Supramolecular Catalysis

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# Charged-Assisted Supramolecular Catalysis**

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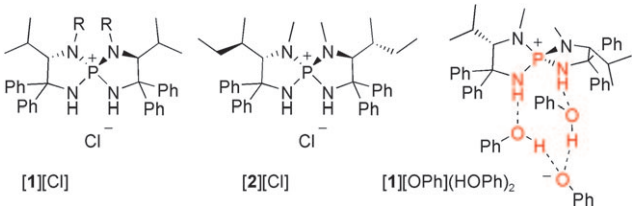
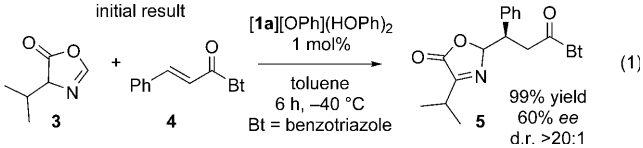
Research in homogeneous supramolecular catalysis has enjoyed sustained attention over the last few years.[1] A supramolecular catalyst associates several components through reversible (e.g., metal–ligand) or noncovalent (electrostatic, van der Waals, hydrogen bonding, π–π stacking, hydrophobic, and solvatophobic) interactions, and the resulting supramolecules are more effective than the subcomponents taken separately. These catalysts have proven to be efficient in numerous metal-mediated catalytic processes, including hydrogenation, hydroformylation, hydroboration, nitroaldol reactions, and hydrations of alkynes and nitriles.[2] Recently, for instance, the chemoselective reduction of aldehydes and the tandem hydroformylation–hydrogenation of terminal alkenes was reported using combined hydrogen-bonding and metal–ligand approaches.[3] In another report, it was shown that a single hydrogen bond between ligands coordinated to a rhodium center results in very effective supramolecular catalysts for asymmetric hydrogenation reactions.[4] Examples of metal-free organocatalytic reactions involving supramolecular structures have also been reported.[5] It is in this context of supramolecular catalysis that an interesting report has recently appeared.

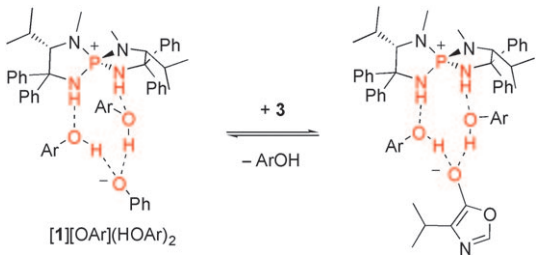
Previously, Ooi and co-workers had reported the six-step synthesis of enantiopure tetraaminophosphonium salts of the type [**1**][Cl] containing a *P*-spirocyclic cationic structure derived from amino acid residues.[6] These salts were "traditional" organocatalysts for enantioselective Henry or Mannich type reactions and hydrophosphonylation of aldehydes (Scheme 1).[6,7] Recently, while attempting to exchange the chloride counterion of salt [**1**][Cl] for a phenoxide anion, Ooi and colleagues realized that larger supramolecular assemblies made of an aminophosphonium cation, two phenols, and a phenoxide anion crystallized.[8] The solid-state structure of the resulting complex [**1**][OPh](HOPh)$_2$ was unambiguously determined by X-ray diffraction analysis. The four components are well-organized through a ten-membered cyclic network of intermolecular hydrogen-bonding interactions. Ooi and co-workers then considered using the neutral phenol molecules to extend the stereochemical information embedded in the chiral spirocyclic cation moiety; the chiral environment is transferred to the phenoxide anion through the H-bonded components.




***Scheme 1.*** Catalytic tetraaminophosphonium species: chloride salts and supramolecular phenol/phenolate complex [**1**][OPh](HOPh)$_2$.

This interesting hypothesis was tested using the synthetically valuable conjugate addition of azlactones of type **3** to α,β-unsaturated acylbenzotriazoles **4** [Eq. (1)]. Azlactone **3** was chosen as a pro-C1 nucleophile with the expectation that it could be activated by hydrogen bonds. The corresponding enolate would also behave as a phenoxide anion equivalent that could be involved in a hydrogen-bonded organization similar to that of [**1**][OPh](HOPh)$_2$ (Scheme 2).




