Review

Rational design of dynamic ammonium salt catalysts towards more flexible and selective function

By Kazuaki ISHIHARA*1,†

(Communicated by Takao SEKIYA, M.J.A.)

Abstract: This review focuses on the development of dynamic ammonium salt catalysis for selective organic transformations conducted in our laboratory since 2002. Several important concepts in designing of catalysts are described with some examples. In particular, the practical synthesis of chiral 1,1'-binaphthyl-2,2'-disulfonic acid (BINSA) and its application in chiral ammonium salt catalysis for the enantioselective direct Mannich-type reaction are described.

Keywords: acid-base combination chemistry, dynamic salt complex, dehydrative condensation, Mannich-type reaction, Diels-Alder reaction, [2+2] cycloaddition reaction

Introduction

The acidity of catalysts can be controlled based on acid–base combination chemistry.1,2 For example, if p-toluenesulfonic acid is too strong as an acid catalyst, pyridinium p-toluenesulfnonate may be chosen. p-Toluenesulfonic acid is a classical single-molecule catalyst, and its ammonium salt behaves as a dynamic complex in solution. Ammonium sulfonates are equilibrated with free amines and free sulfonic acids in solution. Enzymes also function through dynamic complexation between acidic molecules and basic molecules in vivo. It might be possible to create an artificial catalyst taking advantage of the conformational and dynamic flexibility of such salts expecting enzymatic functions such as induced-fit, molecular recognition, cooperative effect, allosteric effect, etc. The key to designing dynamic complexes is non-bonding interactions such as hydrogen-bonding, electrostatic, ionic, π–π, cation–π, cation–n, hydrophobic, hydrophilic interactions, etc. Recently, we developed a new type of catalyst which function through dynamic aggregation of acids and bases. In this article, the potential of dynamic salt complexes as highly functional catalysts is demonstrated with several examples that were developed in our laboratory.

Scheme 1 shows the equilibrium in a solution of an equimolar mixture of a sulfonic acid and a tertiary amine. In this case, a 1:1 complex is expected to be the major species.

Scheme 2 shows the equilibrium in a solution of an equimolar mixture of a sulfonic acid and a secondary amine. In this case, linear or cyclic n:m salt complexes may be formed because secondary ammonium cations have two acidic protons. The selectivity of complexation can be controlled by steric repulsions or other non-bonding interactions.

Scheme 3 shows the equilibrium in a solution of an equimolar mixture of a sulfonic acid and a primary amine. In this case, more complicated n:m salt complexes may have to be considered because primary ammonium cations have three protons. Therefore, it is not easy to control the selectivity of complexation. Nevertheless, a primary ammonium cation may be useful as a building block to construct a three-dimensional structure.

Scheme 1. Dynamic ammonium salts of sulfonic acid with tertiary amine.
Thus, dynamic salt complex catalysts can be prepared in situ from acidic and basic small molecules which are elaborately designed based on acid–base combination chemistry as shown in Schemes 1–3.

The first two examples are the dehydrative condensation reactions catalyzed by dynamic salt complexes of sulfonic acids with secondary amines. These salt catalysts are aggregated like a reverse micelle in non-polar hydrocarbons, and their catalytic activities are much higher than those of the corresponding sulfonic acids themselves due to local hydrophobic function around the ammonium protons of their salts.

The third example is the enantioselective Mannich-type reaction catalyzed by dynamic salt complexes of chiral disulfonic acids with tertiary amines. Interestingly, although ammonium cations are achiral, high enantioselectivity is induced through the chiral counter anion. Chiral dynamic salt complexes can be rapidly optimized to induce high enantioselectivity by a combinatorial approach.

The last three examples are the enantioselective Diels–Alder reactions of dienes with α-(acyloxy)- and α-(N,N-diacylamino)acroleins and the enantioselective [2+2] cycloaddition reactions of alkenes with α-(acyloxy)acroleins catalyzed by dynamic salt complexes of achiral Brønsted acids with chiral amines. A conformationally flexible chiral triamine 24 derived from H-L-Phe-L-Leu-N(CH₂CH₃)₂ is very effective as an amine component of catalysts.
Bulky diarylammonium pentafluorobenzene-sulfonates as mild and extremely active dehydrative esterification catalysts

A great deal of research has been focused on more environmentally benign alternatives to esterification processes, which are in great demand by the chemical industry. In general, the dehydrative condensation reaction of carboxylic acids with alcohols is catalyzed by Brønsted acids such as HCl, H_2SO_4, p-TsOH, etc. for acid-resistant substrates. For acid-sensitive substrates, weak Brønsted acids such as pyridinium p-toluenesulfonate (PPTS) are usually used. However, their catalytic activities are somewhat low, and the reactants that can be used are rather limited. In 2000, Tanabe et al. reported that \(N, N\)-diphenylammonium triflate (1) (1–10 mol%) efficiently catalyzed the esterification reaction of carboxylic acid with equimolar amounts of alcohols under heating at 80 °C without the removal of water (Scheme 4). In 2006, Tanabe et al. reported that pentafluorobenzilinium triflate (2) was more active than 1. However, it is difficult to apply these methods to sterically demanding and acid-sensitive alcohols because 1 and 2 are still strongly acidic salts of a superacid and weak bases. In addition, its turnover is much lower than those of hafnium(IV) and zirconium(IV) catalysts. In 2005, we found bulky \(N, N\)-diarylammonium pentafluorobenzenesulfonates such as 4a, 5a and 6a, which are much milder acids than the corresponding ammonium triflates, as extremely active esterification catalysts. The hydrophobic effect of the bulky ammonium sulfonates effectively promotes the dehydrative condensation reaction, and their steric bulkiness suppresses the dehydrative elimination of secondary alcohols to produce alkenes.

The catalytic activities of various arenesulfonic acids, dimesitylamilonium arenesulfonates, and diarylammonium pentafluorobenzenesulfonates for the esterification reaction of 4-phenylbutyric acid with cyclododecanol in heptane are shown in Figs. 1–3.

In contrast, the catalytic activities of \(N, N\)-diarylammonium alkanesulfonates depended on the structures of ammonium cations and alkanesulfonates (Figs. 2 and 3). These experimental results suggest that ammonium sulfonates function as general acid catalysts. In the case of \(N, N\)-dimesitylammonium...
arenesulfonates (Fig. 2), ammonium tosylate (4b, squares), pentafluorobenzenesulfonate (4a, circles), and mesitylenesulfonate (×) were more active as dehydration catalyst but less acidic than ammonium triflate (+) and 2,4,6-trichlorobenzenesulfonates (triangle).

In the case of N,N-diarylammonium pentafluorobenzenesulfonates (Fig. 3), N,N-diphenylammonium pentafluorobenzenesulfonate (3a, squares) showed lower catalytic activity than C₆F₅SO₃H (circles) due to its weaker acidity. More bulky N,N-diarylammonium pentafluorobenzenesulfonates showed higher catalytic activities than 3a. Surprisingly, N-(2,6-diphenylphenyl)-N-mesitylammonium pentafluorobenzenesulfonate (5a, triangles) exhibited higher catalytic activity than C₆F₅SO₃H. These experimental results suggest that the hydrophobic effect due to bulky N-aryl groups and the S-pentafluorophenyl group of 5a, which surround NH₂⁺ of the catalyst, may synergistically accelerate the dehydrative condensation reaction, and the hydrophobic effect may be more important than the strong acidity of NH₂⁺ in promoting the dehydrative reaction.

Comparative experiments using catalysts 1 and 6a have been performed using the esterification reaction of 4-phenylbutyric acid with 6-undecanol in hexane under reflux conditions without the removal of water and under azotropic reflux conditions with the removal of water (Fig. 4). While the reaction catalyzed by 1 was slightly decelerated under reflux conditions without the removal of water, the reaction catalyzed by 6a proceeded efficiently without the influence of water.¹²⁻¹⁵

Representative results for the esterification catalyzed by 4a (1 mol%) at 80 °C in heptane are shown in Scheme 5. 2-Substituted carboxylic acids, 2-monosubstituted carboxylic acids, and sterically demanding 2,2-disubstituted carboxylic acids were smoothly condensed to produce the corresponding esters. α,β-Unsaturated carboxylic acids and benzoic acids were also transformed into the corresponding

---

Fig. 2. Catalytic activity of N,N-dimesitylammonium alkanesulfonates for the esterification in Fig. 1.

Fig. 3. Catalytic activity of N,N-diarylammonium pentafluorobenzenesulfonates for the esterification in Fig. 1.
esters. 2-Alkoxycarboxylic acids were very reactive probably due to favorable chelation between the substrates and 4a. 4-Oxopentanoic acid was selectively esterified without protecting the ketone moiety. 4a is useful for acid-sensitive alcohols such as benzyl alcohol, allylic alcohols, propargylic alcohols, and secondary alcohols. In particular, esterification with the sterically demanding alcohol 6-undecanol gives the desired esters in good yield with less than 5% of alkenes. Although Lewis-acidic metal salts such as Hf(IV) and Zr(IV) were not adapted to 1,2-diols due to tight chelation with metal ions, these diols were esterified in high yield by 4a. Less-reactive aryl alcohols and 1-adamantan alcohol were also esterified in high yields.

Dehydrative condensation reactions of carboxylic acids with 1.1 equivalents of more-reactive primary alcohols proceeded even at room temperature without any solvents in good yield in the presence of 1 mol% of 4a (Scheme 6). Water was separated as a second phase during the reaction. This is an ultimate atom-economical esterification process.

