Supramolecular Catalysis

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Controlled Assembly of Chiral Tetraaminophosphonium Aryloxide–Arylhydroxide(s) in Solution**

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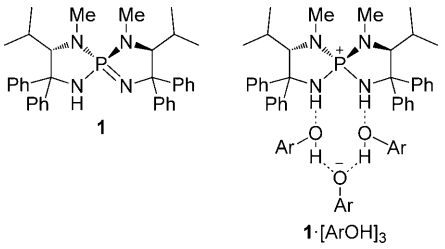
The chemistry at the interface between homogeneous catalysis and supramolecular chemistry, namely supramolecular catalysis, has attracted sustained attention over the last decade.[1] In a departure from early endeavors to create preorganized molecular receptors as an artificial enzyme, the current approach toward understanding and mimicking enzymatic catalysis has focused on the design of systems capable of spontaneously generating well-defined, functional supramolecular architectures by self-assembly. The inner spaces of these assemblies serve as an isolated reaction vessel that can confine the substrates, thus delivering otherwise unattainable reactivity and selectivity.[2] In parallel, new possibilities of supramolecular catalysis have been demonstrated by the marriage of multicomponent assemblies with homogeneous transition-metal catalysis and organic molecular catalysis since the seminal studies of Breit, von Leeuwen, and Reek in 2003.[3] We recently reported that chiral *P*-spiro triaminoiminophosphorane **1** and three equivalents of arylhydroxides (ArOH) spontaneously assembled into the highly organized molecular structure **1**·$[ArOH]_3$ by the formation of an ion-pair-assisted hydrogen-bonding network (Scheme 1).[4,5] Furthermore, the resultant network **1**·$[ArOH]_3$, and particularly that with a 3,5-dichlorophenol component (3,5-$Cl_2C_6H_3OH$; **2**), exerted efficient cooperative catalysis in the stereoselective conjugate addition of an acyl anion equivalent. Although the discrete three-dimensional structure of **1**·$[PhOH]_3$ in solid state was determined by single-crystal X-ray diffraction analysis, the actual behavior of this type of supramolecular catalyst in solution remains an important issue to be resolved. This situation prompted us to conduct a series of spectroscopic analyses of a solution of **1** and **2** in an organic solvent, which revealed not only the effectiveness of the low-temperature ^{31}P NMR spectroscopy measurement for tracing the solution structure, but also unexpected, yet intriguing, phenomenon regarding the mode of molecular association. Herein, we disclose the stepwise and exclusive generation of three types of molecular assemblies, **1**·$[\mathbf{2}]_n$ ($n = 1$–3), in solution by simply adjusting the stoichiometry of **2**. Each structure was unequivocally verified in the solid state by X-ray crystallographic analysis. The finding that the mode of the spontaneous assembly of **1** and **2** can be precisely controlled in solution suggests the possibility of selective use of **1**·$[ArOH]_n$ ($n = 1$–3) as a requisite catalyst for target organic transformations and could also provide a expedient means to gain insights into the structural integrity of the reactive intermediate.



Scheme 1. Chiral *P*-spiro tetraaminophosphonium aryloxide assembly **1**·$[ArOH]_3$.

Initially, ^{31}P NMR spectroscopic analysis of isolated **1**·$[\mathbf{2}]_3$ was performed in toluene (10.0 mM) at −98 °C, and a sharp singlet was observed at $\delta = 32.4$ ppm (Figure 1a, ●). To assess the validity of assigning this signal to **1**·$[\mathbf{2}]_3$ even in solution, the stoichiometry in generating the same signal in situ from iminophosphorane **1** and **2** was probed by varying the amount of **2** to **1**; this method led to some rather surprising yet interesting observations. For a toluene solution of **1** (Figure 1b, ▲) treated with a half equivalent of **2**, two separate signals were detected, at $\delta = 45.0$ and 35.5 ppm (Figure 1c). The new signal that appeared upfield (■) was essentially different from that observed in the case of **1**·$[\mathbf{2}]_3$. As this signal grew as a single peak at $\delta = 35.4$ ppm upon introducing one equivalent of **2** (Figure 1d), it could be assigned to **1**·$[\mathbf{2}]_1$, that is, the simplest ion pair of aminophosphonium cation **1**·H with aryloxide (Figure 2a). Furthermore, treatment of **1** with one and a half equivalents of **2** resulted in the appearance of a new upfield signal with a decrease in the resonance corresponding to **1**·$[\mathbf{2}]_1$ (Figure 1e), and it became an only detectable peak at $\delta = 33.9$ ppm when the amount of **2** was increased to two equivalents (Figure 1f, ▼). This signal was still different from that observed in the case of **1**·$[\mathbf{2}]_3$, and it could correspond to another molecular assembly such as **1**·$[\mathbf{2}]_2$ (▼, Figure 2b). Indeed, a similar tendency was observed when two and a half equivalents of **2** were added (Figure 1g), and the spectrum measured after the treatment of **1** with three equivalents of **2** showed a sharp singlet at $\delta = 32.4$ ppm (Figure 1h, ●), which was identical to the chemical shift observed for isolated **1**·$[\mathbf{2}]_3$. Consequently, there seems to exist a stepwise equilibrium

