Intramolecular cation–π interaction in organic synthesis†

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Controlling molecular conformation is a significantly important issue in a wide variety of organic reactions because the ground state structure is significantly responsible for the transition one. As observed in enzymes and proteins, the cation–π interaction plays a key role in the formation of the tertiary structure and the biochemical processes. Therefore, the cation–π interaction would be a promising conformation-controlling tool not only in large molecules, but also in small molecules due to its stronger interaction force. This article describes the utility of the intramolecular cation–π interaction in various organic syntheses with evidence for the existence of the cation–π interactions.

1. Introduction

It has been well documented that a cation–π interaction[1] plays a crucial role in the recognition of ligands in biochemical processes,[2,3] and in the formation of the tertiary structure of proteins.[4] Moreover, this interaction is one of the key forces for the construction of various host–guest complexes[5,6] and supramolecules.[6] Considerable attention has continued to attract researchers due to its stronger interactive force than those of the other non-bonding aromatic interactions such as the π–π[7] and CH–π[8] interactions.

The metal cation is the most important element of the cationic part in a cation–π interaction due to strong interaction with the aromatic part (Fig. 1a). For example, the stabilization energy for the complex of Na^+ with benzene is reported to be 23 kcal mol^{-1}.[9] On the other hand, organic cations, in particular aromatic cations containing nitrogen, also serve as the cationic parts of the cation–π systems. Although the interaction energy with benzene is lower than that of a metal cation, it is still much higher than the other attractive interactions. The interaction energies for pyridinium–π systems were experimentally estimated to be −0.5 to −2.6 kcal mol^{-1} [10] in solution. Recent *ab initio* molecular orbital calculations estimated about −7.9 to −9.4 kcal mol^{-1} for stabilization energy between the *N*-methylpyridinium cation and benzene with a parallel orientation (Fig. 1b).[11] The origin of this interactive force is evidenced to be electrostatic and inductive forces, which suggests that this interaction is categorized as a cation–π interaction. As the π-component, the aromatic π-system is the most significant part of the cation–π interaction. On the other hand, the other π-systems, such as alkenes[12] and alkynes[13] also act as π-components. In addition, the thiocarbonyl and carbonyl groups also serve as effective π-systems[14] (Fig. 1c).

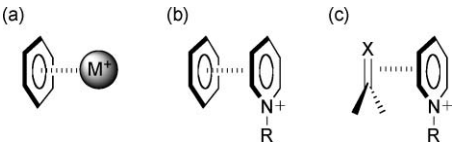

Fig. 1 Cation–π interactions.

In spite of the significant role of the cation–π interactions in the broad fields of chemistry, little application in organic synthesis had been known until recently. From a synthetic point of view, controlling the molecular conformation is a significantly important issue to attain regio- and stereoselectivities in the reactions because the ground state structure is closely related to the transition one. While the π–π interaction has been employed for this purpose,[15] we focused on the intramolecular cation–π

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† This paper is dedicated with the best regards to Professor Hiroshi Suginome on the occasion of his 77th birthday.

Shinji Yamada was born in Sapporo, Japan, in 1959. He received his PhD degree in 1986 from Hokkaido University, under the supervision of Professor Hiroshi Suginome. He was a JSPS research fellow at the same University during 1985 to 1987. He spent three years from 1987 to 1990 in the research laboratory of the KAO Corporation, and he joined the faculty in the Department of Chemistry at Kanagawa University as an Assistant Professor in 1990. During 1993 to 1994 he joined Professor Charles J. Sih's group at the University of Wisconsin as a research fellow. In 1995, he was appointed as an Associate Professor of the Faculty of Science at the Ochanomizu University, and was promoted to Professor in 2003. His recent research interests are stereoselective syntheses based on control of the molecular conformation using intra- and intermolecular interactions.

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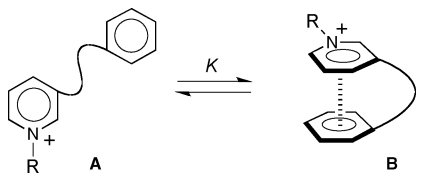
Table 1

ΔG°/kcal mol^{-1}	K_{eq}	A–B (%)
1.0	5.35	16 : 84
2.0	28.6	3.4 : 96.6
3.0	153	0.6 : 99.4

interaction as a conformation-controlling tool due to its stronger interactive force.

$$\Delta G^\circ = -RT \ln K \quad (1)$$

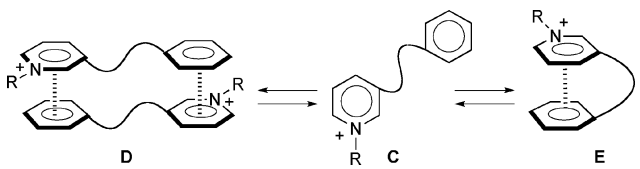
In general, an organic molecule is in equilibrium with several conformers in solution. In order to simplify the system, let us consider a model system in which two conformers, **A** and **B**, are in equilibrium as shown in Scheme 1. The ratio of the conformers is governed by the equilibrium constant K_{eq}, which is correlated to ΔG° by eqn (1). Table 1 shows the relationship between ΔG° and the conformer ratio. It is obvious that 2–3 kcal mol^{-1} of ΔG° is enough to shift the equilibrium to conformer **B**. This strongly suggests that the intramolecular cation–π interaction serves as a promising conformation-controlling tool. This review describes the utility of an intramolecular cation–π interaction in organic synthesis with evidence for the existence of the cation–π interaction in each system.



Scheme 1 Equilibrium of conformers **A** and **B**.

2. Intra- *vs.* intermolecular pyridinium–π interactions

In general, intra- and intermolecular interactions compete with each other in solution. For example, molecule **C**, that has both aromatic and pyridinium rings, is in equilibrium between the dimeric complex **D** and intramolecular complex **E** (Scheme 2). In order for complex **E** to predominate, the entropy term must decrease so that the two rings are close to each other. To this end, the use of an amide linkage is often effective due to its double bond character.



Scheme 2 Competition of intra- and intermolecular interactions.

We clarified that the *cis* and *trans* geometrical differences in the amide linkage significantly affect the interaction modes.[16] A comparison of the $\Delta\delta$**1a** with $\Delta\delta$**2a** values, which are the differences in the ^{1}H NMR chemical shifts between **1a** and **3**, and **2a** and **4**, respectively, suggests that the shielding and deshielding effects of the phenyl ring in **1a** and **2a** are very different from each other (Fig. 2).

