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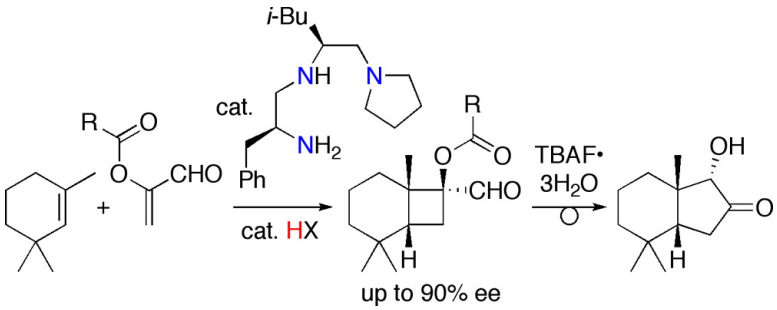

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Enantioselective [2 + 2] Cycloaddition of Unactivated Alkenes with α-Acyloxyacroleins Catalyzed by Chiral Organoammonium Salts

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We have recently developed an enantioselective Diels−Alder reaction of dienes with α-acyloxyacroleins (**3**) induced by chiral organoammonium salts such as H-L-Phe-L-Leu-N$(CH_2CH_2)_2$-reduced triamine (**1**)•2.75$C_6F_5SO_3H$[1a] and (*S*)-1,1′-binaphthyl-2,2′-diamine (**2**)•1.9$HNTf_2$[1b,c] (Scheme 1).[2,3] While examining various asymmetric reactions using these organosalt catalysts, we found that **1**•2.6$HNTf_2$ catalyzes the enantioselective [2 + 2] cycloaddition reaction of unactivated alkenes **4** with **3**, to give optically active 1-acyloxycyclobutanecarbaldehydes **5**. To the best of our knowledge, there are only three previous examples of catalytic enantioselective [2 + 2] cycloaddition reactions for the synthesis of optically active cyclobutanes or cyclobutenes.[4−7] The previous methods were limited to the [2 + 2] cycloaddition of highly nucleophilic alkenyl or alkynyl sulfides[5,6] and sterically demanding alkenes such as norbornene derivatives.[7] We report here the first example of the organocatalytic enantioselective [2 + 2] cycloaddition reaction of **4** with **3** to give optically active **5** and subsequent ring expansion to give optically active 2-hydroxycyclopentanone derivatives **6** and **7**.

First, the [2 + 2] cycloaddition reaction of 2,4-dimethylpent-2-ene (**4a**) with α-benzoyloxyacrolein (**3a**) was examined in the presence of chiral amines (10 mol %) and Brønsted acids (*x* mol %) in nitroethane (Table 1). Although **1**•2.75$C_6F_5SO_3H$ and **1**•2.75TfOH were inert at 0 °C (entries 1 and 2), more acidic **2**•1.9$HNTf_2$ was found to catalyze the cycloaddition even at −78 °C (entry 3). However, the enantioselectivity was moderate (64% ee for major diastereomeric cycloadduct **5aa**). Fortunately, the enantioselectivity was increased to 80% ee with the use of **1**•2.6$HNTf_2$ at 0 °C. Moreover, the enantioselectivity was increased to 85% ee when the reaction temperature was lowered to −20 °C (entry 5). The absolute and relative stereochemistry of **5aa**, which was obtained in the experiments shown in Table 1, was determined to be a (1*S*,3*R*)-*anti* configuration based on the X-ray crystal analysis of (1′*S*)-camphanyl ester **8** derived from **5aa** (see Supporting Information).

Next, several acyloxy groups of **3** were screened for the enantioselective [2 + 2] cycloaddition of **4a** in nitroethane at room temperature in the presence of 10 mol % of **1**•2.6$HNTf_2$ (Table 2). The result indicated that the electronic and steric effects of the acyloxy group of **3** did not greatly influence the enantioselectivity or reactivity. Nevertheless, when 2,6-difluorobenzoyloxyacrolein (**3f**) was used in place of **3a**, the ee value was slightly improved from 73 to 84% (entries 1 and 5).

To explore the generality and scope of the **1**•2.6$HNTf_2$-induced enantioselective [2 + 2] cycloaddition with **3**, structurally diverse alkenes **4** were examined (Table 3). In most cases, cycloadducts **5** were obtained in slightly better yield when the reaction was performed in nitropropane, which is less polar than nitroethane. Cyclic and acyclic trialkylethenes **4a**−**f** were reacted with α-(fluorobenzoyloxy)acroleins **3e**−**g** to give **5** in moderate to good yield with high ee. In contrast, 1,1- and 1,2-dialkylethenes showed no reactivity. However, the cycloaddition of a 1,1-disubstituted styrene derivative, such as **4g** with **3a**, gave **5ag** with 80% ee (entry 12). The absolute and relative stereochemistry of **5ge**, which was obtained in the experiment (entry 10) shown in Table 3, was also determined to be a (1*S*,2*S*,3*R*)-*anti* configuration based on an X-ray crystal analysis (see Supporting Information).

