Chemistry of Ammonium Betaines: Application to Ion–Pair Catalysis for
Selective Organic Transformations

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(Received August 10, 2018; E-mail: tooi@chembio.nagoya-u.ac.jp)

Abstract: The ammonium betaine was developed as an intramolecular ion–pair catalyst for realizing cooperative
catalysis of a cation and anion; i.e. ion–pair catalysis. Combination of the stereocontrolling ability of the
chiral ammonium ion and functions of the pairing aryloxy ion enabled bifunctional organic base catalysis
and ionic nucleophilic catalysis, which facilitate a variety of organic transformations with rigorous stereo-
chemical control. In addition, employing a single–electron–accepting cation as a partner of the basic aryloxy-
late led to the development of a chemical redox catalyst with the capability of proton–coupled electron transfer
(PCET). This research demonstrates a power of the ion–pair catalysis in selective organic synthesis and is
therefore likely to stimulate further study in this field.

1. Introduction

Since a landmark thesis of the Merck research group in 1984 disclosed that cinchona alkaloid–derived chiral ammonium salt could precisely dictate the absolute stereochemistry of alkylation of a prochiral enolate under aqueous–organic biphasic conditions,¹ the chemistry of chiral quaternary onium salts has been placed at the central position in the asymmetric counterion–directed catalysis.² However, the salt has been mainly utilized for phase–transfer catalysis and thus, the potential of its catalytic performance has not yet been fully explored, especially under homogeneous conditions.³ This is largely because of difficulties associated with the understanding of the reaction mechanism that involves dynamic ion exchange under biphasic conditions; that has hampered the application of chiral quaternary onium salt catalysis to a variety of organic transformations in non–specific media.

In the general mode of chiral quaternary onium salt catalysis, the chiral onium ion exchanges its pairing anion with a reactive anion such as an enolate to form the corresponding chiral ion pair, and the ion–paired chiral intermediate participates in downstream bond formation with control of the stereochemical outcome. Accordingly, the cation is a key component responsible for asymmetric catalysis, while the parent anion of the catalyst hardly contributes to the overall reaction, other than to the efficiency of the initial ion–exchange step. In this regard, the catalysis should be classified as chiral cation–directed catalysis, and the development of cooperative catalysis of a cation and anion (ion–pair catalysis) remained elusive, despite its significant potential for expanding the scope of counterion–directed catalysis.³ This situation led us to embark on the development a strategy for establishing true ion–pair catalysis. The simplest approach to this direction was to fix an anion near to a cation by connecting two ions with a covalent bond to form an intramolecular ion pair; thus, we became interested in a betaine.⁴

Betaine is historically reserved for trimethylglycine, but nowadays it is defined as a zwitterionic molecule with a non–protonated cation and any anionic site at non–adjacent positions in a single molecule.⁵ Since the two ionic sites in the betaine are embedded in a spacer scaffold, the structure of the ion pair can be directly regulated through modification of the spacer skeleton, allowing the generation of a structured ion pair. We envisaged that judicious use of the characteristic features of betaine would allow us to design the entire structure of the ion pair for catalytic transformations enabled by the simultaneous function of a cation and anion, thereby opening a door to the ion–pair catalysis. In this account, we describe our efforts toward the development of ion–pair catalysis using ammonium betaines.

