS) structures (Scheme 2).^[6] The dominant secondary π -orbital interactions that are responsible for *endo* selectivity in the Diels–Alder reaction are weaker in the 1,3-dipolar cycloaddition reaction.^[10] The *exo* approach (TS1) of the alkyl vinyl ether to the nitrone substrate is more favored than the *endo* approach (TS2) for the aluminum-catalyzed cycloaddition because of the steric repulsion between the alkoxy group and the bulky Lewis acid.^[6,11] For the Brønsted acid catalyzed reaction, the much smaller acidic proton allows ethyl vinyl ether to approach in an *endo* selective way (TS3). The *exo* selectivity (TS4) might be disfavored because of the steric repulsion between the ethoxy

Table 2: Scope of diaryl nitrones in 1,3-dipolar cycloadditions with ethyl vinyl ether (see Scheme 1).^[a,b]

Entry	R ¹	R ²	T [°C]	Yield [%] ^[c]	<i>endo:exo</i> ^[d]	<i>ee</i> [%] ^[e,f]
1	Ph	Ph	–40	85	96:4	70
2 ^[g]	Ph	Ph	–40	78	95:5	56
3	Ph	4-ClPh	–55	95	97:3	90
4	Ph	4-CF ₃ Ph	–55	69	96:4	92
5	Ph	4-NO ₂ Ph	–55	91	89:11	90
6	Ph	3,5-F ₂ Ph	–50	92	91:9	85
7	4-ClPh	Ph	–55	92	96:4	84
8	4-ClPh	4-ClPh	–55	74	96:4	90
9	4-ClPh	4-CF ₃ Ph	–55	66	93:7	93
10	4-ClPh	4-NO ₂ Ph	–55	98	89:11	92
11	4-ClPh	2-furyl	–50	95	93:7	89
12 ^[h]	4-ClPh	2-thienyl	–50	> 99	96:4	92
13	4-FPh	4-FPh	–40	76	87:13	85
14	4-FPh	4-NO ₂ Ph	–55	> 99	87:13	87
15	4-FPh	2-furyl	–40	90	88:12	87
16 ^[h]	4-FPh	2-thienyl	–40	97	93:7	87

[a] Used 0.2 mmol nitrone and 5 mol % **1e**. [b] Used CHCl₃ as the solvent and the reaction time was 1 h. [c] Yield of isolated cycloadduct. [d] Determined by ¹H NMR spectroscopy. [e] Determined for *endo* product by chiral HPLC methods. [f] For assignment of absolute configurations, see the Supporting Information. [g] Used *tert*-butyl vinyl ether. [h] Reaction time of 6 h.



Scheme 2. Transition-state structures showing the diastereoselectivity of the Brønsted and Lewis acid catalyzed 1,3-dipolar cycloadditions of nitrones.

and R^2 groups. Additionally, hydrogen bonding between the proton of Brønsted acid and the oxygen atom of ethyl vinyl ether may stabilize the *endo* selective transition state (TS3).

In summary, we prepared and used catalyst **1e** in the 1,3-dipolar cycloaddition of diaryl nitrones to ethyl vinyl ether. Only 5 mol % of this air-stable catalyst leads to complete reaction within 1 hour. The *endo* selectivity of the cycloaddition is amenable to the previously reported *exo* selectivity of the aluminum-catalyzed reaction.^[6] These results demonstrate the usefulness of Brønsted acid catalysts for asymmetric synthesis, which is complementary to Lewis acid catalysis.^[12] Additionally, the importance of larger alkyl groups in the *para*

positions of the aryl rings (3,3'-positions) of the binol structure provides important information for future research into the design of these Brønsted acids.

Experimental Section

General procedure for 1,3-dipolar cycloaddition of diaryl nitrones with ethyl vinyl ether catalyzed by **1e**: A solution of nitrone (0.2 mmol) in anhydrous CHCl_3 (5 mL) was cooled to the temperature indicated in Table 2. Ethyl vinyl ether (1.0 mmol, 96 μL) was added by syringe. After stirring the reaction mixture for 10 min, (S)-phosphoramidate **1e** (0.01 mmol, 11 mg) was added. The reaction was monitored by TLC (4:1 hexanes/AcOEt) until all the nitrone was consumed (usually one hour was sufficient). Saturated aqueous Na_2CO_3 (5 mL) was added to the reaction mixture, and the cold mixture was stirred for 10 min. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography on silica gel with hexanes/ Et_2O . The *endo* product eluted immediately after the *exo* product. After concentration of the eluates, the yield of the cycloadduct was determined and the *endo:exo* ratio analyzed by ^1H NMR spectroscopy.

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