A possible stepwise mechanism that accounts for the observed absolute and relative stereochemistries of cycloadducts **5aa** and **5gd** is shown in Scheme 1 and Figure 1.[8] Initially, the enantioselective Michael addition of alkenes to a (*Z*)-iminium intermediate,[9] which would be generated from **3** and **1**•2.6$HNTf_2$, should occur through enantiofacial approach between the *re* face of electron-rich alkenes

Scheme 1. Enantioselective Diels−Alder (ref 1) and [2 + 2] Cycloaddition Reactions with **3**

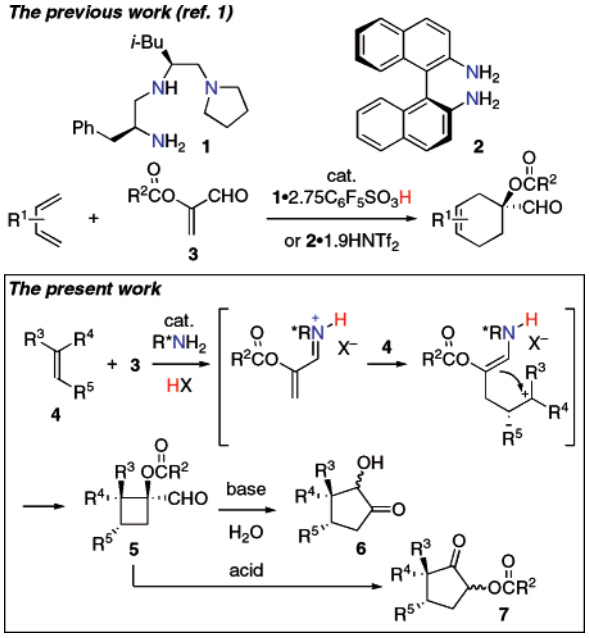
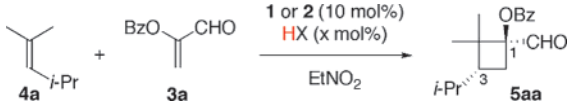


Table 1. Enantioselective [2 + 2] Cycloaddition of **4a** with **3a**[a]



entry	amine•HX	conditions (°C, h)	yield (%)	*syn*:*anti*	ee[b] (%)
1	**1**•2.75$C_6F_5SO_3H$	0, 24	N.R.		
2	**1**•2.75TfOH	0, 24	N.R.		
3	**2**•1.9$HNTf_2$	−78, 36	24	8:92	64
4	**1**•2.6$HNTf_2$	0, 24	71	10:90	80
5	**1**•2.6$HNTf_2$	−20, 48	64	8:92	85

[a] **4a** (2 equiv) and **3a** (1 mmol, 1 equiv) were used in $EtNO_2$ (0.3 mL). [b] The ee value of *anti*-**5aa** was determined by chiral HPLC.

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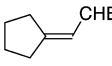
Table 2. Enantioselective [2 + 2] Cycloaddition of **4a** with **3**−**5**[a]

entry	**3**, R^2	time (h)	**5**, yield (%)	*syn*:*anti*	ee[b] (%)
1	**3a**, Ph	7	**5aa**, 74	14:86	73
2	**3b**, *c*-C_6H_{11}	6	**5ba**, 72	13:87	78
3	**3c**, *p*-(MeO)C_6H_4	7	**5ca**, 69	13:87	75
4	**3d**, *p*-FC_6H_4	18	**5da**, 73	13:87	71
5	**3e**, 2,6-$F_2C_6H_3$	12	**5ea**, 80	11:89	84

[a] The reaction of **4a** (2 equiv) with **3** (1 mmol, 1 equiv) was carried out in the presence of **1**•2.6$HNTf_2$ (10 mol %) in $EtNO_2$ (0.3 mL) at room temperature. [b] The ee value of *anti*-**5** was determined by chiral HPLC. (1*S*,3*R*)-*anti*-**5** was the major enantiomer.

Table 3. Enantioselective [2 + 2] Cycloaddition of **4** with **3**−**5**[a]

entry	**4**	**3**	conditions (°C, h)	**5**, yield (%)	*syn*:*anti*	ee (%)[b]
1[c,d]	Me_2C=CH-*i*-Pr, **4a**	**3e**	−20, 48	**5ea**, 63	7 : 93	95
2[e]	Me_2C=CH-*i*-Bu, **4b**	**3g**[f]	−20, 48	**5gb**, 63	6 : 94	89
3[d,e]	Me_2C=CH-*c*-C_6H_{11}, **4c**	**3e**	0, 48	**5ec**, 89	8 : 92	82
4[e,g]		**3e**	−20, 48	**5ec**, 61	9 : 91	85
5[e]	Me_2C=CH-*t*-Bu, **4d**	**3f**[h]	−20, 60	**5fd**, 67	7 : 93	91
6[e,i]		**3g**[f]	−20, 30	**5gd**, 49	7 : 93	87
7[e]	 , **4e**	**3e**	0, 24	**5ee**, 63	5 : 95	82
8[e]		**3f**[h]	0, 48	**5fe**, 77	5 : 95	83
9[e]		**3f**[h]	−10, 48	**5fe**, 57	4 : 96	89
10[e,g,i]		**3g**[f]	−20, 72	**5ge**, 24	4 : 96	90
11[e,i]	 , **4f**	**3e**	−10, 24	**5ef**, 37	17 : 83	87
12[c,d,i,j]	PhMeC=CH_2, **4g**	**3a**	0, 6	**5ag**, 20	16 : 84[k]	80