2. Bifunctional Organic Base Catalysis

If the anion moiety of the betaine abstracts a proton from a pronucleophile as a Brønsted base, the resulting conjugate acid would remain as a hydrogen–bond donating site at a neighboring position to the cationic center and could participate in capturing the nucleophilic anion in cooperation with ionic interaction to form a structured ion pair (Figure 1, lower panel). This contrasts markedly to the conventional intermolecular ion pair, where the parent anion is liberated from the reactive yet fluxional ion pair after the proton transfer event (Figure 1, upper panel).⁶ We envisioned that formation of the structured ion pair could help us design stereoselective catalyst systems through an understanding of the reaction mechanism. Furthermore, the cooperative operation of electrostatic attraction by the ammonium ion and the dual function of the anion moiety could render the betaine a bifunctional organic base catalyst. To assess the validity of this hypothesis, we designed an axially chiral ammonium betaine of type I possessing aryloxy moiety as a basic anionic functionality (Figure 2a).⁷ The structural characteristics of betaine I are as follows: (1) the axially chiral binaphthyl backbone could flexibly adjust the distance of the ammonium ion and aryloxylate; (2) the substituent at the ortho–position of aryloxylate (Ar) would pro-
vide an effective chiral environment around the reaction sphere; (3) the \( \text{ortho} \) substituent of the other naphthyl unit (\( R \)) could restrict the rotation of the ammonium appendage at the benzylic carbon; and (4) the intramolecular ionic interaction would regulate the direction of the cationic site, which could eventually control the position of the nucleophilic anion (see Figure 1).

First, we pursued establishment of a reliable procedure for the formation of the requisite intramolecular ion pair. Chiral ammonium betaines \( 1 \) were quantitatively prepared as a bench stable yellowish solid from its precursor, the quaternary ammonium trifluoroacetate \( 1 \cdot \text{HOCOCF}_3 \), by a simple treatment with a 0.1 M aqueous solution of sodium bicarbonate except for the simplest betaine \( 1a \) (\( R, \text{Ar} = \text{H} \)). Since \( 1a \) is a highly water-soluble molecule, a non-aqueous procedure; i.e. treatment of \( 1a \) with anhydrous tripotassium phosphate in acetone, was required for preparative isolation. Single crystal X-ray diffraction analysis of \( 1b \) (\( R, \text{Ar} = \text{Ph} \)) revealed its three-dimensional structure, where the trimethylammonium cation moiety turned in the same direction as the aryloxide oxygen to form the expected intramolecular ion pair (\( N-O = 4.271 \) Å) (Figure 2b).

2.1 Mannich–type Reaction of \( \alpha \)-Nitro Carboxylates

As a starting point of exploring betaine catalysis, we chose the Mannich–type reaction of \( \alpha \)-nitro carboxylate with \( N\)-Boc aldimine for evaluating the catalytic performance of \( 1 \). Fortunately, the simplest betaine \( 1a \) exhibited an ability to catalyze the Mannich–type reaction at 0 °C in toluene and the adduct was isolated in 40% yield after 20 h of stirring (Table 1, entry 1). However, the stereoselectivity of the reaction was rather poor. As expected, introduction of substituents to the \( 3,3' \)–position of the binaphthyl backbone greatly improved the catalytic activity and stereocontrolling ability, and \( 3,3' \)-phenyl-substituted \( 1b \) gave a diastereomeric mixture of the adduct (syn/anti = 2:1–1) in 92% yield with 90% ee for the syn-isomer (entry 2). Changing the substituent at the \( \text{ortho} \)–position to the ammonium moiety from phenyl to chlorine slightly enhanced the stereoselectivity (entry 3). With respect to the \( \text{ortho} \)–aromatic substituent of aryloxylate, increasing steric bulkiness in the \( \text{para} \)–direction was beneficial, but similar steric demand in the \( \text{meta} \)–direction diminished stereoselectivity (entries 4 and 5). While \( 1 \) consisting of a single binaphthyl backbone displayed excellent enantiomeric selectivity, expanding its molecular structure to a pseudo-\( C_2 \) symmetric form (Figure 3) was found...
to be effective for further improving enantioselectivity. Among the betaines tested, 2d showed highest diastereoselectivity and virtually complete enantioselectivity (entries 6–10). It is noteworthy that the intermolecular–type ammonium arylxoylate 2d provided a nearly racemic adduct, although the reaction efficiency was retained (entry 11), which clearly indicated the importance of the intramolecular ion–pair nature of the ammonium betaine 2 in achieving the absolute stereocostrol.