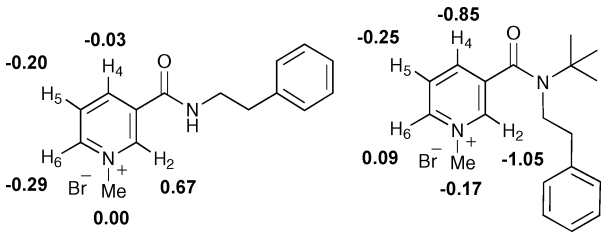
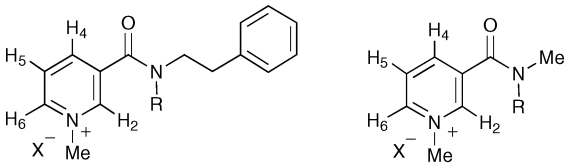


Fig. 2 $\Delta\delta$ Values for **1a** (left) and **2a** (right).



1a: R = H, X = Br
1b: R = H, X = I
2a: R = *t*-Bu, X = Br
2b: R = *t*-Bu, X = I

3: R = H
4: R = *t*-Bu

The ORTEP diagrams of **1b** and **2b** are shown in Fig. 3a and 3b, respectively. The pyridinium and the phenyl rings of **1b** are separated from each other as expected from the ^{1}H NMR studies, and every two molecules of **1b** make a dimeric complex in a face-to-face and head-to-tail manner. The distance of 3.504 Å between C6 and the centroid of the phenyl group is close to the sum of the van der Waals radii of the aromatic carbons. In contrast, the pyridinium ring and the phenyl ring of **2b** lie parallel to each other, the two rings of which are arranged face-to-face (Fig. 3b). The 3.556 Å of the C3 and C14 distance is short enough for the intramolecular pyridinium–π interaction, strongly suggesting the existence of an intramolecular cation–π interaction. This stacking structure can reasonably explain the higher upfield shifts of H2 and H4 observed in the ^{1}H NMR studies. Therefore, it is concluded that inter- and intramolecular cation–π interactions govern the geometries of **1** and **2**, respectively.

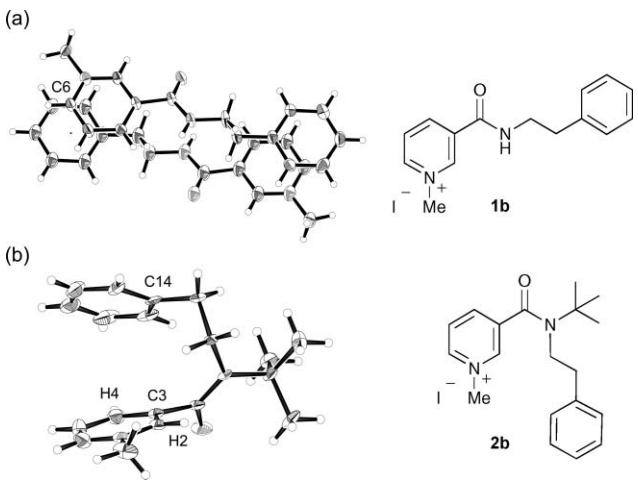


Fig. 3 X-Ray structures of (a) **1b** and (b) **2b**.[16]

The chain length is also an important factor in the equilibrium between the intra- and intermolecular interactions. In the case of amide **5** having a shorter chain length than **1a**, it does not exhibit an intramolecular interaction due to the geometrical restriction.[17] Remarkable is the fact that two significantly

different conformers were observed in the crystal, which form an unsymmetrical molecular dimer with perpendicularly twisted orientation governed by the pyridinium–π interactions (Fig. 4). The origin of these unusual structural features might be the stabilization of the crystal packing by the formation of a three dimensional pyridinium–π interaction network. The substituent effect at the pyridinium ring on the molecular conformation is also reported; in the bis(pyridiniopropyl)benzene derivatives, a bulky substituent disturbs the intermolecular interaction, and as a result, the intramolecular complex is preferentially formed.[18] Interestingly, the pyridinium–π interaction can control not only the conformation of the small molecules but also that of oligomers. *N*-Methylation of the oligomers having dimethylaminopyridine and aromatic moieties causes folding to form a helical motif.[10b,19]

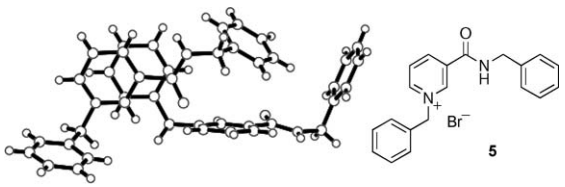
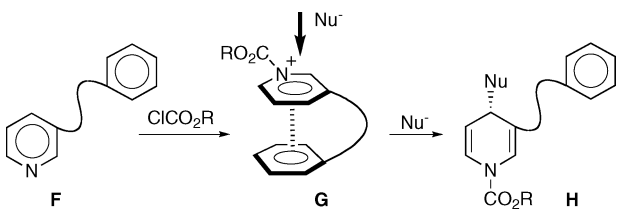


Fig. 4 Two significantly different conformers in the X-ray structure of **5**.[17]

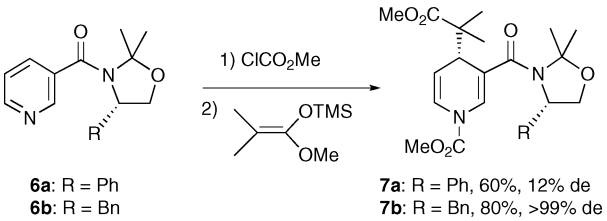
3. Synthesis of chiral dihydropyridines

Chiral 1,4-dihydropyridines[20] have been employed as synthetic intermediates for a wide variety of compounds such as natural products,[21] calcium channel blockers,[22] and NADH models.[23] Moreover, they have the potential utility for obtaining various nitrogen-containing chiral 6-membered heterocycles.[24]

Scheme 3 outlines a strategy for the stereoselective synthesis of 1,4-dihydropyridines *via* a cation–π interaction: (a) conversion of compound **F** containing both a pyridine and a phenyl moiety into a pyridinium salt gives rise to an attractive force between the two entities to form a cation–π complex **G**; (b) the selective shielding of one side of the pyridinium face by the phenyl ring enables nucleophiles to attack the complex only from the non-shielded side, which would stereoselectively give 1,4-dihydropyridine **H**. The addition of a ketene silyl acetal to **6a** and **6b** in the presence of methyl chloroformate in CH_2Cl_2 gave 1,4-adducts **7a** and **7b** as a major product with a small amount of 1,6-adducts, respectively (Scheme 4).[25] Remarkable is the significant difference in the stereoselectivities depending on the chiral auxiliaries; the addition to **6b** produced an excellent selectivity, whereas the selectivity in the case of **6a** was very low. This would be attributable to the geometrical differences between the intermediary pyridinium salts; the benzyl group much more effectively shields one side of the pyridinium face than the phenyl group.