Dehydrative cyclocondensation catalysts

Bulky N,N-diarylammonium pentfluorobenzenesulfonates promote the dehydrative cyclization of 1,3,5-triketones to γ-pyrone much more effectively...
than the dehydrative esterification reaction, since 1,3,5-triketones are generally less polar than carboxylic acids and alcohols. The local hydrophobic environment created around the ammonium protons in ammonium sulfonates is the key to the unusual acceleration of dehydration reactions. We have investigated the relationship between the catalytic activity and the steric and/or stereoelectronic factors of \( N,N \)-diarylammonium arenesulfonate catalysts for the dehydrative cyclization of 1,3,5-triketones, and have discussed the microscopic hydrophobic environment created in aggregated ammonium sulfonates based on a consideration of their X-ray single-crystal structures.

Table 1. Dehydrative cyclization of 7a to 8a catalyzed by 6a or \( C_6F_5SO_3H \)

| entry | solvent | yield [%] of 8a\(^b\) |
|-------|---------|------------------------|
| 1     | heptane | 100 74                 |
| 2     | toluene | 56 55                  |
| 3     | 1,4-dioxane | 64 58          |
| 4     | EtCN    | 64 61                  |

\(^{a}\)Reactions were carried out with 0.2 mmol of 7a and 5 mol % of catalyst in 4 mL of solvent at 80 °C for 8 h without the removal of generated water. \(^{b}\)Determined by HPLC analysis.

The catalytic activities of 6a and \( C_6F_5SO_3H \) in the dehydrative cyclization of 4,6-dimethylnonan-3,5,7-trione (7a) have been compared under heating without the removal of water and under azeotropic reflux conditions with the removal of water (Fig. 5). While the reaction catalyzed by \( C_6F_5SO_3H \) at 80 °C without the removal of water gave \( \gamma \)-pyrone 8a in 74% yield after 8 h (circles, graph A), the reaction under azeotropic reflux conditions in cyclohexane (bp. 80.7 °C) with the removal of water gave 8a in 96% yield after the same reaction time (squares, graph A). The reaction proceeded more smoothly in perfluoromethylcyclohexane, which was a water-repellent solvent, without the influence of water, and gave 6a quantitatively after 8 h (rhombuses, graph A). Fluorous media appear to release the water produced from the active site of the catalyst. In contrast, the reaction catalyzed by 6a at 80 °C gave 8a quantitatively regardless of the above three conditions (graph B). Very importantly, 6a exhibited much higher catalytic activity than \( C_6F_5SO_3H \) under heating conditions without the removal of water despite the weaker acidity of 6a. These experimental results show that the use of 6a gives the same rate-accelerating effect as the use of a Dean–Stark apparatus or hydrophobic perfluoromethylcyclohexane.

The solvent effect for the dehydrative cyclization of 7a catalyzed by 6a or \( C_6F_5SO_3H \) without the removal of water has also been investigated (Table 1). When the reaction catalyzed by 6a was conducted in heptane at 80 °C for 8 h, 8a was obtained in quantitative yield (entry 1). On the other hand, this reac-
Analysis of C$_6$F$_5$SO$_3$H proceeded better in heptane (entries 2–4). Similarly, the reaction catalyzed by toluene, 1,4-dioxane, and EtCN because of no rate-accelerating stable ion pair in polar solvents such as toluene, 1,4-dioxane, and EtCN. Interestingly, 6a catalyzed dehydration reaction can be attributed to the dehydrative cyclization of 4,6,9-trimethyldecan-3,5,7-trione (7b) to γ-pyrone 8b were evaluated by HPLC analysis. rhombuses: [(2,6-Ph$_2$C$_6$H$_3$)MesN$^+$$\cdot$H$_2$]; squares: Mes$_2$N$^+$$\cdot$H$_2$; circles: H$^+$; triangles: [Ph$_2$N$^+$]. The yield of 8b was evaluated by HPLC analysis. rhombuses: [(2,6-Ph$_2$C$_6$H$_3$)MesN$^+$$\cdot$H$_2$]; squares: Mes$_2$N$^+$$\cdot$H$_2$; circles: H$^+$; triangles: [Ph$_2$N$^+$]. The catalytic activities of C$_6$F$_5$SO$_3$H, TsOH and diarylammonium tosylates (graph D) are compared. Compared with C$_6$F$_5$SO$_3$H (circles), 3a showed lower catalytic activity due to its weaker acidity and slight hydrophobicity (triangles), while 5a (rhombuses) and 4a (squares) exhibited significantly higher catalytic activities than C$_6$F$_5$SO$_3$H. In particular, the most bulky catalyst 5a had the highest catalytic activity due to its efficient creation of a local hydrophobic environment. Very interestingly, 5a showed higher catalytic activity than TsOH despite the much weaker acidity of 5a (circles, graph C versus rhombuses, graph D). These experimental results suggest that two bulky N-aryl groups and an S-pentafluorophenyl group, which surround the active site of N$_2$H$_2$O of 5a, synergistically accelerate the dehydration reactions. Based on the results in Figs. 5 and 6 and Table 1, the rate-accelerating effect on the 5aca catalyzed dehydration reaction can be attributed to the local hydrophobic environment in 5a. A similar tendency has been observed in the ester condensation reaction of carboxylic acids with alcohols as well as the dehydrative cyclization of 1,3,5-triketones. However, the latter reaction was promoted much more effectively than the former reaction.

X-ray single-crystal structures of the N,N-diarylammonium sulfonates suggest that a hydrophobic environment in their aggregates may play an important role. Crystal 9 was obtained by the recrystallization of 5a, which was a 1:1 molar mixture of N-(2,6-diphenylphenyl)-N-mesitylamine and C$_6$F$_5$SO$_3$H in CHCl$_3$–hexane (Scheme 7). Surprisingly, X-ray crystallographic analysis revealed that 7 is a supramolecular complex composed of two diarylammonium cations, four pentafluorobenzenesulfonate anions and two oxonium cations (Fig. 7). Two ammonium cations and two oxonium cations in 9 are surrounded by 12 hydrophobic aryl groups, like reverse micelles. Furthermore, the cyclic ion pair is thermodynamically and conformationally stabilized by not only four $^\circ$HN$^+$$\cdot$H$\cdots$O=S=O$^-$ and

![Fig. 6. Dehydrative cyclization of 7b catalyzed by N,N-diarylammonium tosylates (graph C) and N,N-diarylammonium pentafluorobenzenesulfonates (graph D). The yield of γ-pyrones 8b was evaluated by HPLC analysis. rhombuses: [(2,6-Ph$_2$C$_6$H$_3$)MesN$^+$$\cdot$H$_2$]; squares: Mes$_2$N$^+$$\cdot$H$_2$; circles: H$^+$; triangles: [Ph$_2$N$^+$]. The catalytic activities of C$_6$F$_5$SO$_3$H, TsOH and diarylammonium tosylates (graph D) are compared. Compared with C$_6$F$_5$SO$_3$H (circles), 3a showed lower catalytic activity due to its weaker acidity and slight hydrophobicity (triangles), while 5a (rhombuses) and 4a (squares) exhibited significantly higher catalytic activities than C$_6$F$_5$SO$_3$H. In particular, the most bulky catalyst 5a had the highest catalytic activity due to its efficient creation of a local hydrophobic environment. Very interestingly, 5a showed higher catalytic activity than TsOH despite the much weaker acidity of 5a (circles, graph C versus rhombuses, graph D). These experimental results suggest that two bulky N-aryl groups and an S-pentafluorophenyl group, which surround the active site of N$_2$H$_2$O of 5a, synergistically accelerate the dehydration reactions. Based on the results in Figs. 5 and 6 and Table 1, the rate-accelerating effect on the 5aca catalyzed dehydration reaction can be attributed to the local hydrophobic environment in 5a. A similar tendency has been observed in the ester condensation reaction of carboxylic acids with alcohols as well as the dehydrative cyclization of 1,3,5-triketones. However, the latter reaction was promoted much more effectively than the former reaction.

X-ray single-crystal structures of the N,N-diarylammonium sulfonates suggest that a hydrophobic environment in their aggregates may play an important role. Crystal 9 was obtained by the recrystallization of 5a, which was a 1:1 molar mixture of N-(2,6-diphenylphenyl)-N-mesitylamine and C$_6$F$_5$SO$_3$H in CHCl$_3$–hexane (Scheme 7). Surprisingly, X-ray crystallographic analysis revealed that 7 is a supramolecular complex composed of two diarylammonium cations, four pentafluorobenzenesulfonate anions and two oxonium cations (Fig. 7). Two ammonium cations and two oxonium cations in 9 are surrounded by 12 hydrophobic aryl groups, like reverse micelles. Furthermore, the cyclic ion pair is thermodynamically and conformationally stabilized by not only four $^\circ$HN$^+$$\cdot$H$\cdots$O=S=O$^-$ and
six “H$_2$O—H···O=SO$_2$” intermolecular hydrogen bonds but also two intermolecular π–π interactions between mesityl groups and pentafluorophenyl groups, two intermolecular π–π interactions between phenyl groups and pentafluorophenyl groups and two intramolecular π–π interactions between mesityl groups and phenyl groups: the distance between the mesityl and pentafluorophenyl groups is 3.6–3.8 Å and that between the mesityl and phenyl groups is 3.0–3.6 Å. The extremely high catalytic activity of 5a in the ester condensation and dehydrative cyclization of 1,3,5-triketones may be ascribed to the hydrophobic environment around ammonium protons in 7, which includes carboxylic acids or 1,3,5-triketones in place of water.

