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Phosphoric Acid Based Heterodimers in Asymmetric Catalysis

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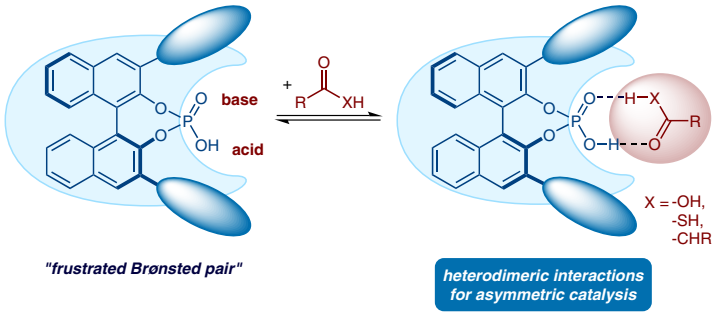

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Abstract Chiral phosphoric acid diesters arguably constitute the most exploited class of catalysts in asymmetric Brønsted acid catalysis. Despite being highly investigated for their acidic properties, these compounds display an amphoteric nature, which has instead been considerably overlooked. The potential of this dichotomous polarity has recently been disclosed and applied to the development of novel reaction modes in organocatalysis. In this account, we present our recent advances in this area, focusing on the establishment of heterodimeric interactions toward the nucleophilic activation of carboxylic acids, thiocarboxylic acids and ketones (via their enols) in asymmetric transformations.

Key words phosphoric acids, non-covalent catalysis, heterodimeric self-assembly, carboxylic acids, enol catalysis, branched ketones

1 Introduction

The year 2004 marked the beginning of an exciting era within asymmetric catalysis. Enantiopure BINOL-derived phosphoric acids were introduced for the first time as powerful organocatalysts and have since helped realize an ever increasing number of catalytic asymmetric transformations of great elegance and practical utility.[1,2] The new field of asymmetric Brønsted acid organocatalysis was born.[3] The enormous potential of this area is not only apparent from the many publications that currently appear,[4] but also from imagining the vast number of transformations which can be catalyzed by Brønsted acids, *e.g.* aldol-, Mannich-, Michael-, Diels–Alder-, Friedel–Crafts-, or Strecker reactions, and a plethora of other transformations proceeding *via* iminium ions, oxonium ions, or carbenium ions in general.[5] All of these important and useful reactions, at least in principle, can now be catalyzed enantioselectively with chiral Brønsted acid catalysts. Arguably, asymmetric Brønsted acid organocatalysis has the potential to even become the most general approach to asymmetric synthesis. But how do chiral phosphoric acids work? Are they really just 'simple' Brønsted acids that protonate substrates,[6] thus promoting chiral counteranion-directed asymmetric transformations, as it is commonly believed? Probably not. It is currently becoming more and more recognized that phosphoric acid diesters are in fact bifunctional catalysts, with the hydroxyl group acting as an acid and the oxo moiety acting as a base. Interestingly, and perhaps less appreciated, the basicity of the oxo functional group is relatively high and thus highly prone to hydrogen bonding and deprotonation.[7] Importantly however, in sterically demanding catalysts (e.g. 3,3′-disubstituted BINOL-derived catalysts), a classical donor–acceptor stabilization is prevented due to their intrinsic structural features, making these molecules effectively 'frustrated' Brønsted pairs.[8] In fact, an intramolecular hydrogen bond within the phosphate moiety (between the P=O and P–OH functionalities) is geometrically precluded. At the same time an intermolecular homodimerization is sterically disfavored (Scheme 1). However, these features generate a characteristic chiral pocket in which heterodimeric associations with small amphoteric molecules are thermodynamically highly favored, thus being particularly effective.

The aim of this account is to illustrate that these non-covalent self-assemblies can actually be beneficial for reactivity and define key elements for the design of new and generic reaction modes in organocatalysis. We herein show how the investigation of these concepts has led to the discovery of a novel activation of carboxylic acids in Brønsted acid catalysis, and how this has allowed the development of a number of useful epoxide and aziridine openings.[4k,9] Furthermore, we describe how this concept has been expanded to other functional groups, ultimately leading to the proposal of 'enol catalysis', which is based upon the ability of phosphoric acid catalysts to promote the enolization of simple, unactivated ketones, enabling their direct and general use as nucleophiles in asymmetric catalysis.[10]

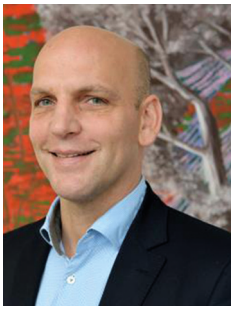
2 Discovery of Heterodimeric Self-Assemblies

In the middle of the last century, investigations by Peppard and co-workers revealed that phosphoric acid diesters exhibit a remarkable tendency to homodimerize in non-polar media.[11] Nowadays this type of self-assembly is well established and it is appreciated to be even more favored than the analogous dimerization tendency of carboxylic acids.[12,13] Surprisingly however, at the onset of our investigation in 2012, the homo-association of BINOL-derived phosphoric acid catalysts had never been observed. This is particularly puzzling considering that apolar solvents, which are usually used in asymmetric Brønsted acid catalyzed re-