The catalysis was applicable to a wide variety of N–Boc aldimines and high yield, moderate diastereoselectivity, and excellent enantioselectivity were generally observed (Scheme 1).


2.2 Mannich–type Reaction of 2–Alkoxythiazol–5(4H)–ones

The highly enantionriched product in the above reaction can serve as a precursor of α,β–diamino acids, yet its diastereo
oselectivity is not synthetically useful. Therefore, we turned our attention to apply the catalysis to another Mannich–type reaction that is more suitable for the preparation of α,β–diamino acids. For this purpose, we selected 2–alkoxythiazol–5(4H)–one (thiazolone) as a nucleophile component with expectation that its rigid structure would be advantageous for precisely dictating the stereochemistry of the bond formation. In addition, we assumed that thiazolone could be converted into N–protected α–amino acid in a facile manner, in contrast to its oxygen–analog, oxazol–5(4H)–one (azlactone). The investigation of the appropriate reaction conditions made it clear that the bifunctional organic base catalysis of betaine 1 was indeed effective for the Mannich–type reaction of thiazolones with N–Boc aldimines. In this reaction, the structure of the 3–substituent on the naphthyl unit of the arylxoylate side was key for rigorously controlling the stereochemical outcome. Extensive survey of the structure–selectivity relationship revealed that betaine 1f possessing an extremely bulky aromatic group was the best catalyst for the present Mannich–type reaction (Scheme 2).

Scheme 2. Chiral ammonium betaine 1f–catalyzed Mannich–type reaction of thiazolones.

With the stereochemically enriched Mannich adduct in hand, we attempted to establish its derivatization into α,β–diamino acid derivatives to demonstrate the synthetic utility of the 1f–catalyzed Mannich protocol (Scheme 3). The thiazolone ring was easily opened upon treatment with basic hydrogen peroxide, and concomitant oxidation of the resulting thiacarbonyl moiety into benzoxycarbonyl afforded differently protected α,β–diamino acid in good yield. Furthermore, we found that the benzyl group could be removed by exposure to methanoic hydrogen chloride to produce 4–tetrasubstituted thiazolidine–2,5–dione. The subsequent aminolysis of the thiazolidine–2,5–dione ring with methylamine furnished an α,β–diamino amide, featuring the reactivity of the thiazolidine–2,5–dione as an acyl–transfer reagent.

Scheme 3. Synthesis of various α,β–diamino acid derivatives from the Mannich adduct of thiazolone.

2.3 Mannich–type Reaction of 3–Aryl Oxindoles

A betaine catalyst is also effective for controlling the stereochemistry of the Mannich–type reaction of 3–aryl oxindoles (Scheme 4). Despite the importance of 3–quaternary chiral oxindoles in the synthesis of biologically relevant molecules, examples of catalytic asymmetric Mannich–type reactions of oxindoles are rare and 3–aryl oxindoles are regarded as a particularly problematic substrate. We solved this problem by utilizing bifunctional organic base catalysis of betaine 1. In fact, the catalytic amount of betaine 1g having 4–tert–butylphenyl groups at 3,3–positions of the binaphthyl backbone promoted smooth Mannich–type reaction and provided the corresponding adducts in high yield with excellent stereoselectivity.


2.4 Mannich–type Reaction of Dihydro–2(1H)–quinolones

The high performance of betaine in the Mannich–type reactions of oxindoles led us to become interested in using dihydro–2(1H)–quinolones as a pronucleophile. Although various annihilation reactions have been introduced to access synthetically valuable chiral dihydroquinolone derivatives, asymmetric modification of their lactam ring remained a chal-

We thus employed 3-nitro-dihydro-2(1H)-quinolone as a nucleophilic component of the Mannich-type reaction under the catalysis of chiral ammonium betaine I. After optimization of the catalyst structure and reaction conditions, a fairly stereoselective system was established with 1h as a requisite catalyst (Scheme 5).

Scheme 5. Chiral ammonium betaine 1h-catalyzed Mannich-type reaction of dihydro-2(1H)-quinolones.

