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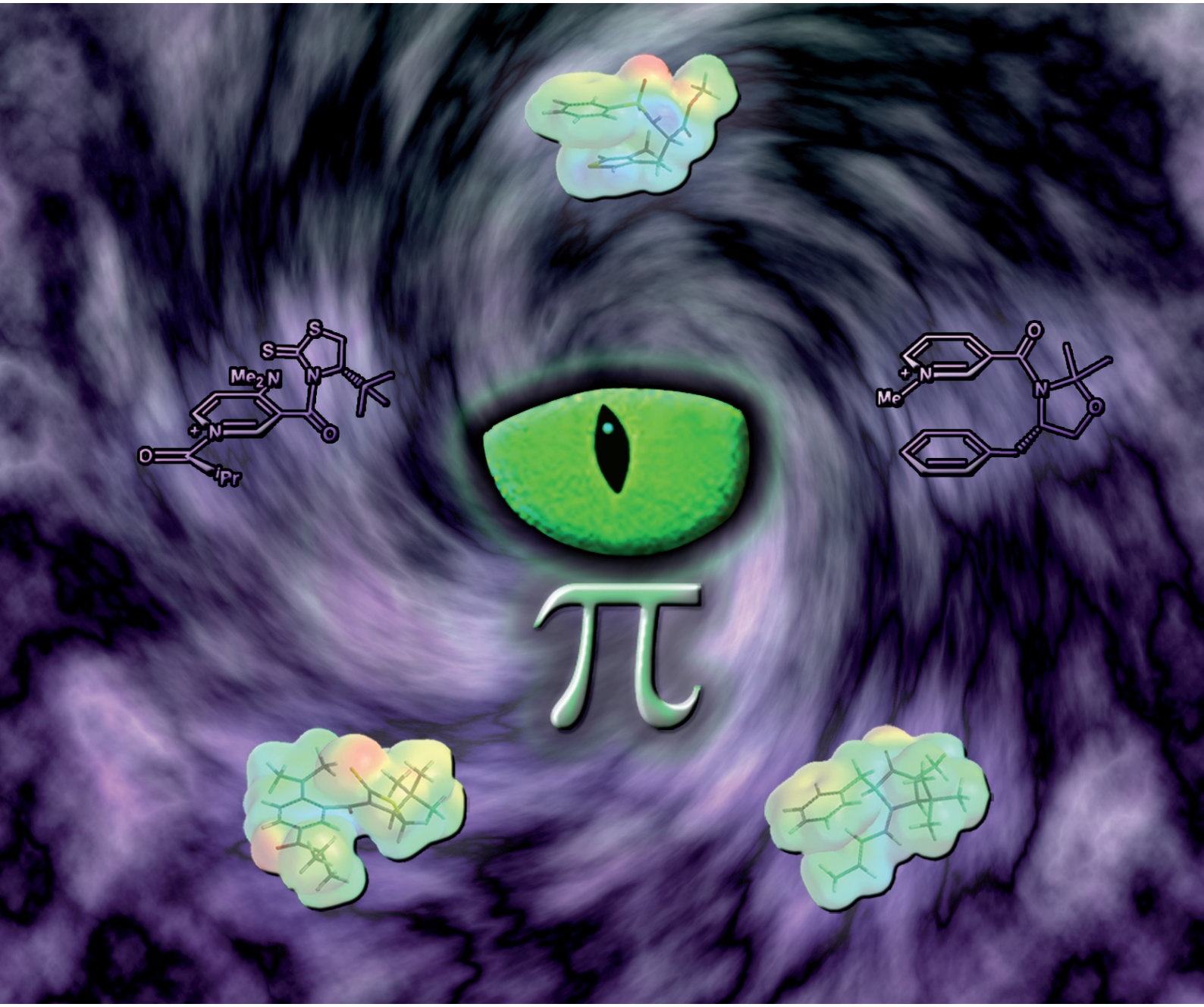

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PERSPECTIVE

Nitrogen cation–π interactions in asymmetric organocatalytic synthesis

Shinji Yamada*[a] and John S. Fossey*[b,c]

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Cation–π interactions have been widely exploited and utilised in the structural biology arena, their fundamental importance in supramolecular chemistry and the pivotal role they play in host guest chemistry has rapidly expanded. In terms of organic synthesis π–π, CH–π and cation–π interactions are often invoked providing hypotheses for observed selectivities and reaction outcomes although fundamental studies of these interactions are less well reported, especially in the organic synthesis arena. This article considers cation–π interactions in the field of asymmetric organocatalysis and provides a summary of cases where such interactions may play an important role. Importantly this article sets out to highlight where such interactions could be operating in order to highlight the potential wealth of investigations to be had in this area rather than categorically claiming such interactions are in operation. For asymmetric catalysis this is particularly important as the geometry of a transition state dictates the stereochemical outcome of the reaction, this article provides a perspective on such phenomena.

