Accounts

Organoammonium Salt-Catalyzed Enantioselective Cycloaddition Reactions with α-(Acyloxy)- or α-Diacylaminoacroleins

Akira Sakakura[1] **and Kazuaki Ishihara***[2]

[1]EcoTopia Science Institute, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603

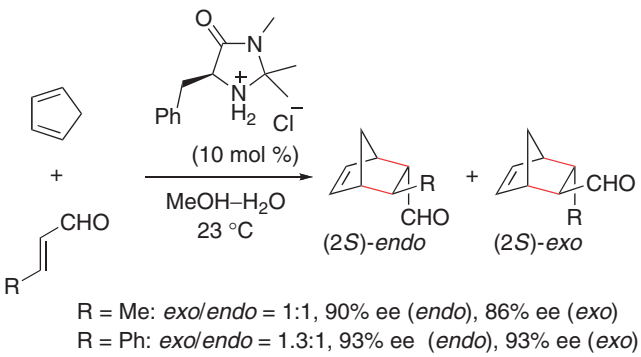
[2]Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603

Received December 28, 2009; E-mail: ishihara@cc.nagoya-u.ac.jp

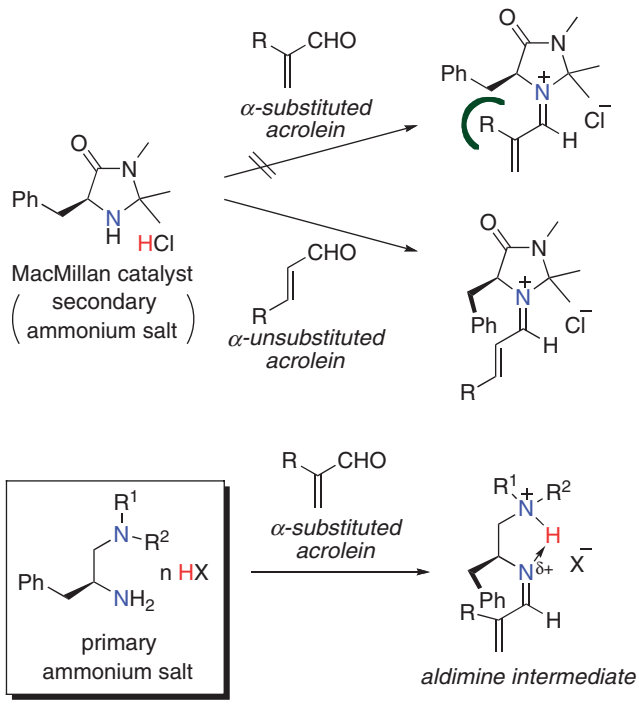
The rational design of small-molecule chiral catalysts is an important subject in the development of practical organic syntheses. We have designed primary ammonium salt catalysts for enantioselective cycloaddition reactions with α-substituted acroleins such as α-(acyloxy)acroleins and α-diacylaminoacroleins. Ammonium salts of an aliphatic triamine derived from H–L-Phe–L-Leu–N(CH_2CH_2)$_2$ successfully promote the Diels–Alder reaction of α-(acyloxy)acroleins and α-(*N*,*N*-diacylamino)acroleins, and the [2 + 2] cycloaddition reaction of α-(acyloxy)acroleins with high enantioselectivity. An ammonium salt of a C_2-symmetric aromatic diamine, 1,1′-binaphthyl-2,2′-diamine, with a superacid is also an efficient catalyst and shows high activity and enantioselectivity for the Diels–Alder reaction of cyclic dienes with α-(acyloxy)acroleins.

1. Introduction

The enantioselective Diels–Alder reaction is one of the most powerful organic transformations and is a versatile tool for the synthesis of many important chiral building blocks for the total synthesis of bioactive natural products.[1] In 2000, the first enantioselective organocatalytic Diels–Alder reaction of dienes with α-unsubstituted acroleins and 2-enones was reported by MacMillan and co-workers (Scheme 1).[2] Their catalysts were chiral ammonium salts of five-membered cyclic secondary amines derived from L-phenylalanine. These ammonium salts, MacMillan catalyst, activate α-unsubstituted acroleins through the reversible formation of aldimine intermediates and promote the Diels–Alder reaction of dienes with high enantioselectivity (Scheme 2).[3] The success of MacMillan and co-workers inspired the development of several chiral organoammonium salt catalysts for enantioselective Diels–Alder reactions.[4,5]



Scheme 1. Diels–Alder reaction with α-unsubstituted acroleins promoted by MacMillan catalyst.



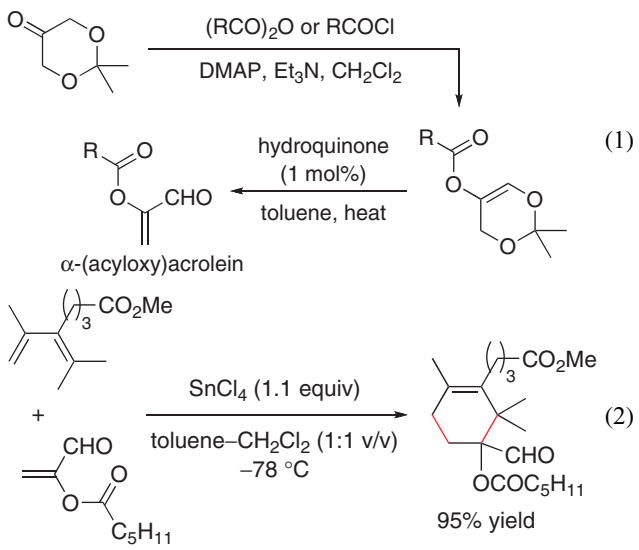
Scheme 2. Rational design of chiral ammonium salt catalysts for the activation of α-substituted acroleins.

Published on the web March 26, 2010; doi:10.1246/bcsj.20090345

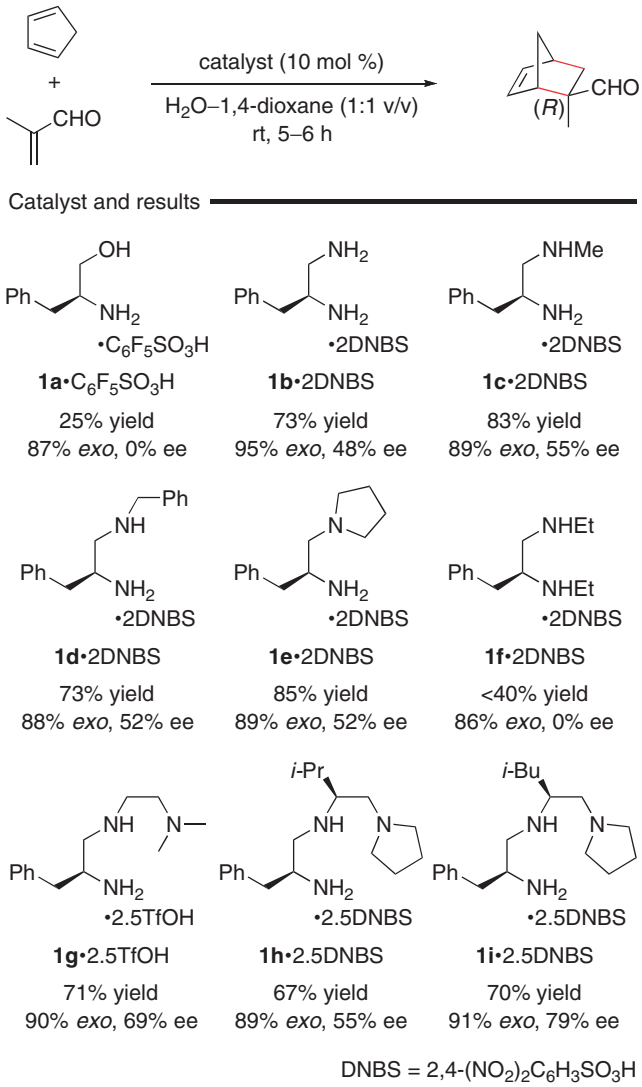
Almost all of them were also secondary ammonium salts and could promote the Diels–Alder reaction with α-unsubstituted acroleins. However, it is difficult to activate α-substituted acroleins with these secondary ammonium salt catalysts, probably because of poor generation of the corresponding aldimine intermediates. The relatively strong basicity and greater bulkiness of the secondary amines were unfavorable for the generation of an iminium ion with α-substituted acroleins. Based on acid–base combination chemistry,[6,7] we attempted to activate α-substituted acroleins through the corresponding aldimines by using catalytic amounts of primary amines and Brønsted acids (HX) (Scheme 2).[8,9] We expected that the chiral ammonium salts of primary amines that were readily derived from L-phenylalanine would generate aldimine intermediates. The phenyl group of the catalysts would effectively shield the *si*-face of a carbon–carbon double bond in the aldimine intermediates to induce asymmetry in the Diels–Alder adducts.