Importantly, no conversion was confirmed when subjecting a β-mono-substituted nitroolefin to the reaction conditions, proving that two β-substituents were essential in this aza-Henry reaction. It is worth noting that the corresponding γ-isomer was never detected, which suggests the intrinsic preference of the vinylogous nitronate during carbon–carbon bond formation with N–Boc aldmines.

Scheme 6. Chiral ammonium betaine 1I-catalyzed aza–Henry reaction of β,β-disubstituted nitroolefins.

The importance of steric repulsion for the facile generation of vinylogous nitronates led us to explore another substitution pattern of nitroolefins pertinent to accelerating the aza-Henry reaction. It was amenable to the stereoselective aza–Henry reaction with N–Boc aldmines. Optimization of the betaine structure and reaction conditions allowed us to selectively obtain the α-adduct in high yield with excellent stereoselectivity under the
influence of 1h (Scheme 7). Here again, γ-adduct formation was not detected and the bond formation at the sterically congested α-position underscored the strong preference of the vinylogous nitronate toward α-addition.

**Scheme 7.** Chiral ammonium betaine 1h-catalyzed Henry reaction of α-aryl β-mono-substituted nitroolefins.

![Scheme 7](image)

2.7 Aza-Henry Reaction of α-Aryl Nitromethanes

The betaine 1-catalyzed aza-Henry protocol was applicable to α-aryl nitromethanes in a similar manner, providing an access to a valuable precursor of 1,2-diarylethylenediamines (Scheme 8). High stereoselectivity was accomplished by using ammonium betaine 1 as a catalyst. The aza-Henry adduct thus obtained was easily converted into the corresponding N-unprotected diamine without loss of stereochemical integrity, demonstrating its synthetic utility. Notably, when the product was treated with triethylamine, facile epimerization at the stereogenic carbon attached to the nitro group took place, resulting in a mixture of a nearly equal amount of diastereomers, while the enantiomeric excesses of both diastereomers remained intact. This observation suggests that the betaine catalyst rigorously discriminates the prochiral faces of N-Boc aldamines at the carbon-carbon bond-forming event.

**Scheme 8.** Chiral ammonium betaine 1i-catalyzed Henry reaction of α-aryl nitromethanes.

![Scheme 8](image)

3. Ionic Nucleophilic Catalysis

In addition to the basic character, aryloxylate functionality of ammonium betaine also exhibits nucleophilicity. This attribute inspired us to conceive that betaine 1 could be evolved into a chiral nucleophilic catalyst through appropriate structural manipulations, despite the fact that most, if not all, of the previously reported nucleophilic catalysts were non-ionic molecules and that development of an ionic nucleophilic catalyst has been elusive.

The nucleophilic catalyst is unique in temporally forming a covalent bond with the substrate to produce a reactive inter-

that the characteristic yellow color of 1j immediately lightened upon the addition of one drop of a solution of the carbonate, which was an indication of acylation of the arylxylate moiety of 1j to form the ammonium enolate. After leaving the mixture for a while without further addition of the carbonate, the original yellow color gradually returned, indicating the regeneration of 1j with concomitant formation of the product. This observation suggests that carbon–carbon bond formation is the rate-limiting step in this catalysis. The introduction of an electron–withdrawing group such as 4-trifluoromethylphenyl (1k) or 3,5-bis(trifluoromethyl)phenyl (1l) to the naphthyl unit bearing the ammonium cation enhanced catalytic efficiency, as indicated by the vivid yellow color remaining throughout the reaction, and improved enantioselectivity further to 95% ee and 97% ee, respectively.

Scheme 9. Evaluation of the performance of ammonium betaine 1 as an ionic nucleophilic catalyst.

![Scheme 9](image)

The optimized betaine 1l exhibited extremely high catalytic performance and a series of carbonates was converted into the corresponding azlactones within 30 min quantitatively with excellent enantiomeric excesses (Scheme 10). Even sterically hindered carbonate (R³=Pr) underwent rearrangement by raising the temperature to 40 °C to afford the product with 95% ee, implying that the prominent nucleophilicity of the anion part and unique structure of the betaine play crucial roles in the nucleophilic catalysis.