When crystal 9 was used as a catalyst instead of a 1:1 molar mixture of C$_6$F$_5$SO$_3$H and N-(2,6-diphenylphenyl)-N-mesitylamine, the ester condensation reaction of 4-phenylbutyric acid with cyclododecanol proceeded more slowly. An equilibrium mixture of 9 and N-(2,6-diphenylphenyl)-N-mesitylamine probably exists in a 1:1 molar solution of C$_6$F$_5$SO$_3$H and N-(2,6-diphenylphenyl)-N-mesitylamine in heptane. The above experimental results suggest that the ratio of 9 in a 1:1 molar solution of C$_6$F$_5$SO$_3$H and N-(2,6-diphenylphenyl)-N-mesitylamine is much higher than that in a 2:1 molar solution.

The X-ray single-crystal structure of 4a is a dimeric complex composed of two N,N-dimesitylammonium cations and two pentafluorobenzenesulfonate anions (Fig. 7). The ammonium cation moiety is surrounded by six aryl groups, and the cyclic ion pair is also stabilized by two intermolecular π–π interactions. The distance between the N-mesityl and pentafluorophenyl groups is 3.5–3.6 Å. N,N-Dimesitylammonium tosylate (4b) also forms a complex composed of two N,N-dimesitylammonium cations and two p-toluenesulfonate anions. In contrast to 9 and 4a, 4b does not exhibit intermolecular π–π interactions between the N-mesityl and tolyl groups. In contrast to the N,N-diaryl ammonium sulfonates, anilinium pentafluorobenzenesulfonate did not form a cyclic ion pair structure. Therefore, N,N-diarylamine structures are important for the formation of cyclic ion pairs in which the ammonium cation moieties are surrounded by aryl groups.

Aggregated cyclic ion pairs 9 and dimeric 4a may be similar to real active species in the dehydra-
tion reactions such as ester condensation and dehydrative cyclization of 1,3,5-triketones. They are stabilized by not only intermolecular hydrogen bondings but also intermolecular π-π interactions between the mesityl and perfluorophenyl groups. Moreover, the use of a less polar solvent such as heptane also promotes tight aggregation between diarylamines and C₆F₅SO₃H, which is less acidic and less polar than TsOH. In contrast, 4b is less active as a dehydration catalyst because of the instability of the cyclic ion pair due to the absence of intermolecular π-π interaction and the more acidic and more polar nature of TsOH. Therefore, it seems that the catalytic activity of 4b is mainly due to its strong acidity. The formation of a stable cyclic ion pair, in which the ammonium protons are located in the local hydrophobic environment, is considered to be crucial for the excellent catalytic activity.

Water molecules produced at the active site of bulky N,N-diarylammonium perfluorobenzenesulfonates are easily exchanged for less polar substrates such as carboxylic acids and 1,3,5-triketones. Once water molecules are released from the ammonium cation moiety, the hydrophobic wall prevents polar water molecules from gaining access to the active site of the catalysts, leading to the inhibition of inactivation of the catalysts by water. In contrast, less polar substrates can easily approach the active site through the hydrophobic wall and is efficiently activated. Thus, bulky N,N-diarylammonium perfluorobenzenesulfonates exhibit remarkable catalytic activities for the dehydration reactions without any loss of catalytic activities even under conditions without the removal of water. In contrast, sulfonic acids interact with water more strongly than with less polar substrates. Therefore, sulfonic acids are inactivated under conditions without the removal of water.

A proposed mechanism for the dehydrative cyclization of 1,3,5-triketones is shown in Scheme 8. Bulky ammonium catalyst 5a coordinates more preferentially with the carbonyl oxygen at the 5-position of 1,3,5-triketones 7 than with that at the 1-position, to avoid the steric hindrance of the substituent group indicated by R (step 1). However, enol intermediate 11 is less stable than 10 because of steric hindrance between the R group and methyl group. Therefore, 7b, which has an isobutyl group, is less reactive than 7a. Compound 11 is reversibly converted to cyclic hemiacetal 12 (step 2). Coordination of 3a with the hydroxy group of 12 makes the hydrophilic hemiacetal moiety of 12 labile in the hydrophobic environment, and the dehydration of 12 (step 3) is promoted. Dehydration is also promoted by the steric hindrance of 5a, and thus 12 is easily converted to the corresponding γ-pyrones 8. The generated water is rapidly released from the active site of 5a and easily exchanged for less polar 7, due to the hydrophobic environment (step 1). Thus, compound 5a exhibits remarkable catalytic activities without being affected by the generated water.

In summary, bulky N,N-diarylammonium perfluorobenzenesulfonates show unusual rate-accelerating effect for dehydration reactions such as the esterification and the cyclization of 1,3,5-triketones. In particular, the most bulky and hydrophobic catalyst 5a shows much higher catalytic activity than C₆F₅SO₃H even though 5a is a weaker acid. It is conceivable that the local hydrophobic environment created by the tight aggregation of 5a in less polar solvent efficiently promotes dehydration reactions. The
X-ray crystallographic analysis of 9, which may be the real active species, suggests that stabilization of the cyclic ion pair by intermolecular π-π interactions between hydrophobic bulky aryl groups is crucial for the creation of the hydrophobic environment.

**Chiral ammonium salts as asymmetric Mannich-type catalysts**

A chiral organic salt which consists of a Brønsted acid and a Brønsted base is one of the most promising catalysts in modern asymmetric syntheses. In general, acid–base combined salts have several advantages over single-molecule catalysts, with regard to the flexibility in the design of their dynamic complexes. Chiral ammonium salts of chiral amines with achiral Brønsted acids are typical examples of these organocatalysts with enantioselective function. 2,2'-Disubstituted 1,1'-binaphthyl is one of the most popular chiral auxiliaries of asymmetric catalysts. However, bulky substituents at the 3,3'-positions of 1,1'-binaphthyl are often required to achieve high enantioselectivity in asymmetric catalysts. In sharp contrast, chiral 1,1'-binaphthyl-2,2'-disulfonylic acid (BINSA, 13) is a promising chiral Brønsted acid, since both the Brønsted acidity and bulkiness can be easily controlled by complexation with achiral amines without substitutions at the 3,3'-positions in a binaphthyl skeleton (Scheme 9). However, despite this potential, there had been no reports on the application of chiral 13 to asymmetric catalyses since the first synthesis of rac-13 in 1928 by Barber and Smiles. In 2008, we developed a practical synthesis of chiral 13 from inexpensive 1,1'-bi(2-naphthol) (BINOL) and efficient enantioselective catalysis in direct Mannich-type reactions using 13-2,6-diarylpyridine (14) combined salts as chiral Brønsted acid–base organocatalysts in situ.

The method used to prepare (R)-13 from (R)-BINOL via the oxidation of dithiol (R)-17 is shown in Scheme 10. Thermolysis in the Newman–Kwart rearrangement of (R)-15 to (R)-16 has been dramatically improved by using a microwave technique at a lower temperature (200°C). The oxidation of thiols (RSH) to sulfonic acids (RSO₂H) is usually accompanied by the generation of disulfides (RS–SR) via intermolecular reactions. In particular, it seems that dithiol (R)-17 bearing two SH groups at...
the 2,2'-positions in a binaophthyl skeleton may be suitable for the formation of an oxidative S-S bond, intramolecularly.\(^{37,38}\) However, the oxidation of \((R)-15\) proceeded smoothly in 82% yield without epimerization under 7 atm of \(\mathrm{O}_2/\mathrm{KOH}\) in HMPA. The chemical structure of the potassium salt of \((R)-13\) had been ascertained by X-ray diffraction analysis of its single crystal. Compound \((R)-13\) was isolated by ion-exchange. Thus, \((R)-13\) was prepared in 51% yield over five steps from \((R)-\text{BINOL}\), or in 82% yield in one step from commercially available \((R)-17\).

The enantioselective direct Mannich-type reaction\(^{27\text{-}29}\) has been examined using \((R)-13\) as a chiral Bronsted acid catalyst (Table 2). Since the reaction between \(N\)-Cbz-phenylaldimine \((18a)\) and acetylacetone \((19a)\) proceeds without catalysts in dichloromethane at 0 °C, the slow addition of \(19a\) is the key to preventing the achiral pathway. However, despite such care, the enantioselectivity of \(20a\) was low (17% ee) when 5 mol % of \((R)-13\) was used (entry 1). Next, chiral \((R)-13\) (5 mol %)–achiral amine (10 mol %) combined salts prepared \textit{in situ} were examined as chiral Bronsted acid–base catalysts. Pyridine, 2-phenylpyridine, and 2,6-lutidine gave \((R)-20a\) in low yield due to the insolvability of the corresponding salts (entries 2–4). In sharp contrast, 2,6-di-tert-butylpyridine improved the enantioselectivity up to 76% ee (entry 5). Moreover, \((R)-13\) with 2,6-diphenylpyridine \((14a)\), which led to a homogeneous catalyst \textit{in situ}, was found to be highly effective, and \((R)-20a\) was obtained in 74% yield with 92% ee (entry 6). \(N\)-Boc-phenylaldimine \((18b)\), which had been reported as a sole protecting group by Terada and co-workers using pioneering chiral phosphoric acids (Scheme 11),\(^{27\text{-}29}\) was compatible with the present reaction conditions using \((R)-\text{13\text{-}14a}_2\), and the corresponding adduct \((R)-20b\) was obtained in 83% yield with 85% ee (entry 7). In their catalytic enantioselective reactions, acetylacetone\(^{27}\) is the sole nucleophile, and \(N\)-Boc protection in aldimes is essential for achieving high enantioselectivities. \((S)-1,1\text{-}\text{Binaphthyl}-2,2\text{-dicarboxylic acid}\text{14a}_2\) (5 mol %) showed low catalytic activity and low enantioselectivity (8% ee) under the same conditions as in entry 6 (entry 8).\(^{26}\)

The molar ratio of \(14a\) (0–15 mol %) to \((R)-13\) (5 mol %) has been optimized for the above direct Mannich-type reaction of \(19a\) with \(18a\) (Table 3). Interestingly, the enantioselectivities of \(20a\) were dramatically improved when a molar ratio of \((R)-\text{13\text{-}14a}_2\) was 1: 0.75 (entries 4–9 vs. entries 1–3). As a result, a 1:1.5 to 1:2.5 ratio of \((R)-\text{11\text{-}12a}\) was effective for achieving both a high yield and a high enantioselectivity (entries 6–8). Probably, the wide range of suitable ratios for \((R)-\text{13\text{-}14a}_2\) is due to the dynamic structure of the catalysts (Scheme 9).