2. Enantioselective Diels–Alder Reaction of α-(Acyloxy)acroleins

α-Haloacroleins are outstanding dienophiles in a catalytic Diels–Alder process because of their high reactivity and the exceptional synthetic versatility of the resulting adducts.[10,11] However, α-haloacroleins are difficult to handle because they are irritants and are unstable at ambient temperature. In contrast, α-(acyloxy)acrolein, which is relatively stable, can be easily prepared from 2,2-dimethyl-1,3-dioxan-5-one via O-acylation followed by thermal retrocycloaddition (eq 1).[12] Furthermore, their reactivity can be controlled by switching the acyloxy group. α-(Acyloxy)acrolein is one of the most promising alternatives to α-haloacrolein. For example, Funk and Yost reported the $SnCl_4$-promoted Diels–Alder reaction of α-(acyloxy)acroleins for the synthesis of functionalized Taxol A-ring synthons (eq 2).[12]



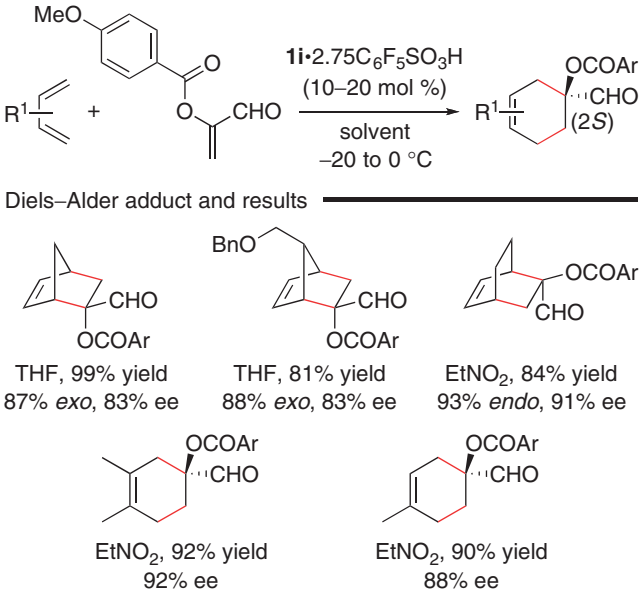
2.1 Chiral Aliphatic Ammonium Salt Catalysts.[13] First, the catalytic activities of several chiral ammonium salts were examined for the Diels–Alder reaction of cyclopentadiene with α-methylacrolein in a 1:1 (v/v) mixture of water and 1,4-dioxane at ambient temperature (Scheme 3). Although the



Scheme 3. Catalytic activities of chiral ammonium salts for the Diels–Alder reaction of cyclopentadiene with α-methylacrolein.

ammonium salt of (*S*)-2-amino-3-phenyl-1-propanol (**1a**) with pentafluorobenzenesulfonic acid ($C_6F_5SO_3H$) gave the racemic adduct, ammonium salts of diamines **1b**–**1e** derived from L-phenylalanine with 2,4-dinitrobenzenesulfonic acid (2,4-$(NO_2)_2C_6H_3SO_3H$) gave (2*R*)-*exo*-adduct with moderate enantioselectivities (48–55% ee). In contrast, the use of an ammonium salt of (*S*)-1-benzyl-*N*,*N*′-diethylethylenediamine (**1f**) gave racemic *exo*-adduct in less than 40% yield. Thus, as expected, the existence of a primary amino group was essential for the present asymmetric Diels–Alder reaction. Next, to improve the enantioselectivity, we further investigated the catalytic activities of ammonium salts of chiral triamines, which were combinatorially prepared based on solid-phase dipeptide synthesis using the oxime resin.[14] As a result, the enantioselectivity was successfully increased to 79% by the use of the chiral triamine **1i** derived from H–L-Phe–L-Leu–$N(CH_2CH_2)_2$.

The ammonium salt of chiral triamine **1i** was expected to be a catalyst for the enantioselective Diels–Alder reaction with

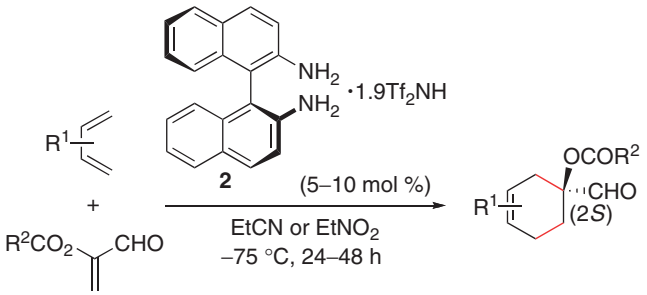


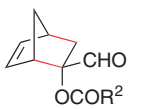
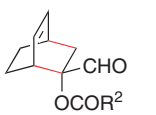
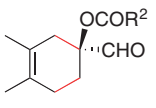
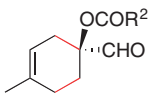
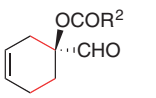
Scheme 4. Diels–Alder reaction with α-(*p*-methoxybenzoyloxy)acrolein.

α-(acyloxy)acrolein (Scheme 4). High enantioselectivity was attained in the Diels–Alder reaction with α-(*p*-methoxybenzoyloxy)acrolein in the presence of **1i**•2.75$C_6F_5SO_3H$. The Diels–Alder reaction of cyclopentadiene and 5-(benzyloxymethyl)cyclopentadiene in THF gave the corresponding (2*S*)-*exo*-adducts as major diastereomers with 83% ee. The latter product is an important intermediate in prostaglandin synthesis.[10a] The Diels–Alder reaction of cyclohexadiene in $EtNO_2$ gave the (2*S*)-*endo*-adduct as a major diastereomer with 91% ee. The adducts of cyclopentadiene and cyclohexadiene can be easily converted to bicyclo[2.2.1]hept-5-en-2-one and bicyclo[2.2.2]oct-5-en-2-one, which are useful common intermediates for the total synthesis of several bioactive compounds.[15,16] The Diels–Alder reaction of not only cyclic but also acyclic dienes, such as 2,3-dimethylbutadiene and isoprene, gave the corresponding adducts with high enantioselectivities (92 and 88% ee). The *endo*/*exo*-selectivity of the reaction in the presence of **1f**•2.75$C_6F_5SO_3H$ showed the same trend as that in the Lewis acid-catalyzed Diels–Alder reaction with other α-substituted acroleins such as α-methylacrolein and α-bromoacrolein.

2.2 Chiral Aromatic Ammonium Salt Catalysts.[17] The enantioselectivity of the chiral triammonium salt **1i**•2.75$C_6F_5SO_3H$ described above for the reaction of cyclopentadiene is slightly low (83% ee, 20 mol % catalyst loading). In addition, the catalytic activity is not so high (10–20 mol % catalyst is loaded at −20 °C to rt) because of its relatively weak acidity. To improve the catalytic activity and the enantioselectivity for the reaction of cyclopentadiene, we focused on more acidic ammonium salts derived from aromatic amines and super Brønsted acids. Thus, we developed a superior asymmetric catalyst, an ammonium salt of (*S*)-1,1′-binaphthyl-2,2′-diamine (**2**) and trifluoromethanesulfonimide (=bis(trifluoromethanesulfon)amide, Tf_2NH) (Table 1). The C_2-symmetric aromatic diammonium salt catalyst could be easily prepared in situ by mixing commercially available **2** and Tf_2NH.

