

Chiral 1,1'-Binaphthyl-2,2'-diammonium Salt Catalysts for the Enantioselective Diels–Alder Reaction with α -Acyloxyacroleins

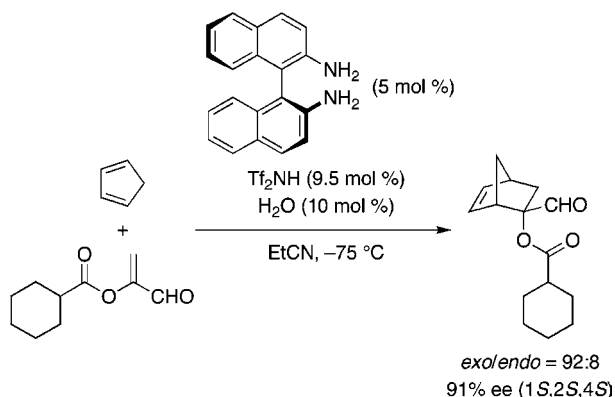
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ABSTRACT



A diammonium salt of chiral 1,1'-binaphthyl-2,2'-diamine and trifluoromethanesulfonimide (Tf_2NH) shows excellent catalytic activity and enantioselectivity for the Diels–Alder reaction of α -acyloxyacroleins with cyclic dienes. For example, in the presence of 5 mol % of the ammonium catalyst, the Diels–Alder reaction of α -(cyclohexanecarbonyloxy)acrolein with cyclopentadiene proceeded in EtCN at $-75\text{ }^\circ\text{C}$ to give the adducts in 88% yield with 92% *exo* and 91% ee. This catalyst can be easily prepared *in situ* by mixing the commercially available chiral diamine and Tf_2NH .

The enantioselective Diels–Alder reaction is one of the most powerful organic transformations and is a versatile method for the synthesis of many important chiral building blocks for the total synthesis of bioactive natural products.¹ Recently, the development of methods based on metal-free organocatalysis has attracted great attention in this area.^{2–4} MacMillan

and co-workers reported the first enantioselective organocatalytic Diels–Alder reaction of dienes with α -unsubstituted acroleins and 2-enones.² Their catalysts, which were chiral ammonium salts of HCl or HClO_4 with secondary amines derived from *L*-phenylalanine, gave good results for the Diels–Alder reaction of α -unsubstituted acroleins and 2-enones. However, it is difficult to activate α -substituted acroleins with the catalysts, probably because of poor generation of the corresponding iminium cations. The relatively greater bulkiness of the secondary amines was

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(3) For chiral organocatalysts for Diels–Alder reactions, see: (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b) Kim, K. H.; Lee, K. S.; Lee, D.-W.; Ko, D.-H.; Ha, D.-C. *Tetrahedron Lett.* **2005**, *46*, 5991. (c) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141.

(4) For a recent review on hydrogen-bonding catalysis, see: Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.

thought to be unfavorable for generating an iminium ion with α -substituted acrolein.⁵

Recently, we reported the enantioselective organocatalytic Diels–Alder reaction with α -acyloxyacrolein.⁶ α -Acyloxyacrolein is an important alternative to α -haloacrolein⁷ and has versatile synthetic utility as a dienophile.⁸ Our catalyst is the chiral ammonium salt of pentafluorobenzenesulfonic acid ($C_6F_5SO_3H$)⁹ with the chiral triamine **1** bearing a primary amino group (Figure 1). The Diels–Alder reactions

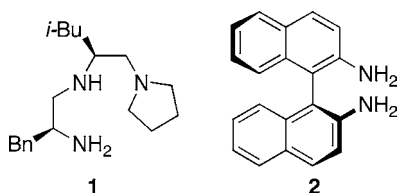


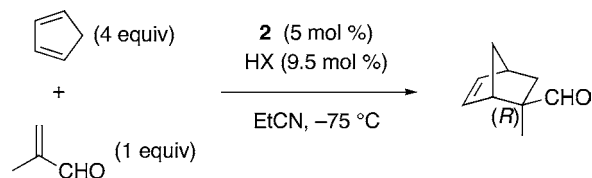
Figure 1. Chiral aliphatic triamine **1** including a primary amino group and aromatic primary diamine **2**.