Introduction

In recent years small molecule organocatalysis has graduated from an emerging to a semi-mature field in organic synthesis that offers a number of advantages over metal or enzyme centred catalysis.[1] One of the many advantages is the relative ease of synthetic access to structurally diverse catalyst architectures, facilitating the design and synthesis of tailor-made catalysts. In the design of asymmetric organocatalysts, the key subject is organisation of molecules to realise *enantio*-differentiation in the transition state. Both intra- and intermolecular interactions can be effective for controlling molecular organisation in the transition state, notably hydrogen bonding may be described as the most powerful tool in organocatalysis.[2]

Since the reports of Dougherty,[3] cation–π interactions have been widely observed, exploited and utilised in the structural biology arena,[4] and their fundamental importance in supramolecular chemistry and the pivotal role they play in host–guest chemistry has rapidly expanded.[4–5] In organic synthesis, the role of cation–π interactions has only just started to be well recognised,[6] despite the fact that cation–π-interaction energies are generally much larger than those of the other π–interactions.[7]

Herein the authors of this article have selected cases from leading references where cation–π interactions may explain asymmetric induction in organocatalysed reactions.[8] Several representative examples are shown on the basis of the categorisation of interaction modes, iminium–π, pyridinium–π, imidazolium–π and thiazolium–π interactions. Common feature of these examples are that central chirality of the catalyst induces planar chirality in the corresponding cationic intermediates through cation–π interactions, which enables remote asymmetric induction even if the source of initial central chirality is molecularly distant from the reaction centre. Although there are a number of reported examples of ammonium–π interactions in various biological systems[9] and supramolecular systems,[5a,5b] this article introduces reactions which either evidence or support the assertion of a cation–π interactions influencing reaction selectivities. The focus is on organocatalysed reactions involving cationic intermediates to disclose, correlate and contrast the role of cation–π interactions in these systems.

Among the various organocatalytic reactions, chiral amine catalysed reactions that proceed *via* nitrogen-containing cationic intermediates are of particular relevance; *e.g.* iminium, pyridinium, imidazolium and thiazolium intermediates (Fig. 1).

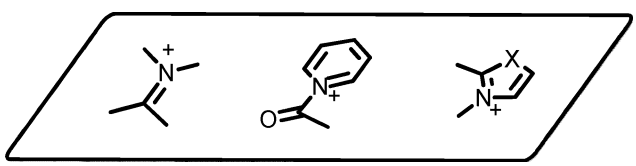

Fig. 1 Planar pyridinium, imidazolium and thiazolium intermediates in organocatalysis.

These intermediates are generally planar, therefore distinguishing the *re* and *si* faces through cation–π interactions can be an effective approach for *enantio*-differentiation in a reaction, Scheme 1a and b. When an intramolecular face-face cation–π

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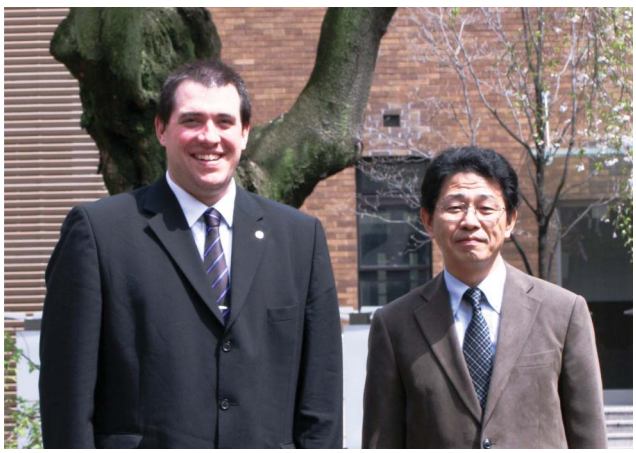
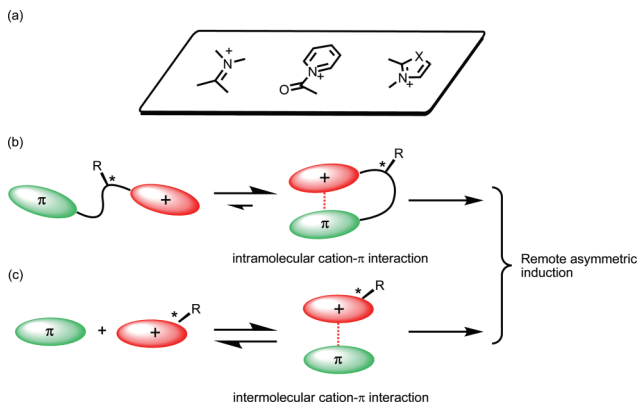
Professor Shinji Yamada is currently the head of Chemistry at Ochanomizu University, was born in 1959 in Sapporo, Japan. He obtained his PhD from Hokkaido University in 1986, under the supervision of Professor Hiroshi Suginome. He was a JSPS research fellow at the same University from 1985 to 1987. He spent 1987 to 1990 at the KAO Corporation, and in 1990 he joined the faculty in the Department of Chemistry at Kanagawa University as an Assistant Professor. From 1993 to 1994 he worked with Professor Charles J. Sih's group at the University of Wisconsin as a research fellow. In 1995, he became 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.