Scheme 10. Chiral ammonium betaine 1l–catalyzed enantioselective Steglich rearrangement.

![Scheme 10](image)

An interesting aspect of the present reaction system is the dependence of enantioselectivity on substrate concentration, and low concentration of the carbonate appeared to be key for attaining high enantiomeric excess. In fact, enantioselectivity of the reaction decreased from 97% to 87% when 1l was added to a solution of the phenylalanine–derived carbonate under otherwise identical conditions. This outcome suggests that two reaction pathways exist in the 1l–catalyzed Steglich rearrangement. One is the expected pseudo–intramolecular “rearrangement” with high enantioselectivity (Figure 6a, cycle I) and the other is the less stereoselective intermolecular reaction of the ammonium enolate with the external carbonate (cycle II). The possible influence of this undesired intermolecular pathway on the reaction profile was assessed by investigating the reactivity of the carbonate as an acyl–transfer reagent to an ammonium enolate. Namely, the addition of the carbonate to a solution of in situ generated tetrabutylammonium β-naphthoxide (20 mol%) produced azlactone in 85% yield along with 2,2,2-trichloroethyl β-naphthyl carbonate in 15% yield (Figure 6b). This result indicates that the intermediary ammonium enolate, which was generated via initial nucleophilic addition of β-naphthoxide to the carbonate, directly reacted with the carbonate to give azlactone. In other words, the chiral ammonium enolate could also provide azlactone via direct addition to the external carbonate; this process would compete with the desired pseudo–intramolecular bond formation. Consequently, maintaining low substrate concentration is a prerequisite for controlling the reaction pathway and achieving high enantioselectivity.

Figure 6. (a) Plausible reaction mechanisms of the chiral ammonium betaine 1l–catalyzed Steglich rearrangement. (b) Intramolecular “Steglich rearrangement”.

3.2 Aldol Reaction of Oxindole–derived Enol Carbonates

During the course of the study on the nucleophilic catalysis of ammonium betaines, we became interested in the moderate stability of the intermediary formed ammonium enolate, which eventually reacts with the aryl carbonate moiety pseudo–intramolecularly to give the “rearranged” product (Figure 7, path A). The possible intervention of the competing intermolecular reaction with the coexisting carbonate suggests that the transient enolate ion could be trapped by an external electrophile such as aldehyde, followed by O–acylation of the resulting alkoxylic acid, giving rise to a fully protected aldol adduct (path B).25 To examine this possibility, the aldol reaction of oxindole–derived vinyl carbonates with aldehydes was selected as a model reaction. Despite the oxindole core being commonly found in biologically relevant molecules, the catalytic asymmetric aldol reaction of oxindoles is scarcely developed and essentially limited to systems using highly activated aldehydes as requisite electrophiles.25,26 This is probably because aldol
adducts of oxindoles tend to racemize under basic conditions via the retro-aldol reaction. With this respect, our approach would be generically advantageous because of the concurrent in situ acyl transfer to afford the aldol adduct as a stable, protected form.

The presumed aldol reaction of O-\textsuperscript{2,2,2}-trichloroethoxy-carbonyl enolate and benzaldehyde (2.0 equiv) was attempted with chiral ammonium betaine 1j as a nucleophilic catalyst. Fortunately, the expected adduct was obtained as a diastereomeric mixture (dr=6:1) in 77% yield with 34% ee for the major diastereomer, albeit notable amount of Steglich product was also isolated (aldol vs. Steglich 8:1) (Table 2, entry 1).

