Organocatalysis

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Activation of Carboxylic Acids in Asymmetric Organocatalysis**

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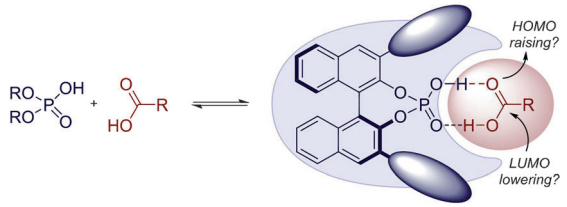
Abstract: *Organocatalysis, catalysis using small organic molecules, has recently evolved into a general approach for asymmetric synthesis, complementing both metal catalysis and biocatalysis.[1] Its success relies to a large extent upon the introduction of novel and generic activation modes.[2] Remarkably though, while carboxylic acids have been used as catalyst directing groups in supramolecular transition-metal catalysis,[3] a general and well-defined activation mode for this useful and abundant substance class is still lacking. Herein we propose the heterodimeric association of carboxylic acids with chiral phosphoric acid catalysts as a new activation principle for organocatalysis. This self-assembly increases both the acidity of the phosphoric acid catalyst and the reactivity of the carboxylic acid. To illustrate this principle, we apply our concept in a general and highly enantioselective catalytic aziridine-opening reaction with carboxylic acids as nucleophiles.*

Carboxylic acids, including all amino acids, tartaric acid, lactic acid, mandelic acid, and pyruvic acid, to name just a few, are ubiquitous molecules in life. They feature both a hydrogen-bond donor and a hydrogen-bond acceptor, which can stabilize each other by self-association. The dimerization of carboxylic acids was first observed at the beginning of the 20th century and is now well appreciated to be a general phenomenon.[4] In the middle of the last century, a similar interaction was observed for phosphoric acid diesters and the strength of the dimerization was found to be even larger for these species on account of the dipolar nature of the P=O bond and their higher acidity.[5,6] In the meantime, chiral binaphthol-derived phosphoric acid diesters have been used as remarkably general asymmetric Brønsted acid catalysts that activate not only imines but also certain carbonyl compounds and related substrates.[7] Interestingly, carboxylic acids have not previously been utilized as substrates in asymmetric phosphoric acid catalysis. We speculated that in mixtures of phosphoric acids and carboxylic acids, in addition to the two expected homodimers, an equilibrium favoring the corresponding and previously undescribed heterodimer may exist. We were intrigued about the nature of the electronic structure of such a hypothetical heterodimer. On the one hand, protonation of the carboxylic acid is expected to lower its LUMO, generating a more reactive electrophile. On the other hand, the well-established basicity of the oxygen atom within the P=O bond of the phosphoric acid catalyst should lead to a partial deprotonation of the carboxylic acid, which would increase the energy of the HOMO and provide a more nucleophilic species. Potentially, both activation modes could even occur simultaneously (Scheme 1).



Scheme 1. Activation of carboxylic acids by heterodimerization with phosphoric acids.

The concept proposed here originated from the observation that in contrast to simple and small phosphoric acid diesters, which readily form dimers,[8] their sterically much more demanding binol-derived congeners are generally monomeric in solution. Presumably, their dimerization is sterically hindered. Dimerization also appears to be difficult in the solid state.[9] For example, in the crystal structure of the popular phosphoric acid catalyst TRIP, a water molecule is required to bridge the dimer. On this basis, we hypothesized that the heterodimerization with a small carboxylic acid, which could enter the catalytic pocket in the absence of repulsive forces, might be a highly favorable process.

Indeed, initial NMR studies supported our hypothesis (for details, see the Supporting Information). A stoichiometric amount of benzoic acid significantly shifted the signals of TRIP in the ^{1}H NMR spectrum. In addition, the signal of the phosphoric acid in the ^{31}P NMR spectrum was shifted considerably downfield. To gain further evidence of the suggested heterodimerization, diffusion-ordered spectroscopy (DOSY) measurements were performed.[10] The translational diffusion coefficient of the two molecules significantly decreased upon self-assembly. As expected, the effect on the smaller carboxylic acid is larger due to the higher variation of its hydrodynamic volume (Figure 1 a).