***Scheme 2.*** Proposed assembly mode of two phenols, **1**, and the azlactone enolate.

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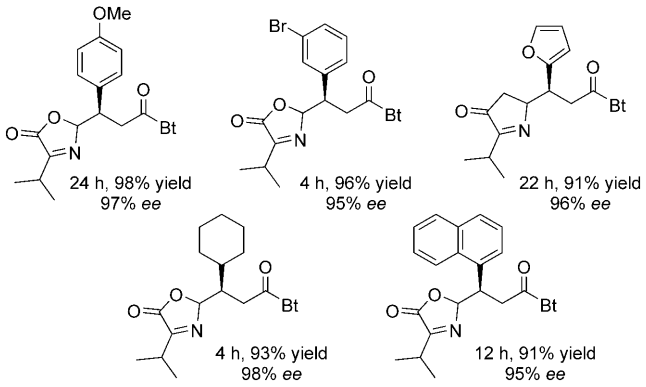
Using complex [**1**][OPh](HOPh)$_2$ as catalyst (1 mol%), compounds **3** and **4** reacted readily at low temperature to yield product **5** in excellent yield and decent enantioselectivity [60% *ee*, Eq. (1)]. Significantly, a lower asymmetric induction (34% *ee*) was reached in the absence of the two phenol moieties. However, quite high enantiomeric excess values were obtained using chlorine-substituted derivatives, in particular 3,5-dichlorophenol (80% *ee*), in place of regular phenol. Increased catalyst loading and decreased solvent volume further improved the enantioselectivity (89% *ee*); all of these elements point towards the possible role of a supramolecular assembly. Switching cation **1** to L-leucine-derived **2** was also favorable (up to 95% *ee*).

Both electron-donating and electron-withdrawing groups on the aryl substituent of the α,β-unsaturated acylbenzotriazoles **4** are tolerated (Scheme 3). Fused and heteroaromatic




***Scheme 3.*** Representative products of type **5**. Bt = benzotriazole.

substituents as well as alkyl groups exert little influence on the stereochemical outcome, although the reactivity may be affected. Finally, adducts **5** can be selectively transformed into various functional groups without any loss of selectivity, as demonstrated by a successful synthesis of scalemic methylsuccinic acid in four steps.[8]

This reactive combination of an aminophosphonium cation, two phenols, and a phenoxide is noteworthy for a number of reasons. The proposed four-component structure of the catalyst allows a modular approach to its design, as the reactivity and selectivity can be tuned by astute modifications on each subcomponent (e.g., chlorine substituents on the phenols, the nature of the amino acid backbone on the phosphonium cation). The concentrated reaction medium (1M in toluene) limits the amount of solvent used, which is favorable for the sustainability of the reaction. Also, preorganization of the supramolecular assembly prior to the reaction is not required. This feature greatly facilitates the experimental procedure. Overall, the current system is a very significant contribution to the field of enantioselective catalysis.

What remains to be seen is how broad the reactivity scope will be and how well the ten-membered cyclic network of intermolecular hydrogen-bonding interactions and its role in solution will be defined. Deep understanding of the mechanism at play may prove to be necessary to unravel the cooperativity of the subcomponents. A detailed kinetic analysis, for instance, will be helpful. Precise determination of a rate law and of enthalpy and entropy of activation may give many clues to the nature of the assembly of the catalyst in (or prior to) the rate-determining step. Modern NMR spectroscopic techniques, React-IR spectroscopy, and computational studies will also be useful. For instance, diffusion data from pulse-field gradient spin echo (PGSE) experiments ($^1$H, $^{31}$P) will give useful information on the integrity of the supramolecular structure prior to and during the reaction.[9] The three-dimensional solution structure—and the H-bond network in particular—might be accessible by homonuclear NOESY experiments. These two sets of experiments will further help characterize the "ion pairing" situation at play, as it is not clear whether complex [**1**][OPh](HOPh)$_2$ can be accurately described as an ion pair.[10–12] Salts that contain strong secondary interactions between the ions, and directional H-bonds in particular, are charge-assisted supramolecular entities rather than ion pairs in the strict sense of the term;[11] complex [**1**][OPh](HOPh)$_2$ would then be a new type of charge-assisted supramolecular catalyst.

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[12] An ion pair is defined to exist when a cation and an anion are close in space and share a common solvation shell; the energy

  

associated with their electrostatic attraction is larger than the thermal energy ($RT$) available to separate them. The ions must also stay associated longer than the time required for Brownian motion to separate non-interacting species. Only strict electrostatic interactions should occur between the ions. No interactions other than the Coulombic attraction should formally exist upon the association of the charges, which existed prior to the interaction and remain unchanged in the interaction.