Scheme 3 Face-selective addition to a pyridinium complex.



Scheme 4 Addition of ketene silyl acetal to **6**.

Intramolecular interaction was also observed in the model compound **8b** having a similar framework structure to **2b**. The existence of the intramolecular cation–π interaction in solution was evidenced by CD spectroscopy as well as ^{1}H NMR spectroscopy. Interesting is the significant difference in the CD curves between **8a** and **8b** in spite of a small structural difference between them (Fig. 5).[26] The CD spectrum of **8b** exhibits an exciton couplet in the 200–260 nm region with the first strong positive exciton Cotton effect at around 236 nm and the second strong negative exciton Cotton effect at around 214 nm. This suggests that the conformational flexibility of **8b** is significantly diminished by an intramolecular cation–π interaction.

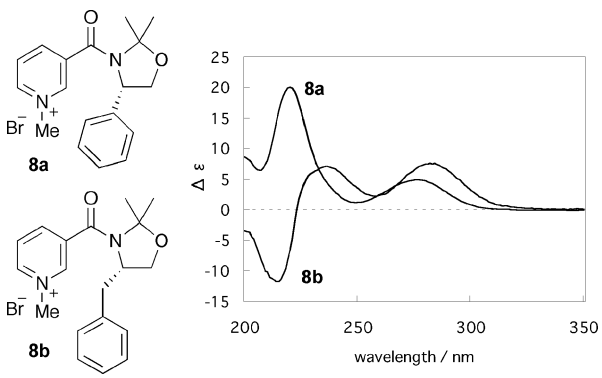


Fig. 5 CD spectra for **8a** and **8b**.

X-Ray analyses clarified significant geometrical differences between **6b** and **8b** (Fig. 6). The remarkable feature in **8b** is that the pyridinium and the phenyl rings lie parallel to each other and the two rings are arranged face-to-face, the distance between them being about 3.4 Å. On the other hand, the pyridine and the phenyl moieties of **8a** are far apart from each other. The fact that the geometry significantly depends on whether the pyridine nucleus has a cationic charge or not is unambiguous evidence that a cation–π interaction governs the conformation of **6b**. Although in

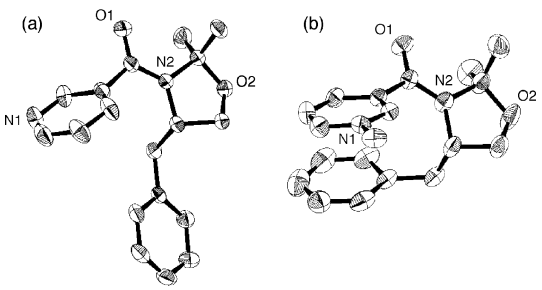
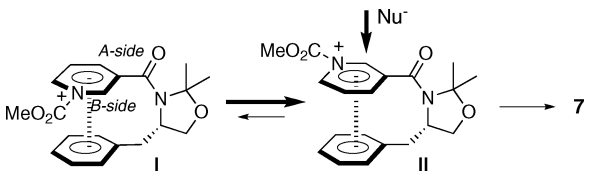


Fig. 6 ORTEP drawings for (a) **6b** and (b) **8b**.[25] The bromo anion of **8b** was omitted for clarity.

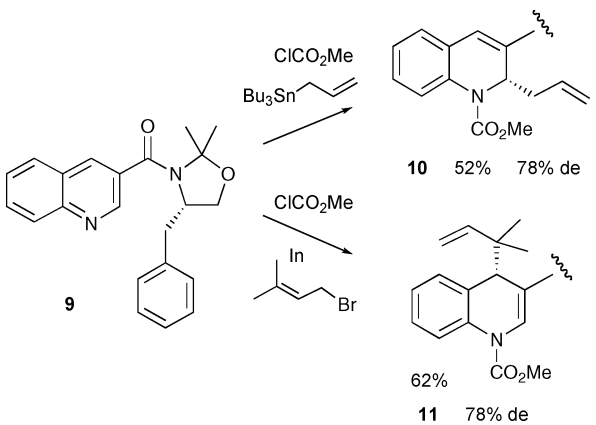
several pyridinium–π systems a major attractive force is considered to be charge transfer energy,[27] no charge transfer absorption was observed in the present complex **8b**.

A working model was proposed as shown in Scheme 5 based on the structural optimization of the intermediary pyridinium cation by *ab initio* calculations at the RHF/3-21G* level, where conformer **II** is 2.1 kcal mol^{-1} more stable than conformer **I**. Therefore, the equilibrium between conformers **I** and **II** favors **II**; as a result, a nucleophile will attack conformer **II** from the non-shielded side to give a chiral dihydropyridine with good stereoselectivity. A similar stereoselective addition was also performed for a related nicotinic amide system.[28]



Scheme 5 Working model for nucleophilic addition to a cation–π complex.

Allylmetal reagents also serve as nucleophiles for pyridinium and quinolinium salts. The addition of allyltributyltin and prenylindium reagents resulted in good stereoselectivities. The addition of allyltributyltin reagent to the quinolinium salt of **9** gave **10** as a major product in 78% de.[29] On the other hand, the reaction with prenylindium reagent gave a 1,4-adduct **11** in 78% de (Scheme 6).[29] X-Ray analysis of *N*-methylquinolinium salt **12** clearly showed the effective blocking of the quinolinium plane by the benzyl group through an intramolecular cation–π interaction (Fig. 7). The quinolinium and the phenyl rings lie parallel to each other and the two rings are arranged face-to-face, the distance between them being about 3.4 Å.



Scheme 6 Face-selective addition of allylmetal reagents to **9**.