Dr John S. Fossey (left) and Professor Shinji Yamada (right)

Dr John S. Fossey is a lecturer at the University of Birmingham, he obtained an MChem degree from Cardiff University in 2000, after which he obtained a PhD from Queen Mary University of London, under the direction of Dr Christopher J. Richards. He was next awarded a Japan Society for the Promotion of Science (JSPS) overseas research fellowship to work with Professor Shū Kobayashi in the Graduate School of Pharmaceutical Sciences, University of Tokyo. After three years as a temporary faculty member at the University of Bath he became a lecturer at the University of Birmingham in 2008. In 2010 he was an inaugural recipient of a JSPS Re-Invitation Bridge Fellowship hosted by Professor Shinji Yamada (co-author of this paper) at Ochanomizu University in Tokyo. He has been a visiting associate professor at Tokyo Metropolitan University, and is a visiting professor at East China University of Science and Technology, and has recently been awarded an NSFC fellowship. His current research interests are in catalysis and sensing, and the development of self-reporting synthetic systems.



Scheme 1 (a) Planar pyridinium, imidazolium and thiazolium intermediates in organocatalysis. (b) Representation of an intramolecular cation–π interaction. (c) Representation of an intermolecular cation–π interaction.

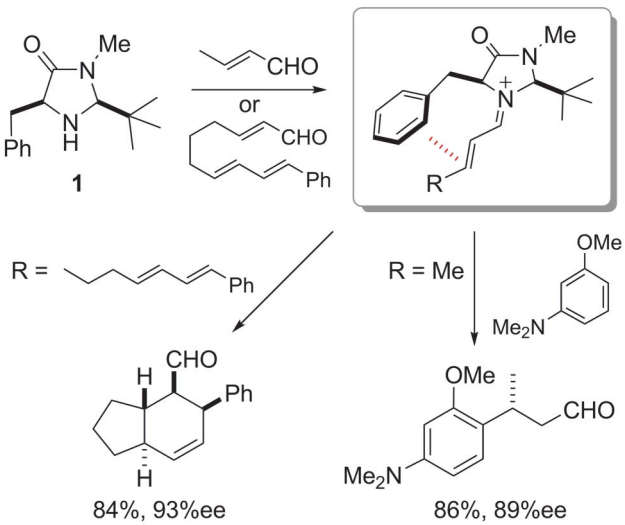
interaction selectively shields one face of the planar part of a cationic intermediate a reaction may occur on the opposite exposed face, Scheme 1a. On the other hand, when the intermediate has no opportunity for interaction with an intramolecular π–component, it may be possible to form an intermolecular cation–π complex with an aromatic moiety of a substrate or reagent is produced as shown in Scheme 1b. In both cases, central chirality has the potential to induce transient planar chirality through cation–π interactions, thus allowing remote asymmetric induction.

It should be noted that a cation–π interaction has much larger interaction energy than related π–π and CH–π interactions. The interaction energy between benzene and *N*-methylpyridinium is predicted to be –9.36 kcal mol^{-1} by molecular orbital calculations,[7] whereas the interaction energies in a benzene-pyridine complex and a benzene dimer were calculated to be –3.04 and 2.48 kcal mol^{-1}, respectively. Calculations have also predicted that electrostatic and induction interactions are major forces in pyridinium–π interactions, which confirms that pyridinium–π interactions may be categorised as cation–π interactions.[6]

Herein several asymmetric organocatalytic reactions in which a cation–π interaction apparently play a key role in establishing stereoselectivity are surveyed, and categorised according to the type of interaction so as to disclose the role of these interactions in asymmetric organocatalytic reactions. For the purposes of this article cation–π interactions are restricted to those where the cation consists of an unsaturated nitrogen-containing cation which displays charge delocalisation.

