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Design of Chiral *N*-Triflyl Phosphoramide as a Strong Chiral Brønsted Acid and Its Application to Asymmetric Diels−Alder Reaction

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Metal-free chiral Brønsted acid catalysis has recently emerged as a new class of chiral organic catalysis. Several quite nice chiral Brønsted acids, such as urea/thiourea, alcohol, and phosphoric acid, have already been reported as a chiral electron acceptor of carbonyl and imine compounds.[1] However, compared with chiral metal Lewis acid catalysts, the utility of chiral Brønsted acid catalysts is still limited to the reactive substrates. This drawback can be overcome by designing a Brønsted acid catalyst with higher acidity. To increase the acidity of Brønsted acids, it is necessary to increase the stability of the counteranion. Koppel and co-workers reported that introduction of a strong electron acceptor group, such as ═NTf, into an acid system instead of an ═O group increased the stability of counteranions and their acidity (Figure 1).[2] For example, the pK_a of *N*-triflyl benzamide in acetonitrile (11.06) is much lower than that of benzoic acid (20.7). Recently, Akiyama and Terada's chiral phosphoric acid was reported to be a most powerful chiral Brønsted acid.[3] Unfortunately, however, the relatively low acidity of phosphoric acid makes this excellent catalyst of rather limited use in future applications. We expected that strong chiral Brønsted acid would be achieved by introduction of a ═NTf group into the phosphoric acid.[4]

Metal Lewis acid-catalyzed asymmetric Diels−Alder reaction is one of the most studied reactions. However, chiral metal Lewis acid-catalyzed asymmetric Diels−Alder reaction of α,β-unsaturated ketone is still rare because the recognition of two lone pairs and the control of the s-*cis*/s-*trans* conformation of α,β-unsaturated ketone are difficult.[5,6] Recently, we reported that Brønsted acid is a suitable catalyst for the Diels−Alder reaction of α,β-unsaturated ketone.[7] Herein we describe the preparation of a new designer chiral strong Brønsted acid and its application to the asymmetric Diels−Alder reaction of α,β-unsaturated ketone.[8]

As shown in Scheme 1, chiral *N*-triflyl phosphoramides **2** and **3** were easily synthesized from optically active BINOL derivatives by phosphorylation with $POCl_3$ and amidation between resultant phosphoryl chloride and $TfNH_2$.

First, to compare the catalytic activity of chiral Brønsted acids **1**−**3**, the asymmetric Diels−Alder reactions of ethyl vinyl ketone were investigated; the results are summarized in Table 1. Although, using 5 mol % of **1** with **4**, no reaction was observed (entry 1 in Table 1), **2** and **3** gave desired Diels−Alder product in high yield with moderate enantiomeric excess (entries 2 and 3 in Table 1). Thus, the reactivity was enhanced dramatically by the introduction of a ═NTf group into the phosphoric acid. Even with the more reactive **5**, **1** showed no catalytic activity (entry 4 in Table 1). However, whereas **2** gave a trace amount of Diels−Alder product, **3** provided the desired product in quantitative yield with high enantiomeric excess (entries 5 and 6 in Table 1).[9] This observed significant difference of reactivity between **2** and **3** is explained by the rapid quenching of catalyst with **5**. In fact, the same reaction using 5 mol % of **3**, pretreated with TIPS enol ether of acetophenone, gave no desired product (Scheme 2);[10] silylated **3** has no catalytic activity.[11] In entry 5, **2** was initially silylated by **5** under the reaction conditions, whereas, in entry 6, silylation of **3** might be much slower than **2** because of the overwhelming bulkiness adjacent to the acidic proton.

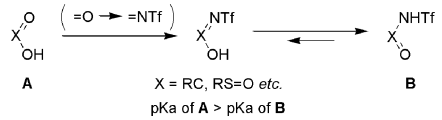


Figure 1. Enhancement of the acidity of Brønsted acid by a strong electron acceptor.

Scheme 1. Preparation of Chiral Phosphoramide

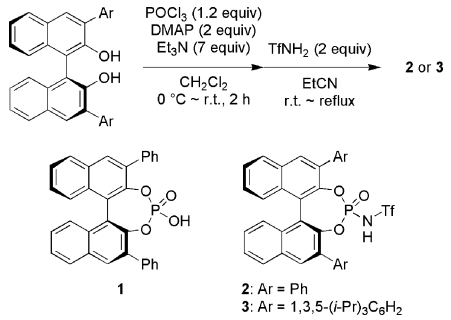
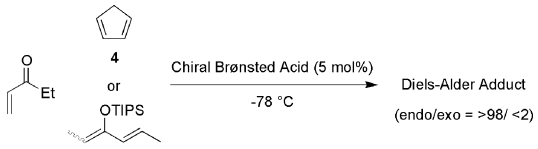


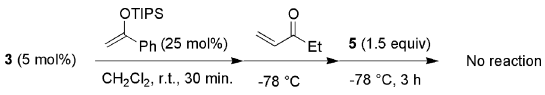
Table 1. Reactivity for the Diels−Alder Reactions[a]



en try	diene (equiv)	chiral Brønsted acid	solvent	time (h)	yield (%)	ee[b] (%) (config.)
1	**4**	**1**	CH_2Cl_2	2	0	n.d.
2	(1.2)	**2**	CH_2Cl_2	2	91	9 (*S*)
3		**3**	CH_2Cl_2	1	86	32 (*R*)
4	**5**[c]	**1**	toluene	3	0	n.d.
5	(1.5)	**2**	toluene	3	<10	n.d.
6		**3**	toluene	3	95[d]	92

[a] Only endo product was observed by ^{1}H NMR. [b] Enantiomeric excess was determined by GC analysis. [c] (*Z*,*E*):(*E*,*E*) = 86:14. [d] Mixture of olefin regio isomer; see Table 2.