Table 1. Diels–Alder Reaction with α-(Acyloxy)acrolein Catalyzed by 1,1′-Binaphthyl-2,2′-diammonium Salts



Adduct	R^2	Yield /%	*Exo*/*endo*	Ee/%[a] [config]
	*p*-$MeOC_6H_4$	48	93:7	94 [2*S*]
	c-C_6H_{11}	88[b]	92:8	91 [2*S*]
	p-$TIPSOC_6H_4$	76	93:7	94 [2*S*]
	*c*-C_6H_{11}	90	<1:>99	91 [2*S*]
	*c*-C_6H_{11}	88	—	70
	p-$TIPSOC_6H_4$	85	—	85
	*c*-C_6H_{11}	67	>99:<1[c]	71
	p-$TIPSOC_6H_4$	85	>99:<1[c]	82
	*c*-C_6H_{11}	65	—	68
	p-$TIPSOC_6H_4$	77	—	82

a) Enantiomeric excess of the major diastereomer. b) The reaction was conducted in the presence of H_2O (10 mol %). c) Regioisomeric ratio.

In the presence of 5 mol % of the aromatic ammonium catalyst **2**•1.9Tf_2NH, the Diels–Alder reaction of cyclopentadiene with α-(*p*-methoxybenzoyloxy)acrolein proceeded in propionitrile (EtCN) at −75 °C and gave the *exo*-adduct with high enantioselectivity (94% ee) in moderate yield (48%). The low reactivity of α-(*p*-methoxybenzoyloxy)acrolein was mainly attributed to its poor solubility in EtCN at −75 °C. Indeed, α-(cyclohexanecarbonyloxy)acrolein and α-[*p*-(triisopropylsilyloxy)benzoyloxy]acrolein, which could be dissolved in EtCN at −75 °C, showed good reactivities (88 and 76% yield) and the corresponding *exo*-adducts were obtained with high enantioselectivities (91 and 94% ee). Both cyclic dienes, such as cyclopentadiene and cyclohexadiene, and acyclic dienes, such as 2,3-dimethylbutadiene, isoprene, and butadiene, could be converted to the corresponding adducts in good yield (65–90%) with high enantioselectivities (68–91% ee). In particular, α-[*p*-(triisopropylsilyloxy)benzoyloxy]acrolein, which had a good electron-donating *p*-(triisopropylsilyloxy)phenyl group, gave the adducts in high yield with high enantioselectivity.

According to an X-ray crystal structure analysis of α-(*p*-methoxybenzoyloxy)acrolein, the plane of the *s-trans* acrolein

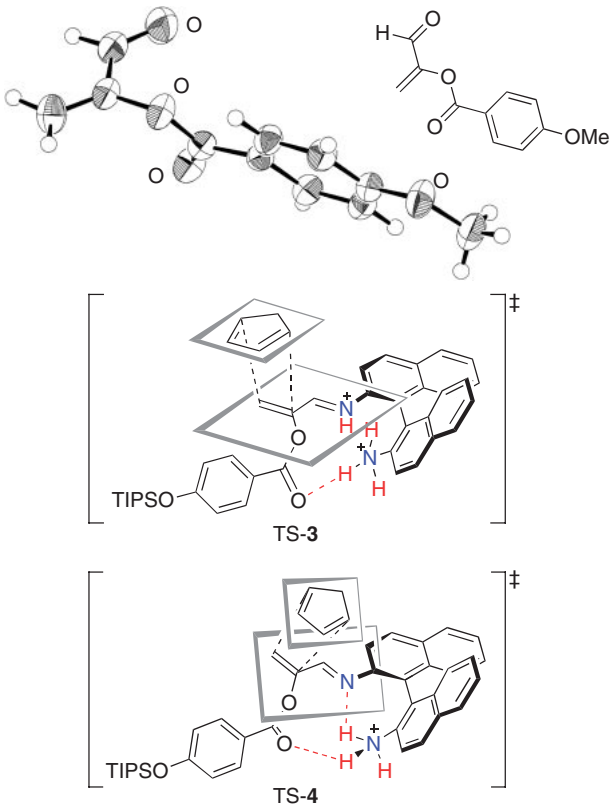


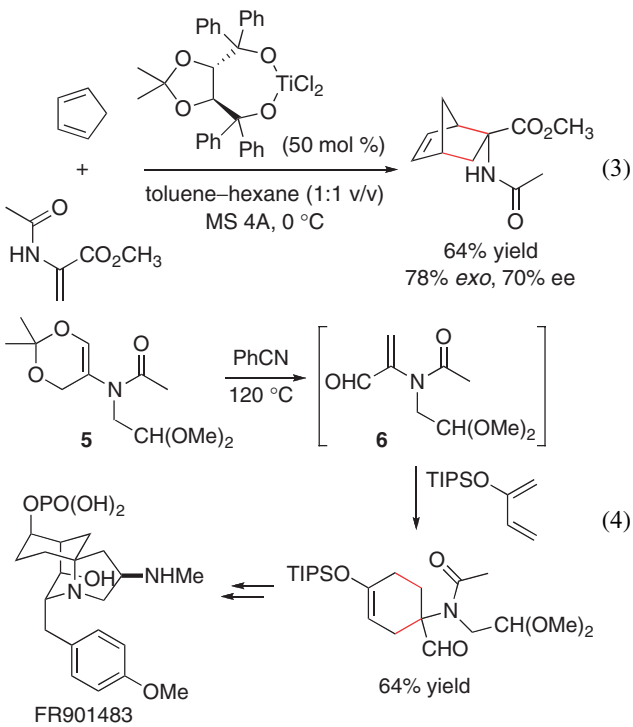
Figure 1. ORTEP plot of α-(*p*-methoxybenzoyloxy)-acrolein (top) and proposed transition-state assemblies (bottom). Counter anions (Tf_2N^-) are omitted for clarity.

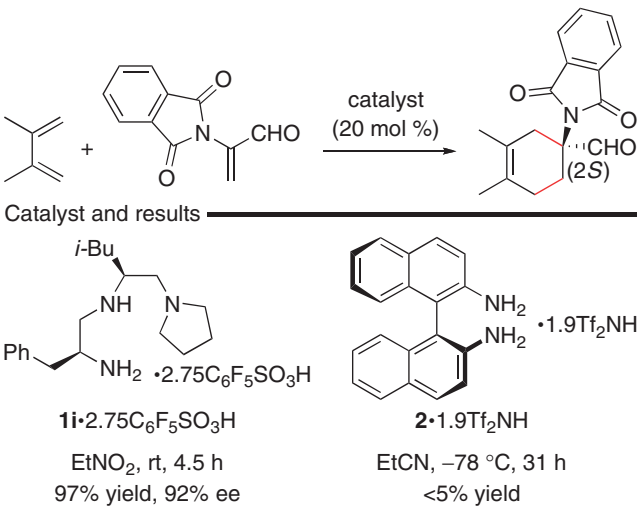
moiety and the plane of the acyloxy group can be distorted (Figure 1, top). A transition state (TS) was proposed based on a ^{1}H NMR study[18] and the X-ray crystal structure analysis of α-(*p*-methoxybenzoyloxy)acrolein, as shown in Figure 1. The present Diels–Alder reaction might proceed via TS-**3** or TS-**4**. In each transition-state assembly, one of the amino groups of the diamine forms an aldimine with α-(acyloxy)acrolein and the other amino group forms an ammonium salt with Tf_2NH. In TS-**3**, the aldimine is activated by the other molecule of Tf_2NH, to be the active dication intermediate. Moreover, the acyloxy group should be activated by linear intramolecular hydrogen bonding with a proton of the ammonium group in the same molecule. In TS-**3**, the diene should approach the *si*-face of the dienophile from the less-hindered side, to give the (2*S*)-*exo*-adduct. On the other hand, in TS-**4**, the aldimine and the acyloxy group are both 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 (N···H–N) and the carbonyl oxygen of the acyloxy group with a proton of the ammonium group (O···H–N) are not linear. Therefore these hydrogen bondings are weak, and TS-**4** is conformationally unstable. Moreover, the aldimine of TS-**4** is activated by the weakly acidic ammonium group while the aldimine of TS-**3** is activated by superacidic Tf_2NH. Indeed, the reaction catalyzed by 5 mol % of **2**·Tf_2NH, which should proceed via TS-**4**, gave low reactivity and low enantioselectivity. Therefore, these results suggested that the present Diels–Alder reaction proceeded via TS-**3**.