[a] Unless otherwise noted, **3** (1.0 mmol, 1.0 equiv) and **4** (1.2 equiv) were used in $PrNO_2$ (1.0 mL) in the presence of **1**•2.6$HNTf_2$ (10 mol %). [b] The ee value of *anti*-**5** was determined by chiral HPLC. [c] $EtNO_2$ was used. [d] **4** (2.0 equiv) was used. [e] **1**•2.6$HNTf_2$ (20 mol %) was used. [f] **3g** (R^2 = C_6F_5). [g] $PrNO_2$ (2.0 mL) was used. [h] **3f** (R^2 = 2,4,6-$F_3C_6H_2$). [i] 1,1,2,2,3,3-Hexafluoropropane-1,3-disulfonimide was used in place of $HNTf_2$. [j] Water (2.0 equiv) was added. [k] The relative stereochemistry of **5ag** is unknown.

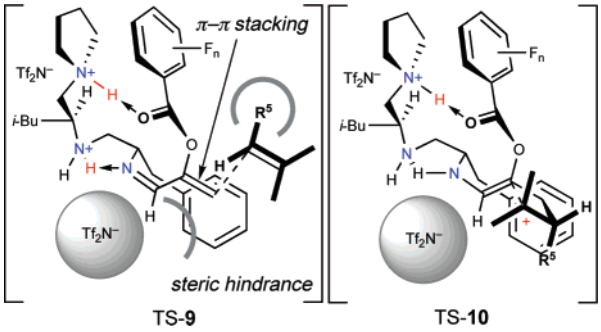
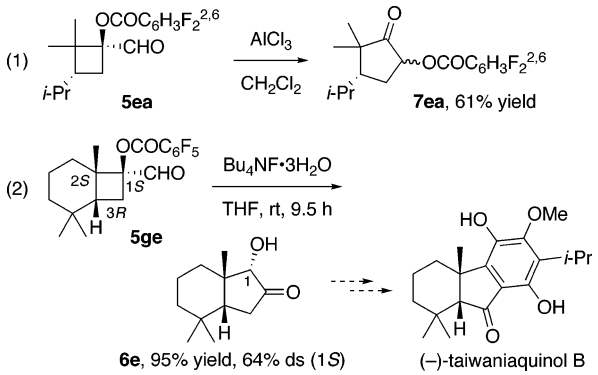


Figure 1. Possible TS **9** and TS **10** for the present [2 + 2] cycloaddition.

and the *si* face of the electron-deficient (*Z*)-iminium intermediate in an extended transition-state assembly (TS) **9**. The (*Z*)-iminium isomer of **9** is expected to be more stabilized by intramolecular hydrogen-bonding interactions between R^2−C═*O* or *o*-*F* substituents in R^2 and *H*−$N^+(CH_2CH_2)_2$. Subsequently, the resulting tertiary carbocation intermediate would be intramolecularly cyclized through a folded TS **10**. The high *anti*-selectivity of cycloadducts might also be achieved by an intramolecular hydrogen-bonding interaction in **9** and **10**.

To demonstrate the synthetic utility of cycloadducts **5**, **5ea** was expanded to 2-acyloxycyclopentanone **7ea** by treatment with $AlCl_3$ (1.2 equiv) through successive 1,2-shifts of a tertiary alkyl group and a hydride (eq 1).[10] On the other hand, **5ge** was expanded to 2-hydroxycyclopentanone **6e** in 95% yield with 64% ds by treatment with Bu_4NF•$3H_2O$ (2 equiv) through hydrolysis and the subsequent 1,2-shift of a tertiary alkyl group (eq 2). It is expected that **6e** may become a new chiral common intermediate candidate in the enantioselective total syntheses of 4a-methylhydrofluorene diterpenoids such as (−)-taiwaniquinol B.[11,12]



In summary, we have described a novel and useful formal [2 + 3] cycloaddition of **4** with **3** by an organocatalytic enantioselective [2 + 2] cycloaddition and subsequent ring expansion to give optically active **6** or **7** with high ee.

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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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(9) It was ascertained by ^{1}H NMR spectral analysis that a new species was generated from **1**•2.6$HNTf_2$ and **4** in CD_3CN in ca. 10% conversion. However, we could not clearly assign it as an iminium salt intermediate. Therefore, we cannot deny the possibility of chiral Brønsted acid catalysis through hydrogen bonding.
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