Iminium–π interactions

MacMillan and co-workers have developed a series of chiral imidazolidinones as powerful enantioselective catalysts for carbon-carbon bond-forming reactions of α,β-unsaturated carbonyl compounds.[10] These catalysts are supremely effective for various kinds of asymmetric reactions such as Diels–Alder,[11] 1,3-dipolar cycloaddition,[12] Friedel–Crafts,[13] and conjugate addition[14] reactions. A crucial aspect to the success of the amine catalysts' design is its ability to distinguish between the two faces of the iminium intermediate, thus achieving a highly diastereoselective transition state. The benzyl group of catalyst **1** (Scheme 2) effectively blocks one face of the iminium plane, which enables face-selective



Scheme 2 Enantioselective organocatalytic 1,4-addition reaction to an α,β-unsaturated aldehyde and an intramolecular Diels–Alder reaction.

addition of the nucleophiles and enophiles, delivering products in high enantiomeric excess.

Scheme 2 shows the enantioselective organocatalytic 1,4-addition reaction of an electron-rich benzene to an α,β-unsaturated aldehyde[14a] and an intramolecular Diels–Alder reaction of a trienal.[11b] In the presence of 10 mol% of catalyst **1**, a chiral aldehyde was obtained in 86% yield in 89% ee. The first step of this reaction is the formation of the intermediary iminium ion from reaction of the catalyst with α,β-unsaturated aldehydes, followed by face-selective addition of the electron rich benzene derivative to the iminium ion. The subsequent intramolecular Diels–Alder reaction proceeds to give a [4.3.0]bicyclic aldehyde bearing forming four stereogenic centres in 84% yield and 93% ee.

These high selectivity can be explained by the MM3 geometry of the intermediary cation,[1a] which predicts the benzyl group on the catalyst framework shields the *re* face of the iminium plane, leaving the *si* face exposed to attack by the nucleophile. Calculations by Houk reveal a structure that also apparently supports the geometry assertions of proposed iminium intermediates.[15]

Fig. 2a shows two stable conformers **A** and **B** obtained by DFT calculations for the same iminium ion with ΔE values, indicating that conformer **A** is more stable than conformer **B**.[15,16] To add weight to the presumption that cation–π interactions lead to the calculated confirmation preference in the stabilisation of the conformer **A**, structure optimisations for the corresponding non-charged C-analogues were carried out for comparison. As shown in Fig. 2b, conformer **B′** is more stable than conformer **A′**. These results strongly suggest that a cation–π interaction plays a key role in controlling the stability of the stacked iminium conformer **A**.[16]

Jørgensen reported conjugate additions of nitroalkanes[17] and malonates[18] to α,β-unsaturated enones using amine catalyst **2** to give the corresponding adducts with good stereoselectivities, a similar interaction to that proposed in Scheme 3 is proposed. The reaction of the enone with the catalyst produces an iminium intermediate, the energy minimisation (PM3) study of which provided the lowest energy conformer with a geometry one could interpret as *stacked*, a geometry similar to that reported by MacMillan

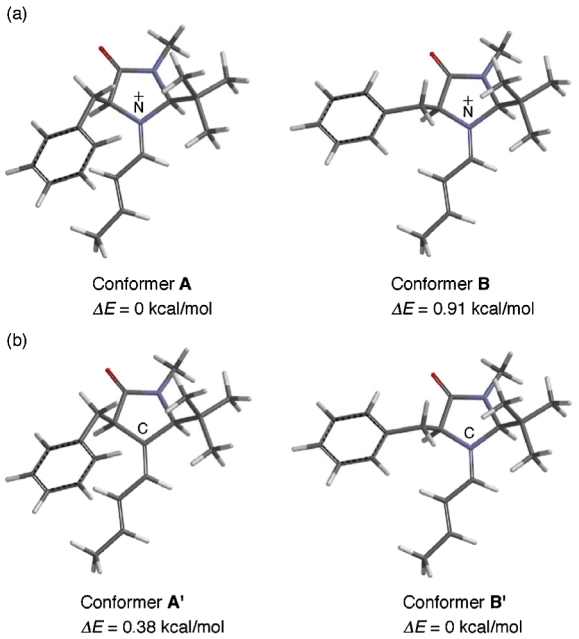
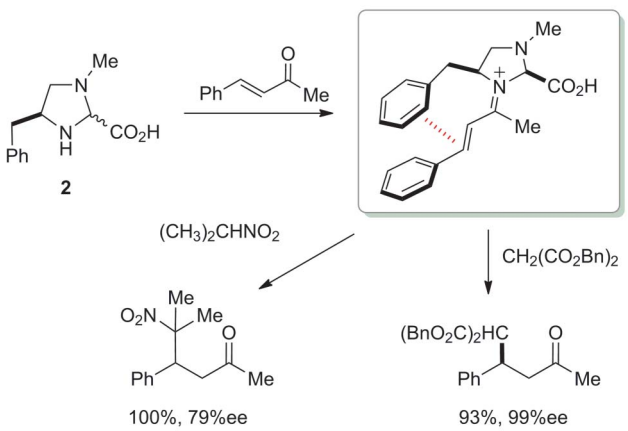


Fig. 2 DFT calculations for (a) iminium intermediates and (b) corresponding C-analogues.