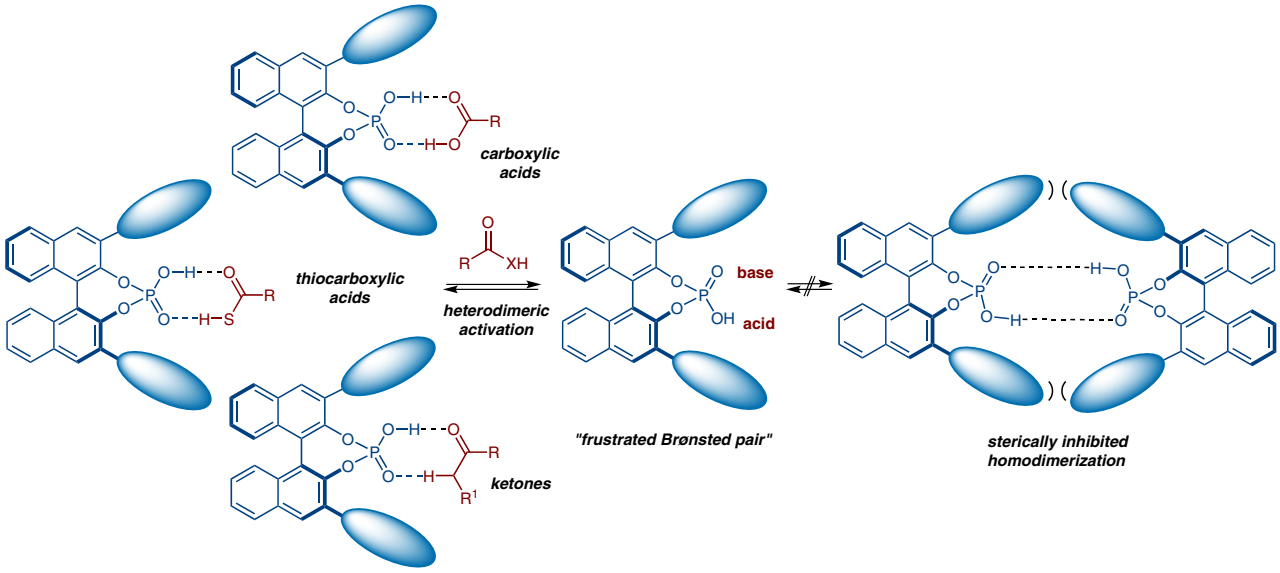
Biographical Sketches

Mattia Riccardo Monaco was born in Naples, Italy, in 1987. He studied Chemistry at 'Sapienza' University of Rome, where he took his first steps in the field of organocatalysis in the research group of Dr. Marco Bella. After obtaining his Master's degree in 2011, he joined the group of Prof. Dr. Benjamin List at the Max-Planck-Institut für Kohlenforschung, focusing his doctoral studies on the development of heterodimeric activation strategies in Brønsted acid catalysis. In 2016, having obtained his Ph.D., he moved to Zürich, Switzerland, where he joined the group of Prof. Dr. Helma Wennemers as a post-doctoral researcher.

Gabriele Pupo was born in Torino, Italy, in 1989. He studied chemistry at the Università degli Studi di Torino, Italy, where he received his Master's degree in Advanced Chemical Methodologies in 2012 under the supervision of Prof. Cristina Prandi. In 2013, he started his Ph.D. studies as a Kekulé fellow of the Fonds der Chemischen Industrie in the group of Prof. Dr. Benjamin List, where he is currently working on novel activation modes in Brønsted acid catalysis.



Benjamin List was born in 1968 in Frankfurt, Germany. He graduated from Freie University Berlin (1993) and received his Ph.D. (1997) from the University of Frankfurt. After postdoctoral studies (1997–1998) as a Feodor Lynen Fellow of the Alexander von Humboldt foundation at The Scripps Research Institute, he became a Tenure Track Assistant Professor at the same institute in January 1999. Subsequently, he developed the first proline-catalyzed asymmetric intermolecular aldol-, Mannich-, Michael-, and α-amination reactions. He moved to the Max-Planck-Institut für Kohlenforschung in 2003 as a group leader (until 2004), and became director in 2005. He was the managing director of the institute from 2012 until 2014, and has served as an honorary professor at the University of Cologne since 2004. His research interests are new catalysis concepts and chemical synthesis in general. He has pioneered and contributed several concepts including aminocatalysis, enamine catalysis, and asymmetric-counteranion-directed catalysis (ACDC). His accomplishments have been recognized with several awards including the Astra Zeneca Research Award in Organic Chemistry, the Otto Bayer Award, the Mukaiyama Award, the Arthur C. Cope Scholar Award, and most recently, the Leibniz Award.



Scheme 1 Chiral sterically demanding phosphoric acids: inhibited homodimerization and novel heterodimeric activation

actions not only favor the formation of tight ion-pairs, but should also support this type of dimeric self-assembly. Presumably, the homo-association is hindered with encumbered phosphoric acids, which, in contrast to their less sterically demanding congeners, are monomers in solution. However, in the solid state, the dimerization tendency of the 3,3′-bis(2,4,6-triisopropyl-phenyl)-BINOL-derived phosphoric acid (**TRIP**), a frequently employed acid catalyst, can be observed. A molecule of water is incorporated in a hydrogen-bonding network bridging within the homodimer (Figure 1).[14] On this basis, we hypothesized that a small-sized amphoteric molecule (i.e., a carboxylic acid) may, in solution, enter the pocket of the catalyst, thus providing stabilization in the absence of large repulsive forces.