Scheme 2. Denial of Chiral Silyl Lewis Acid



Next we optimized the reaction condition for the asymmetric Diels−Alder reaction with **5**. Basically aromatic solvent, such as toluene, is suitable for this reaction. Ethylbenzene and chlorobenzene gave almost the same results as toluene (entries 1−3 in Table 2). Using CH_2Cl_2 as a solvent, the yield was suddenly decreased probably due to the dimerization of diene (entry 4 in Table 2). In

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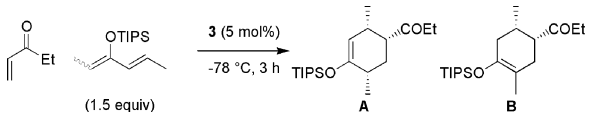
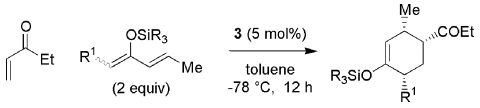
Table 2. Solvent Effect for Asymmetric Diels−Alder Reaction



entry	solvent	yield (%)	**A**:**B**[b]	ee (%)[a]
1	toluene	95	76:24	92
2	ethylbenzene	83	78:22	93
3	chlorobenzene: toluene = 1:2	95	71:29	93
4	CH_2Cl_2	55	n.d.	81
5	hexane	99	85:15	80

[a] Enantiomeric excess was determined by GC analysis after cleavage of the TIPS group. [b] Ratio of **A**:**B** was determined by ^{1}H NMR.

Table 3. Substrate Scope[a]



entry	R_3Si[b]	R^1	yield (%)	ee (%)[c]
1	TBS	Me	43	92
2[d]	TIPS	Me	95[e]	92
3[f]	TIPS	H	43[g]	88
4	TIPS	Bn	>99	85
5	TIPS	(4-TBSOC$_6$H$_4$)CH$_2$	>99	92
6	TIPS	(4-MOMOC$_6$H$_4$)CH$_2$	>99	87
7	TIPS	(4-HOC$_6$H$_4$)CH$_2$	35	82
8	TIPS	BzOCH$_2$CH$_2$	>99	91

[a] (*Z*,*E*)-Silyloxydiene is major. [b] TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl. [c] Enantiomeric excess was determined by GC analysis after cleavage of silicon or by HPLC analysis directly (see Supporting Information). [d] Reaction time was 3 h. [e] 76:24 mixture of olefin regio isomer. [f] **3** (15 mol %) and ethyl vinyl ketone (3 equiv) were used. [g] Yield was determined after the cleavage of the TIPS group because the compound is almost a 1:1 mixture of olefin regio isomer.

the nonpolar solvent, such as hexane, the reaction still proceeded cleanly, but the enantiomeric excess was slightly decreased (entry 5 in Table 2).

The substrate scope of the asymmetric Diels−Alder reactions between ethyl vinyl ketone and silyloxydienes is summarized in Table 3. The bulkiness of the silyl group did not affect the enantioselectivity. The yields of reactions are, however, quite sensitive to the stability of silyloxydienes due to the protonation of diene and deactivation (silylation) of catalyst (entries 1 and 2 in Table 3).[12] For the same reason, α-nonsubstituent silyloxydiene gave relatively low yield but still maintained the high enantiomeric excess value (entry 3 in Table 3). Interestingly, the olefin migration was not observed under the reaction conditions when *tert*-butyldimethylsilyloxydiene was used or when R^1 was a sterically hindered group, such as a benzyl (entries 1 and 4−8 in Table 3). The acid-sensitive groups, such as a silyl ether and methoxymethyl ether, are tolerant in this reaction (entries 5 and 6 in Table 3). Usually, the free hydroxyl group is not compatible with the chiral metal Lewis acid catalyst; however, it is noteworthy that the reaction tolerates this group with chiral Brønsted acid catalyst (entry 7 in Table 3). The Lewis basic functional group, ester moiety, did not affect either the reactivity or the enantioselectivity (entry 8 in Table 3).

In conclusion, we have developed a highly reactive and acidic chiral Brønsted acid catalyst, chiral *N*-triflyl phosphoramide. Highly enantioselective Diels−Alder reaction of α,β-unsaturated ketone with silyloxydiene was demonstrated using this chiral Brønsted acid catalyst. Further applications of *N*-triflyl phosphoramide to other organic reactions are underway in our laboratory.

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Supporting Information Available: Experimental procedure and spectroscopic data of new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

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