Face-selective addition reactions toward pyridine,[30] β-carboline[31] and isoquinoline[32] systems have also been performed, in which a pyridinium–π interaction with chiral auxiliaries at the *N*-acyl moieties, was postulated. Interesting is that the interaction plays a key role in the catalytic enantioselective reaction. In the intramolecular annulation of 2-(5-oxopentyl)isoquinolinium iodide using a chiral amine, a favorable interaction between the isoquinolinium moiety and a phenyl ring of the catalyst is anticipated in the transition state.[33]

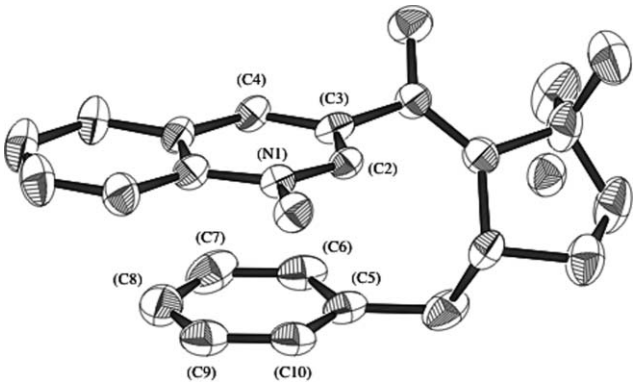
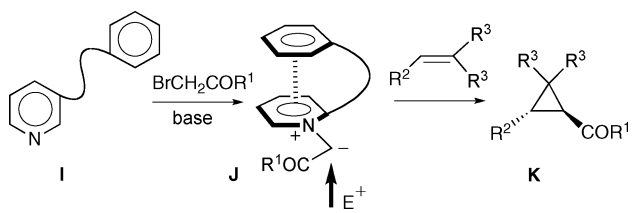


Fig. 7 ORTEP drawing of **12**.[29]

4. Enantioselective cyclopropanation

The previous section dealt with nucleophilic addition to the pyridinium ring. In this section, the electrophilic addition reaction to the pyridinium ylide is described, in which the pyridinium ylide serves as a nucleophile. Scheme 7 shows our strategy; a conformationally fixed pyridinium ylide **J** arising from a pyridinium–π interaction would attack an electron deficient olefin at the less-hindered side to give a cyclopropane **K** with recovery of the framework pyridine **I**. Although diastereoselective cyclopropanation of the pyridinium ylide has been reported,[34] an enantioselective cyclopropanation was performed according to this concept for the first time.

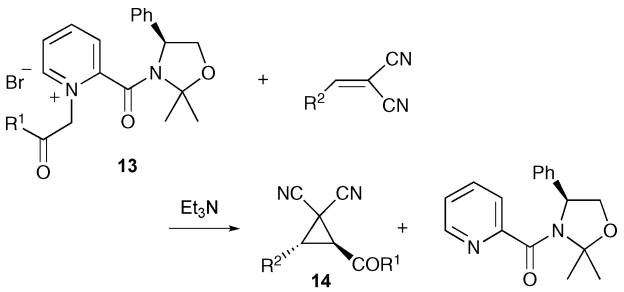


Scheme 7 Reaction of a conformationally fixed pyridinium ylide with an alkene.

The cyclopropanation reaction of benzylidene malononitrile with a pyridinium salt **13** was carried out in the presence of Et_3N at rt to yield the *trans*-cyclopropane **14** in a good enantiomer ratio with recovery of the chiral auxiliary.[35] The reaction of *tert*-butylmalononitrile resulted in the highest enantioselectivity (Scheme 8).

An X-ray structural analysis of pyridinium **15** as a model compound elucidated the existence of the pyridinium–π interaction. Fig. 8 clearly shows that the pyridinium and the phenyl rings of **15** are very close to each other with a face-to-face arrangement. The phenyl ring blocks the N1 atom, and the distances between the centroid of the phenyl group and N1 and C7 are 3.678 and 3.677 Å, respectively.[35]

A working model for the stereoselective formation of the cyclopropanes is outlined in Scheme 9. An electron-deficient olefin will approach the cation–π complex, which is predicted by structural optimization, from the less-hindered *A*-side. Two



Scheme 8 Cyclopropanation reaction of electron deficient alkenes using a pyridinium ylide.

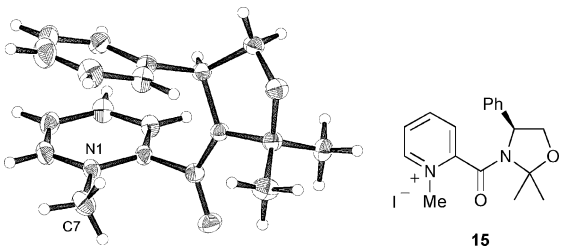
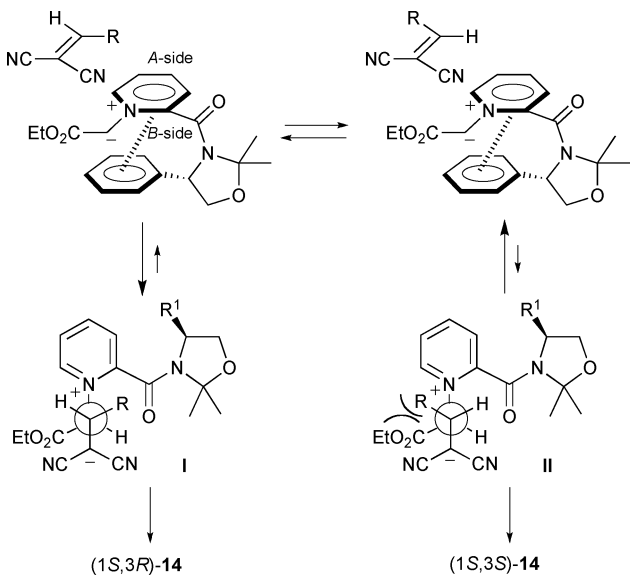


Fig. 8 ORTEP drawing of compound **15**.[35]



Scheme 9 Plausible reaction pathway toward (1*S*,3*R*)-**14**.

intermediates **I** and **II** can be produced depending on whether the ylide attacks the *Re* or *Si* face of the olefin. The equilibrium between **I** and **II** would shift to **I** so as to avoid a severe steric repulsion between the CO_2Et and the R groups in **II**; consequently, (1*S*,3*R*)-**14** was produced as the major product.

5. Cation–π interaction between a thiocarbonyl group and a pyridinium ring

While most of the reported cation–π interactions are observed between a cationic moiety and an aromatic π-component, only a few examples are known for a non-aromatic π-system, such as the ethylene-ammonium cation[12] and acetylene-Ca^+ systems.[13] Therefore, disclosure of a new type of cation–π interaction would be of significant interest.