of acyclic dienes and cyclohexadiene with α -(*p*-methoxybenzoyloxy)acrolein give the adducts with high enantioselectivities. But unfortunately, the enantioselectivity for the reaction of cyclopentadiene is up to 83% ee (20 mol % of catalyst loading). In addition, the catalytic activity is not so high (10~20 mol % of catalyst is loaded at -20 °C to rt) because of its relatively weak acidity. The adducts of cyclopentadiene with α -acyloxyacrolein can be converted to bicyclo[2.2.1]hept-5-en-2-one, which is a promising synthetic intermediate for the total synthesis of several bioactive compounds,¹⁰ and the development of a practical method for the synthesis of the compound in an enantiomerically pure form is strongly needed. To improve the catalytic activity and the enantioselectivity for the Diels–Alder reaction of cyclopentadiene, the use of the ammonium salt of a weakly basic aromatic amine with a super Brønsted acid⁹ at a lower reaction temperature would be desirable. In this paper, we

report a new organocatalyst, an ammonium salt of (*S*)-2,2'-diamino-1,1'-binaphthyl (**2**) with trifluoromethanesulfonimide (Tf_2NH), for the enantioselective Diels–Alder reaction of cyclic dienes with α -acyloxyacroleins (Figure 1).

First, we examined the Diels–Alder reaction of cyclopentadiene (4 equiv) with methacrolein using chiral ammonium salts of commercially available chiral aromatic diamine **2** (5 mol %) and several Brønsted acids (HX, 9.5 mol %) in propionitrile (EtCN) at -75 °C (Table 1). The

Table 1. Diels–Alder Reaction of Cyclopentadiene with Methacrolein^a



entry	HX	time (h)	yield (%)	exo/endo	ee ^b (%)
1	$C_6F_5SO_3H$	15	8	90:10	45
2	TfOH	6	27	97:3	39
3	Tf_2NH	6	13	97:3	61

^a The Diels–Alder reaction of cyclopentadiene (4 mmol) with methacrolein (1 mmol) in EtCN (2 mL) was carried out at -75 °C. ^b Enantiomeric excess of the exo adduct.

ammonium salt of **2** and $C_6F_5SO_3H$ gave (*2R*)-exo adduct as a major diastereomer in a conversion yield of 8% with 45% ee (entry 1). The use of trifluoromethanesulfonic acid (TfOH) gave an enantioselectivity (39% ee) similar to that of $C_6F_5SO_3H$ (entry 2). The use of other sulfonic acids such as (+)-camphorsulfonic acid and 2,4,6-triisopropylbenzenesulfonic acid gave the adducts with low enantioselectivities (<13% ee). On the other hand, ammonium salt of **2** and Tf_2NH gave the Diels–Alder adduct with better enantioselectivity (61% ee) (entry 3).

We then investigated several ammonium salts of *N*-monosubstituted or *N,N'*-disubstituted 2,2'-diamino-1,1'-binaphthyls and Tf_2NH . But unfortunately, they all gave the adduct with lower enantioselectivity (<13% ee).

Next, we examined the Diels–Alder reaction of cyclopentadiene (4 equiv) with α -acyloxyacroleins catalyzed by the ammonium salt of **2** (5 mol %) and Tf_2NH (9.5 mol %) (Table 2). The Diels–Alder reaction with α -(*p*-methoxybenzoyloxy)acrolein, which gave the highest enantiomeric excess (83%) in the Diels–Alder reaction of cyclopentadiene catalyzed by the ammonium salt of **1** and $C_6F_5SO_3H$,⁶ gave the corresponding (*2S*)-exo adduct as a major diastereomer with higher enantiomeric excess (94%) in moderate yield (48%) (entry 1). This result prompted us to investigate the Diels–Alder reaction of cyclopentadiene with several α -acyloxyacroleins catalyzed by the ammonium salt of **2** and Tf_2NH . After screening of several α -acyloxyacroleins, we found that α -(cyclohexanecarbonyloxy)acrolein gave the corresponding adduct with good enantioselectivity (86% ee) and in good yield (80%) (entry 2). The use of the ammonium

(5) MacMillan failed to activate methacrolein with a secondary ammonium salt: Kunz, R. K.; MacMillan D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240.