We commenced our studies focusing on the detection of an interaction between **TRIP** (**1a**) and acetic acid (**2a**) or benzoic acid (**2b**) (Scheme 2).[9a] Indeed, initial NMR measurements showed that the resonance signals of the phosphoric acid molecule are strongly influenced by the presence of the carboxylic acid in solution (Scheme 2a).

In fact, a remarkable shift downfield of the phosphorus signal in the ^{31}P NMR spectrum was observed, and a careful examination of the ^{1}H NMR spectrum suggested the presence of the guest molecule within the catalyst pocket. As shown in Scheme 2a, the overlap of non-equivalent proton signals of the 3-3′ substituents is cleared in the presence of acetic acid, thus suggesting a lower rotational freedom of the C–C bond between the naphthalene backbone and the aryl moiety (2.5–3.0 ppm; 6.9–7.1 ppm).[15] Intrigued by this qualitative analysis, a DOSY (diffusion-ordered spectroscopy) experiment was performed to evaluate the change of the hydrodynamic volume of the solvated species in solution.[16] The translational diffusion coefficients of the two in-

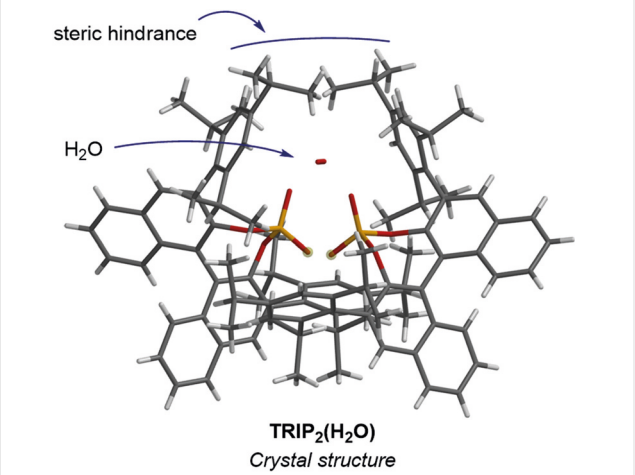
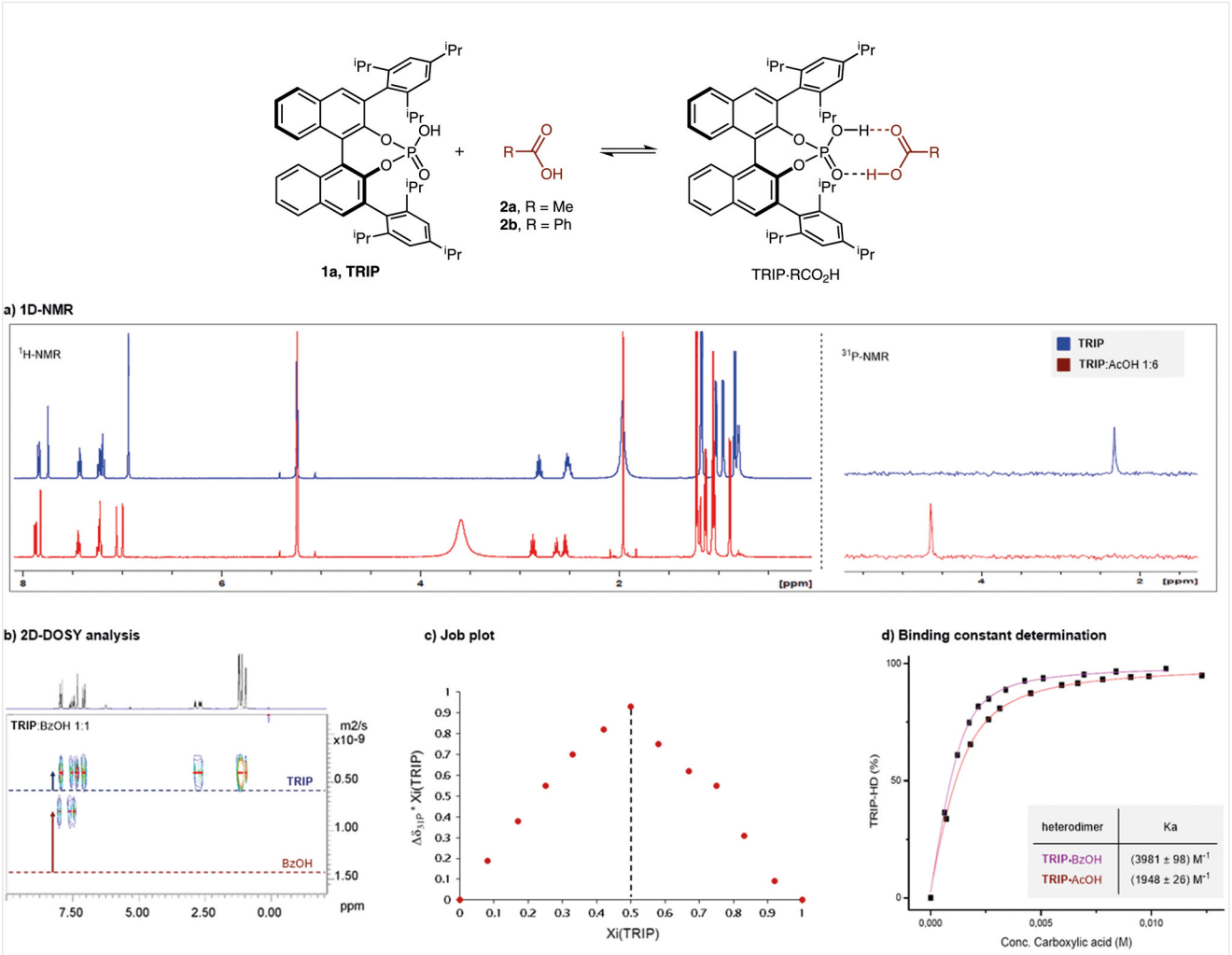