Fortunately, \((R)-20a\) was obtained in 91% yield with 90% ee with the use of 1 mol % of \((R)-\text{13\text{-}14a}_2\) in the presence of MgSO\(_4\), which prevented the decomposition of \(18a\) (1.5 equiv) due to adventitious

Table 2. Ammonium salts of \((R)-13\) as tailor-made catalysts\(^a\)

| entry | amine | yield [%] | ee [%] |
|-------|-------|----------|--------|
| 1 | \(18a\) (R = Cbz) | 81 | 17 |
| 2 | \(18a\) | 8 | 5 |
| 3 | \(18a\) | 11 | 10 |
| 4 | \(18a\) | 19 | 0 |
| 5 | \(18a\) | 32 | 76 |
| 6 | \(18a\) | 74 | 92 |
| 7 | \(18b\) | 83 | 85 |
| 8\(^b\) | \(18a\) | 85 | 8 (S) |

\(^a\)Acetylacetone \(19a\) was added at 0 °C over 1 h, and the resultant mixture was stirred for 30 min. \(^b\)\((S)-1,1\text{-}\text{Binaphthyl}-2,2\text{-dicarboxylic acid}\) was used instead of \((R)-13\). After being stirred at 0 °C for 30 min, the reaction mixture was further stirred at room temperature for 4 h.

Scheme 11. Example of the enantioselective direct Mannich reaction using a single-molecule catalyst.
moisture (Table 4, entry 1). Under these optimized conditions, N-Boc-Mannich product (R)-20b was obtained in 99% yield with 84% ee (entry 2). From 19a and a variety of N-Cbz-arylaldimines bearing electron-donating or electron-withdrawing groups in the aryl or heteroaryl moiety, the corresponding adducts (20c–j) were obtained in excellent yields with high enantioselectivities (entries 3–8). When other diketones such as 3,5-heptanone (19b) and 1,3-diphenylpropane-1,3-dione (19c) were reacted with 18a, 20i and 20j were obtained with 95% ee and 84% ee, respectively (entries 9 and 10).

The absolute stereochemistry of the products 20a and 20b has been determined by following Terada’s procedure, which includes Baeyer–Villiger oxidation.27 However, unexpected tertiary alcohols 21 were obtained exclusively instead of the Baeyer–Villiger products when Mannich adducts 20 were oxidized under the same reaction conditions as reported by Terada.27 Compound 21f was determined by X-ray analysis (Scheme 12).

Moreover, cyclic 1,3-diketone 19d could also be used, and the corresponding adduct 20k with a quaternary carbon center was obtained in 98% yield with a syn/anti diastereomer ratio (dr) of 83/17 and high enantioselectivity (91% ee and 96% ee, respectively) (Scheme 13).

A suitable chiral ammonium salt is easily tailormade for a ketoester equivalent such as 3-acetoacetyl-2-oxazolidinone (22) (Scheme 14). Chiral ammonium salt (R)-13•14a2, which was optimized for the reaction of diketones 19 with 18, was not effective, and the desired product 23 was obtained in 86% yield ee.

Table 3. Effect of the ratio of (R)-13•14a

| entry | 13•14a | yield [%] | ee [%] |
|-------|--------|-----------|--------|
| 1     | 13     | 81        | 17     |
| 2     | 13•14a0.25 | 82      | 17     |
| 3     | 13•14a0.5  | 83      | 34     |
| 4     | 13•14a0.75 | 81      | 79     |
| 5     | 13•14a1.0  | 82      | 84     |
| 6     | 13•14a1.5  | 84      | 90     |
| 7     | 13•14a2.0  | 74      | 92     |
| 8     | 13•14a2.5  | 76      | 95     |
| 9     | 13•14a3.0  | 68      | 86     |

Table 4. Catalytic enantioselective direct Mannich-type reaction

| entry | 18 (R, Ar) | 19 | 20 | yield [%] | ee [%] |
|-------|------------|----|----|-----------|--------|
| 1     | 18a (Cbz, Ph) | 19a | 20a | 91 | 90 (R) |
| 2     | 18b (Boc, Ph) | 19a | 20b | 99 | 84 (R) |
| 3     | 18c (Cbz, o-MeC6H4) | 19a | 20c | 93 | 96 |
| 4     | 18d (Cbz, m-MeC6H4) | 19a | 20d | 93 | 89 |
| 5     | 18e (Cbz, p-MeOC6H4) | 19a | 20e | 95 | 96 |
| 6     | 18f (Cbz, p-BrC6H4) | 19a | 20f | 92 | 98 (R) |
| 7     | 18g (Cbz, 1-Naph) | 19a | 20g | 99 | 96 |
| 8     | 18h (Cbz, 3-Thionyl) | 19a | 20h | 98 | 98 |
| 9     | 18a (Cbz, Ph) | 19b | 20i | 95 | 95 |
| 10    | 18a (Cbz, Ph) | 19c | 20j | >99 | 84 |

Scheme 12. Unexpected oxidation of 20f and X-ray analysis of 21f.
yield with low diastereo- and enantioselectivities. In contrast, the enantioselectivity of 23 increased to 93% ee when 2,6-dimesitylpyridine (14b) was used in place of 14a. In this way, tailor-made salts (R)-13 make it possible to avoid preparing single-molecule catalysts in advance and offered a quick solution to this type of optimization problem.

Compound 23 could be easily transformed to β-amino carbonyl compound 24 via deprotection of the oxazolidinone moiety without a loss of enantioselectivity (Scheme 15).

In summary, BINSA (R)-13 is a highly effective chiral Brønsted acid that can be combined with an achiral Brønsted base. The combination of the achiral bulky 2,6-diarylp yridine 14 with the simple disulfonic acid (R)-13 circumvents the trouble of having to build bulky substituents at the 3,3'-positions, as is normally required in analogous biphenyl phosphoric acid catalysts. In the presence of 1 mol% of (R)-13 and 2 mol% of 14, highly enantioselective direct Mannich-type reactions of a variety of 1,3-diketones and a 1,3-ketoester equivalent with arylaldimines proceed smoothly with high enantioselectivities. BINSA 13 is a powerful chiral auxiliary like BINOL, BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthalene), BINAM, etc., and is expected to trigger a new frontier in acid-base chemistry in asymmetric catalyses.44)

Chiral ammonium salt catalysts for the enantioselective Diels–Alder reaction with α-(acyloxy)acroleins

The first enantioselective organocatalytic Diels–Alder reaction of dienes with α-unsubstituted acroleins was reported by MacMillan et al. (Scheme 16).45,46) Their organocatalysts, which are chiral ammonium salts of HCl or HClO4 with cyclic secondary amines derived from L-phenylalanine, are almost inactive for the Diels–Alder reaction with α-substituted acroleins, due to poor generation of the corresponding iminium ions.

In 2005, we succeeded in the first enantioselective Diels–Alder reaction of dienes with α-substituted acroleins catalyzed by chiral ammonium salts of acyclic primary amines derived from L-phenylalanine and Brønsted acids.30) α-Substituted acroleins are readily activated through the corresponding aldimes by catalytic amounts of primary amines and
Bronsted acids. For example, the ammonium salt of (S)-N\(^-\)benzyl-3-phenylpropane-1,2-diamine (10 mol%) with 2,4-dinitrobenzenesulfonic acid (20 mol%) catalyzed the Diels–Alder reaction of cyclopentadiene with methacrolein to afford the corresponding exo-adduct with 52% ee in 73% yield. The enantioselectivity was further increased to 79% ee by using chiral triamine (24) derived from H-L-Phe-L-Leu-N(CH\(_2\)CH\(_2\))\(_2\) instead of the diamine. The increase in enantioselectivity can be explained by the preference for the cis-iminium transition state due to the steric bulkiness of R as shown in Scheme 17.

