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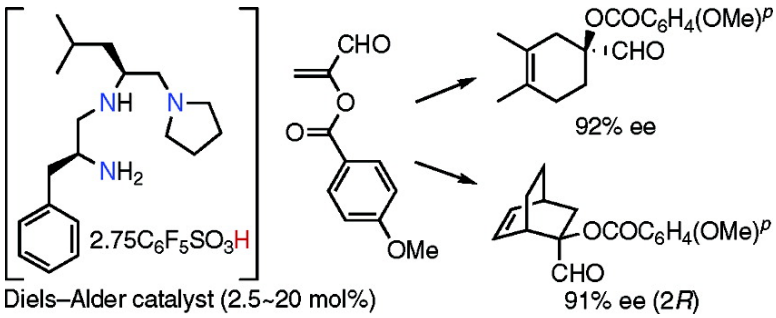

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Design of an Organocatalyst for the Enantioselective Diels−Alder Reaction with α-Acyloxyacroleins

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The first enantioselective organocatalytic Diels−Alder (DA) reactions of dienes with α-unsubstituted acroleins and 2-enones were reported by MacMillan et al.[1,2] Their catalysts were chiral ammonium salts of HCl or $HClO_4$ with *secondary* amines derived from L-phenylalanine. We report here a new organocatalyst for the enantioselective DA reaction with α-substituted acroleins. This organocatalyst was an ammonium salt of $C_6F_5SO_3H$ with chiral triamine **1k** bearing a *primary* amino group (Figure 1). To the best of our knowledge, this is the first example of the enantioselective DA reaction with α-acyloxyacroleins,[3] which were useful as synthetic equivalents of α-haloacroleins.[4,5]

According to our preliminary experimental results, it is difficult to activate α-substituted acroleins with *secondary* amines and Brønsted acids (HX) probably because of poor generation of the corresponding iminium ions.[6] We attempted to activate them through the corresponding aldimines by catalytic amounts of *primary* amines and HX. Our strategy for the design of organocatalyst **1**•HX is shown in Scheme 1. We expected that the chiral ammonium salt of 1,2-diamine **1** readily derived from L-amino acid and HX induces its asymmetry to DA adducts through five-membered cyclic *cis*- or *trans*-transition state (TS) **2**. If *cis*-TS **2** is more favorable than *trans*-TS **2** by $\pi-\pi$ attractive interaction between R^1 and $H_2C{=}CY$ and steric hindrance between X^- and $H_2C{=}CY$, the DA adduct might be obtained with high enantiomeric excess. If steric hindrance occurs not only between X^- and Y but also between R^1 and $H_2C{=}CY$ in TS **2**, the α-face addition of diene to the *s-cis* rotamer of *trans*-TS **2** would be preferable to lead to the same enantiomeric product.

First, several chiral ammonium salts prepared from diamine **1** (10 mol %) and 2,4-$(NO_2)_2C_6H_3SO_3H$ (20 mol %)[7] were examined for the DA reaction between cyclopentadiene and methacrolein in a 1:1 (v/v) mixed solvent of water and 1,4-dioxane at room temperature under air (Table 1). The use of **1** (R^1 = arylmethyl group) gave (2*R*)-*exo*-adduct with relatively good enantioselectivity (entry 2), while **1** (R^1 = aliphatic group) gave quite low enantioselectivity (entry 5). Diamine **1** (R^1 = Bn) derived from L-phenylalanine gave the best result. The absolute stereochemical course via **1a**−**c** could be understood by $\pi-\pi$ attractive interaction between a phenyl group and the *re* face of an isopropenyl group in *cis*-TS **2**. R^2 and R^3 in **1** (R^1 = Bn) were also screened. When either or both of them were primary alkyl groups, higher enantioselectivities were observed (entries 2 and 3 versus entries 1 and 4). When (*S*)-1,2-di(*N*-ethylamino)-3-phenylpropane (*N*-Et-**1f**) was used instead of **1a**, racemic *exo*-adduct was obtained in less than 40% yield (entry 6). Thus, the existence of a primary amino group in **1** was essential for the present asymmetric DA catalysis.

Next, R^2 and R^3 of **1** (R^1 = Bn) were further screened to attain higher enantioselectivity. We expected that chiral triamines **1g**−**j** (R^1 = Bn, $R^2 = (CH_2)_nNR^4R^5$) might be more effective than diamines **1b** and **1c** because of the instability of *trans*-TS **2** due to the steric bulkiness of $(CH_2)_nNR^4R^5$•HX (Figure 1). Actually, the

Scheme 1. Design of a New Organocatalyst for the Enantioselective DA Reaction with α-Substituted Acroleins