Scheme 3 Jørgensen's iminium catalyst for conjugate addition reactions of conjugate additions of nitroalkanes and malonates.

et al.[19] in their related systems. It should be noted Jørgensen and co-workers discussed the role of the of the enone's spectator substituent and pointed out that steric interactions attenuate the rate but not the selectivity of the reaction. A significant feature of these reactions is that a 1,5-asymmetric induction is achieved through fixed conformer stabilised by apparent cation–π interactions. Importantly, it is not the assertion of this article to claim cation–π interactions alone are the origins of the exquisite selectivity observed in MacMillan-type catalysis, rather a potential contributor, indeed there are even examples where no cation–π interactions are possible that still give rise to very high ee products in similar catalysed reactions.[19]

Pyridinium–π interactions

Dougherty clarified details of an interaction between a pyridinium species and a phenyl group in 1988.[20] A cyclophane host **3** binds

N-methylquinolinium more tightly than quinoline by 2.5 kcal mol^{-1} in water, even though the cationic guest is much better solvated than quinoline (Fig. 3). Additionally, the existence of an intramolecular cation–π interaction between a pyridinium and a phenyl group was also revealed by one of the authors.[21] Intramolecular pyridinium–π interactions play an essential role in the facial-selectivity of nucleophilic addition reactions toward pyridinium **4**, where X-ray structural analysis, ^{1}H NMR spectroscopy and CD spectra elucidated a stacked geometry,[21–22] such interactions may also be probed by fluorescence spectroscopy.[23]

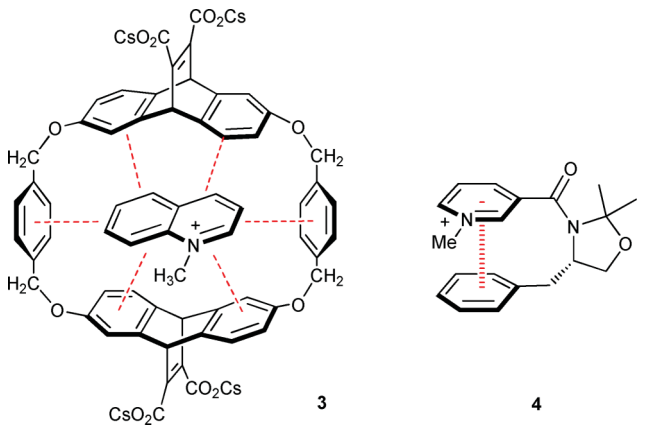


Fig. 3 Supramolecular guest-host ensemble **3**, utilising pyridinium–π interactions and a Yamada pyridinium–π construct **4**.

Dimethylaminopyridine (DMAP) is a powerful acylation catalyst for alcohols and amines, chiral DMAP derivatives have been developed as asymmetric acylating catalysts.[24] In the design of the chiral DMAP catalysts, distinguishing between the two faces of the intermediate acylated pyridinium species is a key to attaining high selectivity factors in the kinetic resolution of secondary alcohols. In 1997, Kawabata reported an enantioselective acyl transfer catalyst **5** based on the 4-pyrrolidinopyridine (PPY).[25] Compound **5** catalysed the kinetic resolution of racemic α-acyloxy alcohols using (*i*-PrCO)$_2$O as the acylating agent, with good selectivity factors (Scheme 4a). On the basis of NOE experiments, Kawabata hypothesised conformation changes in the catalyst before and after *N*-acylation. Namely, upon acylation of the pyridine nitrogen a *closed* conformation was adopted, as such the proposed transition state relies on both an intramolecular cation–π interaction to construct a highly selective environment and an intermolecular cation–π interaction organises the approach of the reactive enantiomer of secondary alcohol substrate.