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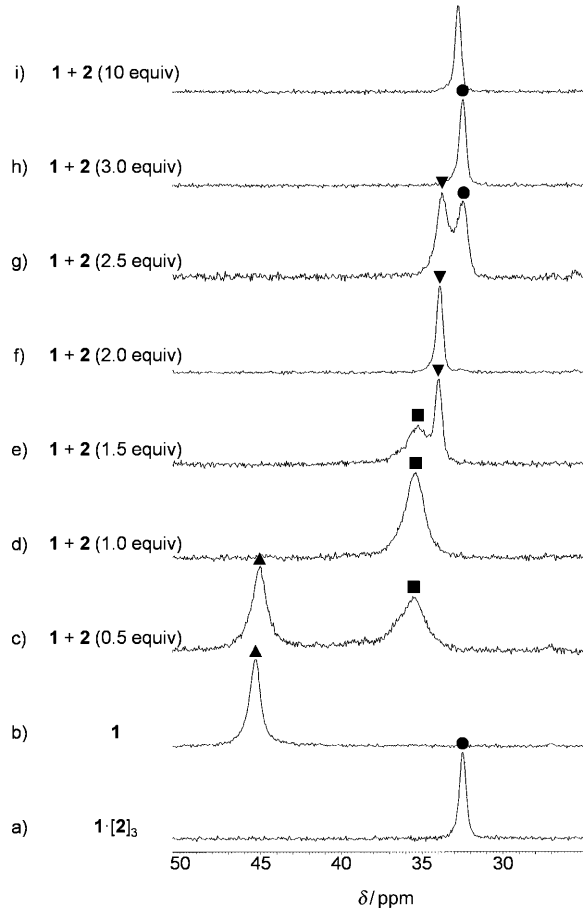


Figure 1. ^{31}P NMR spectra of in situ generated molecular assemblies of triaminoiminophosphorane **1** and 3,5-$Cl_2C_6H_3OH$ (**2**) at −98 °C in toluene.

between **1** and **1**·[**2**]$_3$ depending on the stoichiometry of **2**, and each assembly could be predominantly organized under the influence of a requisite least equivalent (1–3 equiv) of **2**. It should be noted that the presence of large excess of **2** did not significantly affect the mode of assembly (Figure 1 i), and thus **1**·[**2**]$_3$ would be a terminal assembly.

On the basis of these observations, we attempted to obtain further compelling evidence for the intervention of each plausible mode of assembly. Fortunately, we found that each molecular assembly was sufficiently stable to be crystallized from a solution of **1** and **2** in an appropriate molar ratio. The X-ray diffraction analyses of these single crystals show the three dimensional structures of **1**·[**2**]$_1$, **1**·[**2**]$_2$ and **1**·[**2**]$_3$ (ORTEP diagrams in Figure 2).[6] Moreover, the ^{31}P NMR spectroscopic analyses of toluene solutions prepared from each single crystal at −98 °C provided a signal at exactly the same chemical shift as that of the in situ generated assembly. These results unambiguously confirm the contribution of the stepwise equilibrium and suggest that k_1 is substantially greater than k_2 for all the steps. Thus, it would be possible to precisely control the mode of the spontaneous assemblies of chiral tetraaminophosphonium aryloxide–arylhydroxide(s) in solution by adjusting the stoichiometry of each component.