During our studies on the face-selective addition of nucleophiles to pyridinium salts bearing a 1,3-thiazolidine-2-thione moiety,[36] we presumed that the resulting face-selectivities are caused by a conformational rigidity arising from an intramolecular interaction between the pyridinium ring and the thiocarbonyl group (Fig. 9).[14,37] The existence of attractive intra- and intermolecular (C=S)···Py^+ interactions of **17** was elucidated by ^1H and ^{13}C NMR spectroscopies, and X-ray crystallographic analyses. The superimposed X-ray structures are shown in Fig. 10 in an effort to better understand the geometrical differences between pyridine and pyridinium derivatives. Fig. 10 clearly shows that the S1 atoms of **16** and **17** occupy positions significantly different from each other; while the S1 atom of **16** is on the side of the pyridine ring, the S1 atom of **17** is located on the pyridinium plane. These results strongly suggest the existence of attractive interactions between the C=S group and the pyridinium ring.

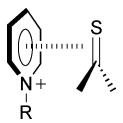


Fig. 9 A new class of cation–π interactions.

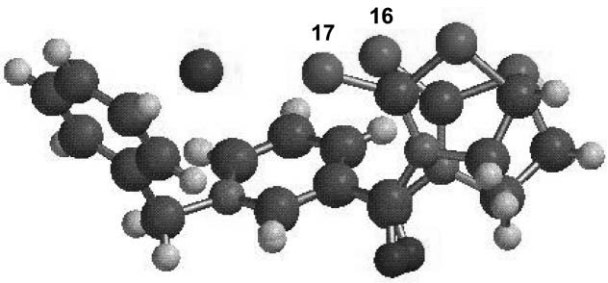
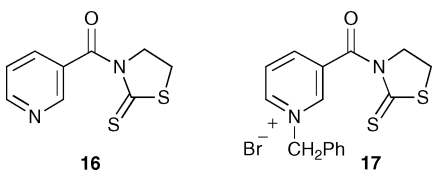


Fig. 10 Superimposition of the X-ray structures of **16** and **17**.[14,37]



The X-ray structures of **16** and **17** were compared to those optimized at the HF/6-311G** level. The optimized geometries shown in Fig. 11 are very close to the corresponding X-ray structures. The S1···C3 distance of the optimized **17** (3.20 Å) is shorter than that of **16** (3.35 Å). This trend is comparable with

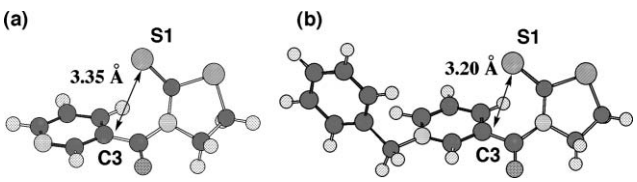


Fig. 11 Structural optimization of (a) **16** and (b) **17**.

their X-ray geometries, supporting the attractive interaction of the C=S group with the pyridinium ring.

The interaction energies of the model system were calculated to elucidate the origin of the (C=S)···Py$^+$ interaction (Fig. 12).[14] The model system is composed of two essential parts, *N*-methylpyridinium and thioformamide. Fig. 12 shows the calculated interaction energy profiles of the model systems. R is the distance between the C4 and the S atom. The total interaction energy (E_{MP2}) was calculated at the MP2/6-311G** level. E_{es} and E_{ind} are the electrostatic and induction energies, respectively. E_{corr} ($= E_{MP2} - E_{HF}$) is the contribution of the electron correlation to the calculated interaction energy, which is mainly the dispersion energy. E_{rep} ($= E_{HF} - E_{es} - E_{ind}$) is mainly the exchange-repulsion energy, but it also includes other terms. The E_{MP2} values of the two model systems (HCHS···$C_5H_5NMe^+$) at the potential minima are -2.60 kcal mol^{-1} ($R = 4.0$ Å), respectively. The potential energy curve of E_{MP2} indicates that a substantial attraction still exists even when the molecules are well separated ($R > 5.0$ Å), which shows that the major source of the attraction in these systems are long-range interactions, such as induction and electrostatic interactions.

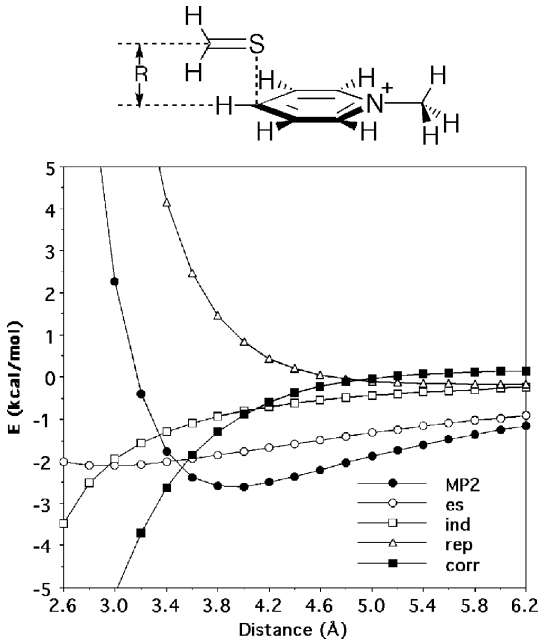
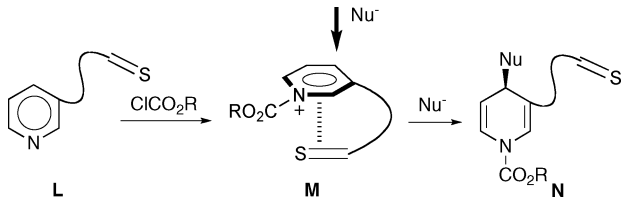


Fig. 12 Interaction energy of the complex between CH_2S and $C_5H_5NMe^+$.

Indeed, the major contributors for the attraction are E_{es} and E_{ind}. It has been reported that the electrostatic interaction is the major source of the attraction in the cation–π interaction. Therefore, the present (C=S)···Py$^+$ interactions are grouped with a cation–π interaction, though the interactive energies are much smaller than the aromatic-π and the metal cation interactions. A similar interaction was observed between the carbonyl group and the pyridinium ring.[14]

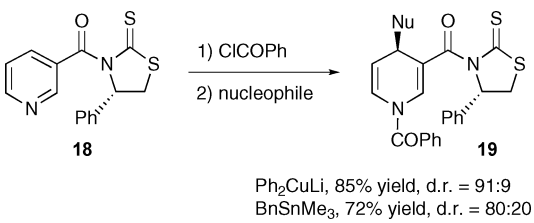
6. Asymmetric synthesis of dihydropyridines and piperidines through (C=S)···Py$^+$ interaction

A regioselective nucleophilic 1,4-addition to the intermediary pyridinium ring has been established using a variety of nucleophiles such as ketene silyl acetal, organocuprate and trimethylbenzyltin. Using the intramolecular (C=S)···Py$^+$ interaction described in the previous section would achieve stereoselective addition to a pyridinium salt as outlined in Scheme 10. When a pyridine compound **L** having a thiocarbonyl group is converted to the corresponding pyridinium salt **M**, face-selective addition of various nucleophiles toward the pyridinium salt **M** was performed to give the corresponding dihydropyridines **N**.