We were also able to determine the binding isotherms of the association of TRIP with benzoic acid and with acetic acid by following the shift of the phosphorus signal in a ^{31}P NMR titration experiment (Figure 1 b). The constants K_a were

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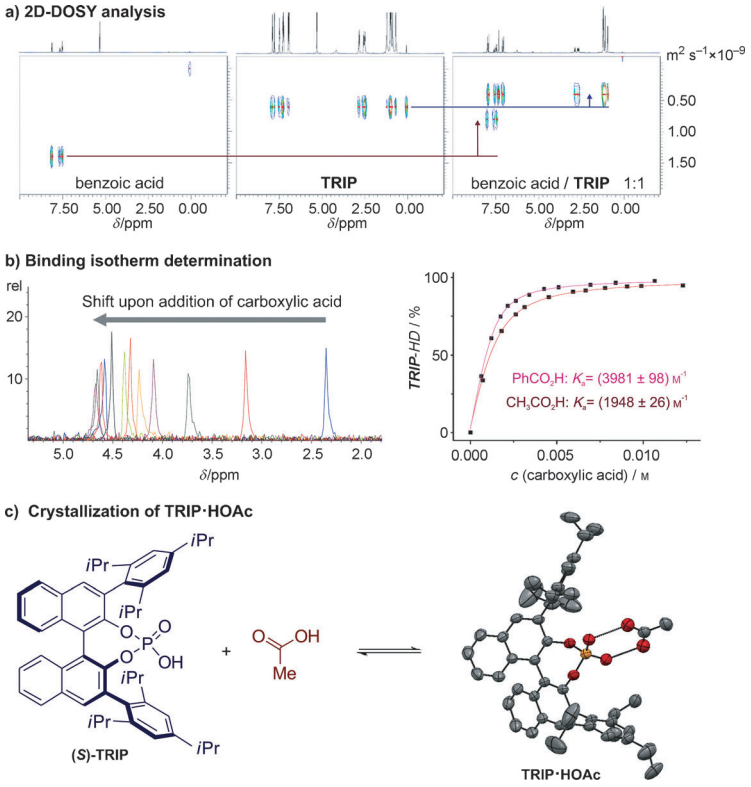


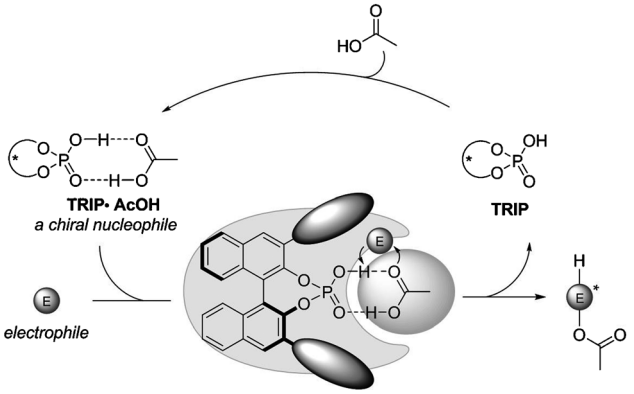
Figure 1. Physical characterization: a) 2D-DOSY analysis; b) Binding isotherm determination; c) Crystal structure of TRIP·AcOH. TRIP-HD = heterodimer of TRIP with a carboxylic acid.

determined by a nonlinear regression approach in which the heterodimer was treated as a 1:1 host–guest system.[11] The measured K_a values (TRIP·BzOH $K_a = (3981 \pm 98)\,M^{-1}$, TRIP·AcOH $K_a = (1948 \pm 26)\,M^{-1}$) are consistent with this kind of interaction and lie between the binding constants for the homodimerization of carboxylic acids (10–100 M^{-1}) and those of phosphoric acids (usually above $10^5\,M^{-1}$). The stronger association with benzoic acid may be explained on the basis of the dual contribution of the aromatic ring, which increases the availability of the lone pairs on the carbonyl moiety and the acidity of the hydroxy group. A final confirmation of heterodimer formation was obtained by cocrystallizing acetic acid and TRIP, which gave a crystal suitable for X-ray diffraction. The resulting structure (Figure 1c) shows that this interaction is not only favored in solution, but also in the solid state.