The structural modification of 1 had a clear impact on the distribution of the products as well as stereoselectivity. Concretely, replacing the N\textsuperscript{+}methyl substituent with sterically demanding groups dramatically improved selectivities, and 1o possessing a 3,5\textsuperscript{-bis(tert-butyldimethylsilyl)}benzyl group enabled a promising level of control of both reaction pathway and stereochemical outcome (entries 3 and 4). Increasing the steric bulkiness of the aromatic substituent on the naphthyl unit (1p) further enhanced selectivities (entry 5). Because the parent structure of 1 is converted to O-\textsuperscript{acyl} ammonium enolate upon the acyl-transfer reaction, the carbon-\textsuperscript{carbon} bond forming process is controlled by the O-\textsuperscript{acyl} ammonium ion. Therefore, we investigated effect of the structure of R\textsuperscript{1} in the substrate on selectivity profile (entries 6–8). When the trichloroethoxy moiety was exchanged with a benzyl group, enantioselectivity was enhanced to 92%, but the turnover frequency was markedly diminished (entry 6). This problem was overcome by introducing electron-withdrawing groups to the benzyl moiety, which improved reaction efficiency without affecting selectivities (entries 7 and 8). Eventually, use of the 3,5\textsuperscript{-bis(trifluoromethyl)}-benzyl carbonate in combination with 1p as a catalyst led to virtually complete discrimination of the reaction pathway with excellent stereocontrol (entry 8).

Table 2. Optimization of conditions for the chiral ammonium betaines 1-\textsuperscript{catalyzed aldol reaction.}

| entry | R\textsuperscript{1} | yield (\%) | dr | aldol/steglich (%)
|-------|----------------------|------------|----|----------------------|
| 1j    | Cl\textsubscript{3}CCH\textsubscript{3} | 77 | 6:1 | 8:1 (34)
| 1m    | Cl\textsubscript{3}CCH\textsubscript{3} | 67 | 7:1 | 4:1 (39)
| 1n    | Cl\textsubscript{3}CCH\textsubscript{3} | 79 | 15:1 | 15:1 (71)
| 1o    | Cl\textsubscript{3}CCH\textsubscript{3} | 82 | 15:1 | 11:1 (78)
| 1p    | Cl\textsubscript{3}CCH\textsubscript{3} | 86 | 20:1 | 13:1 (89)
| 6\textsuperscript{*} | 1p | PhCH\textsubscript{2} | 51 | 20:1 | 20:1 (92)
| 5p    | 4-FC\textsubscript{4}CH\textsubscript{2}CH\textsubscript{3} | 88 | 20:1 | 20:1 (93)
| 8p    | 3,5-\text{(CF\textsubscript{3})\textsubscript{2}}C\textsubscript{6}H\textsubscript{3}CH\textsubscript{2} | 89 | 20:1 | 20:1 (95)

\*Reaction time was 12 h.

Figure 7. Working hypothesis for the chiral ammonium betaine 1-catalyzed aldol reaction.

As described, embedding an aryloxylate unit to a chiral ammonium ion has enabled ion–pair catalysis effective for achieving otherwise difficult highly stereoselective organic transformations. The judicious combination of functions of the aryloxylate, such as nucleophilicity, basicity, and the hydrogen-bonding capability of the conjugate acid, with the stereocontrolling ability of the ammonium ion allowed us to generate and control unique yet reactive ionic species. Based on these findings, we next turned our attention to another function of cationic species to further expand the potential of ion–pair catalysis of the betaine molecules by changing the structure of the cation component.

As an initial step toward this direction, we selected 9-\text{mesityl} acridinium ion, which was discovered by Fukuzumi in 2004 to be a redox active molecule having extremely long excited-
state lifetime as a functional cationic subunit and designed an intramolecular ion pair of type 3, acridinium betaine, as a single-electron-transfer catalyst (Figure 8). We hypothesized that the combination of the basic character of the aryloxylate moiety of 3 and the relatively high reduction potential of the acridinium ion at the ground state could facilitate proton-coupled electron transfer (PCET) in its hydrogen-bonding complex with an acidic substrate. Moreover, the resulting radical species could be utilized for downstream bond formation. PCET is one of the basic mechanisms of chemical and biological transformations, where simultaneous transfer of one electron and one proton between given substrates generates high-energy radical intermediates. Essentially, PCET is known to proceed via a more stable transition state than that expected in iterative electron–proton (or proton–electron) transfer processes. Therefore, in order to catalytically promote the PCET reaction, the reduction/oxidation potential of the catalyst is expected to be much lower than that of the two–step reaction, and the resulting reduced (or oxidized) catalyst should be restored under accessible conditions. Although fulfilling these requirements could lead to the development of a catalytically operative chemical redox reagent, this possibility has not yet been experimentally explored.