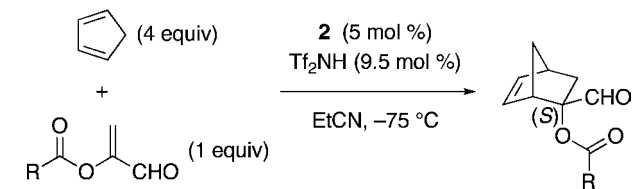
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Table 2. Diels–Alder Reaction of Cyclopentadiene with α -Acyloxyacroleins^a

entry	R	time (h)	yield (%)	exo/endo	ee ^b (%)
1	<i>p</i> -MeOC ₆ H ₄	28	48	93:7	94
2	<i>c</i> -C ₆ H ₁₁	24	80	94:6	86
3 ^c	<i>c</i> -C ₆ H ₁₁	24	72	91:9	71
4 ^d	<i>c</i> -C ₆ H ₁₁	24	88	92:8	91
5 ^d	<i>c</i> -C ₅ H ₉	24	95	92:8	88

^a Unless otherwise noted, the Diels–Alder reaction of cyclopentadiene (1.6 mmol) with α -acyloxyacrolein (0.4 mmol) in EtCN (0.8 mL) was carried out at -75°C . ^b Enantiomeric excess of the exo adduct. ^c The reaction was conducted in the presence of **2** (5 mol %) and Tf_2NH (5 mol %). ^d The reaction was conducted in the presence of 10 mol % of water.

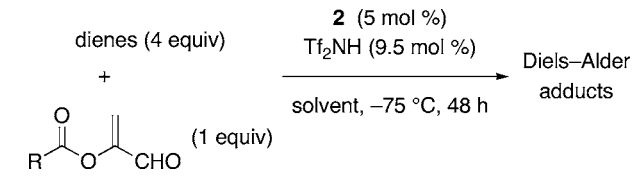
salt of **2** (5 mol %) and Tf_2NH (5 mol %) as a catalyst gave a lower yield (72%) and enantioselectivity (71%) (entry 3). When the reaction with α -(cyclohexanecarbonyloxy)acrolein was conducted in the presence of 10 mol % of water,¹¹ the yield and enantioselectivity were increased (88% yield and 91% ee) (entry 4). α -(Cyclopentanecarbonyloxy)acrolein also gave good results (95% yield, 88% ee) (entry 5).

To explore the generality and scope of the Diels–Alder reaction with α -acyloxyacroleins catalyzed by the ammonium salt of **2** and Tf_2NH , the Diels–Alder reaction of not only cyclic dienes but also acyclic dienes was examined (Table 3). For the Diels–Alder reaction of cyclohexadiene (CH) with α -(cyclohexanecarbonyloxy)acrolein in EtCN , 10 mol % of the catalyst was used because the reactivity of cyclohexadiene was lower than that of cyclopentadiene and gave the corresponding (2*S*)-*endo*-adduct as a major diastereomer (>99% de) in 92% yield with 91% ee (entry 1). The use of EtNO_2 as a solvent increased the reactivity, and 5 mol % of the catalyst was active enough for the Diels–Alder reaction of cyclohexadiene (90% yield, 91% ee) (entry 2).¹² α -(Cyclopentanecarbonyloxy)acrolein also gave good results (97% yield, 87% ee) (entry 3). The Diels–Alder adducts of cyclohexadiene with α -acyloxyacrolein can be converted to bicyclo[2.2.2]oct-5-en-2-one, which is also useful as a common intermediate for the total syntheses of several bioactive compounds.¹³ The Diels–Alder reaction

(11) The reaction conducted in the presence of water (100 mol %) gave similar results. When the reaction was carried out in the presence of more than 500 mol % of water, solvent was partially frozen and the reactivity was decreased.

(12) When the Diels–Alder reaction of cyclopentadiene with α -acyloxyacroleins was conducted in EtNO_2 , cyclopentadiene polymerized and the Diels–Alder adducts were obtained with low enantioselectivity.