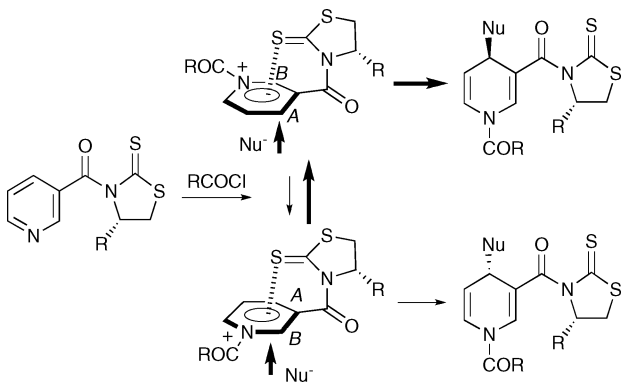


Scheme 10

The addition of the ketene silyl acetal to the intermediary pyridinium salts formed from **18** possessing a chiral thiazolidine-2-thione with benzoyl chloride gave 1,4-adduct **19** as the major product with good stereoselectivities (Scheme 11).[36,38] In the case of the quinolinic amide, the addition of the ketene silyl acetal produced the corresponding 1,4-dihydroquinolines in good regio- and stereoselectivities.[39] The selectivity can be explained by a working model outlined in Scheme 12; the intramolecular interaction restricts the molecular motion and hinders one of the pyridinium faces. Nucleophiles attack from the less hindered side to give the 1,4-dihydropyridines. It is interesting to note that the stereochemistry of the products is opposite to that obtained in the reaction of the oxazolidine derivatives having the same chirality like the thiazolidine-2-thione derivatives described in section 3.



Scheme 11 Competition of intra- and intermolecular interaction.



Scheme 12 Plausible reaction pathway through cation–π complex formation.

This methodology can be applied to the synthesis of 3-substituted-4-arylpiperidines,[40] such as (−)-paroxetine[41] and (+)-femoxetine (Fig. 13).[42] Since they are a significantly important class of serotonin reuptake inhibitors, extensive efforts have been made for the efficient synthesis of (−)-paroxetine and (+)-femoxetine. Although various methods for the construction of the piperidine ring system have been developed, little has been reported for an approach using pyridine derivatives as the substrates, despite their easy availability.

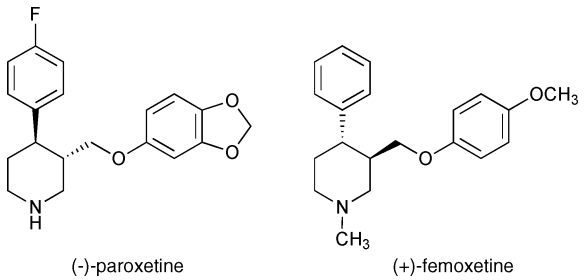
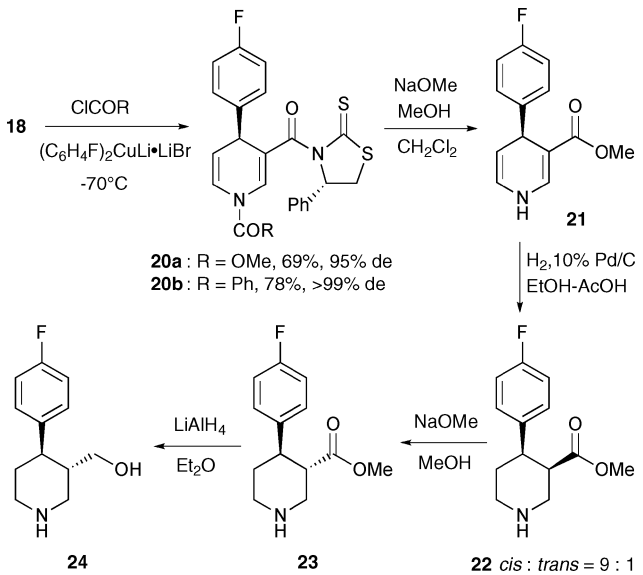


Fig. 13 Representative serotonin reuptake inhibitors.

The face-selective addition of a 4-fluorophenylcuprate toward nicotinic amide **18** according to our methodology[38] gave 1,4-adduct **20b** in 78% yield with 99% de. Removal of the chiral auxiliary with NaOMe–MeOH and hydrogenation of the dihydropyridine **21** in the presence of Pd/C gave tetrahydropyridine **22**. The isomerization of *cis*-piperidine **22** into *trans*-piperidine **23** and reduction of the ester moiety of **23** provided piperidine alcohol **24**,[43] which is the reported precursor of (−)-paroxetine (Scheme 13).[44] A similar reduction of the *cis*-piperidine **22** afforded the corresponding *cis*-alcohol.

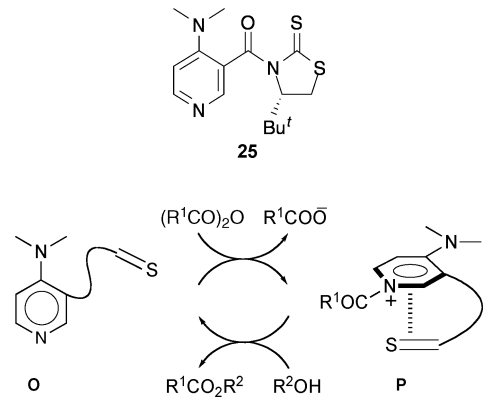


Scheme 13 Formal synthesis of (−)-paroxetine.