α-[*p*-(Triisopropylsilyloxy)benzoyloxy]acrolein bearing a good electron-donating *p*-(triisopropylsilyloxy)phenyl group exhibited very high enantioselectivity, which could be attributed to the formation of strong intramolecular hydrogen bonding in the transition state, due to the higher basicity of the carbonyl oxygen of the acyloxy group.

3. Enantioselective Diels–Alder Reaction of α-Diacylaminoacroleins[19]

As described in the previous section, the aliphatic triammonium salt **1i**·2.75$C_6F_5SO_3H$ and the aromatic diammonium salt **2**·1.9Tf_2NH successfully promote the Diels–Alder reaction with α-(acyloxy)acroleins to give α-quaternary α-hydroxy acid equivalents, which are valuable chiral synthons that bear two functional groups, with high enantioselectivity. In contrast, to the best of our knowledge, there has been only one reported example of the enantioselective Diels–Alder reaction with α-acylaminoacroleins: in 1991, Cativiela and co-workers reported the Diels–Alder reaction of cyclopentadiene with methyl α-acetamidoacrylate promoted by 50 mol % of chiral titanium(IV) Lewis acid (64% yield, 78% *exo*, 70% ee (*exo*)) (eq 3).[20,21] The Diels–Alder reaction with α-acylaminoacroleins has significant synthetic versatility. Funk and co-workers successfully used the Diels–Alder reaction with α-acylaminoacroleins for the synthesis of racemic polycyclic alkaloids.[22] For example, the immunosuppressant substance FR901483 was synthesized using the Diels–Alder reaction of 2-(triisopropylsiloxy)butadiene with α-acylaminoacrolein **6**, which was prepared in situ by the thermal decomposition of **5** (eq 4).[22a] In this section, we describe the catalytic and highly enantioselective Diels–Alder reaction with α-diacylamino- or α-acylaminoacroleins to give optically active cyclic α-quaternary α-amino acid precursors. Conformationally constrained α-amino acids are valuable in biochemistry as modified peptides, enzyme inhibitors, and ligands for probing receptor recognition.[21,23,24]





Scheme 5. Catalytic activities of the chiral ammonium salts for the Diels–Alder reaction with α-phthalimidoacrolein.

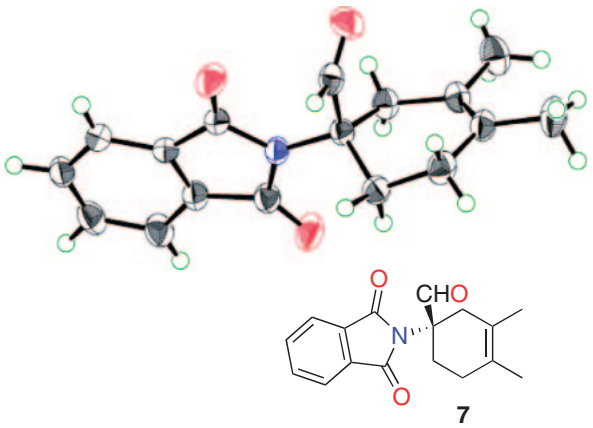
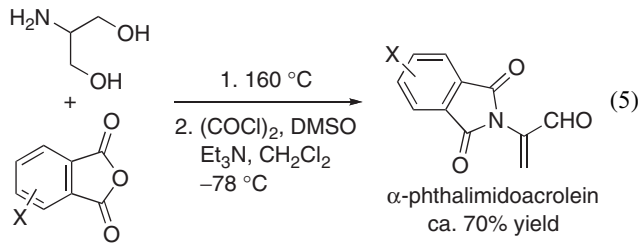


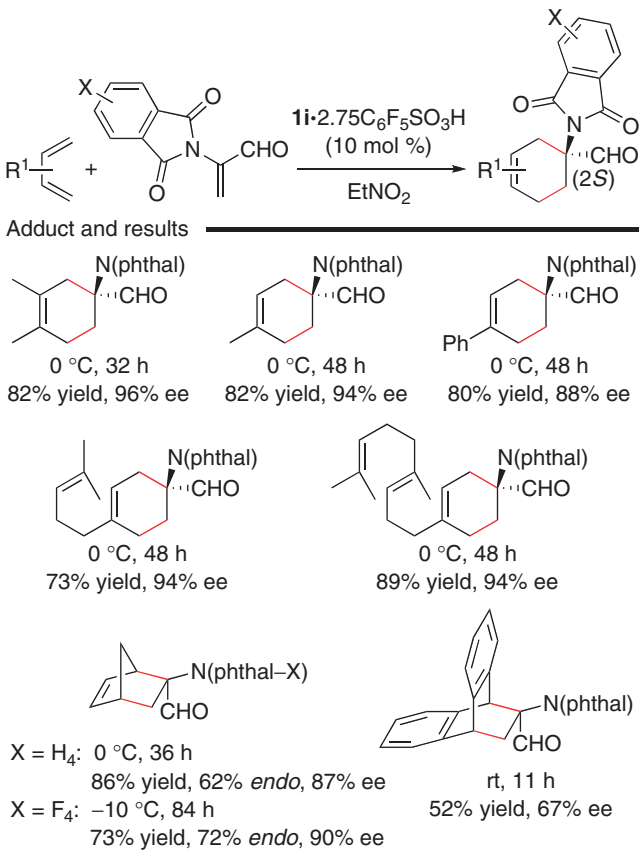
Figure 2. ORTEP illustration of (2*S*)-cycloadduct **7** with thermal ellipsoids drawn at a 50% probability level (Flack parameter = 0.1228).

We first examined the catalytic activities of the aliphatic triammonium salt (**1i**•2.75$C_6F_5SO_3H$) and the aromatic diammonium salt (**2**•1.9Tf_2NH) for the Diels–Alder reaction of 2,3-dimethylbutadiene with α-phthalimidoacrolein (Scheme 5). α-Phthalimidoacrolein was prepared by a one-pot dehydrative condensation between 2-amino-1,3-propanediol and phthalic anhydride and subsequent oxidative dehydration under Swern conditions (eq 5). As a result, **1i**•2.75$C_6F_5SO_3H$ showed good catalytic activity (97% yield) and excellent enantioselectivity (92% ee). In contrast, **2**•1.9Tf_2NH did not catalyze the Diels–Alder reaction with α-phthalimidoacrolein because **2** reacted irreversibly with the dienophile even at −78 °C. The absolute configuration of the cycloadduct **7**, which was obtained as a major enantiomer in Scheme 5, was determined to be (2*S*) by X-ray crystallographic analysis, as shown in Figure 2.



(5)

To explore the generality and scope of the **1i**•2.75$C_6F_5SO_3H$-catalyzed enantioselective Diels–Alder reaction with α-phthalimidoacrolein, several dienes were examined (Scheme 6). When the reaction of 2,3-dimethylbutadiene was conducted at 0 °C, the enantioselectivity was increased to 96% ee. Isoprene, 2-phenylbutadiene, myrcene, and (*E*)-farnesene also reacted smoothly to give the desired 4-substituted cyclohex-3-enecarbaldehydes with >99% regioselectivity and 88–94% ee. The reaction of cyclopentadiene with α-(tetrafluorophthalimido)acrolein gave *endo*-formylbicycloadduct with 72% ds and 90% ee. In general, the Diels–Alder reaction of cyclopentadiene with α-substituted acroleins predominantly gives *exo*-adducts. However, the **1i**•2.75$C_6F_5SO_3H$-catalyzed



Scheme 6. Enantioselective Diels–Alder reaction with α-phthalimidoacrolein.

Diels–Alder reaction of cyclopentadiene with α-phthalimidoacrolein gave the *endo*-adduct as a major diastereomer. Anthracene, which was much less reactive, could also be used as a diene, although the chemical yield and enantioselectivity were moderate (52% yield, 67% ee).