Figure 8. Structure and properties of acridinium betaine 3 and working hypothesis for generating a radical species via the PCET process.

The single-electron transfer reaction by chemical redox reagents is a powerful means for generating radical species, while it generally requires an over-stoichiometric amount of strong reductants (or oxidants), such as low-valent metal salts, which produce non-reusable waste after the reaction. Because external energy infusion is not necessary, the chemical redox reaction is highly reliable and it is still frequently used for the synthesis of complex molecules. Therefore, the advent of new catalysts or catalytic systems of chemical redox reactions using a clean terminal oxidant such as oxygen is in high demand from the viewpoint of sustainable process development. However, the exploration of catalytically relevant chemical redox reagents has been scarce, presumably because of difficulties associated with regeneration of the catalyst. Generation of reactive radical species from stable compounds requires high–energy redox–active reagents, which would make it difficult to regenerate the catalyst by commonly utilized terminal oxidants/reductants. We anticipated that a catalytic PCET reaction based on the use of 3 could offer a platform for overcoming this dilemma because the acridinium ion is known to be robust to the single–electron redox process and is regenerated via autoxidation of its reduced radical form.

Acridinium betaine 3 was synthesized as a stable solid in a straightforward manner and its physical properties were analyzed. The reduction potential of 3 was determined to be $-0.60 \text{ V (vs. SCE)}$ by cyclic voltammetry (CV) in MeCN and its $pK_a$ (23.7 in MeCN) value was derived from the change in UV–Vis absorbance during acid–base titration with 3-HCl/DBU or 3-acetic acid. According to these physical data, 3 can oxidize organic compounds containing an active proton (bond–dissociation free energy (BDFE) = 64.8 kcal/mol) through the PCET process. As a model reaction for evaluating the catalytic property of 3, we selected homodimerization of $N$–PMP–3–aryl–oxindole (BDFE = 64.8 kcal/mol, calculated at PCM(MeCN)–UB3LYP/6–311++G(2df,2p) level) via a radical enolate. The viability of our hypothesis was initially investigated by treatment of $N$–PMP–3–phenyl–oxindole with 3 (2 mol%) in toluene at room temperature under oxygen atmosphere (Table 3, entry 1). The reaction proceeded smoothly and the expected dimer was isolated in good yield after 3 h of stirring. While a similar result was obtained under atmospheric conditions, the reaction was completely suppressed under argon atmosphere (entries 2 and 3). This observation clearly indicates that oxygen is essential for the reaction. The critical importance of the structure of 3, with respect to both the redox-active unit and the basic site embedded in the same molecular framework, was confirmed by the following reactions (entries 4–6). A simple base catalyst, pyridinium betaine (betaine), did not afford the homodimerized product under similar conditions (entry 4). On the other hand, acridinium salt (acr) subtly promoted the coupling reaction and certain acceleration was observed under binary catalysis of acr and betaine; however, the rates were markedly slower than that in the 3–catalyzed reaction (entries 5 and 6). The relative configuration of the dimer was unambiguously determined by X–ray diffraction analysis to be meso-isomer.

Table 3. Reaction conditions.