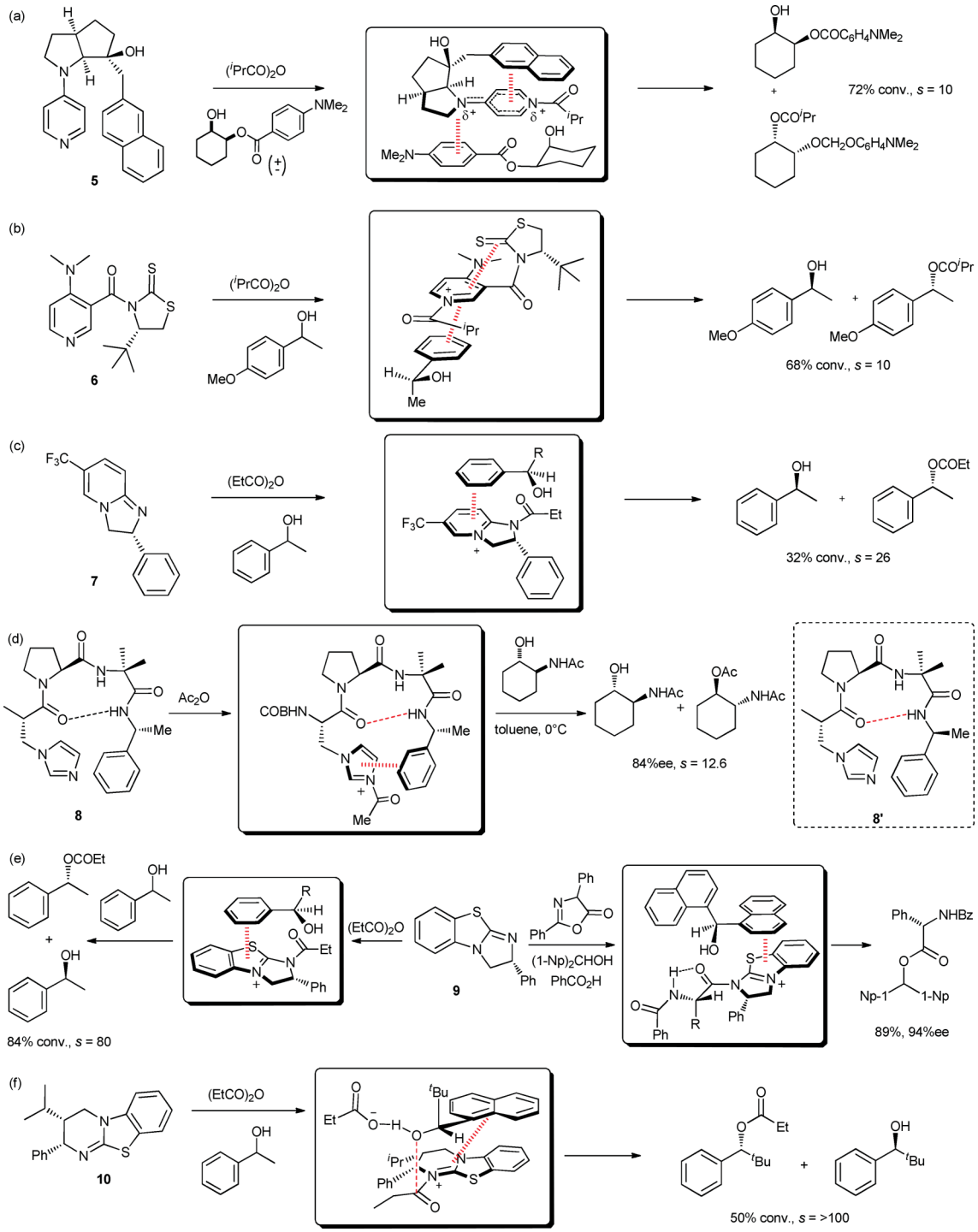
One of the authors has designed a chiral DMAP equivalent (**6**) possessing a chiral thiazolidine-2-thione moiety at the 3-position of the pyridine nucleus (Scheme 4b) as a catalyst.[26] The interaction between the pyridinium and the N–C═S moieties[27] mirrors that of cation–π interaction due to the fixed conformation of the *N*-acylpyridinium intermediate. This leads to the development of an enhanced chiral environment around the pyridinium, which allows enantiomer selective acylation of *sec*-alcohols. The kinetic resolution of racemic 1-(4-methoxyphenyl)ethanol was performed with good selectivity using (*i*-PrCO)$_2$O in the presence of 0.05 mol% of catalyst **6**. X-Ray structural analyses, ^{1}H NMR spectroscopic studies and DFT calculations for the *N*-substituted catalysts elucidated the fixed conformation; the C3···S═C distance of the pyridinium is much shorter than that of parent catalyst **9**.[26b] The same catalyst can be applied to desymmetrisation of diols[26b] and dynamic kinetic resolution of hemiaminals.[28] A significant feature of these catalytic reactions is that remote stereogenic centres far from the point of reaction have a profound influence on reaction outcomes, cation–π interactions serve to facilitate a chiral relay[29] effect within the catalyst framework. In addition to intramolecular cation–π interactions, intermolecular cation–π interactions between the pyridinium intermediates and aromatic substrates also appear to be significantly important for differentiation of enantiomeric alcohols.