Phthalimido groups of Diels–Alder adducts were deprotected in high yield by treatment with hydrazine after conversion to the corresponding methyl esters (eq 6). Norbornene (=bicyclo[2.2.1]hept-2-ene) derivatives are particularly valuable as opti-

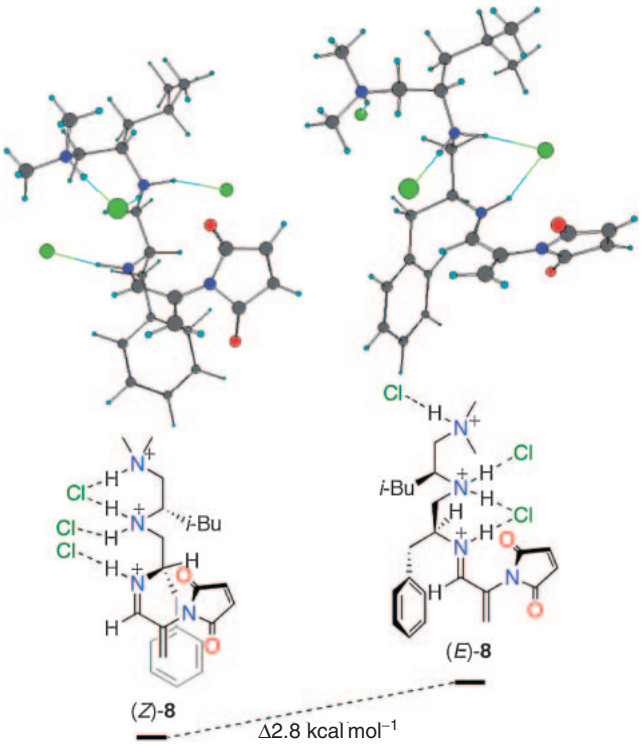
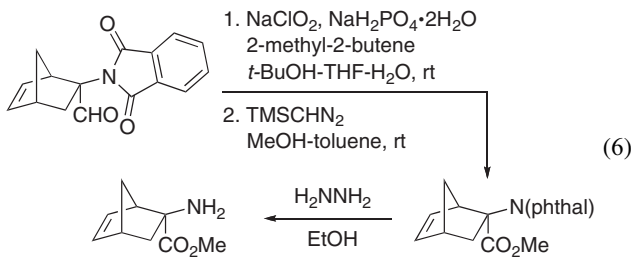


Figure 3. Difference in energy of the (*E*)- and (*Z*)-geometries of aldiminium salt **5** based on theoretical calculations.

cally active intermediates for the synthesis of bioactive alkaloids such as (5-amino-5-norbornenyl)methanol derivatives[25] and (−)-altemicidin.[26]



(6)

Since **1i**·$2C_6F_5SO_3H$ was much less active than **1i**·$2.75C_6F_5SO_3H$ as a catalyst for the Diels–Alder reaction with α-phthalimidoacroleins as well as α-(acyloxy)acroleins, we assumed that **1i**·$3C_6F_5SO_3H$ might be the actual active catalyst. **1i**·$3C_6F_5SO_3H$ would activate α-phthalimidoacroleins through the formation of aldiminium salts, although we cannot exclude the possibility of chiral Brønsted acid catalysis through hydrogen bonding. A (*Z*)-isomeric preference of aldiminium salts was proposed based on theoretical calculations of the geometries of their analogous aldiminium salts **8** derived from α-maleimidoacrolein and H–L-Phe–L-Leu–NMe_2-reduced triamine·3HCl.[27] The geometries of **8** were optimized by DFT calculations with B3LYP,[28] using the 6-31+G(d,p) basis set (Figure 3). After satisfactory geometry optimization, the vibrational spectrum of each species was calculated. As shown in Figure 3, the relative energy of (*Z*)-**8** is 2.8 kcal mol^{-1} lower than that of (*E*)-**8**, and the *re*-face of the enimide moiety of

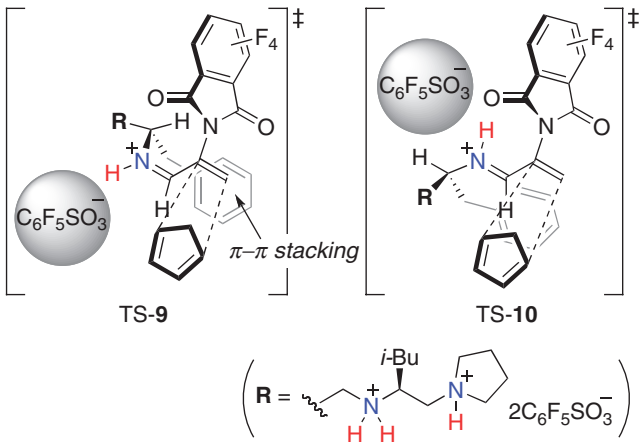
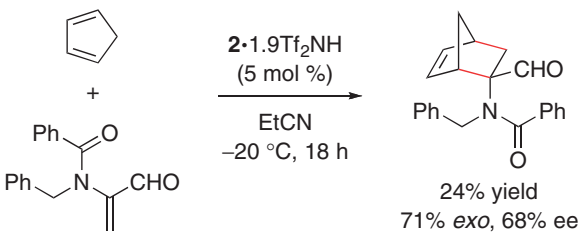


Figure 4. Proposed transition-state assemblies.

(*Z*)-**8** is sterically shielded by the benzyl substituent. Cyclopentadiene should approach the *si*-face of the electron-deficient enimide moiety enantioselectively to give *endo*-(2*S*)-adduct as a major isomeric product. Thus, along with the (*Z*)-isomeric preference of **8**, we expected that the (*Z*)-transition-state assembly (TS-**9**) would be preferred to the (*E*)-transition-state assembly (TS-**10**) (Figure 4).

The aliphatic ammonium salt **1i**·$2.75C_6F_5SO_3H$ has a flexible structure. It is conceivable that this flexibility could lead to an efficient chiral environment in the aldimine intermediate via hydrogen bonding to give Diels–Alder adducts with high enantioselectivity. In contrast, the conformation of ammonium salt **2**·Tf_2NH is rather rigid and is not suitable for the construction of an efficient chiral environment in the aldimine intermediate with α-(*N*-acylamino)-acroleins.

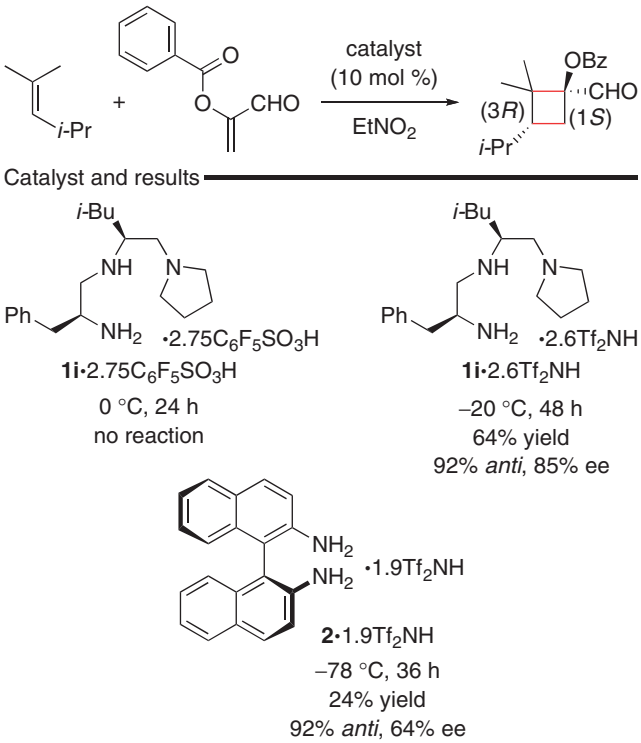
In the course of our investigation on the Diels–Alder reaction with α-acylaminoacroleins, we found that 5 mol % of **2**·$1.9Tf_2NH$ could catalyze the reaction of cyclopentadiene with α-(*N*-benzylbenzamido)acrolein to give the corresponding *exo*-adduct with moderate enantioselectivity (68% ee), albeit the yield of the adduct was poor (24% yield) (eq 7).