\(\text{Scheme 17. Design of chiral ammonium salt catalysts for the enantioselective Diels–Alder reaction with } \alpha\text{-methacrolein.}\)

**a**-Haloacroleins are outstanding dienophiles in the asymmetric Diels–Alder process because of their high reactivity and the exceptional synthetic versatility of the resulting adducts.\(^{31},32,47\)–49 However, \(\alpha\)-haloacroleins are difficult to handle because they are irritants and are unstable even at ambient temperature. In contrast, our chiral ammonium salt catalyst 24\(\cdot\)2.75C\(_6\)F\(_5\)SO\(_3\)H was highly effective for the enantioselective Diels–Alder reaction of dienes with \(\alpha\)-(p-methoxybenzoyloxy)acrolein (25a), which were synthetic equivalents of \(\alpha\)-haloacroleins. Representative results are shown in Scheme 18. The Diels–Alder reaction of not only cyclic but also acyclic dienes gave the Diels–Alder adducts with high enantioselectivities. Interestingly, THF was more suitable than nitroethane as solvent for the Diels–Alder reaction of cyclopentadiene, while nitroethane was more suitable than THF for the Diels–Alder reactions of cyclohexadiene and acyclic dienes. The endo/exo selectivity had the similar tendency with that of Lewis acid-catalyzed Diels–Alder reaction with other \(\alpha\)-substituted acroleins such as methacrolein and \(\alpha\)-bromoaacrolein.

To improve the catalytic activity and the enantioselectivity for the Diels–Alder reaction of cyclopentadiene, we developed a superior asymmetric catalyst, an ammonium salt of (S)-2,2'-diamino-1,1'-binaphthyl (26) with trifluoromethanesulfonimide, both of which are commercially available, for the enantioselective Diels–Alder reaction of cyclic dienes with 25 (Scheme 19).\(^{50},51\) The Diels–Alder reaction
of α-(cyclohexanecarbonyloxy)acrolein (25b) with cyclopentadiene proceeded in EtCN at -75 °C in the presence of 5 mol% of 26·1.9HNTf₂ to give the adducts in 88% yield with 92% exo and 91% ee. In a similar manner, the Diels–Alder reaction of cyclohexadiene in nitroethane gave (2S)-endo-adduct as a major diastereomer (>99% de) in 92% yield with 91% ee.

According to an X-ray structural analysis of 25a, the plane of the s-trans acrolein moiety and the plane of the acyloxy group can be distorted (Fig. 8, top). The transition-state (TS) structures 27 and 28 have been proposed based on a 1H NMR study and the X-ray structure of 25a, as shown in Fig. 8 (bottom). In each TS, one of the amino groups of 26 forms an aldime with 25b and the other amino group forms an ammonium salt with Tf₂NH. In TS-27, the aldime is activated by the other molecule of Tf₂NH to be an 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-27, the diene approaches the si-face of the dienophile from the less-hindered side to give the (2S)-exo adduct. On the other hand, in TS-28, both the aldime and the acyloxy group are activated by the ammonium protons in the same molecule. However, the two intramolecular hydrogen bondings of the nitrogen of aldime 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-28 is conformationally unstable. Moreover, the aldime of TS-28 is activated by the weakly acidic ammonium group, while the aldime of TS-27 is activated by superacidic Tf₂NH. Therefore, it is suggested that the present Diels–Alder reaction proceeds via TS-27.

Chiral ammonium salt catalysts for the enantioselective [2+2] cycloaddition of unactivated alkenes with α-(acyloxy)acroleins

In 2007, we found that 24·2.6HNTf₂ catalyzed the enantioselective [2+2] cycloaddition reaction of unactivated alkenes 28 with 25, to give optically active 1-(acyloxy)cyclobutanecarbaldehydes (29), and the subsequent ring expansion of 29 gave optically active 2-hydroxycyclopentanone derivatives 30 and 31 (Scheme 20).52 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.53–57 The previous methods are limited to the [2+2] cycloaddition of highly nucleophilic...
Table 5. Enantioselective [2+2] cycloaddition of 28a with 25c

| entry | amines-HX | conditions | yield | syn | anti | ee |
|-------|-----------|------------|-------|-----|------|----|
| 1     | 24•2.75HX | 0, 24      | N.R.  | -   | -    | -  |
| 2     | 24•2.75HX | 0, 24      | N.R.  | -   | -    | -  |
| 3     | 26•1.9HX  | -78, 36    | 24    | 8 : 92 | 64 |
| 4     | 24•2.6HX  | 0, 24      | 71    | 10 : 90 | 80 |
| 5     | 24•2.6HX  | -20, 48    | 64    | 8 : 92 | 85 |

*28a (2 equiv) and 25c (1 mmol, 1 equiv) were used in EtNO₂ (0.3 mL). bHX = C₂F₅SO₃H, HX = TfOH, HX² = HNTf₂. cThe ee value of anti-29ac was determined by chiral HPLC.

Table 6. Enantioselective [2+2] cycloaddition of 28a with 25 to 29

| 25, R² | time | yield [%] | syn | anti | ee [%] |
|--------|------|-----------|-----|------|--------|
| 25c, Ph | 7    | 29ac, 74  | 14 : 86 | 73  |
| 25b, c-C₅H₁₁ | 6 | 29bc, 72 | 13 : 87 | 78  |
| 25a, p-(MeO)C₆H₄ | 7 | 29ac, 69 | 13 : 87 | 75  |
| 25d, p-FC₆H₄ | 18 | 29dc, 73 | 13 : 87 | 71  |
| 25e, 2.6-F₂C₆H₄ | 12 | 29ec, 80 | 11 : 89 | 84  |

The reaction of 28a (2 equiv) and 25 (1 mmol, 1 equiv) was carried out in the presence of 24•2.6HNTf₂ (10 mol%) in EtNO₂ (0.3 mL) at room temperature. bThe ee value of anti-29 was determined by chiral HPLC. (1S,3R)-anti-29 was the major enantiomer.

 niektores of electron-rich alkenes and the steric hindrance of substrates. Initially, the enantioselective Michael addition of alkenes to a (Z)-iminium intermediate, which is generated from 25 and 24•2.6HNTf₂, occurs through enantiofacial approach between the re-face of electron-rich alkenes and the si-face of the electron-deficient (Z)-iminium intermediate in an extended TS assembly 32. The (Z)-iminium isomer of alkenyl or alkynyl sulfides and sterically demanding alkenes such as norbornene derivatives. 57)

First, the [2+2] cycloaddition reaction of 2,4-dimethylpent-2-ene (28a) with α-(benzyloxy)acrolein (25c) has been examined in the presence of chiral amines (10 mol%) and Brønsted acids (x mol%) in nitroethane (Table 5). Although 24•2.75C₂F₅SO₃H and 24•2.75TfOH were inert at 0 °C (entries 1 and 2), more acidic 26•1.9HNTf₂ catalyzed the cycloaddition even at -78 °C (entry 3). However, the enantioselectivity was moderate (64% ee for major diastereomeric cycloadduct 29ac). Fortunately, the enantioselectivity was increased to 80% ee with the use of 24•2.6HNTf₂ 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 29ac, which was obtained in the experiments shown in Table 5, was determined to be a (1S,3R)-anti configuration based on the X-ray crystal analysis of (1'S)-camphyl ester derived from 29ac.

Next, several acyloxy groups of 25 have been screened for the enantioselective [2+2] cycloaddition of 28a in nitroethane at room temperature in the presence of 10 mol% of 24•2.6HNTf₂ (Table 6). The result indicates that the electronic and steric effects of the acyloxy group of 25 do not have greatly influence the enantioselectivity or reactivity. Nevertheless, when α-(2,6-difluorobenzoyloxy)acrolein (25e) was used in place of 25c, the ee value was slightly improved from 73% to 84%.

To explore the generality and scope of the 24•2.6HNTf₂-induced enantioselective [2+2] cycloaddition with 25, structurally diverse alkenes 28 have been examined (Table 7). In most cases, cycloadducts 29 were obtained in slightly better yield when the reaction was performed in nitropropane, which was less polar than nitroethane. Cyclic and acyclic trialkylethenes 28a-f were reacted with α-(fluorobenzoyloxy)acroleins 25e-g to give 29 in moderate to good yield with high ee. In contrast, 1-, 1.1-, and 1.2-dialkylethenes showed no reactivity. However, the cycloaddition of a 1,1-disubstituted styrene derivative such as 28g with 25c gave 29cg with 80% ee (entry 12). The absolute and relative stereochemistry of 29cg, which was obtained in the experiment (entry 10), was also determined to be a (1S,2S,3R)-anti configuration based on an X-ray crystal analysis.

A possible stepwise mechanism that accounts for the observed absolute and relative stereochemistries of cycloadducts 29ca and 29gd is shown in Scheme 20 and Fig. 9. The possibility of a concerted [π2s+π2s] cycloaddition 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 because of the steric hindrance of substrates. Initially, the enantioselective Michael addition of alkenes to a (Z)-iminium intermediate, which is generated from 25 and 24•2.6HNTf₂, occurs through enantiofacial approach between the re-face of electron-rich alkenes and the si-face of the electron-deficient (Z)-iminium intermediate in an extended TS assembly 32. The (Z)-iminium isomer of...
32 is expected to be more stabilized by intramolecular hydrogen-bonding interactions between R²-C=O or o-F substituents in R² and H-N⁺(CH₂CH₂)₂. Subsequently, the resulting tertiary carbocation intermediate is intramolecularly cyclized through a folded TS-33. The high anti-selectivity of cycloadducts may also be achieved by an intramolecular hydrogen-bonding interaction in 32 and 33.

To demonstrate the synthetic utility of cycloadducts 29, 29ea was expanded to 2-(acyloxy)cyclopentanone 31ea by treatment with AlCl₃ (1.2 equiv) through successive 1,2-shifts of a tertiary alkyl group and a hydride (Eq. 1). On the other hand, 29ge was expanded to 2-hydroxycyclopentanone 30e in 95% yield with 64% ds by treatment with Bu₄NF·3H₂O (2 equiv) through hydrolysis and the subsequent 1,2-shift of a tertiary alkyl group (Eq. 2).