Figure 1 Crystal structure of (*R*)-**TRIP** phosphoric acid

teracting acids were found to be significantly lowered with respect to the values measured on two previous independent analyses, giving an additional confirmation to our hypothesis (Scheme 2b). As expected, the change is larger for the smaller carboxylic acid molecule than for **TRIP**, witnessing the higher variation of its hydrodynamic volume. Next the stoichiometry of the host–guest complexation was assigned to be 1:1 using the method of continuous variations (Job plot) (Scheme 2c) and the determination of the association strength was obtained by titration of the shift of the phosphorus signal in the ^{31}P NMR spectrum upon addition of the carboxylic acid (Scheme 2d).[17,18] The binding isotherms for the formation of dimers **TRIP**–AcOH and **TRIP**–BzOH were plotted and the corresponding association con-



Scheme 2 (a) NMR measurement of **TRIP** (blue) and of a mixture of **TRIP**–AcOH (1:6) (red). (b) 2D-DOSY measurement of a mixture of **TRIP**–BzOH (1:1) which shows the change of the diffusion coefficients of the species with respect to the normal values. (c) Job plot of the association **TRIP**–BzOH. (d) Binding isotherms for the dimerization of **TRIP** with BzOH (magenta) and AcOH (red), and the relative binding constants obtained *via* the linear regression approach

stants were derived *via* a non-linear regression approach. Remarkably, the values obtained for our heterodimers significantly matched with expectations [K_a (**TRIP**–AcOH) = 1948 M^{-1}; K_a (**TRIP**–BzOH) = 3981 M^{-1}), lying between those of carboxylic acid and phosphoric acid homodimers.[19]

Finally, a single crystal X-ray diffraction analysis gave unambiguous confirmation of the nature of the dimeric interaction and suggested that such association is also favored in the solid state (Figure 2).

To the best of our knowledge, this crystal structure represents the first reported example of a defined heterodimeric association between these acidic moieties.[20]

3 Activation of Carboxylic Acids

Encouraged by the qualitative and quantitative characterization of this novel class of heterodimers, we set out an investigation of their reactivity. The field of phosphoric acid catalysis is generally based on the association of the chiral catalyst with basic compounds; however, in sharp contrast, our studies had delivered a novel association in which a second Brønsted acidic molecule was bound. We were intrigued by this combination since no obvious prediction on the reactivity was possible at first sight. Nevertheless, we speculated that an increase of the overall acidity of the species could occur due to a heteroconjugation effect. Upon deprotonation, the additional hydrogen-bonding interaction accounts for a higher stabilization of the phosphate anion.[21] Qualitative findings on the increased overall acidity of

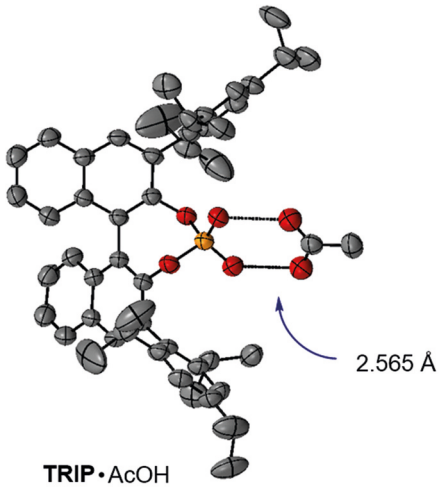
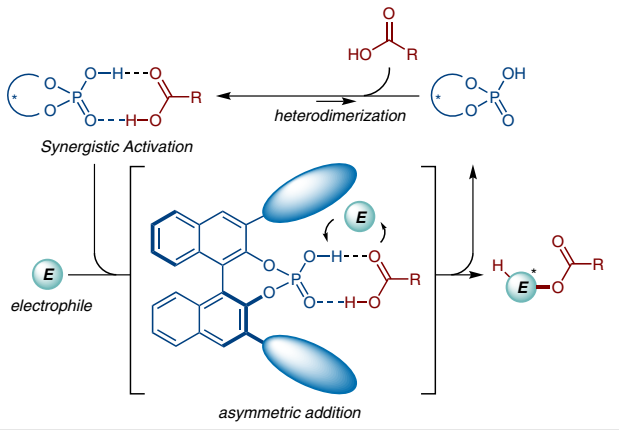