Interestingly, carboxylic acids have previously been used as additives in chiral phosphoric acid catalyzed asymmetric reactions. In 2006, the Akiyama group described the beneficial effect of a stoichiometric amount of acetic acid in a TRIP-catalyzed aza-Diels–Alder reaction without further investigating its role.[12] Later Rueping and co-workers described a Mannich reaction, in which acetic acid was crucial for the reactivity and suggested that its role would be to promote the enolization of the nucleophile, while the chiral phosphoric acid was suggested to activate the electrophile.[13]

Although other explanations cannot be excluded, we propose here that in both cases the more acidic heterodimer served as the actual catalyst (heteroconjugation phenomenon).[14–16] Moreover, as the association has not previously been recognized, its real potential, especially for the activation of carboxylic acids, has remained untapped. We were particularly intrigued by the upfield shift of the proton signals in the NMR spectrum of the carboxylic acids. This appears to indicate the somewhat counterintuitive possibility that heterodimerization with a phosphoric acid raises the energy of the HOMO. In other words, the (stronger) phosphoric acid would formally behave like a base within the dimer. Thus, upon self-assembly a synergistic activation may take place: the nucleophilicity of the carboxylic acid and the acidity of the catalyst are both increased. This observation suggested to us the possibility of designing a catalytic system in which the heterodimeric species acts as a source of nucleophilic carboxylic acids (Scheme 2).

Specifically, we decided to investigate whether the system could facilitate an asymmetric ring opening of aziridines to afford protected amino alcohols. Molecules containing a vicinal amino alcohol moiety are interesting synthetic targets, due to their abundance in naturally occurring molecules and pharmacologically active compounds, and their application as chiral ligands, auxiliaries, and catalysts in asymmetric transformations.[17,18] Stereoselective transformations of aziridines have



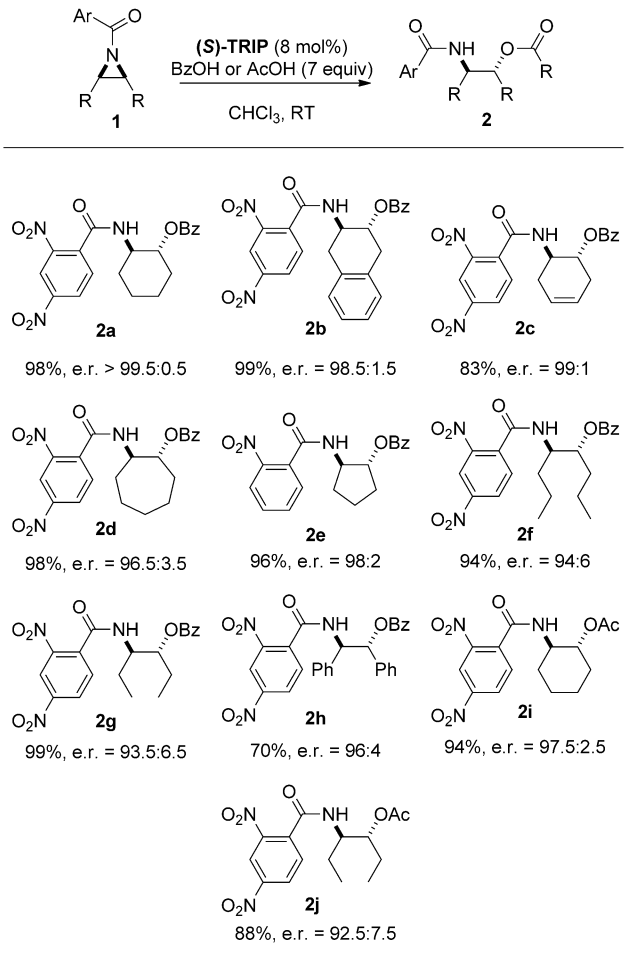
Scheme 2. A catalytic cycle that utilizes TRIP·AcOH as a chiral and nucleophilic source of AcOH.

been widely investigated in the last few years but an asymmetric catalytic conversion that leads to amino alcohols, that is, a hydrolytic kinetic resolution or desymmetrization, has not yet been developed.[19,20] We therefore anticipated that the designed reaction would be an ideal testing ground for our new carboxylic acid activation.