It is expected that 30e may become a new chiral common intermediate candidate in the enantioselective total syntheses of 4a-methylhydro/C₁₃uorene diterpenoids such as (−)-taiwaniquinol B.

In summary, we have developed a novel and useful formal [2+3] cycloaddition of 28 with 25 by an

![Fig. 9. Possible TS-32 and TS-33 for the present [2+2] cycloaddition.](image)

Table 7. Enantioselective [2+2] cycloaddition of 28 with 25 to 29

| entry | 28       | 25 | conditions [°C, h] | 29, yield [%] | syn:anti | ee [%] |
|-------|----------|----|-------------------|---------------|----------|-------|
| 1c,d  | Me₂C=CH-i-Pr, 28a | 25e | −20, 48           | 29ea, 63      | 7 : 93   | 95    |
| 2e    | Me₂C=CH-i-Bu, 28b | 25g | −20, 48           | 29gb, 63      | 6 : 94   | 89    |
| 3d,e  | Me₂C=CH-o-C₆F₅, 28c | 25e | 0, 48             | 29ec, 89      | 8 : 92   | 82    |
| 4e,g  | Me₂C=CH-o-C₆H₁₁, 28c | 25e | −20, 48           | 29ec, 61      | 9 : 91   | 85    |
| 5e    | Me₂C=CH-t-Bu, 28d | 25f | −20, 60           | 29fd, 67      | 7 : 93   | 91    |
| 6e,i  | Me₂C=CH-t-Bu, 28d | 25f | −20, 30           | 29gd, 49      | 7 : 93   | 91 87 |
| 7e    | Me₂C=CH-t-Bu, 28d | 25e | 0, 24             | 29ge, 63      | 5 : 95   | 82    |
| 8e    | Me₂C=CH-t-Bu, 28d | 25h | 0, 48             | 29fe, 77      | 5 : 95   | 83    |
| 9e    | Me₂C=CH-t-Bu, 28d | 25g | −10, 48           | 29ge, 57      | 4 : 96   | 89    |
| 10e,h | Me₂C=CH-t-Bu, 28d | 25g | −20, 72           | 29ge, 24      | 4 : 96   | 90    |
| 11e,i | PhMeC=CH₂, 28i | 25c | 0, 6              | 29cg, 20      | 16 : 84  | 80    |

aUnless otherwise noted, 25 (1.0 mmol, 1.0 equiv) and 28 (1.2 equiv) were used in PrNO₂ (1.0 mL) in the presence of Na₂HNTf₂ (10 mol%). bThe ee value of anti-29 was determined by chiral HPLC. cEtNO₂ was used. d28 (2.0 equiv) was used. e24·2.6HNTf₂ (20 mol%) was used. f25g (R²=C₆F₅). gPrNO₂ (2.0 mL) was used. h25f (R²=2,4,6-F₃C₆H₂). i1,1,2,2,3,3-Hexa/C₁₃uoropropane-1,3-disulfonimide was used in place of HNTf₂. jWater (2.0 equiv) was added. kThe relative stereochemistry of 29cg is unknown.
organocatalytic enantioselective [2+2] cycloaddition and subsequent ring expansion to give optically active 30 or 31 with high ee.

Chiral ammonium salt catalysts for the enantioselective Diels–Alder reaction of dienes with α-(N-acylamino)acroleins

Optically active α-amino acids as well as α-hydroxy acids are valuable chiral synthons that bear two functional groups. Chiral ammonium salts 24•2.75HX and 26•1.9HNTf₂ activate α-(acyloxy)acroleins 25 as an aldiminium cation intermediate to react with dienes or monoalkenes to provide cycloaliphatic α-quaternary α-hydroxy acid equivalents with high enantioselectivity. In contrast, to the best of our knowledge, there has been only one example of the enantioselective Diels–Alder reaction with α-(N-acylamino)acrolein derivatives: in 1991, Cativiela et al. reported the Diels–Alder reaction of cyclopentadiene with methyl α-(N-acetylamino)acrylate promoted by 50 mol % of chiral titanium(IV) Lewis acid (64% yield, 78% exo, 70% ee (exo)). In 2008, we developed the catalytic and highly enantioselective Diels–Alder reaction of dienes with α-(N,N-diacylamino) or α-(N-acylamino)acroleins 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.

Table 8. Diels–Alder reaction of 2,3-dimethylbutadiene with 34 or 35 catalyzed by 24•2.75HX or 26•1.9HNTf₂

| entry | dienophile (R¹, R²) | catalyst | conditions | product |
|-------|-------------------|----------|------------|---------|
| 1d    | 34 (Bz, H)        | 24•2.75C₆F₅SO₃H | EtNO₂, 0, 36 to rt, 24 | yield [%]b ee [%]c |
| 2     | 35a (phthal)      | 24•2.75C₆F₅SO₃H | EtNO₂, rt, 4.5 | 97     92 |
| 3     | 35a (phthal)      | 24•2.75C₆F₅SO₃H | MeNO₂, rt, 4.5 | 77     89 |
| 4     | 35a (phthal)      | 24•2.75C₆F₅SO₃H | MeCN, rt, 4.5 | 86     89 |
| 5     | 35a (phthal)      | 24•2.75C₆F₅SO₃H | THF, rt, 4.5 | 71     93 |
| 6     | 35a (phthal)      | 24•2.75C₆F₅SO₃H | DME, rt, 4.5 | 74     94 |
| 7     | 35a (phthal)      | 24•2.75C₆F₅SO₃H | DMF, rt, 4.5 | 41     74 |
| 8     | 35a (phthal)      | 24•2.75C₆F₅SO₃H | EtNO₂, rt, 84 | 43     42 |
| 9     | 35a (phthal)      | 24•2.75C₆F₅SO₃H | EtNO₂, rt, 4.5 | 91     90 |
| 10    | 35a (phthal)      | 24•2.75C₆F₅SO₃H | EtNO₂, rt, 4.5 | 90     89 |
| 11    | 35a (phthal)      | 24•2.75C₆F₅SO₃H | EtNO₂, rt, 3 | <5f  – |
| 12    | 35a (phthal)      | 24•2.75C₆F₅SO₃H | EtCN, –78, 31 | <5f  – |
| 13    | 35a (phthal)      | 24•2.75C₆F₅SO₃H | EtNO₂, –78, 24 | 0      – |

aUnless otherwise noted, the reaction of 2,3-dimethylbutadiene (0.6 mmol) with 34 or 35 (0.5 mmol) was carried out in a solvent (0.5 mL). bIsolated yield. cDetermined by chiral HPLC analysis. d2,3-Dimethylbutadiene (1.0 mmol) was used in EtNO₂ (156 µL). eArSO₃H = 2,4-(NO₂)₂C₆H₄SO₃H. fA complex mixture was obtained.
Fig. 10. ORTEP illustration of (S)-36a with thermal ellipsoids drawn at the 50% probability level (flack parameter = 0.1228).

Table 9. Enantioselective DA reaction of dienes with 35

| entry | diene | 35 | cat. [mol %] | conditions [M, °C, h] | yield [ %] | product endo:exo ee [%] |
|-------|-------|----|-------------|----------------------|-----------|-----------------------|
| 1     | 35a   | 10 | 0.7, 0, 32 | 36a, 82              | –         | 96 (S)                |
| 2     | 35a   | 2.5| 1, rt, 48  | 36a, 91              | –         | 92 (S)                |
| 3     | 35a   | 10 | 0.7, 0, 48 | 37a, 82              | >99:1d    | 94                    |
| 4     | 35a   | 10 | 1, 0, 48   | 38a, 80              | >99:1d    | 88                    |
| 5     | 35a   | 10 | 0.7, 0, 48 | 39a, 73              | >99:1d    | 94                    |
| 6     | 35a   | 10 | 1, 0, 48   | 40a, 89              | >99:1d    | 94                    |
| 7     | 35a   | 10 | 1, RT, 48  | 41a, 55              | –         | 83                    |
| 8     | 35a   | 10 | 1, 0, 36   | 42a, 86              | 62:38     | 87b                   |
| 9     | 35b   | 10 | 1, −10, 84 | 42b, 73              | 72:28     | 90 (2S)h,i            |
| 10    | 35a   | 10 | 1, RT, 11t | 43a, 52              | –         | 67                    |

*Unless otherwise noted, the reaction of diene (0.6 mmol) with 35 (0.5 mmol) was carried out in EtNO₂. Isolated yield. 
*EE of major diastereomer determined by chiral HPLC analysis. Ratio of 4- and 3-alkyl isomers. The stereochemistry of 38a was determined by X-ray diffraction analysis. THF was used instead of EtNO₂. Diene (2 equiv) was used. H-L-[3-(2-Naph)Ala]-L-Leu-N(CH₂CH₂)₂-reduced triamine was used instead of 24. 54% ee (exo-42a), 57% ee (exo-42b). The relative and absolute stereochemistries of major diastereomer of 42b were determined by X-ray diffraction analysis after its derivation to (R)-N-phenylethylamide. 11 days.
Scheme 22. Deprotection of the phthalimido group of 42a.

also examined as HX of 24·2.75HX (entries 2, 8–11): most sulfonic acids were effective, but on the other hand trifluoroacetic acid and superacidic triflylimide were not suitable. Another candidate 26·1.9HNTf$_2$ did not catalyze the Diels–Alder reaction with 35a because 26 irreversibly reacted with 35a even at −78°C in the presence of triflylimide (entry 12). 24·1.9C$_6$F$_5$SO$_3$H did not catalyze the Diels–Alder reaction with 35a at −78°C (entry 13), and did not induce high enantioselectivity at room temperature.