(7)

4. Enantioselective [2 + 2] Cycloaddition Reaction of α-(Acyloxy)acroleins[29]

The [2 + 2] cycloaddition reaction is the most popular method for the synthesis of cyclobutanes and cyclobutenes.[30] However, to the best of our knowledge, there are only three previous examples of a catalytic enantioselective [2 + 2] cycloaddition reaction.[31] The previous methods were limited to the [2 + 2] cycloaddition of highly nucleophilic alkenyl or alkynyl sulfides[32,33] and sterically demanding alkenes such as norbornene derivatives.[34] In this section, we describe the first



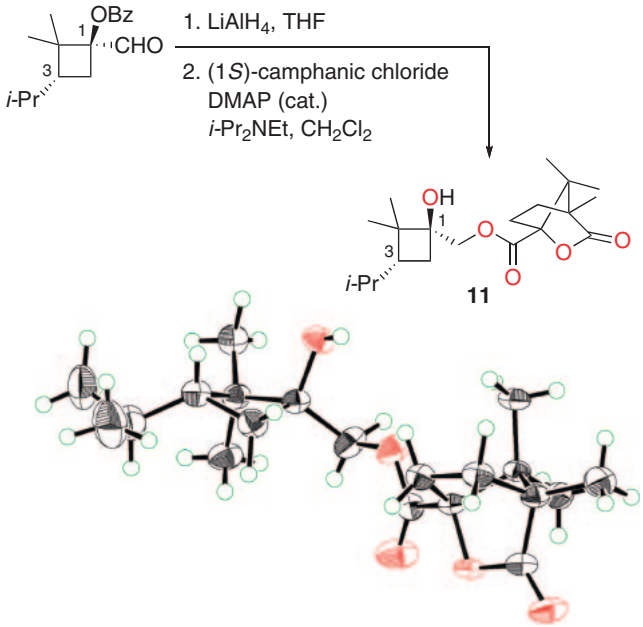
Scheme 7. Catalytic activities of chiral ammonium salts for enantioselective [2 + 2] cycloaddition with α-(benzoyloxy)acrolein.

example of the organocatalytic enantioselective [2 + 2] cycloaddition reaction of simple trisubstituted alkenes with α-(acyloxy)acroleins to give optically active cyclobutanes.

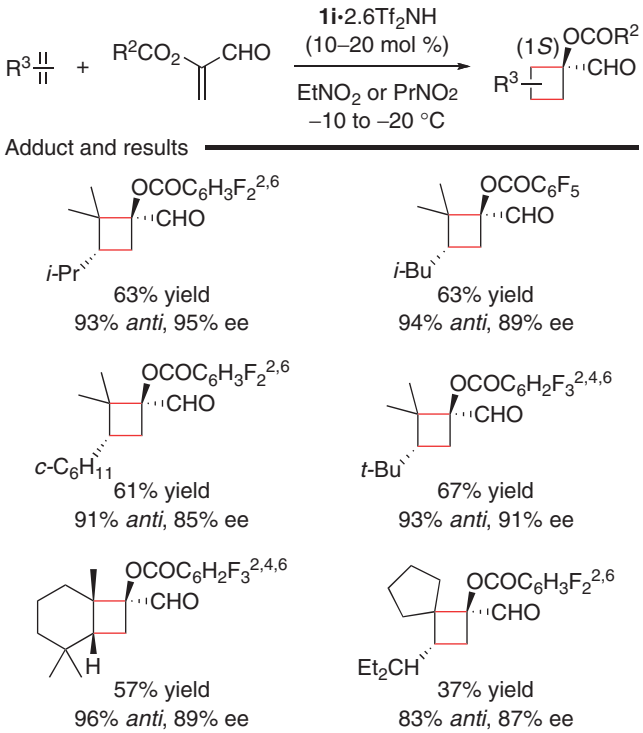
First, the [2 + 2] cycloaddition reaction of 2,4-dimethylpent-2-ene with α-benzoyloxyacrolein was examined in the presence of chiral ammonium salt catalysts (10 mol %) in $EtNO_2$ (Scheme 7). While the aliphatic ammonium salt **1i**•2.75$C_6F_5SO_3H$ was inert at 0 °C, more acidic **1i**•2.6Tf_2NH catalyzed the reaction at −20 °C to give the corresponding *anti*-cycloadduct with good enantioselectivity (85% ee). When the reaction was conducted with **2**•1.9Tf_2NH, the *anti*-cycloadduct was obtained in low yield with moderate enantioselectivity (24% yield, 64% ee). The absolute and relative stereochemistry of the cycloadduct, which was obtained in Scheme 7, was determined to be a (1*S*,3*R*)-*anti* configuration based on an X-ray crystal analysis after conversion to (1′*S*)-camphanic acid ester **11** (Scheme 8).

To explore the generality and scope of the **1i**•2.6Tf_2NH-induced enantioselective [2 + 2] cycloaddition with α-(acyloxy)acroleins, structurally diverse alkenes were examined (Scheme 9). Cyclic and acyclic trialkylethenes were reacted with α-(fluorobenzoyloxy)acroleins to give the corresponding *anti*-cycloadducts in moderate to good yield (37–67%) with high enantioselectivity (83–96% ee). In contrast, 1,1- and 1,2-dialkylethenes, except for α-substituted styrene derivatives, were inert.

To demonstrate the synthetic utility of the cycloadducts, we examined their derivatization. When adduct **12** was treated with $AlCl_3$ (1.2 equiv), 2-acyloxycyclopentanone **13** was obtained via successive 1,2-hydride shifts of a tertiary alkyl group and a



Scheme 8. Absolute and relative stereochemistry of the [2 + 2] cycloadduct.



Scheme 9. Enantioselective [2 + 2] cycloaddition with α-(acyloxy)acroleins.

hydride (eq 8).[35] In contrast, **14** was expanded to 2-hydroxycyclopentanone **15** 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 9). Compound **15** may be a new chiral intermediate in the enantioselective syntheses of 4a-methylhydrofluorene diterpenoids such as (−)-taiwaniaquinol B.[36,37]

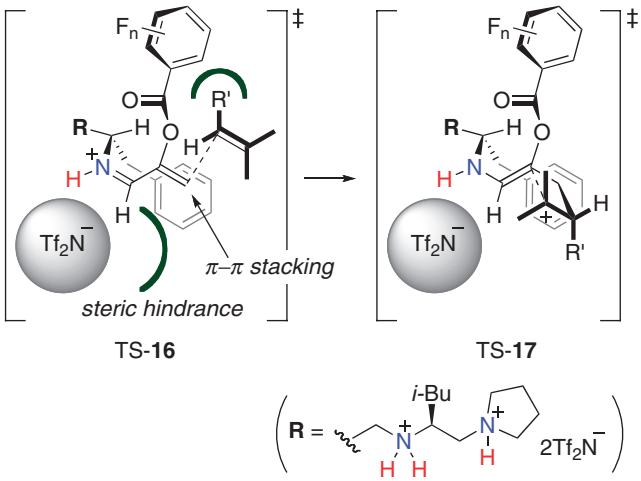
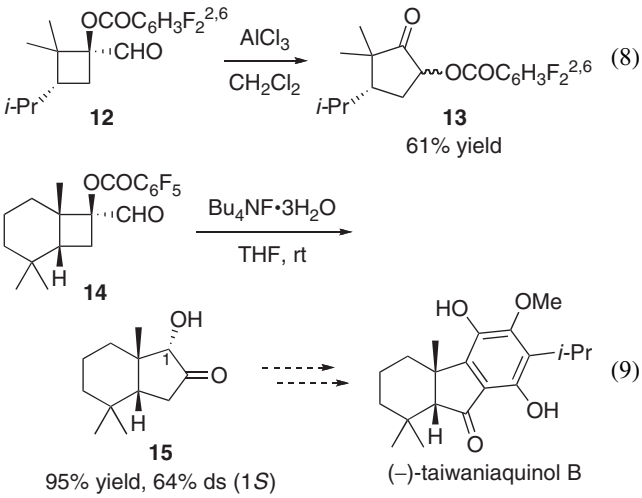


Figure 5. Proposed transition-state assemblies.



A possible stepwise mechanism that accounts for the observed absolute and relative stereochemistries of the cycloadducts is shown in Figure 5. We previously reported that (*Z*)-aldiminium salt derived from **1i**·2Tf$_2$NH and α-(acyloxy)acrolein would be a key intermediate.[29] However, as described in previous sections, a (*Z*)-aldiminium salt derived from **1i**·3Tf$_2$NH and α-(acyloxy)acrolein may be more favorable.[38] Initially, the enantioselective Michael addition of alkenes to a (*Z*)-aldiminium salt, which would be generated from α-(acyloxy)acroleins and **1i**·2.6Tf$_2$NH, should occur through an enantiofacial approach between the *re*-face of electron-rich alkenes and the *si*-face of the electron-deficient (*Z*)-aldiminium salt in an extended TS-**16**. Subsequently, the resulting tertiary carbocation intermediate would be intramolecularly cyclized through a folded TS-**17**. The possibility of a concerted [π2s + π2s] cycloaddition reaction and the possibility of a folded transition state for the initial Michael addition step are forbidden by orbital symmetry considerations. The possibility of a concerted [π2s + π2a] pathway is also excluded due to the steric hindrance of substrates.