Birman *et al.* developed a new class of enantioselective acyl transfer catalysts,2,3-dihydroimidazo[1,2-*a*]pyridines.[30] Kinetic resolution of various aryl alkyl carbinols with Ac$_2$O or (EtCO)$_2$O in the presence of catalyst **7** provides (*R*)-esters in high stereoselectivities. In these reactions, intermolecular cation–π interactions play an essential role; the aryl group of the substrate alcohol stacks on the less hindered side of the pyridinium face (Scheme 4c).[31,32] The (*R*)-alcohols more favourably form complexes than their (*S*) congeners to predominantly give (*R*)-esters. The fact that less polar solvents are important for the enantiomer selectivity strongly supports the suggestion that cation–π interactions are important. Calculations of the transition state of the acylation of (*R*)-1-phenylethanol with the *N*-propionyl intermediate by Houk *et al.* supported the hypothesised intermolecular pyridinium–π interaction between the catalyst and the substrate. A slipped-parallel geometry for the phenyl and the pyridinium rings, and close contact of the centroid of the phenyl and the pyridinium nitrogen (3.74 Å) indicates an electrostatic attraction between them.[33]

Jørgensen reported an annulation reaction of 2-(5-oxopentyl)isoquinolinium iodide using 10 mol% of chiral pyrrolidine catalyst **11** resulted in enantioselective annulation to give a chiral tricyclic compound in high selectivity through 1,9-asymmetric induction.[34] The stereoselectivity can be explained by a transition state, corroborated by calculations, where the isoquinolinium and a phenyl ring are stacked through a cation–π interaction (Scheme 5). The cation–π interaction allows the *re* face of the intermediate enamine double bond to approach the *si* face of the iminium double to deliver the corresponding tricyclic product in high ee.

Imidazolium, thiazolium and related structure–π interactions

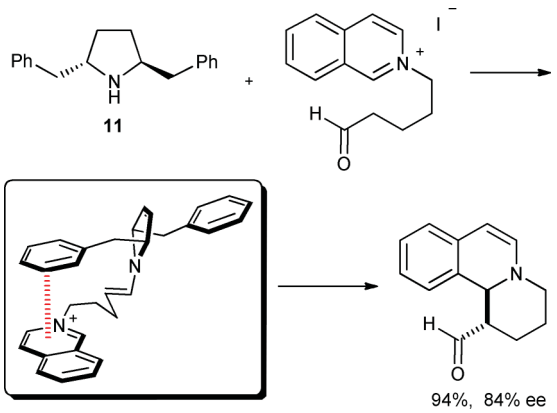
It has been well documented that acylimidazoliums are reactive intermediates for acylation reaction of alcohols.[35] Miller has developed a biomimetic enantioselective acyl transfer tripeptide catalyst containing 3-(imidazolyl)-(*S*)-alanine as the catalytic core (Scheme 4d).[36] This peptide has a β-turn structure defined by a proline-(*R*)-aminoisobutyric acid framework, the C-terminus of which bears a (*R*)-methylbenzylamide moiety. Kinetic resolution of racemic *trans*-2-(*N*-acetylamino)cyclohexan-1-ol was performed with good selectivity (s = 12.6) by acetylating with acetic anhydride in the presence of 0.05 equivalents of peptide catalyst **8**. On the other hand, when using catalyst **8′** having (*S*)-methylbenzylamide at the C-terminus resulted in much lower



Scheme 4 Cation–π interactions in secondary alcohol kinetic resolutions (KR) (a) Kawabata's chiral DMAP equivalent for KR. (b) Yamada's chiral DMAP equivalent for KR. (c) Birman's chiral Imidazole equivalent for KR. (d) Miller's peptidic catalyst for KR. (e) Birman's sulfur containing catalyst for asymmetric KR. (f) Smith's catalyst for secondary alcohol K.R.

selectivity ($s = 3.5$). The significant difference in the selectivities as a consequence of the absolute configuration of the methylbenzyl moiety suggests the close proximity of the *N*-acylimidazolium and the benzyl moieties *via* an intramolecular cation–π interaction during the key bond forming step. The intermolecular cation–π interaction between the imidazolium ring and toluene has been investigated through the combination of NMR spectroscopy and computational techniques, the nature of these intramolecular interactions was observed to be dependent on the propensity for self aggregation of the imidazolium moiety.[37]

Birman found that the commercially available pharmaceutical, tetramisole (Fig. 4), serves as an enantioselective acylation catalyst for the kinetic resolution of aryl alky carbinols.[38] On the basis of this finding, a new catalyst **9** was developed, the π-system was