Initially, we focused our attention on the development of a desymmetrization strategy for *meso*-aziridines with benzoic acid as the nucleophile and the designed system was indeed found to be effective in the transformation. We selected an electron-poor benzamide moiety with two nitro groups in the

ortho and *para* positions as the protecting group since the simple one-step deprotection of both ester and amide moieties of the products would afford the "naked" 1,2-amino alcohols. Optimization of the reaction conditions (see the Supporting Information) revealed that the transformation proceeds smoothly when the association between the phosphoric acid catalyst and the carboxylic acid is promoted by an excess of the carboxylic acid. Degradation of the catalyst by means of direct attack of the phosphate on the aziridine was observed when equilibrium was not reached.[21] With seven equivalents of benzoic acid, ring opening of the six-membered-ring-fused aziridine **1a** to give the expected protected amino alcohol **2a** occurred with quantitative yield and essentially perfect enantioselectivity (98% yield, e.r. > 99.5:0.5, Scheme 3).

Several different cyclic and acyclic *meso*-aziridines **1a–h** were successfully employed in the transformation. The corresponding cyclic products **2a–e** were generally obtained with good to excellent yields and enantioselectivities. Importantly, the methodology seems to be only slightly influenced by the ring strain and the size of the starting materials.



Scheme 3. Reactions were performed on a 0.2 mmol scale. Substrate **1a** was reacted on a 1 mmol scale. Substrate **1e** was reacted at −10 °C. The loading of AcOH was increased to 10 equivalents in the reactions to products **2i,j**. Enantiomeric ratios were determined by HPLC on a chiral stationary phase.

Compound **2e**, bearing only one nitro group on the benzamide moiety, required lower reaction temperature (−10 °C) and more dilute conditions.

Acyclic substrates were also tolerated although with a slight loss in stereocontrol. Protected amino alcohols **2f,g** could be obtained in excellent yield and good enantiocontrol when the reaction was simply performed under more dilute conditions. Notably, product **2h** was also delivered smoothly from the challenging *cis*-stilbene-derived aziridine **1h** in good yield and excellent stereoselectivity. The reaction also tolerates other carboxylic acids. For example, acetic acid gives similarly high yield and enantioselectivity (products **2i** and **2j**). The longer reaction time required and higher nucleophile concentration may suggest that the affinity between TRIP and the carboxylic acid plays a role in the transformation.

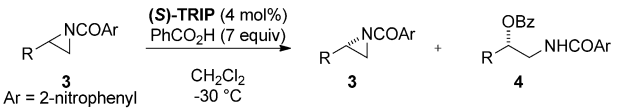
Chiral terminal aziridines are considered linchpins for the synthesis of important building blocks such as 1,2-amino alcohols, 1,2-diamines, and 1,2-amino thiols.[22] Therefore, having shown the potential of TRIP/carboxylic acid heterodimers in the desymmetrization of *meso*-aziridines, we decided to also apply our activation concept to the kinetic resolution of racemic terminal aziridines. It is noteworthy that in this transformation both the product and the unreacted starting material are potentially useful.

We found that our catalyst system was indeed also effective in this reaction. Lowering the temperature to −30 °C and employing terminal aziridines with only one nitro group in the benzamide protecting group, we could obtain the desired products and the unreacted starting materials with excellent selectivity factors ($S = 37$–51, Table 1). The preliminary scope of this transformation is shown in Table 1. Not only the linear-chain aziridines **3a–c** proved to be suitable for the resolution, but even the branched compound **3d** reacted smoothly.

As expected for ring-opening reactions occurring in acidic media, the nucleophilic attack exclusively occurs on the internal carbon of the aziridine substrate. The reason for the perfect regioselectivity may be due to a partial positive charge on the aziridine fragment in the transition state (vide infra) and no regioisomeric product could be detected in any case.

