Asymmetric Synthesis

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

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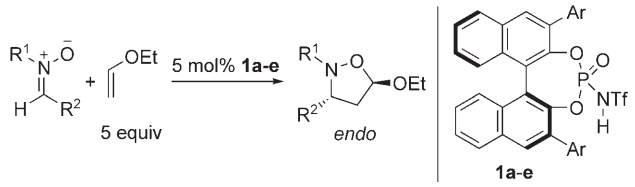
Chiral Brønsted acid catalysis has recently become attractive because of its wide application in various asymmetric syntheses.[1] Among these catalysts, chiral phosphoric acids represent an outstanding example.[2] Whereas phosphoric acids are used to activate imine type compounds, we reported the first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



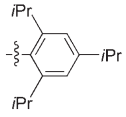
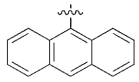
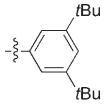
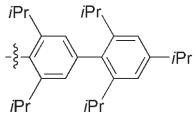
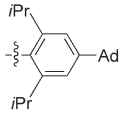
Scheme 1. Chiral phosphoramide-catalyzed 1,3-dipolar cycloaddition of diaryl nitrones with ethyl vinyl ether. Tf = trifluoromethanesulfonyl.

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 phosphoramide 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 phosphoramide 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 phosphoramide 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 CH_2Cl_2, 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] $CHCl_3$ gave the best results with respect to both the diastereo- and enantioselectivities of the products (Table 1, entry 1).

Next, we compared chiral phosphoramides 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]	*endo*:*exo*[d]	*ee* [%][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 substitutents: R^1 = 4-ClPh and R^2 = Ph. Ad = adamantyl. [b] $CHCl_3$ was used as the solvent and reactions were run at −55 °C for 1 h. [c] Yield of isolated cycloadduct. [d] Determined by ^{1}H 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 crystollographic 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

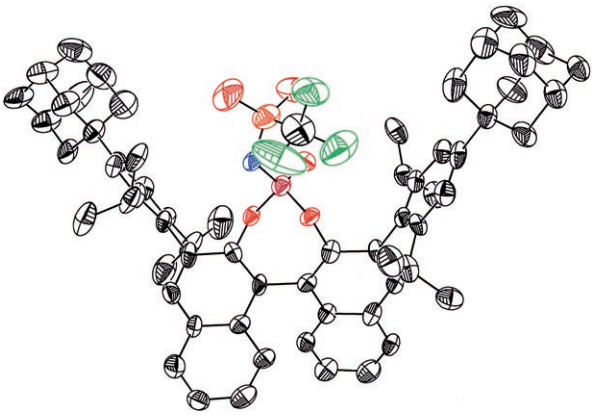


Figure 1. ORTEP view (50% probability level) of catalyst **1e** in anion form (O red, S yellow, F green, N blue, P purple, C gray).

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.

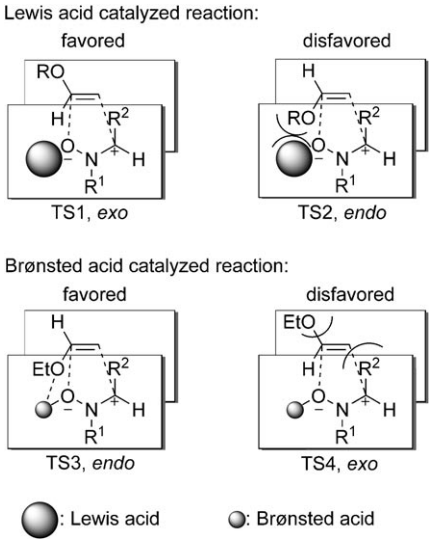
The scope of the nitrones in 1,3-dipolar cycloaddition was examined by using catalyst **1e** (Table 2). In most cases (the exceptions are Table 2, entries 12 and 16) the reaction was complete within 1 hour and gave the *endo* products predominantly and with high enantioselectivities. For diphenyl nitrones 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 AlMe–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]	*endo*:*exo*[d]	*ee* [%][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_3Ph	−55	69	96:4	92
5	Ph	4-NO_2Ph	−55	91	89:11	90
6	Ph	3,5-F_2Ph	−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_3Ph	−55	66	93:7	93
10	4-ClPh	4-NO_2Ph	−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_2Ph	−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 $CHCl_3$ as the solvent and the reaction time was 1 h. [c] Yield of isolated cycloadduct. [d] Determined by ^{1}H 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*)-phosphoramide **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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