7. Asymmetric acylation of *sec*-alcohols with a DMAP catalyst having a conformation switch system

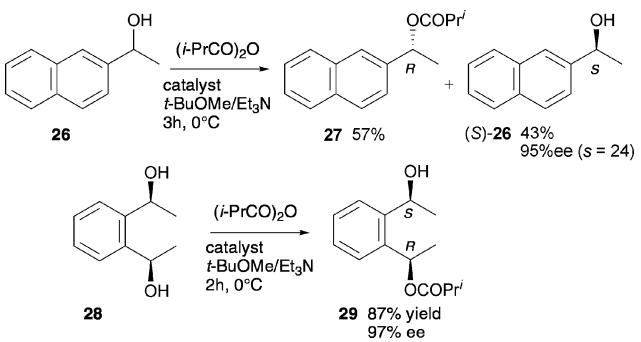
4-Dimethylaminopyridine (DMAP) and 4-pyrrolidinopyridine (PPY) derivatives are some of the most important organocatalysts for the acyl transfer reaction of various types of alcohols.[45] The chiral versions of the DMAP and PPY derivatives have been extensively developed over the last decade due to the significant importance of the asymmetric acylation of alcohols for the production of chiral alcohols. The key feature of these DMAP catalysts is selective blocking of the pyridinium face with an aromatic moiety in order to generate the planar chirality required for discrimination of the enantiomeric alcohols.[46]

We designed a new type of catalyst **25** possessing a thiocarbonyl group because the $(C{=}S)\cdots Py^+$ interaction described earlier would be effective for blocking one side of the pyridinium face. The characteristic feature of this catalyst is that the conformation is changed according to the acylation and deacylation steps as outlined in Scheme 14. Acylation of catalyst **O** gives the conformationally fixed *N*-acylpyridinium salt **P** through the $(C{=}S)\cdots Py^+$ interaction,[14] which provides a chiral environment around the *N*-acyl moiety. The reaction of racemic *sec*-alcohols with this intermediate **P** would allow the enantio discrimination to give the corresponding chiral esters with recovery of the catalyst. The recovered catalyst with restored conformational freedom is smoothly available for the next cycle. We anticipated that this conformational switch process would satisfy both the selectivity and reactivity.



Scheme 14 Conformation switch system triggered by acylation and deacylation steps.

Kinetic resolution of 1-(2-naphthyl)ethanol (**26**) with isobutyric anhydride was performed in a high selectivity in the presence of 5 mol% of catalyst **25** in *t*-BuOMe at 0 °C (Scheme 15).[47,48] Decreasing the catalyst amount to 0.05 mol% gave a similar selectivity. This method can be applicable to a variety of *sec*-alcohols.



Scheme 15 Kinetic resolution of **26** and desymmetrization of *meso*-diol **28**.

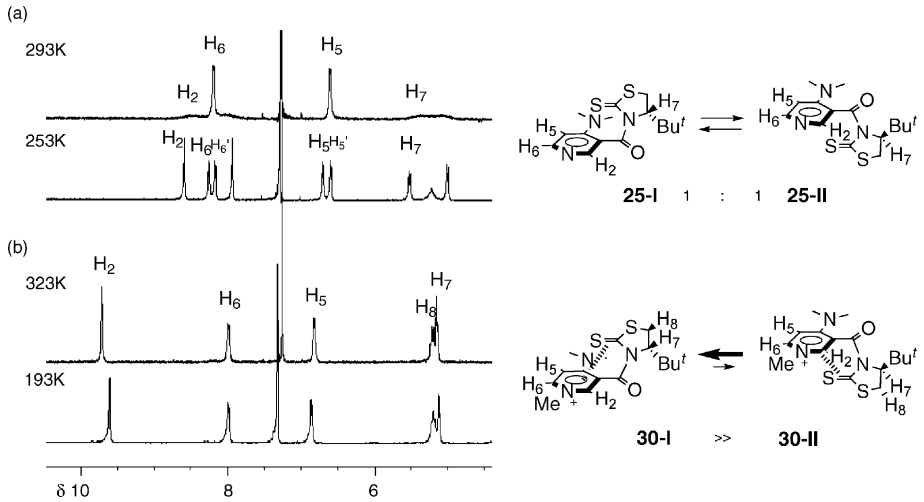


Fig. 14 ^{1}H NMR spectra for (a) **25** at 253 K and 293 K and (b) **30** at 193 K and 323 K and their schematic equilibrium equations.

Asymmetric desymmetrization of *meso*-diols was also achieved using the same catalyst.[48] Acylation of 1,4-diol **28** afforded a monoester **29** in good yield with a higher enantiomeric excess. The product monoesters are valuable synthetic intermediates due to possessing two different functional groups.

Dynamic NMR experiments showed the conformational change process during the catalysis. Comparison of the behavior of **25** and the corresponding *N*-methylpyridinium **30** as a model compound in $CDCl_3$ showed significant differences between them. Fig. 14 depicts the ^{1}H NMR spectra of them. The spectrum of **25** at 253 K clearly shows two rotamers with respect to the C–(C=O) bond, the ratio of which is about 1 : 1. The equilibrium between the two rotamers was supported by the fact that the ^{1}H NMR spectrum at 293 K shows coalescence of the two rotamers. On the other hand, only one rotamer appears in the spectra of **30** in the range of 193 K to 323 K, strongly suggesting that the equilibrium shifts toward one of the two rotamers.

Fig. 15 outlines a plausible catalytic cycle. One of the enantiomers of the racemic *sec*-alcohols preferentially attacks the intermediate **I** from the *B*-side to give the corresponding ester with recovery of the catalyst. The catalyst with the restored conformational freedom is smoothly available for *N*-acylation of the next cycle.

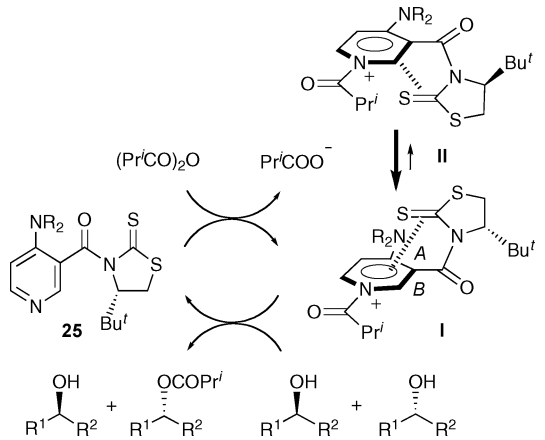


Fig. 15 Plausible catalytic cycle for asymmetric acylation of *sec*-alcohols.