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Table 3. Diels–Alder Reaction of Dienes with α -Acyloxyacroleins^a

entry	diene	R	solvent	yield (%)	exo/endo	ee ^b (%) [config]
1 ^c	CH ^d	<i>c</i> -C ₆ H ₁₁	EtCN	92	<1:>99	91 [2 <i>S</i>]
2	CH ^d	<i>c</i> -C ₆ H ₁₁	EtNO_2	90	<1:>99	91 [2 <i>S</i>]
3	CH ^d	<i>c</i> -C ₅ H ₉	EtNO_2	97	<1:>99	87 [2 <i>S</i>]
4 ^c	DMB ^d	<i>c</i> -C ₆ H ₁₁	EtNO_2	88		70 [-]
5 ^c	DMB ^d	<i>c</i> -C ₅ H ₉	EtNO_2	98		65 [-]

^a Unless otherwise noted, the Diels–Alder reaction of dienes (1.6 mmol) with α -acyloxyacroleins (0.4 mmol) in solvent (0.8 mL) was carried out at -75°C . ^b Enantiomeric excess of the major diastereomer. ^c The reaction was conducted in the presence of **2** (10 mol %), Tf_2NH (19 mol %), and water (10 mol %). ^d See text.

of acyclic dienes, such as 2,3-dimethylbutadiene (DMB), gave the corresponding adducts in high (88–98%) yield with moderate (65–70%) enantioselectivities (entries 4 and 5).

Next, a ¹H NMR study was conducted to explore the reaction mechanism. In the case of the present Diels–Alder reaction, two reaction mechanisms can be proposed. One reaction mechanism includes reversible formation of the aldimine intermediate activated by a Brønsted acid, as reported by us.⁶ The other is chiral Brønsted acid catalysis, as reported by Rawal.¹⁴ Thus, we examined whether the aldimine could be formed from α -acyloxyacrolein and **2**·1.9*Tf*₂NH by an ¹H NMR study. α -(Cyclohexanecarbonyloxy)acrolein was mixed with **2** (1 equiv) and Tf_2NH (1.9 equiv) in CD_3CN and analyzed by ¹H NMR. Three new singlets corresponding to an aldimine proton (8.96 ppm, $-\text{CH}=\text{NH}^+-$) and protons of an *exo*-methylene group (6.68 and 6.60 ppm, $\text{CH}_2=\text{C}-$) appeared in the spectra, which suggested formation of the aldimine, albeit only a small amount (ca. 5%). The fact that a catalytic amount of water promoted the Diels–Alder reaction also suggested the formation of the aldimine as an active intermediate.

According to an X-ray structural analysis of α -(*p*-methoxybenzoyloxy)acrolein, the plane of the *s-trans* acrolein moiety and the plane of the acyloxy group can be distorted (Figure 2, top).¹⁵ A transition state was proposed on the basis of the ¹H NMR study and the X-ray structure of α -(*p*-methoxybenzoyloxy)acrolein as shown in Figure 2 (bottom). The present Diels–Alder reaction might proceed via **TS-1** or **TS-2**. In each transition-state assembly, one of the amino groups of the diamine forms the aldimine with α -acyloxyacrolein, and the other amino group forms the ammonium salt with Tf_2NH . In **TS-1**, the aldimine is activated by the other molecule of Tf_2NH to be the active dication intermedi-

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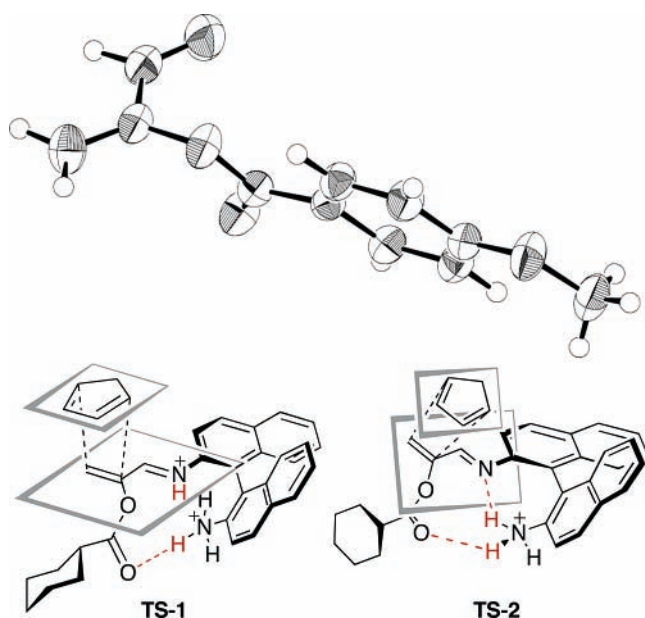