Figure 2 Crystal structure of **TRIP**–AcOH

carboxylic acids with phosphoric acids can be traced back to previous reports by Akiyama, Rueping, and Antilla.[22] Despite the general interest of the scientific community toward enhancement of catalyst activity,[23] our focus was instead mainly aimed at exploring a new activation mode for enantioselective transformations of carboxylic acids. Indeed, our spectroscopic analysis had suggested the significant role of the Lewis basic site of the catalyst in a partial deprotonation, thus revealing a possible activation of the carboxylic acid as a nucleophile. On this basis we investigated a novel approach based on self-assembly organocatalysis, which involves the heterodimeric species as the crucial intermediate. We designed an unprecedented catalytic cycle in which the twofold effect of the heterodimerization is exploited: the increased acidity of the catalyst and the enhanced nucleophilicity of the carboxylic acid (Scheme 3).[9a]



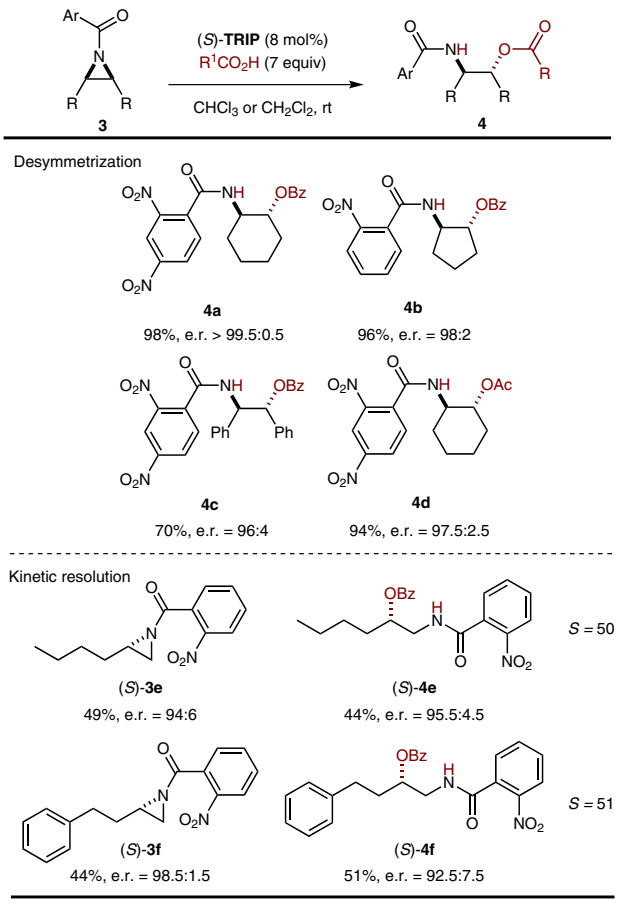
Scheme 3 Design of a catalytic cycle which exploits the heterodimeric activation

The heterodimer is proposed to engage in a nucleophilic attack on the electrophile, which may additionally benefit from hydrogen-bond activation in the transition state. With these ideas in mind, we focused on the investigation of the carboxylysis of aziridines and epoxides, which had previously been elusive electrophiles in asymmetric Brønsted acid catalysis.

3.1 The Enantioselective Carboxylysis of Aziridines

Chiral 1,2-aminoalcohol scaffolds are incorporated in a large variety of biologically active molecules, and therefore the development of novel routes for their enantioselective synthesis is of perpetual interest in medicinal chemistry.[24,25] On the other hand, aziridines are considered key intermediates in stereoselective synthesis and their ring-opening reactions have been widely explored in asymmetric catalysis.[26,27] Interestingly however, no success with oxygen nucleophiles had been reported before our studies. Since aziridines can be readily obtained from the corresponding olefins,[28] an enantioselective conversion into 1,2-aminoalcohols is of significant synthetic value and thus we selected this transformation as testing ground for the novel activation strategy.

The major challenge that our investigation had to overcome was the instability of the catalyst toward these very reactive electrophiles: phosphoric acids are known to react readily with aziridines, leading to an alkylated species and thus preventing the possible turnover in a classical Brønsted acid catalytic cycle.[29] Importantly however, according to our design, the high tendency toward the heterodimerization with carboxylic acids could effectively prevent this undesired catalyst deactivation pathway. Therefore, we initially focused our attention on the ring-opening desymmetrization of *meso*-aziridines **3** possessing an electron-poor 2,4-dinitrobenzamide protecting group due to the possible one-step deprotection of the products into 1,2-aminoalcohols. Indeed, using **TRIP** as the catalyst and benzoic acid as the nucleophile, we observed a very fast formation of the desired products **4** in excellent enantiomeric ratio (Scheme 4). Moreover, a careful analysis of the reaction mixture confirmed that upon saturation of the heterodimeric association with an excess of the carboxylic acid, the above-mentioned catalyst alkylation was completely avoided, highlighting the potential of this novel concept in organocatalysis. Notably, the methodology was found to be general and robust, and to be only slightly affected by the electronic and steric properties of the aziridine substrate. A large variety of *meso*-aziridines, bearing cyclic or acyclic scaffolds, was converted into the corresponding protected aminoalcohols, always in very high yields and enantioselectivity. Aliphatic carboxylic acids, such as acetic acid, were also successfully employed in the transformation giving the product in very high optical purity, albeit with slightly reduced reactivity.