Having been able to selectively utilize **1**·[ArOH]$_n$ (n = 1–3) as a catalyst, we evaluated the synthetic relevance of this possibility in the conjugate addition of 2-unsubstituted azlactone **3** to cinnamoyl benzotriazole (Figure 3).[4] The reactions were carried out at −60 °C in toluene, with catalysts prepared by the treatment of **1** (1 mol %) with **2** (n mol %, n = 0–3). As we presumed, the enantioselectivity was significantly enhanced as the number of **2** incorporated in the catalyst assembly was increased, and reached 90 % *ee* when **1**·[**2**]$_3$ was employed. Notably, however, the selectivity was almost saturated under these conditions after 2 mol % of **2** (n = 2) was used for the catalyst preparation,[7] in sharp contrast to the nearly proportional increase from 51 % *ee* with **1** (n = 0) to 89 % *ee* with **1**·[**2**]$_2$ (n = 2). This observation provides an important clue to the nature of the assembly of the reactive intermediate (Scheme 2).[8]

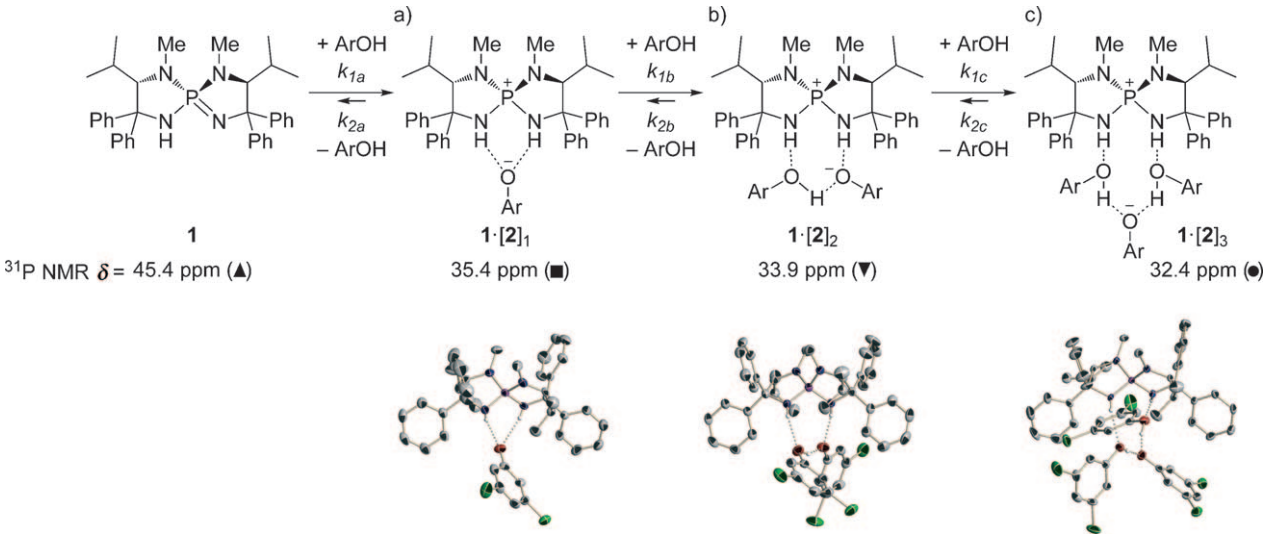
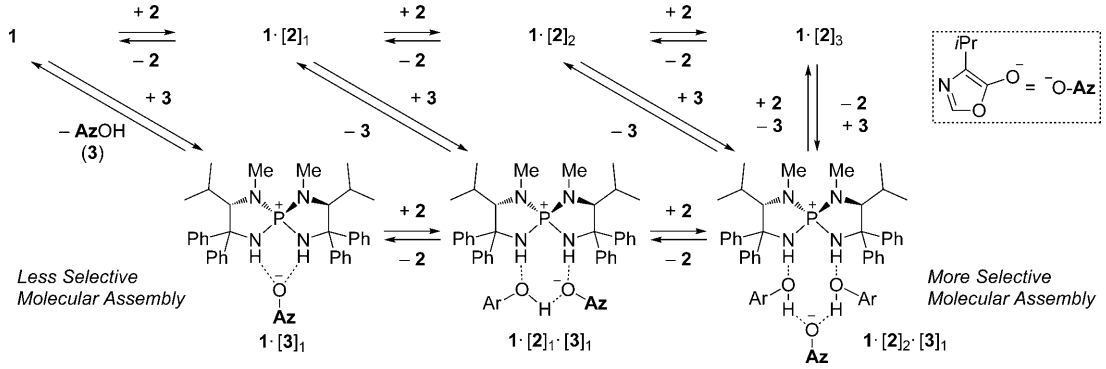


Figure 2. Equilibrium between molecular assemblies **1**·[**2**]$_n$ (n = 1–3, Ar = 3,5-$Cl_2C_6H_3$) and ORTEP diagrams of each assembly. Calculated hydrogen atoms are omitted for clarity. P purple, N blue, O red, Cl green, C gray.