Figure 2. ORTEP plot of α -(*p*-methoxybenzoyloxy)acrolein (top) and proposed transition-state assemblies (bottom). Counteranions (Tf_2N^-) are omitted for clarity.

ate. Moreover, the acyloxy group should be activated by a linear intramolecular hydrogen bonding with a proton of the ammonium group in the same molecule. In **TS-1**, the diene should approach the *si*-face of the dienophile from the less-hindered side to give the (*2S*)-*exo* adduct. On the other hand, in **TS-2**, both the aldimine and the acyloxy group are activated by the ammonium protons in the same molecule. However, the two intramolecular hydrogen bondings of the nitrogen of aldimine with a proton of the ammonium group ($\text{N}\cdots\text{H}-\text{N}$) and the carbonyl oxygen of the acyloxy group with a proton of the ammonium group ($\text{O}\cdots\text{H}-\text{N}$) are not linear; therefore, these hydrogen bondings are weak, and **TS-2** is conformationally unstable. Moreover, the aldimine of **TS-2** is activated by the weakly acidic ammonium group, while the aldimine of **TS-1** is activated by superacidic $\text{Tf}_2\text{-}$

NH. Therefore, **TS-2** should be less reactive than **TS-1**. Indeed, the reaction catalyzed by the ammonium salt of **2** (5 mol %) and Tf_2NH (5 mol %), which should proceed via **TS-2**, gave the low reactivity and low enantioselectivity (Table 2, entry 3). Therefore, it is suggested that the present Diels–Alder reaction proceeded via **TS-1**.

In conclusion, we have developed the chiral ammonium salt of binaphthyl-based diamine **2** with Tf_2NH as a catalyst for the enantioselective Diels–Alder reaction. The use of a small amount (5 mol %) of this chiral ammonium catalyst at a lower reaction temperature ($-75\text{ }^\circ\text{C}$) allowed better reactivity and enantioselectivity than with the ammonium salt of triamine **1** with $\text{C}_6\text{F}_5\text{SO}_3\text{H}$ in the Diels–Alder reaction of cyclic dienes with α -acyloxyacroleins. The ammonium catalyst could be easily prepared in situ by mixing commercially available 2,2'-diamino-1,1'-binaphthyl **2** and $\text{Tf}_2\text{-NH}$.

Acknowledgment. Financial support for this project was provided by JSPS KAKENHI(15205021) and the 21st Century COE Program of MEXT.

Supporting Information Available: Experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) Crystal data for α -(*p*-methoxybenzoyloxy)acrolein: Bruker SMART APEX diffractometer with CCD detector (graphite monochromator, Mo $\text{K}\alpha$ radiation, $\lambda = 0.71073\text{ \AA}$). The structure was solved by direct methods and expanded using Fourier techniques: formula $\text{C}_{11}\text{H}_{10}\text{O}_4$, colorless, crystal dimensions $0.20 \times 0.20 \times 0.20\text{ mm}^3$, monoclinic, space group $P2_1(\#4)$, $a = 6.437(2)\text{ \AA}$, $b = 7.173(3)\text{ \AA}$, $c = 22.181(8)\text{ \AA}$, $\beta = 95.980(7)^\circ$, $V = 1018.5(7)\text{ \AA}^3$, $Z = 4$, and $D_{\text{calc}} = 1.345\text{ g cm}^{-3}$, $F(000) = 432$, $\mu = 0.103\text{ mm}^{-1}$, $T = 223(2)\text{ K}$. 2635 reflections collected, 2022 independent reflections with $I > 2\sigma(I)$ ($2\theta_{\text{max}} = 29.07^\circ$), and 176 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. $R_1 = 0.0542$ and $wR_2 = 0.1613$, GOF = 1.063. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk]. Supplementary publication no. CCDC-286812.