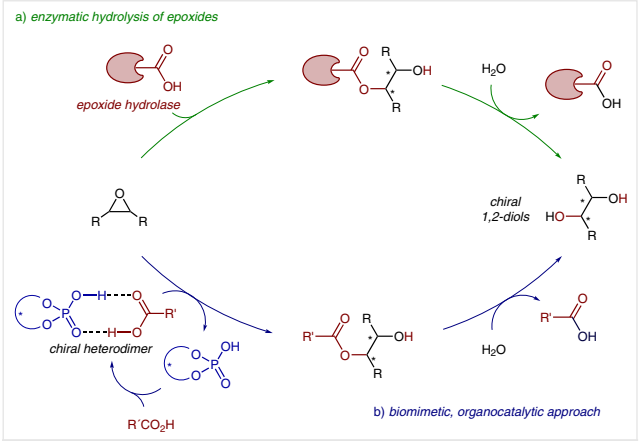
Scheme 4 Selected examples of the asymmetric carboxylysis of aziridines

The interest toward enantiopure aziridines as chiral building blocks for the stereoselective synthesis of 1,2-diamines, 1,2-aminoalcohols, and 1,2-aminothiols prompted us to test the catalytic system for a related kinetic resolution strategy.[30] Remarkably, under cryogenic conditions, our system was indeed able to effectively discriminate between enantiomeric aziridine starting materials (Scheme 4). When a racemic mixture of terminal aziridine was subjected to the reaction conditions, the transformation was promoted with high selectivity factors (*S* from 37 to 51) delivering the ring-opened products and the unreacted starting materials in good enantiopurity. Interestingly, the ring-opening reaction was found to occur selectively at the higher substituted carbon center, suggesting the presence of a partial cationic charge in the transition state. An asynchronous S_N2 reaction pathway, which proceeds with a Walden inversion of configuration, is in accordance with our observations.[31]

3.2 An Asymmetric Hydrolysis of Epoxides

Having identified the potential of the heterodimeric system for the ring opening of aziridines, we turned our attention to epoxides.[9b] Chiral vicinal diols are ubiquitous as secondary metabolites and very commonly incorporated into the scaffolds of pharmaceuticals.[32] Therefore, developing asymmetric epoxide hydrolyses has long been recognized as a valuable synthetic target.[33,34]

At the onset of this study we were particularly inspired by the enzymatic mechanism of epoxide hydrolases. In the biopathway, an aspartate residue performs the nucleophilic attack on the activated epoxide generating an enzyme-bound intermediate, which is subsequently hydrolyzed to give the 1,2-diol product.[35] Interestingly, coupling an asymmetric carboxylysis reaction *via* chiral heterodimers with an *in situ* saponification of the ester product would entirely mimic the natural process (Scheme 5).[36]

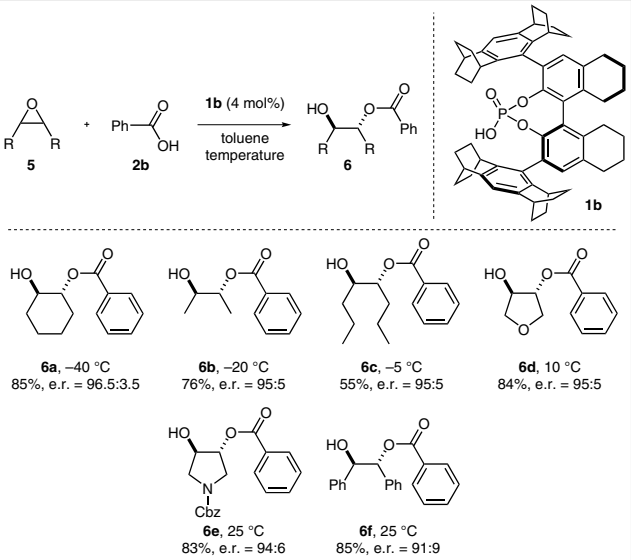


Scheme 5 Design of a biomimetic hydrolysis of epoxides using chiral heterodimers

Intrigued by this biomimetic hydrolysis, we focused on the ring-opening desymmetrization of *meso*-epoxides **5** with benzoic acid **2a**. In the presence of **TRIP**, the transformation proceeded smoothly delivering the desired monobenzoylated glycols in good yield, albeit with only moderate selectivity. This result suggested to us that the nitrogen protecting group of the aziridine had a significant influence on the enantioselectivity of its ring-opening reaction. In order to overcome the lack of this important stereocontrolling element, we explored a novel class of confined BINOL-derived phosphoric acid catalysts, bearing both *ortho* and *meta* aliphatic fragments on the 3-3′-aryl substituents. Importantly, catalyst **1b**, with a rigid polycyclic substituent and a partially saturated backbone, significantly outperformed the previous catalysts giving outstanding results. In fact, using toluene as the solvent, the scope of this asymmetric methodology turned out to be wide and several different *meso*-

epoxides successfully underwent the transformation although a judicious selection of the reaction temperature was required (Scheme 6).