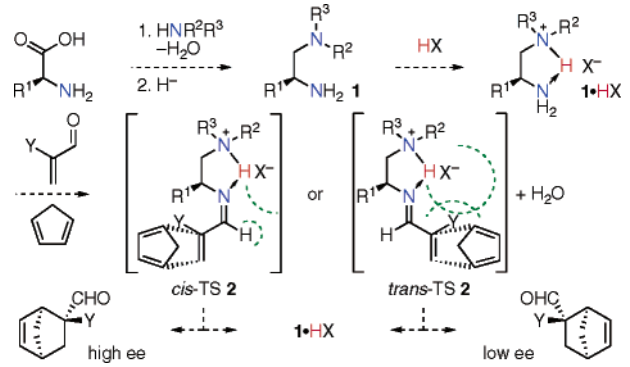
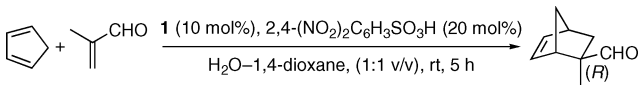


Table 1. DA Reaction of Cyclopentadiene with Methacrolein[a]



entry	**1** [R^1, R^2, R^3]	yield (%)	*exo*:*endo*	ee (%)[b]
1	**1a** [Bn, H, H]	73	95:5	48
2	**1b** [Bn, Bn, H]	73	88:12	52
3	**1c** [Bn, $(CH_2)_2$, $(CH_2)_2$]	85	89:11	52
4	**1d** [Bn, *i*-Pr, *i*-Pr]	67	87:13	0
5	**1e** [*i*-Pr, Bn, H]	66	89:11	21
6	*N*-Et-**1f** [Bn, Et, H][c]	<40	86:14	0

[a] The DA reaction of cyclopentadiene (3.2 mmol) with methacrolein (0.8 mmol) in H_2O (0.25 mL)/1,4-dioxane (0.25 mL) was carried out. [b] Enantiomeric excess of the *exo*-adduct. [c] For *N*-Et-**1f**, see text.

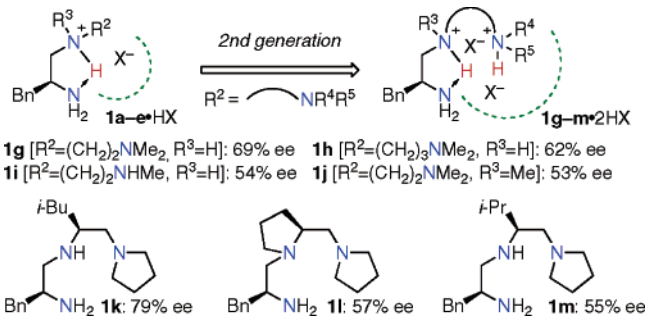


Figure 1. Enantiomeric excess of the *exo*-DA adduct of cyclopentadiene and methacrolein [catalyst: **1g**−**m** (10 mol %) + 2,4-$(NO_2)_2C_6H_3SO_3H$ (25 mol %); the same conditions as in Table 1].

enantiomeric excess of the *exo*-adduct of cyclopentadiene and methacrolein was increased from 52 to 69% by changing R^2 of **1b** from a Bn group to $(CH_2)_2NMe_2$. Chiral triamine **1g** ($R^2 = (CH_2)_2NMe_2$, R^3 = H) was superior to **1h** ($R^2 = (CH_2)_3NMe_2$, R^3 = H), **1i** ($R^2 = (CH_2)_2NHMe$, R^3 = H), and **1j** ($R^2 = (CH_2)_2NMe_2$, R^3 = Me). Fortunately, a chiral N^1-(2-amino)ethyl-1,2-diamino-3-phenylpropane library, which includes **1g**, could be prepared from dipeptides by solid- or liquid-phase synthesis.[8] The oxime resin

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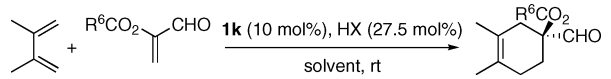
Table 2. DA Reaction of 2,3-Dimethylbutadiene with α-Acyloxyacrolein[a]



entry	R^6	HX	solvent	time (h)	yield (%)	ee (%)
1	*p*-$MeOC_6H_4$	$C_6F_5SO_3H$	$EtNO_2$	8	>99	90
2	Ph	$C_6F_5SO_3H$	$EtNO_2$	16	97	87
3	Ph	$C_6F_5SO_3H$	no solvent	12	95	85
4	Ph	2,4-$(NO_2)_2C_6H_3SO_3H$	$EtNO_2$	12	85	85
5	Ph	2,4-$(NO_2)_2C_6H_3SO_3H$	H_2O	20	81	82
6	Ph	2,4-$(NO_2)_2C_6H_3SO_3H$	$H_2O-C_4H_8O_2$[b]	20	67	80
7	Ph	TsOH	$EtNO_2$	15	60	78
8	Me	2,4-$(NO_2)_2C_6H_3SO_3H$	$EtNO_2$	24	56	83

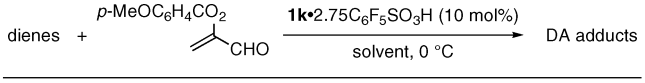
[a] Unless otherwise noted, the DA reaction of 2,3-dimethylbutadiene (3.2 mmol) with α-acyloxyacrolein (0.8 mmol) in solvent (0.25 mL) was carried out. [b] H_2O (0.25 mL) and 1,4-dioxane (0.25 mL) were used.

developed by Kaiser and DeGrado[9] was used in the solid-phase dipeptide synthesis. The resin allows the preparation of dipeptides using the BOC strategy and their subsequent cleavage from the support by nucleophilic displacement with pyrrolidine at the carboxyl terminus. Representative examples are shown in Figure 1. The enantiomeric excess was further increased to 79% by the use of **1k** derived from H-L-Phe-L-Leu-N(CH_2CH_2)$_2$. The *i*-Bu group of **1k** probably helps to stabilize the conformation of R^2.