Scheme 5

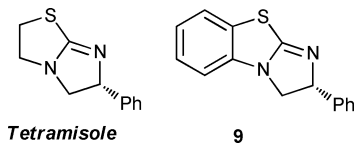


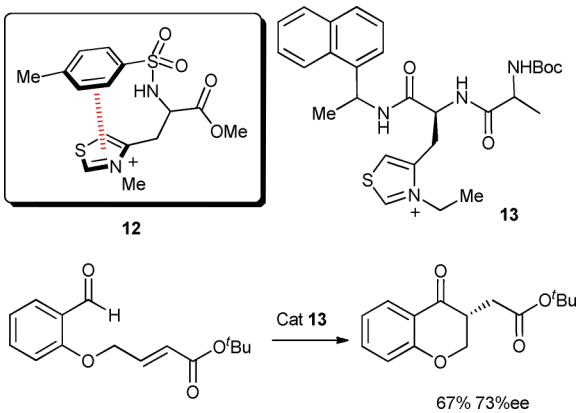
Fig. 4 Comparison between the structures of Tetramisole and compound **7**.

extended which also served to remove the hydrogens that might perturb accessibility of the substrate toward the intermediate *N*-acyl cation.[39] The kinetic resolution of various *sec*-benzylic alcohols catalysed by **9** has been achieved with the extremely high selectivity factors in the range of 100–355, the same catalyst is effective for the kinetic resolution of oxazolidinones (Scheme 4e).[39]

These high selectivities are reasoned to be due not only to the elimination of the steric repulsion by extending π-system, but also the enhanced cation–π interaction the extended aromatic area affords. Recently, this catalyst has been applied to dynamic kinetic resolution of azalactones *via* the acyl transfer mechanism,[40] where an intermolecular cation–π interaction between an *N*-acyl intermediate and di-(1-naphthyl)methanol discriminates between the diastereomeric intermediates.

Smith recently introduced an extraordinarily selective organocatalyst for secondary alcohol acylation, based on a homobenzotetramisole (HBTM) core where the introduction of an isopropyl substituent afforded catalyst (**10**) which was able to achieve selectivity factors of $s > 100$ for certain secondary alcohol substrates.[41] A stacked transition state was suggested by Smith *et al.* in order to explain high selectivity. Whilst the ferrocene derived catalysts fall outside the remit of true organocatalysis, functionalised metallocenes have also been studied as chiral DMAP equivalents by Fu[42] and others,[43] and in a recent development Hu *et al.* conceived a Fu–Birman hybrid catalyst that operates through an exclusively stacked transition state which clearly invokes a cation–π interaction. Selectivity factors for the catalytic kinetic resolution of bulky arylalkyl carbinols in that system reached up to $s = 1892$ (at –40 °C).[44]

A thiazolium moiety is observed in vitamin B1 and its analogues, which serve as catalysts for the benzoin condensation and related reactions.[45] Miller has developed peptide catalysts, having thiazole moieties as active sites.[46] The Stetter cyclisation of aromatic aldehydes with catalysts **12** and **13** gave a chroman-4-one in good enantioselectivity, Scheme 6. The X-ray crystal structure of catalyst **12** revealed that the aryl and the thiazolium rings lie in a parallel face-to-face arrangement in the solid state, indicating the potential existence of an intramolecular cation–π interaction. As such a charge separated zwitter ionic intermediate, which is produced by the addition of the *N*-heterocyclic carbene to an aldehyde, has the potential to form a cation–π complex during the face-selective 1,4-addition reaction.



Scheme 6

Conclusions

In this article the importance of potential cation–π interactions in asymmetric organocatalysis is proposed. In the rapidly maturing field of asymmetric organocatalysis many of its mysteries remain to be revealed, aromatic cation–π interactions are, possibly very important in many organocatalytic transformations, as this report aims to illuminate. Utilisation and appreciation of the fundamentally important interactions that govern selectivity in catalysis will permit the design of ever more exciting catalyst constructs with the ability to tackle the most challenging transformations in organic chemistry. In addition to the examples described here, there are bound to be unnoticed examples involving the participation of cation–π interactions in a variety of organocatalytic processes. Disclosure and delineation of such hidden features will provide valuable insight for the design of new organocatalytic reaction ensembles.

Note added after first publication

This article replaces the version published on 13 June 2011, which contained errors in Scheme 3.

Acknowledgements

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8 It is important to note that the authors of this article have collated representative examples where, in their opinion, cation-pi interactions play an important role. Such interpretation and categorisation is offered in the spirit of fostering further inquiry, and does not represent any definitive conclusion.
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