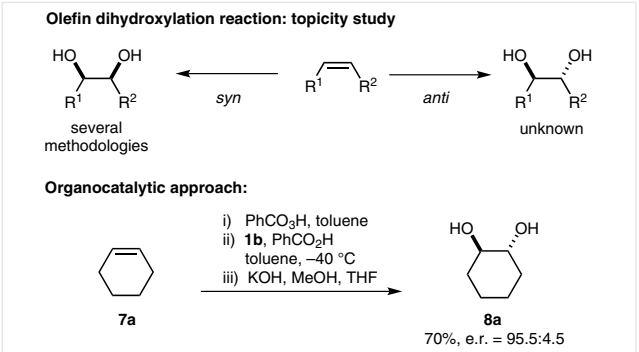
Notably, not only chiral cyclic protected glycols were obtained in very high enantioenrichment, but also epoxides derived from acyclic olefins performed well under the reaction conditions, generally delivering the desired products in high yields and enantiopurities. It is noteworthy that even the small epoxide **5b** was converted into the corresponding product **6b** in 95:5 enantiomeric ratio, highlighting the potential of the new sterically confined catalyst.[37] Furthermore, substrates containing heteroatoms were also found to be suitable for the transformation, which proceeded with good yields and high levels of stereoselectivities.



Scheme 6 Selected examples of the asymmetric carboxylysis of epoxides

This asymmetric carboxylysis of epoxides could also be successfully applied to the development of an organocatalytic *anti*-dihydroxylation of simple olefins. Although asymmetric *syn*-dihydroxylation strategies have been widely investigated over many years,[38,39] a similar transformation proceeding with *anti*-selectivity had been entirely elusive (Scheme 7).

We realized that the Prilezhaev oxidation of an alkene yields the corresponding epoxide with a stoichiometric amount of carboxylic acid byproduct. By simply adding the phosphoric acid catalyst **1b** to the reaction mixture, the asymmetric ring opening is performed and a subsequent hydrolysis under mild basic conditions delivers the desired chiral 1,2-diol. As shown in Scheme 7, our designed process converted cyclohexene (**7a**) into *trans*-cyclohexan-1,2-diol (**8a**) in 70% yield and 95.5:4.5 enantiomeric ratio in a simple, one-pot process.



Scheme 7 Non-enzymatic *anti*-dihydroxylation of olefins

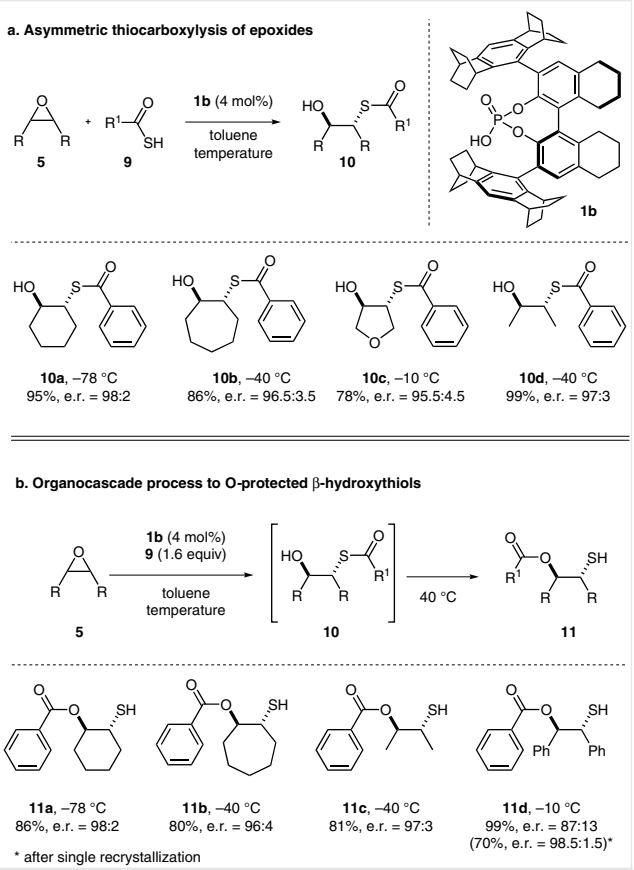
4 Activation of Thiocarboxylic Acids

Having discovered the potential of the heterodimeric self-assembly for the activation of carboxylic acids, we started wondering whether chiral phosphoric acid catalysts could promote similar activation modes for other bifunctional molecules. In particular, we immediately realized the possibility to broaden these concepts to thiocarboxylic acids.[9c]

Sulfur is a frequent constituent of pharmaceuticals and, in particular, the chiral β-hydroxythiol framework is present in several bioactive molecules.[40] Despite the interest toward a straightforward enantioselective access to this moiety, the asymmetric sulfhydrolysis of epoxides is still an unsolved challenge.[41] Intrigued by the possibility to deliver an effective alternative route, we investigated the first highly enantioselective thiocarboxylytic ring-opening reaction. Indeed, catalyzed by confined acid **1b**, the desymmetrization of *meso*-epoxides leading to *S*-protected β-hydroxythiols proceeded in excellent yields and with remarkable selectivity (Scheme 8a).