α-Haloacrolein is known to be an outstanding dienophile in a catalytic DA process because of its high reactivity and the exceptional synthetic versatility of the resulting adducts.[4,5] However, α-haloacrolein is an irritant and is unstable at ambient temperature. In contrast, α-acyloxyacrolein is relatively stable, and its reactivity can be controlled by switching the acyloxy group.[3] Ammonium salt of **1k** and HX was expected to be a catalyst for the enantioselective DA reaction between 2,3-dimethylbutadiene and α-acyloxyacrolein at room temperature (Table 2). The highest enantiomeric excess (90%) and quantitative yield were attained in the DA reaction with α-(*p*-methoxybenzoyloxy)acrolein in the presence of 10 mol % of **1k** and 27.5 mol % of $C_6F_5SO_3H$ in $EtNO_2$ (entry 1); 25−30 mol % of HX per 10 mol % of **1k** was suitable for the enantioselective DA reaction. Interestingly, this reaction proceeded with high enantioselectivity regardless of the concentration of the reactants (entries 2 and 3). Furthermore, this reaction occurred even in water without a serious reduction in enantioselectivity (entry 5 versus entries 4 and 6).

To explore the generality and scope of the DA reaction with α-(*p*-methoxybenzoyloxy)acrolein catalyzed by **1k**•2.75$C_6F_5SO_3H$, the DA reactions of representative dienes were examined at 0 or −20 °C (Table 3). The DA reaction of cyclopentadiene (CP) and 5-(benzyloxymethyl)cyclopentadiene (BMCP) in THF gave the (2*S*)-*exo*-adducts as major diastereomers with up to 83% ee (entries 1−4). With respect to the enantioselectivity, THF was more suitable than $EtNO_2$ as solvent for these two examples. The latter product (entries 3 and 4) is an important intermediate for prostaglandin synthesis.[4a] The DA reaction of cyclohexadiene (CH) gave the (2*R*)-*endo*-adduct as a major diastereomer with 91% ee (entry 5). Bicyclo[2.2.2]oct-5-en-2-one derived from this product (entry 5) is useful as a common intermediate for the total syntheses of several biologically active compounds.[10] These results can be understood through our predictive mechanistic model (*cis*-TS **2**) shown in Scheme 1. The DA reaction of not only cyclic but also acyclic dienes, such as 2,3-dimethylbutadiene (DMB) and isoprene (IP), gave the DA adducts with high enantioselectivities (entries 6−8). It is noted that 2.5 mol % of the catalyst was active enough for the DA reaction of DMB (entry 7).

Table 3. DA Reaction of Dienes with α-(*p*-Methoxybenzoyloxy)acrolein[a]



entry	diene	solvent	time (h)	yield (%)	*exo*:*endo*	ee (%)[b] [config]
1	CP[c]	THF	11	97	86:14	80 [2*S*]
2[d]	CP[c]	THF	48	99	87:13	83 [2*S*]
3	BMCP[c]	THF	24	72	81:19	74 [2*S*]
4[d]	BMCP[c]	THF	28	81	88:12	83 [2*S*]
5	CH[c]	$EtNO_2$	48	84	7:93	91 [2*R*]
6	DMB	$EtNO_2$	24	92		92 [−]
7[e]	DMB	$EtNO_2$	12	95		88 [−]
8	IP[c]	$EtNO_2$	48	90	99:1[f]	88 [−]

[a] Unless otherwise noted, the DA reaction of dienes (1.6 mmol) with α-acyloxyacrolein (0.8 mmol) in THF (0.25 mL) or $EtNO_2$ (0.125 mL) was carried out. [b] Enantiomeric excess of major diastereomer. [c] See text. [d] **1k**•2.75$C_6F_5SO_3H$ (20 mol %) at −20 °C. [e] DA reaction of DMB (3.2 mmol) with α-acyloxyacrolein (1.6 mmol) in $EtNO_2$ (0.125 mL) was carried out in the presence of **1k**•2.75$C_6F_5SO_3H$ (2.5 mol %) at room temperature. [f] The molar ratio of 4-methyl and 3-methyl isomers is indicated.

In summary, we have realized the first enantioselective organocatalytic DA reactions with α-substituted acroleins, such as α-acyloxyacroleins.[11] Further studies are in progress to elucidate the mechanism and the origin of the enantioselectivity.

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

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(7) When 10 mol % of diamine **1** and 2,4-$(NO_2)_2C_6H_3SO_3H$ were used, similar enantioselectivities were observed, but the catalytic activity was reduced.
(8) For details, see the Supporting Information.
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