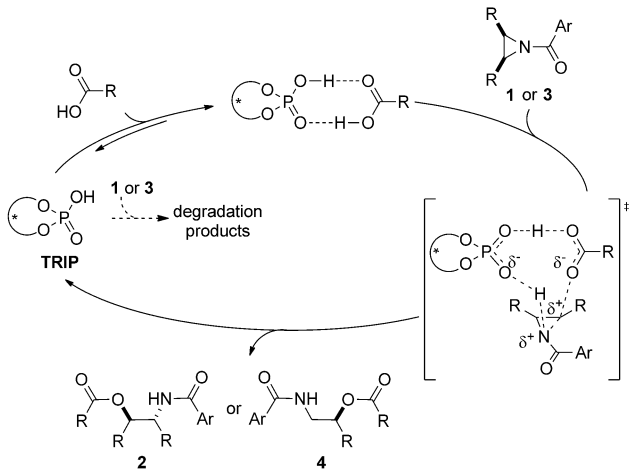
On the basis of the results obtained during our investigation, a catalytic cycle can be proposed (Scheme 4). Accordingly, the initial equilibrium between the free phosphoric acid and the heterodimer is shifted to the right due the high concentration of the carboxylic acid. This saturation of TRIP suppresses its degradation through reaction with the aziridine. Thus, the carboxylic acid plays a dual role in the reaction by both performing the ring opening as well as protecting the catalyst from degradation. The heterodimer then engages in the nucleophilic attack, which possibly occurs through a concerted transition state, in which the aziridine is subject to additional Brønsted acid activation. While the heterodimer has in principle two different possible nucleophilic sites, the carboxylate and the phosphate, the reactivity of the phosphate moiety is sterically hindered. Based on the experimental results we speculate that the reaction might occur by means of an asynchronous S_N2 pathway. The presence of a carbocationic species in the catalytic cycle is unlikely because of the exclusivity of the *trans* product in the

Table 1: Kinetic resolution of terminal aziridines.[a]



Entry	Aziridine	Product	Yield [%]	e.r.[b]	S[c]
1	*rac*-**3a**	(*S*)-**4a**	48	92.5:7.5	48
		(*S*)-**3a**	42	98:2	
2	*rac*-**3b**	(*S*)-**4b**	49	94:6	50
		(*S*)-**3b**	46	95.5:4.5	
3	*rac*-**3c**	(*S*)-**4c**	51	92.5:7.5	51
		(*S*)-**3c**	44	98.5:1.5	
4	*rac*-**3d**	(*S*)-**4d**	28	96:4	37
		(*S*)-**3d**	58	71.5:28.5	

[a] Reactions were performed on 0.1 mmol scale in 0.016 M solution. [b] Determined by HPLC on a chiral stationary phase. [c] Measured by Kagan's equation.



Scheme 4. Proposed catalytic cycle for the TRIP·RCO_2H-mediated ring opening of aziridines.

desymmetrization, while the complete regioselectivity of the kinetic resolution indicates the presence of a strong localized δ^+ charge at the reacting carbon center (for mechanistic investigations see the Supporting Information).

As suggested above, the success of organocatalysis relies on the possibility to design novel transformations based on established activation modes. Our activation of carboxylic acids is not an exception and it is potentially broadly applicable. A related catalytic system has been developed concurrently in our laboratories for the first asymmetric organocatalytic carboxylysis of epoxides.[23]

In conclusion a new concept for the activation of carboxylic acids in asymmetric catalysis has been designed and realized, which involves their heterodimerization with chiral sterically hindered phosphoric acids. This interaction may open new perspectives by not only providing a new highly acidic motif for asymmetric Brønsted acid catalysis, but also by providing a generic activation mode for carboxylic acids in organocatalysis. The system was shown to be effective in the first highly enantioselective ring opening of aziridines to afford protected amino alcohols. Further investigations to define the scope of this catalyst system are currently in progress in our laboratories.

Experimental Section

Catalytic asymmetric synthesis of **2a**: In a dried screw-cap vial a solution of benzoic acid (855 mg, 7 equiv) and TRIP (60 mg, 8 mol %) was prepared in chloroform (6 mL). The mixture was stirred at the reaction temperature for 20 min and then a solution of the aziridine **1a** (291 mg, 1 mmol) in chloroform (2 mL) was added at once. When the reaction was determined to be complete (thin-layer chromatography), the reaction mixture was diluted with hexanes/MTBE (1:1) and the products were directly purified by column chromatography. For complete experimental details and characterization of compounds, see the Supporting Information.

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