The absolute configuration of cycloadduct 36a, which was obtained as a major enantiomer in Table 8, was determined to be (S) by X-ray crystallographic analysis, as shown in Fig. 10.

α-Phthalimidoacrolein 35a, which was a novel compound, was prepared by a one-pot procedure of dehydrative condensation between 2-amino-1,3-propanediol and phthalic anhydride, and subsequent oxidative dehydration under Swern conditions (Scheme 21).

Phthalimido groups of Diels–Alder adducts 36–43 were deprotected in high yield by the treatment with hydrazine after conversion to the corresponding methyl esters (Scheme 22). Norbornene derivatives are particularly valuable as important optically active synthetic intermediates of bioactive alkaloids such as norborne-2-aminoo-2-methanol derivatives and (-)-altemicidin.

Considering that 24·2C$_6$F$_5$SO$_3$H is much less active than 24·2.75C$_6$F$_5$SO$_3$H as a catalyst for the Diels–Alder reaction of dienes with 35 as well as α-(acyloxy)acroleins, we assume that 24·3C$_6$F$_5$SO$_3$H may be a real active catalyst, which activates 35b as aldiminium salt (46) with 24·3C$_6$F$_5$SO$_3$H. In our previous papers, it was assumed that (Z)-aldiminium salt derived from 24·2HX and 25 would be a key intermediate. However, an aldiminium salt derived from 26·3HX and 25 may be more favorable. The (Z)-isomeric preference of 46 is supposed based on theoretical calculations of geometries of its analogous aldiminium salt (47) derived from α-(maleimido)acrolein and 24·3HCl. The geometries of 47 have been optimized at DFT calculations with B3LYP using the 6-31+G(d,p) basis set (Fig. 11). The relative energy of (Z)-47 is 2.8 kcal/mol lower than that of (E)-47, and the re-face of the enimide moiety of (Z)-47 is sterically shielded by the benzyl substituent.

Cyclopentadiene approaches enantioselectively the si face of the electron-deficient enimide moiety to give endo-(2S)-42b as a major isomeric product. Thus, as well as the (Z)-isomeric preference of 47, it is expected that (Z)-TS-48 is preferred to (E)-TS-48 (Fig. 12).

In summary, we have developed a catalytic and highly enantioselective Diels–Alder reaction of dienes with 35 to provide cyclic α- quaternary α-amino acid precursors for the first time. Chiral triamine 24, which is configurationally more flexible than 26, could be used as a catalyst ligand for cycloadditions for not only 25 but also 35.
Conclusion and prospect

The dynamic ammonium salt catalysis for selective organic transformations conducted in our laboratories is reviewed. Bulky N,N-diarylammonium pentfluorobenzenesulfonates show unusual rate-accelerating effect for dehydration reactions such as the esterification and cyclization of 1,3,5-triketones. The role of the locally created hydrophobic environment is reasonable for the observed high conversion reactions. Currently our efforts are focused on exploring this overall mechanism in greater detail. Chiral ammonium salts of achiral amines with chiral BINSA are effective as asymmetric Mannich-type catalysts. Chiral ammonium salts of chiral amines with achiral Brønsted acids are effective as asymmetric [2+4] and [2+2] cycloaddition catalysts. Further studies on the exploration and applications of dynamic ammonium salts as functional catalysts are actively underway in our laboratory.

References

1) Erkkilä, A., Majander, I. and Pihko, P. M. (2007) Iminium catalysis. Chem. Rev. 107, 5416–5470.
2) Ishihara, K., Sakakura, A. and Hatano, M. (2007) Design of highly functional small-molecule catalysts and related reactions based on acid–base combination chemistry. Synlett, no. 5, 686–703.
3) Ishihara, K. (2009) Dehydrative condensation catalyses. Tetrahedron 65, 1085–1109.
4) Wakasugi, K., Misaki, T., Yamada, K. and Tanabe, Y. (2000) Diphenylammonium triflate (DPAT): Efficient catalyst for esterification of carboxylic acids and for transesterification of carboxylic esters with nearly equimolar amounts of alcohols. Tetrahedron Lett. 41, 5249–5252.
5) Funatomi, T., Wakasugi, K., Misaki, T. and Tanabe, Y. (2006) Pentafluorophenylammonium Triflate (PFPAT): An efficient, practical, and cost-effective catalyst for esterification, thioesterification, transesterification, and macrolactone formation. Green Chem. 8, 1022–1027.
6) Ishihara, K., Ohara, S. and Yamamoto, H. (2000) Direct condensation of carboxylic acids with alcohols catalyzed by hafnium(IV) salts. Science 290, 1140–1142.
7) Ishihara, K., Nakayama, M., Ohara, S. and Yamamoto, H. (2001) A green method for the selective esterification of primary alcohols in the presence of secondary alcohols or aromatic alcohols. Synlett 7, 1117–1120.
8) Ishihara, K., Nakayama, M., Ohara, S. and Yamamoto, H. (2002) Direct ester condensation from a 1:1 mixture of carboxylic acids and alcohols catalyzed by hafnium(IV) or zirconium(IV) salts. Tetrahedron 58, 8179–8188.
9) Nakayama, M., Sato, A., Ishihara, K and Yamamoto, H. (2004) Water-tolerant and reusable catalysts for direct ester condensation between equimolar amounts of carboxylic acids and alcohols. Adv. Synth. Catal. 346, 1275–1279.
10) Sato, A., Nakamura, Y., Maki, T., Ishihara, K. and Yamamoto, H. (2005) Zr(IV)–Fe(III), Zn(III), Ga(III),...
25) Nakashima, D. and Yamamoto, H. (2006) Design of chiral N-triflyl phosphoramides as a strong chiral Brønsted acid and its application to asymmetric Diels–Alder reaction. J. Am. Chem. Soc. 128, 9626–9627.

26) Hashimoto, T. and Maruoka, K. (2007) Design of axially chiral dicarboxylic acid for asymmetric Mannich reaction of arylaldehyde N-Boc imines and diazo compounds. J. Am. Chem. Soc. 129, 10054–10055.

27) Uruguchi, D. and Terada, M. (2004) Chiral Brønsted acid-catalyzed direct Mannich reactions via electrophilic activation. J. Am. Chem. Soc. 126, 5356–5357.

28) Terada, M., Sorimachi, K. and Uruguchi, D. (2006) Phosphoramidic acid as a novel structural motif of Brønsted acid catalysts for direct Mannich reaction of N-acetyl imines with 1,3-dicarbonyl compounds. Synlett, no. 1, 133–136.

29) Gridnev, I. D., Kouchi, M., Sorimachi, K. and Terada, M. (2007) On the mechanism of stereoselection in direct Mannich reaction catalyzed by BINOL-derived phosphoric acids. Tetrahedron Lett. 48, 497–500.

30) Ishihara, K. and Nakano, K. (2005) Design of an organocatalyst for the enantioselective Diels–Alder reaction with α-acetoxyacetone. J. Am. Chem. Soc. 127, 10504–10505, 13079 (additions and corrections).

31) Corey, E. J. and Loh, T.-P. (1991) First application of attractive intramolecular interactions to the design of chiral catalysts for highly enantioselective Diels–Alder reactions. J. Am. Chem. Soc. 113, 8966–8967.

32) Ishihara, K., Gao, Q. and Yamamoto, H. (1993) Enantioselective Diels–Alder reaction of α-bromo-α,β-unsaturated ketones with dienes under catalysis by CAB. J. Org. Chem. 58, 6917–6919.

33) Barber, H. J. and Smiles, S. (1928) Cyclic disulfoxides derived from diphenyl. J. Chem. Soc. 1141–1149.

34) Armarego, W. L. F. and Turner, E. E. (1957) Biarylphosphorodiamidic acid as a novel structural motif of Brønsted acid catalysts for direct Mannich reactions via electrophilic activation. J. Am. Chem. Soc. 119, 3463–3472.

35) Takahashi, K. and Fujii, K. (2005) Preparation of optically active binaphthylsulfonylcarbonyl compounds. Synlett, no. 1, 133–136.

36) Hatan, M., Maki, T., Moriyama, K., Arinobe, M. and Ishihara, K. (2008) Pyridinium 1,1′-binaphthyl-2,2′-disulfonates as highly effective chiral Brønsted acid–base combined salt catalysts for enantioselective Mannich-type reaction. J. Am. Chem. Soc. 130, 16858–16860.

37) Fabbri, D., Delogu, G. and De Lucchi, O. (1993) Preparation of enantioselectively pure 1,1′-binaphthalene-2,2′-diod and 1,1′-binaphthalene-2,2′-dithiol. J. Org. Chem. 58, 1748–1750.

38) Bandarage, U. K., Simpson, J., Smith, R. A. J. and Weavers, R. T. (1994) Conformational polymorphism and thermorearrangement of 2,2′-bis-(N,N-dimethylcarbamato)-1,1′-binaphthalene. A facile synthesis of 1,1′-binaphthalene-2,2′-dithiol. J. Org. Chem. 58, 3463–3472.

39) Moseley, J. D., Lenden, P., Lockwood, M., Ruda, K., Sherlock, J.-P., Thomson, A. D. et al. (2008) A comparison of commercial microwave reactors for
scale-up within process chemistry. Org. Process Res. Dev. 12, 30–40.