The *R*-selectivity in the kinetic resolution and desymmetrization could be explained by comparing the two plausible transition state models, TS-I and TS-II, for the acylation of the (*R*)- and (*S*)-2-phenylethyl alcohols, respectively (Fig. 16). Each hydroxy group would approach the *B*-side of the pyridinium in a face-to-face manner due to the intermolecular cation–π interaction between the pyridinium and the phenyl rings.[16,17] While the (*R*)-alcohol can effectively attack the *N*-acyl group, the (*S*)-alcohol receives considerable steric repulsion with the chiral auxiliary; therefore, the acylation would preferentially proceed through TS-I to give the (*R*)-ester. There are a few catalysts in which an intramolecular $Py^+ \cdots Ar$ interaction is postulated to play a key role in blocking the pyridinium face.[49,50] The intermolecular cation–π interaction of the aromatic ring with the pyridinium ring of the acylated catalyst was also postulated for the enantiomer selective acylation with 2,3-dihydroimidazo[1,2-*a*]pyridine catalyst.[51]

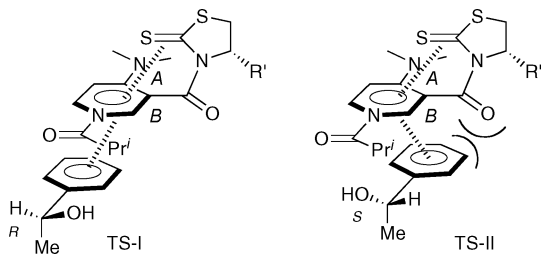
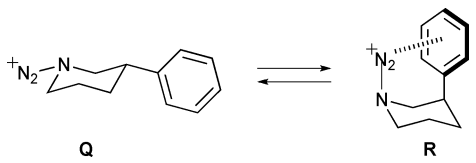


Fig. 16 Comparison of TS-I and TS-II.

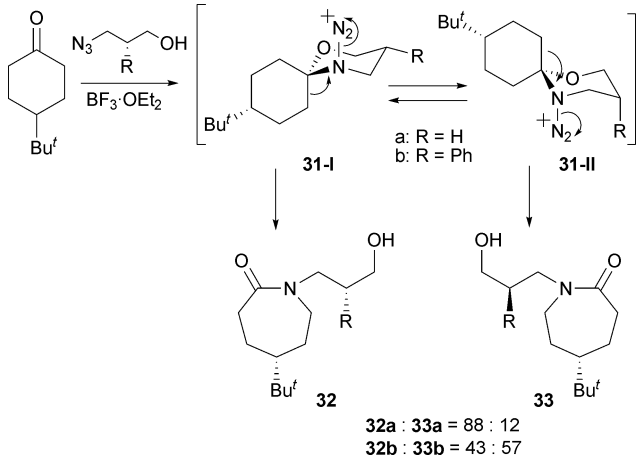
8. Regioselective rearrangement *via* conformation-control of cyclic compounds

The conformation of a cyclic compound can also be controlled by the cation–π interaction. In the six-membered ring system shown in Scheme 16, 1,3-diaxial conformer **R** generally receives severe steric repulsion, and as a result, **Q** is the major contributor in this type of system. If an attractive interaction exists between the two moieties and it mainly contributes to govern the conformation, the equilibrium position may shift to conformer **R**. Hydrogen bonding often allows this type of equilibrium shift.[52]



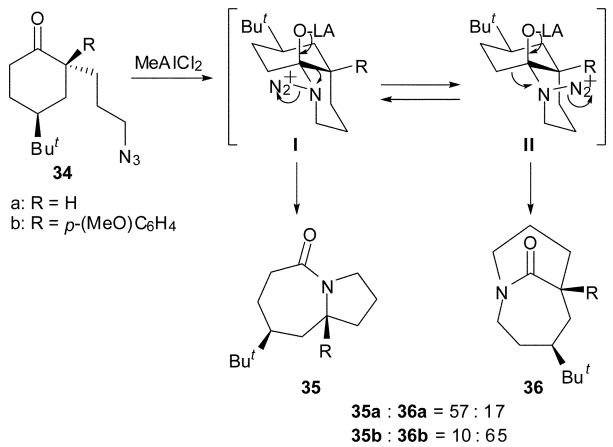
Scheme 16 Equilibrium of the conformation of a cyclic compound.

Aubé and Katz have shown that the product ratio in the Schmidt reaction of **31** significantly underwent a substituent effect.[53] The rearrangement of **31a** produced **32a** as the major product, whereas the reaction of **31b** yielded **32b** and **33b** in a ratio of 43 : 57, suggesting a preference for conformer **II** rather than conformer **I** due to stabilization by the intramolecular $N_2^+ \cdots Ar$ interaction despite steric repulsion (Scheme 17).



Scheme 17 Schmidt reaction *via* the equilibrium between **31-I** and **31-II**.

A similar interaction was used for the regioselective formation of bridged bicyclic lactams.[54] The successive cyclization and rearrangement reaction of compound **34a** gave **35a** and **36a** in 57% and 17% yields, respectively, depending on the orientation of the N_2^+ moiety as shown in Scheme 18. On the other hand, the reaction of **34b** provided **36b** as the major product through conformer **II**, suggesting the cation–π interaction between the N_2^+ moiety and the aryl group.



Scheme 18 Substituent effect on the product ratio in the Schmidt reaction.

9. Concluding remarks

This perspective review article described the utility of the intramolecular cation–π interaction in organic synthesis with evidence for the participation of the cation–π interaction. Although the importance of the cation–π interaction in various fields of chemistry has been recognized in this decade, its synthetic applications have only recently started. The key feature of the stereo-controlled syntheses described in this article is controlling the molecular conformation by the intramolecular cation–π interaction. The high interaction energy of the cation–π interaction enables control of the substrate conformation, not only in the ground state but also in the transition one, which leads to the stereoselectivities. This article mainly focuses on the pyridinium–π interaction due to its having several merits in organic synthesis as follows: (1) the planarity allows one to have a stacked orientation against a π-component. (2) The pyridinium cation serves as an electrophile, whereas the pyridinium ylide serves as a nucleophile. (3) The pyridinium is readily available from pyridines. (4) The pyridinium cation is very stable compared to other cations. These features allowed a variety of stereoselective reactions. The conformation of a cyclic six-membered ring system was also controlled by the $N_2^+ \cdots \pi$ interaction, which allowed selective Schmidt reactions. This conformation-controlling concept is also applicable to catalytic reactions. The fact that non-bonding interactions play an essential role in enzyme structure and function suggests the effectiveness of this concept in the design of organocatalysts.

Although this article did not deal with the utility of an *intermolecular* cation–π interaction in organic synthesis, it is also a promising tool for stereoselective synthesis. In the field of photochemistry, the intermolecular interaction between a metal cation with an aromatic ring has recently been employed for stereo-controlled photoisomerization.[55] There might be a number of unnoticed examples involving the participation of a cation–π interaction in a variety of synthetic processes. Therefore, determining such hidden features would provide an insight into the design of new systems effective for stereo-controlled synthesis. Further developments of new types of conformation-controlling systems based on the cation–π interaction and their application to organic synthesis will be expected.

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