5. Conclusion

In conclusion, we have developed chiral primary ammonium salt catalysts for enantioselective cycloaddition reactions with α-(acyloxy)acroleins and α-diacylaminoacroleins. The present results demonstrate that rationally designed ammonium salts of chiral primary amines can create a flexible but efficient asymmetric environment through hydrogen bonding and ionic bonding. This flexible asymmetric environment would be essential for the cycloaddition reaction with sterically hindered substrates such as α-substituted acroleins. Since we developed chiral primary ammonium salt catalysts, several primary ammonium salt-catalyzed enantioselective cycloaddition reactions have been reported.[4g,4h,8]

References

1 For recent reviews, see: a) P. Merino, E. Marqués-López, T. Tejero, R. P. Herrera, *Synthesis* **2010**, 1. b) S. Reymond, J. Cossy, *Chem. Rev.* **2008**, *108*, 5359. c) E. J. Corey, *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. d) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

2 a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243. b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458. c) R. M. Wilson, W. S. Jen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 11616. d) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79.

3 a) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416. b) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267.

4 a) K. H. Kim, S. Lee, D.-W. Lee, D.-H. Ko, D.-C. Ha, *Tetrahedron Lett.* **2005**, *46*, 5991. b) M. Lemay, W. W. Ogilvie, *Org. Lett.* **2005**, *7*, 4141. c) M. Lemay, W. W. Ogilvie, *J. Org. Chem.* **2006**, *71*, 4663. d) M. Lemay, L. Aumand, W. W. Ogilvie, *Adv. Synth. Catal.* **2007**, *349*, 441. e) T. Kano, Y. Tanaka, K. Maruoka, *Org. Lett.* **2006**, *8*, 2687. f) T. Kano, Y. Tanaka, K. Maruoka, *Chem. Asian J.* **2007**, *2*, 1161. g) T. Kano, Y. Tanaka, K. Osawa, T. Yurino, K. Maruoka, *Chem. Commun.* **2009**, 1956. h) R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 2422. i) H. Gotoh, Y. Hayashi, *Org. Lett.* **2007**, *9*, 2859. j) Y. Hayashi, S. Samanta, H. Gotoh, H. Ishikawa, *Angew. Chem., Int. Ed.* **2008**, *47*, 6634. k) H. He, B.-J. Pei, H.-H. Chou, T. Tian, W.-H. Chan, A. W. M. Lee, *Org. Lett.* **2008**, *10*, 2421.

5 For a hydrogen bonding catalysis for the enantioselective Diels–Alder reaction, see: Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146.

6 For our account, see: K. Ishihara, A. Sakakura, M. Hatano, *Synlett* **2007**, 686.

7 For a recent review of bifunctional acid–base catalysts, see: M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491.

8 a) F. Peng, Z. Shao, *J. Mol. Catal. A: Chem.* **2008**, *285*, 1. b) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807.

9 Ha and co-workers reported ammonium salts of 1,2-diamino-1,2-diphenylethane as catalysts for the enantioselective Diels–Alder reaction.[4a] Although their catalysts are primary ammonium salts, the enantioselectivity was low for the reaction with α-substituted acroleins.

10 a) E. J. Corey, T.-P. Loh, *J. Am. Chem. Soc.* **1991**, *113*, 8966. b) E. J. Corey, C. L. Cywin, *J. Org. Chem.* **1992**, *57*, 7372. c) E. J. Corey, T.-P. Loh, *Tetrahedron Lett.* **1993**, *34*, 3979. d) E. J. Corey, A. Guzman-Perez, T.-P. Loh, *J. Am. Chem. Soc.* **1994**, *116*, 3611. e) J. A. Marshall, S. Xie, *J. Org. Chem.* **1992**, *57*, 2987. f) E. J. Corey, T. Shibata, T. W. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 3808.

11 a) K. Ishihara, Q. Gao, H. Yamamoto, *J. Org. Chem.* **1993**,

58, 6917. b) K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 1561. c) K. Ishihara, H. Kurihara, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 3049. d) K. Ishihara, H. Kurihara, M. Matsumoto, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 6920.

12 R. L. Funk, K. J. Yost, III, *J. Org. Chem.* **1996**, *61*, 2598.

13 K. Ishihara, K. Nakano, *J. Am. Chem. Soc.* **2005**, *127*, 10504; Additions and corrections: K. Ishihara, K. Nakano, *J. Am. Chem. Soc.* **2005**, *127*, 13079.

14 a) W. F. DeGrado, E. T. Kaiser, *J. Org. Chem.* **1980**, *45*, 1295. b) W. F. DeGrado, E. T. Kaiser, *J. Org. Chem.* **1982**, *47*, 3258. c) N. Voyer, A. Lavoie, M. Pinette, J. Bernier, *Tetrahedron Lett.* **1994**, *35*, 355.

15 a) A. E. Greene, C. Le Drian, P. Crabbé, *J. Am. Chem. Soc.* **1980**, *102*, 7583. b) R. G. Salomon, N. D. Sachinvala, S. Roy, B. Basu, S. R. Raychaudhuri, D. B. Miller, R. B. Sharma, *J. Am. Chem. Soc.* **1991**, *113*, 3085. c) C. Marschner, J. Baumgartner, H. Griengl, *J. Org. Chem.* **1995**, *60*, 5224. d) G. T. Wang, S. Wang, Y. Chen, R. Gentles, T. Sowin, *J. Org. Chem.* **2001**, *66*, 2052. e) X.-F. Zhu, F. Nydegger, A. Gossauer, *Helv. Chim. Acta* **2004**, *87*, 2245.

16 a) D. A. Evans, A. M. Golob, N. S. Mandel, G. S. Mandel, *J. Am. Chem. Soc.* **1978**, *100*, 8170. b) A. P. Kozikowski, R. J. Schmiesing, *J. Org. Chem.* **1983**, *48*, 1000. c) M. Demuth, S. Chandrasekhar, K. Schaffner, *J. Am. Chem. Soc.* **1984**, *106*, 1092. d) A. B. Smith, III, J. R. Empfield, R. A. Rivero, H. A. Vaccaro, J. J.-W. Duan, M. M. Sulikowski, *J. Am. Chem. Soc.* **1992**, *114*, 9419.

17 a) A. Sakakura, K. Suzuki, K. Nakano, K. Ishihara, *Org. Lett.* **2006**, *8*, 2229. b) A. Sakakura, K. Suzuki, K. Ishihara, *Adv. Synth. Catal.* **2006**, *348*, 2457.

18 When α-(cyclohexanecarbonyloxy)acrolein was mixed with **2** (1 equiv) and Tf_2NH (1.9 equiv) in CD_3CN, three new singlets which might correspond to an aldimine proton (8.96 ppm, –C*H*=NH^+–) and protons of an *exo*-methylene group (6.68 and 6.60 ppm, CH_2=C–) appeared in the spectra, albeit in only a small amount (ca. 5%). However, we cannot exclude the possibility of chiral Brønsted acid catalysis through hydrogen bonding.