40) Gillay, J. P., Lenden, P., Moseley, J. D. and Cox, B. G. (2008) The Newman-Kwart rearrangement: A microwave kinetic study. J. Org. Chem. 73, 3130–3134.

41) Wallace, T. J. and Schriesheim, A. (1965) The base-catalysed oxidation of aliphatic and aromatic thiols and disulphides to sulphonic acids. Tetrahedron 21, 2271–2280.

42) Agami, C., Prince, B. and Puchot, C. (1990) A convenient access to chiral sulfonylic acids. Synth. Commun. 20, 3289–3294.

43) House, H. O. and Gannon, W. F. (1958) Reaction of \( \beta \)-diketones with peracids. J. Org. Chem. 23, 879–884.

44) García-García, P., Lay, F., García-García, P., Raba-\( \lambda \)kos, C. and List, B. (2009) A powerful chiral counteranion motif for asymmetric catalysis. Angew. Chem., Int. Ed. 48, 4363–4366.

45) Arendt, K., Borths, C. J. and MacMillan, D. W. C. (1965) The base-catalysed oxidation of aliphatic and aromatic thiols and disulphides to sulphonic acids. Tetrahedron 21, 2271–2280.

46) Northrup, A. B. and MacMillan, D. W. C. (2002) The first general enantioselective catalytic Diels–Alder reaction with simple \( \alpha,\beta \)-unsaturated ketones. J. Am. Chem. Soc. 124, 2458–2460.

47) Ishihara, K. and Yamamoto, H. (1994) Brønsted acid assisted chiral Lewis acid (BLA) catalyst for asymmetric Diels–Alder reaction. J. Am. Chem. Soc. 116, 1561–1562.

48) Ishihara, K., Kurihara, H. and Yamamoto, H. (1996) A new powerful and practical BLA catalyst for highly enantioselective Diels–Alder reaction: An extreme acceleration of reaction rate by Brønsted acid. J. Am. Chem. Soc. 118, 3049–3050.

49) Ishihara, K., Kurihara, H., Matsumoto, M. and Yamamoto, H. (1998) Design of Brønsted acid-assisted chiral Lewis acid (BLA) catalysts for highly enantioselective Diels–Alder reactions. J. Am. Chem. Soc. 120, 6920–6930.

50) Sakakura, A., Suzuki, K., Nakano, K. and Ishihara, K. (2006) chiral 1,1’-binaphthyl-2,2’-diammonium salt catalysts for the enantioselective Diels–Alder reaction with \( \alpha \)-acyloxyacroleins. Org. Lett. 8, 2229–2232.

51) Sakakura, A., Suzuki, K. and Ishihara, K. (2006) Enantioselective Diels–Alder reaction of \( \alpha \)-acyloxyacroleins catalyzed by chiral 1,1’-binaphthyl-2,2’-diammonium salts. Adv. Synth. Catal. 348, 2457–2465.

52) Ishihara, K. and Nakano, K. (2007) Enantioselective [2+2] Cycloaddition of unactivated alkenes with \( \alpha \)-acyloxyacroleins catalyzed by chiral organoammonium salts. J. Am. Chem. Soc. 129, 8930–8931.

53) Narasaka, K., Hayashi, Y., Shimadzu, H. and Nishihata, S. (1992) Asymmetric [2+2] cycloaddition reaction catalyzed by a chiral titanium reagent. J. Am. Chem. Soc. 114, 8869–8885.

54) Ito, H., Hasegawa, M., Takenaka, Y., Kobayashi, T. and Iguchi, K. (2004) Enantioselective total synthesis of (+)-tricyclochavulone. J. Am. Chem. Soc. 126, 4520–4521.

55) Takenaka, Y., Ito, H., Hasegawa, M. and Iguchi, K. (2006) Catalytic enantioselective [2+2]-cycloaddition reaction of 2-methoxy-carbonyl-2-cyclopentenone by a chiral copper catalyst. Tetrahedron 62, 3380–3388.

56) Takenaka, Y., Ito, H. and Iguchi, K. (2007) Enantioselective formal synthesis of (+)-precapnelladiene by chiral copper-catalyzed asymmetric [2+2]-cycloaddition reaction. Tetrahedron 63, 510–513.

57) Shibata, T., Takami, K. and Kawachi, A. (2006) Rh-catalyzed enantioselective [2+2] cycloaddition of alkyne esters and norborne derivatives. Org. Lett. 8, 1343–1345.

58) Davies, H. M. L. and Dai, X. (2004) Lewis acid induced tandem Diels–Alder reaction/ring expansion as an equivalent of a [4+3] cycloaddition. J. Am. Chem. Soc. 126, 2692–2693.

59) Dai, X. and Davies, H. M. L. (2006) Formal enantioselective [4+3] cycloaddition by a tandem Diels–Alder reaction/ring expansion. Adv. Synth. Catal. 348, 2449–2456.

60) Fillion, E. and Fishlock, D. (2005) Total synthesis of (+)-taivaniaquinol B via a domino intramolecular friedel–crafts acylation/carbonylation \( \alpha \)-tert-alkylation reaction. J. Am. Chem. Soc. 127, 13144–13145.

61) Banerjee, M., Mulhopadiyay, R., Achari, B. and Banerjee, A. K. (2006) General route to 4a-methyl-hydrofluore diterpenoids: Total syntheses of (+)-taivaniaquinones D and H, (+)-taivaniaquinol B, (+)-dichroanal B and (+)-dichroane. J. Org. Chem. 71, 2787–2796.

62) Liang, G., Xu, Y., Sieple, I. B. and Trauner, D. (2006) Synthesis of taiwaniaquinoids via Nazarov triation. J. Am. Chem. Soc. 128, 11022–11023.

63) McFadden, R. M. and Stoltz, B. M. (2006) The catalytic enantioselective, protecting group-free total synthesis of (+)-dichroane. J. Am. Chem. Soc. 128, 7738–7739.

64) Cativiela, C., López, P. and Mayoral, J. A. (1991) Asymmetric synthesis of 2-amino-2,5-dihydroxybenzene-2-carboxylic acids by Diels–Alder reaction. Tetrahedron: Asymmetry 2, 1295–1304.

65) Ishihara, K., Nakano, K. and Akakura, M. (2008) Organocatalytic enantioselective Diels–Alder reaction of dienes with \( \alpha \)-((N,diaicylamino)acroleins. Org. Lett. 10, 2893–2896.

66) Clerici, F., Gelmi, M. L. and Gambini, A. (1999) A highly diastereoselective approach to conformationally constrained serine analogues: Synthesis of an \( \alpha \)-amino-\( \beta \)-hydroxycyclohexanecarboxylic acid and derivatives. J. Org. Chem. 64, 5764–5767.

67) Kotha, S., Ganesh, T. and Ghosh, A. K. (2000) Diels–Alder approach to tetraline-based constrained \( \alpha \)-amino acid derivatives. Bioorg. Med. Chem. Lett. 10, 1755–1757.

68) Clerici, F., Gelmi, M. L., Gambini, A. and Nava, D. (2001) Carbocyclic serine analogues: Regio- and diastereoselective syntheses of new 1-amino-2,5-dihydroxycyclohexanecarboxylic acids. Tetrahedron 57, 6429–6438.
69) Yang, B. V. and Doweyko, L. M. (2005) Highly regioselective Diels–Alder reactions of 9-substituted anthracenes and 2-acetamidoacrylate: Synthesis of conformationally constrained α-amino acids. Tetrahedron Lett. 46, 2857–2860.
70) Cativiela, C. and Díaz-de-Villegas, M. D. (2000) Stereoselective synthesis of quaternary α-amino acids. Part 2: Cyclic compounds. Tetrahedron: Asymmetry 11, 645–732.
71) Harada, H., Morie, T., Hirokawa, Y. and Kato, S. (1996) An efficient synthesis of 6-substituted aminohexahydro-1H-1,4-diazepines from 2-substituted aminopropenals. Chem. Pharm. Bull. 44, 2205–2212.
72) Iwasaki, T., Yamazaki, H., Nishitani, T. and Sato, T. (1991) A synthesis of 2-endo-amino-2-exo-hydroxymethynorbornenes having inhibitory activity against protein kinase C. Chem. Pharm. Bull. 39, 527–529.
73) Yamazaki, H., Horikawa, H., Nishitani, T., Iwasaki, T., Nosaka, K. and Tamaki, H. (1992) Syntheses and antiulcer activities of 2-aminonorbornene derivatives. Chem. Pharm. Bull. 40, 102–108.
74) Kende, A. S., Liu, K. and Jos Brands, K. M. (1995) Total synthesis of (−)-altemicidin: A novel exploitation of the Potier-Polonovski rearrangement. J. Am. Chem. Soc. 117, 10597–10598.

(Received June 12, 2009; accepted July 23, 2009)

Profile

Kazuki Ishihara was born in Aichi, Japan, in 1963, and 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 for three months 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 (15 months beginning in 1991), he returned to Japan and joined Professor Hisashi 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. Dr. Ishihara 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 and Sustainable Chemistry Award from the Ministry of Education, Culture, Sports, Science and Technology (2003), the JSPS Prize (2005), the BCSJ Award (2005), the International Conference on Cutting-Edge Organic Chemistry in Asia Lectureship Award (2006), Japan/UK GSC Symposium Lectureship (2007), the IBM Japan Science Prize (2007), and the Mukaiyama Award (2009). His research interests include asymmetric catalysis, biomimetic catalysis induced by artificial enzymes, dehydrative condensation catalysis towards green and sustainable chemistry, and acid–base combination chemistry.