<table>
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To gain a mechanistic insight into the 3–catalyzed dimerization of oxindole, the kinetic profile was analyzed by monitoring the reaction progress with in situ IR measurement. Comparison of the initial rate between the 3–catalyzed reaction and that under the binary catalysis of betaine and acr revealed that the intramolecular ion–pair structure of 3 was...
crucial for enhancing catalytic efficiency. The order of the reaction on each component was then determined as: 1st order on 1, -0.85th order on oxindole, and 0.5th order on O₂. The observed non-integer orders suggest the intervention of equilibrium in the rate-limiting step, and a possible mechanism is shown in Figure 9. The negative dependence on oxindole concentration could be accounted for by that SET from the oxindole enolate to the acridinium unit would be much more sluggish than PCET, and generation of the acridinium enolate may impede regeneration of 3, where the effective concentration of 3 was decreased in the presence of excess amount of the oxindole. The role of O₂ as the single-electron oxidant for liberating the radical enolate of oxindole and formation of H₂O₂ was experimentally proved, providing further evidence for the proposed reaction mechanism. Although additional study is still required to clarify the detailed mechanism, the above observations support the PCET catalysis of 3 depicted in Figure 9.

5. Conclusion

As a unique means for realizing a cooperative catalysis of a cation and anion, an ion-pair catalysis, we developed an ammonium betaine of type I as an intramolecular ion-pair catalyst and unveiled its catalytic performance in achieving a series of selective organic transformations. With particular focus on the functions of the anionic moiety, an arylxylate, both bifunctional base catalysis and ionic nucleophilic catalysis were established in the development of highly stereoselective bond-forming reactions. Upon giving an eye to the function of the cationic moiety, the organic chemical-redox catalyst 3 was elaborated by employing the acridinium ion as a requisite cationic unit having single-electron redox capability. The nature of these catalyses is distinct from ordinary bifunctionalonium salt catalysis and represents a true ion-pair catalysis. Our studies on the chemistry of betaines demonstrate the potential of the catalysis that relies on imparting an appropriate yet discrete structure to an ion pair in selective organic synthesis and will stimulate further research efforts for understanding and exploitation of ion-pair catalysis.

Acknowledgements

The authors would like to express their sincere apprecia-

citation to all past and present members of the betaine team in the laboratory for the chemistry of organic reaction (Ooi group) at Nagoya University for their vital contributions. Financial support was provided by CREST-JST (JPMJCR13L2; 13418441), a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” from MEXT, the Program for Leading Graduate Schools “Integrative Graduate Education and Research Program in Green Natural Sciences” in Nagoya University, and Grants of JSPS for Scientific Research.

References

9) When an anionic component of the betaine precursor was trifluoroacetate CF₃CO₂⁻, complete conversion to the corresponding betaine 1 could be confirmed by disappearance of the signal of CF₃CO₂⁻ in ¹H NMR analysis.
Daïsuke Uraguchi is an Associate Professor of Nagoya University. He was born in 1974 in Hokkaido and received his B.Sc. (1997) and Ph.D. degree (2002) from Hokkaido University under the guidance of Professor Keiji Maruoka. He gained substantial experience working as a postdoctoral fellow of JSPS (2002–2004) with Professor P. Andrew Evans at Indiana University and with Professor Masahiro Terada at Tohoku University. Then, he moved to the Sagan chemical research center (2004–2006). In 2006, he was appointed as Assistant Professor of the research group of Professor Takashi Ooi at Nagoya University, and promoted to Associate Professor in 2008. He has received the Takeda Pharmaceutical Co., Ltd. Award in SSOCI (2008), The CSJ Award for Young Chemist (2010), The Young Scientists’ Prize from MEXT (2011), Banyu Chemist Award (2012), Lectureship Award MBLA (2013), and Thieme Chemistry Journal Award (2014). His current research interests include the chemistry of organic ion–pair catalysis.

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27. When a betaine lacking 3-substituent of the arylxylate side was prepared, a methanolic solution of its conjugate acid salt was passed through a column of ion-exchange resin (OH form).
32. The enantioselective excess of the Steglich rearrangement product was not analyzed.
39. The reason for the observed diastereopreference is unclear yet.