19 K. Ishihara, K. Nakano, M. Akakura, *Org. Lett.* **2008**, *10*, 2893.

20 C. Cativiela, P. López, J. A. Mayoral, *Tetrahedron: Asymmetry* **1991**, *2*, 1295.

21 For the diastereoselective Diels–Alder reaction with chiral α-amino acrylic acid derivatives, see: a) C. Cativiela, P. López, J. A. Mayoral, *Tetrahedron: Asymmetry* **1990**, *1*, 61. b) C. Cativiela, P. López, J. A. Mayoral, *Tetrahedron: Asymmetry* **1990**, *1*, 379. c) C. Cativiela, P. López, J. A. Mayoral, *Tetrahedron: Asymmetry* **1991**, *2*, 449. d) W. Sankhavasi, S. Kohmoto, M. Yamamoto, T. Nishio, I. Iida, K. Yamada, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 935. e) C. Cativiela, J. I. Carcía, J. A. Mayoral, E. Pires, A. J. Royo, F. Figueras, *Appl. Catal., A* **1995**, *131*, 159. f) C. Cativiela, J. I. García, J. A. Mayoral, E. Pires, A. J. Royo, F. Figueras, *Tetrahedron* **1995**, *51*, 1295. g) R. Chinchilla, L. R. Falvello, N. Galindo, C. Nájera, *Tetrahedron: Asymmetry* **1999**, *10*, 821. h) T. Abellán, C. Nájera, J. M. Sansano, *Tetrahedron: Asymmetry* **2000**, *11*, 1051. i) R. Chinchilla, L. R. Falvello, N. Galindo, C. Nájera, *J. Org. Chem.* **2000**, *65*, 3034. j) B. A. Burkett, C. L. L. Chai, *Tetrahedron Lett.* **2001**, *42*, 2239. k) T. Abellán, B. Mancheño, C. Nájera, J. M. Sansano, *Tetrahedron* **2001**, *57*, 6627. l) F. Caputo, F. Clerici, M. L. Gelmi, S. Pellegrino, D. Pocar, *Tetrahedron: Asymmetry* **2006**, *17*, 1430. m) T. A. Cernak, J. L. Gleason, *J. Org. Chem.* **2008**, *73*, 102.

22 a) J.-H. Maeng, R. L. Funk, *Org. Lett.* **2001**, *3*, 1125. b) J.-H. Maeng, R. L. Funk, *Org. Lett.* **2002**, *4*, 331. c) Y. He, R. L. Funk, *Org. Lett.* **2006**, *8*, 3689.

23 H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406.

24 a) F. Clerici, M. L. Gelmi, A. Gambini, *J. Org. Chem.* **1999**, *64*, 5764. b) S. Kotha, T. Ganesh, A. K. Ghosh, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1755. c) F. Clerici, M. L. Gelmi, A. Gambini, D. Nava, *Tetrahedron* **2001**, *57*, 6429. d) B. V. Yang, L. M. Doweyko, *Tetrahedron Lett.* **2005**, *46*, 2857. For a review of the stereoselective synthesis of cyclic tertiary α-amino acids, see: e) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **2000**, *11*, 645.

25 a) T. Iwasaki, H. Yamazaki, T. Nishitani, T. Sato, *Chem. Pharm. Bull.* **1991**, *39*, 527. b) H. Yamazaki, H. Horikawa, T. Nishitani, T. Iwasaki, K. Nosaka, H. Tamaki, *Chem. Pharm. Bull.* **1992**, *40*, 102.

26 A. S. Kende, K. Liu, K. M. Jos Brands, *J. Am. Chem. Soc.* **1995**, *117*, 10597.

27 Theoretical calculations were performed using the Gaussian 03 program: M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03, Revision C.02*, Gaussian, Inc., Wallingford CT, **2004**.

28 a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648. b) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623.

29 K. Ishihara, K. Nakano, *J. Am. Chem. Soc.* **2007**, *129*, 8930.

30 For a review, see: E. Lee-Ruff, G. Mladenova, *Chem. Rev.* **2003**, *103*, 1449.

31 After our report (Ref. 29) was published, Corey and Canales reported catalytic enantioselective [2 + 2] cycloaddition reaction of highly nucleophilic enol ethers. E. Canales, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 12686.

32 For the titanium-catalyzed enantioselective [2 + 2] cycloaddition reaction of acryloyl oxazolidinone derivatives with alkenyl sulfides and alkynyl sulfides (10–30 mol % catalyst loading, 30 to >99% yield, 80 to >98% ee), see: K. Narasaka, Y. Hayashi, H. Shimadzu, S. Niihata, *J. Am. Chem. Soc.* **1992**, *114*, 8869.

33 For the copper-catalyzed enantioselective [2 + 2] cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one with phenylthioacetylene (20 mol % catalyst loading, 67% yield, 73% ee), see: a) H. Ito, M. Hasegawa, Y. Takenaka, T. Kobayashi, K. Iguchi, *J. Am. Chem. Soc.* **2004**, *126*, 4520. b) Y. Takenaka, H. Ito, M. Hasegawa, K. Iguchi, *Tetrahedron* **2006**, *62*, 3380. c) Y. Takenaka, H. Ito, K. Iguchi, *Tetrahedron* **2007**, *63*, 510.

34 For the rhodium-catalyzed enantioselective [2 + 2] cycloaddition reaction of alkynyl esters with norbornene derivatives (5 mol % catalyst loading, 54 to >99% yield, 55–99% ee), see: T.

Shibata, K. Takami, A. Kawachi, *Org. Lett.* **2006**, *8*, 1343.

35 a) F. Tanaka, N. Mase, C. F. Barbas, *J. Am. Chem. Soc.* **2004**, *126*, 3692. b) X. Dai, H. M. L. Davies, *Adv. Synth. Catal.* **2006**, *348*, 2449.

36 For syntheses of (±)-4a-methylhydrofluorene diterpenoids, see: a) E. Fillion, D. Fishlock, *J. Am. Chem. Soc.* **2005**, *127*, 13144. b) M. Banerjee, R. Mukhopadhyay, B. Achari, A. K. Banerjee, *J. Org. Chem.* **2006**, *71*, 2787. c) G. Liang, Y. Xu, I. B. Seiple, D. Trauner, *J. Am. Chem. Soc.* **2006**, *128*, 11022.

37 For the synthesis of (±)-dichroanone, see: R. M. McFadden, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 7738.

38 It was ascertained by ^{1}H NMR spectral analysis that a new species was generated from **1i**·2.6Tf_2NH and α-(acyloxy)acrolein in CD_3CN in ca. 10% conversion. However, we could not clearly assign it as an iminium salt intermediate. Therefore, we cannot exclude the possibility of chiral Brønsted acid catalysis through hydrogen bonding.

Kazuaki Ishihara was received his Ph.D. from Nagoya University in 1991 under the direction of Professor Hisashi Yamamoto. He had the opportunity to work under the direction of Professor Clayton H. Heathcock at the University of California, Berkeley, as a visiting graduate student in 1988. He was a JSPS Fellow under the Japanese Junior Scientists Program from 1989 to 1991. After completing his postdoctoral studies with Professor E. J. Corey at Harvard University, he returned to Japan and joined Professor H. Yamamoto's group at Nagoya University as an assistant professor in 1992, and became associate professor in 1997. In 2002, he was appointed to his current position as a full professor at Nagoya University. He has received the Inoue Research Award for Young Scientists (1994), the Chemical Society of Japan Award for Young Chemists (1996), the Thieme Chemistry Journal Award (2001), the Green & Sustainable Chemistry Award from the Ministry of Education, Culture, Sports, Science and Technology (2003), the JSPS Prize (2005), the BCSJ Award (2005), the Japan IBM Science Prize (2007), and the Mukaiyama Award (2009). His research interests include asymmetric catalysis, biomimetic catalysis induced by artificial enzymes, dehydrative condensation catalysis, and acid–base combination chemistry.

Akira Sakakura was born in 1970 in Mie Prefecture, Japan, and received his Ph.D. degree from Nagoya University in 2000 under the direction of Professor Yoshihiro Hayakawa. After doing postdoctoral studies with Professor Shizuaki Murata at Nagoya University for nine months from 2000, he joined Professor Hideo Kigoshi's group at University of Tsukuba as an assistant professor in 2001. In 2003, he joined Professor Kazuaki Ishihara's group at Graduate School of Engineering, Nagoya University as an associate professor. In 2007, he appointed to his current position of an associate professor at EcoTopia Science Institute, Nagoya University. He has received Incentive Award from Tokai Branch of the Society of Synthetic Organic Chemistry, Japan (2005), Banyu Pharmaceutical Award in Synthetic Organic Chemistry, Japan (2005), Lectureship Award of Young Generation Special Forum from the Chemical Society of Japan (2006), Thieme Chemistry Journal Award (2006), and Incentive Award in Synthetic Organic Chemistry, Japan (2007), Banyu Chemist Award (BCA) (2009). His research interests include biomimetic synthesis of bioactive natural products, catalytic dehydrative condensation towards green & sustainable chemistry, and acid–base combination chemistry.