Scheme 2. Plausible molecular assemblies of **1**, **2**, and azlactone **3** in solution (Ar = 3,5-$Cl_2C_6H_3$).

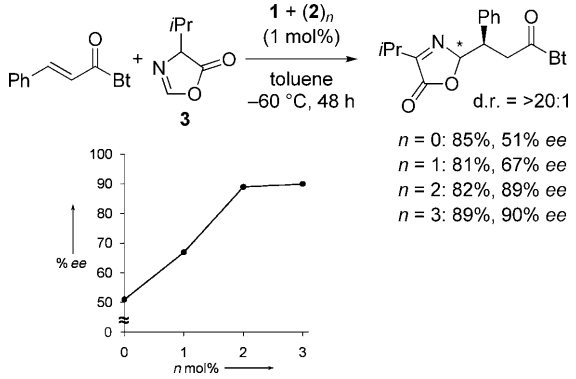


Figure 3. Asymmetric conjugate addition of **3** to cinnamoyl acylbenzotriazole (Bt = benzotriazol-1-yl) catalyzed by in situ generated chiral *P*-spiro tetraaminophosphonium aryloxide assembly **1**·[**2**]$_n$ (n = 0–3).

In the reactions we attempted with **1**·[**2**]$_n$ (n = 0–2), initial deprotonation of **3** by **1**·[**2**]$_n$ would give a reactive intermediate incorporating an enolate of **3** ($^-$O-**Az**) in the form of **1**·[**2**]$_n$·[**3**]$_1$, each of which was responsible for the stereochemical control in its addition to cinnamoyl benzotriazole. Judging from the fact that **1**·[**2**]$_3$ is a terminal assembly even in the presence of excess **2**, the reaction under the influence of **1**·[**2**]$_3$ would involve the generation of **1**·[**2**]$_2$·[**3**]$_1$ through the formal replacement of **2** by **3** in the deprotonation event. Thus, both **1**·[**2**]$_2$ and **1**·[**2**]$_3$, upon reacting with **3**, would afford the same molecular assembly, **1**·[**2**]$_2$·[**3**]$_1$, thus accounting for the observed similar enantioselectivity.

In conclusion, by using low-temperature ^{31}P NMR spectroscopy and X-ray crystallographic analysis, we have successfully revealed that chiral *P*-spiro iminophosphorane **1** and 3,5-$Cl_2C_6H_3OH$ (**2**) assemble into three types of discrete molecular associations, **1**·[**2**]$_1$, **1**·[**2**]$_2$, and **1**·[**2**]$_3$ in a stepwise manner depending on the stoichiometry of **2**. This process enables a facile and selective generation of a requisite mode of assembly in solution, which could not only amplify the structural diversity of this type of chiral supramolecular catalysts but also constitute a basis for the mechanistic elucidation of their catalyses as demonstrated in the asymmetric conjugate addition of 2-unsubstituted azlactone **3** to cinnamoyl benzotriazol. The present study offers a new, yet fruitful, opportunity for the design and application of supramolecularly assembled, chiral organic molecular catalysts.

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[6] See Supporting Information for details of X-ray analysis, particularly in view of the presence of another H_2O-bridged structure in the unit cells of **1**·[**2**]$_1$ and **1**·[**2**]$_2$, respectively. CCDC 801437 (**1**·[**2**]$_1$), CCDC 801438 (**1**·[**2**]$_2$), CCDC 801439 (**1**·[**2**]$_3$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[7] When the reaction was conducted at higher temperature (−40 °C), use of **1**·[**2**]$_3$ was crucial for attaining a highest level of enantioselectivity[4] probably because an excess amount of **2** would be necessary for shifting the equilibrium to the terminal assembly in order to ensure the intervention of **1**·[**2**]$_2$·[**3**]$_1$.
[8] Attempts to detect the equilibrium between the enolate assemblies by the low temperature ^{31}P NMR analysis were unsuccessful primarily due to the higher pK_a of **3** than that of **2**.