Gratifyingly, this novel, enantioselective ring-opening reaction was found to be only slightly influenced by the electronic and steric features of the substrates: both cyclic and acyclic products were obtained and the presence of heteroatoms was tolerated effectively (products **10a**–**d**, Scheme 8a).

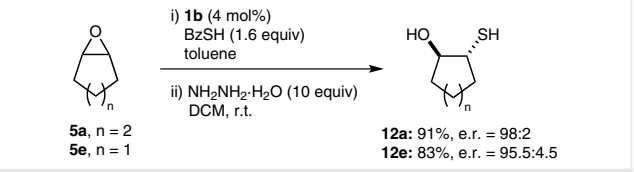
Intriguingly, the careful analysis of the reaction mixture revealed that a subsequent acid-catalyzed transesterification reaction may occur thus providing the O-protected β-hydroxythiol isomers. We then focused our attention on this organocascade process and reinvestigated our protocol by simply elevating the reaction temperature after full consumption of the epoxide starting material (Scheme 8b).[42] This methodology was found to be robust giving products **11** in excellent yield and enantiomeric purity. It is noteworthy that a simple modification of the reaction conditions offers the opportunity to address the same scaffold, protected



Scheme 8 (a) Asymmetric thiocarboxylysis of epoxides. (b) Organocascade process to O-protected β-hydroxythiols

either on sulfur or on oxygen. We envision that such an orthogonal approach will be particularly suitable for synthetic applications. The only significant limitation to this cascade reaction was observed for five-membered ring substrates: due to the high energy *trans*-fused bicyclooctane intermediates, the acyl transfer step was not observed.

Remarkably, by developing this novel activation of thiocarboxylic acids, we could ultimately provide an effective alternative for the long sought after asymmetric sulfhydrolysis of epoxides. In fact, the deprotection of the products can be performed *in situ* under mild reaction conditions, thus affording the 'naked' β-hydroxythiol moiety (Scheme 9).

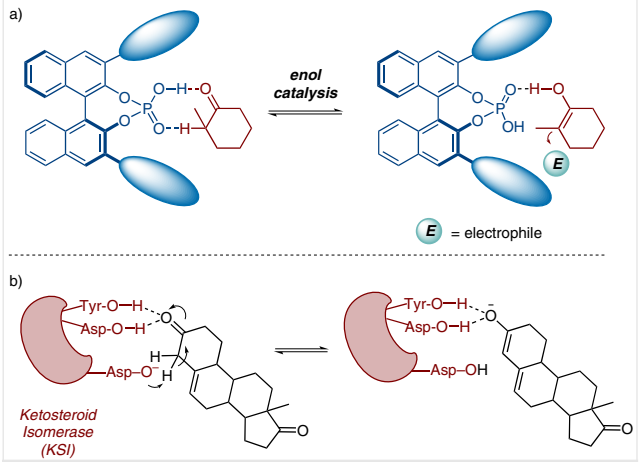


Scheme 9 A one-pot alternative to the asymmetric sulfhydrolysis of epoxides

5 Enol Catalysis

Having designed a new activation mode for carboxylic acids and established a new supramolecular heterodimerization as its key feature, we became interested in activating less acidic substrates. In particular, ketones drew our attention due to their structural similarities with carboxylic acids (the acidic OH moiety is replaced with an acidic C–H bond). We speculated that the chiral phosphoric acid could potentially interact both with the lone pair of the carbonyl and the α-proton, *via* its acidic P–OH and basic P=O substructure, respectively (Scheme 10a). This heterodimeric interaction may be weaker than that of carboxylic acids, but was speculated to lead to the *enolization* of the ketone substrate.

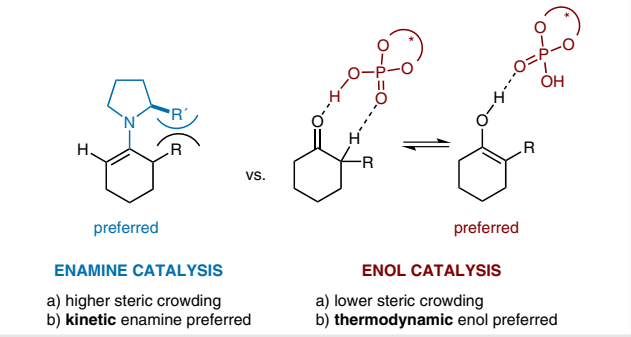
Numerous studies on the mechanism of acid-catalyzed enolizations of ketones have been reported,[43] and interestingly, a similar phenomenon can be found in certain enzymatic enolizations in which basic and acidic amino acid residues work synergistically *via* a concerted or stepwise mechanism to promote enol formation,[44] e.g., ketosteroid isomerase (Scheme 10b).[45] We hypothesized that once formed, the 'chiral enol–phosphate complex would further interact with an electrophile *via* hydrogen bonding, eventually leading to an asymmetric α-functionalization reaction (Scheme 10a). This design, 'enol catalysis', represents an expansion of Brønsted acid catalysis, in which ketones are activated as nucleophiles rather than as electrophiles.



Scheme 10 (a) Organocatalytic enolization with branched ketones (enol catalysis). (b) Enzymatic enolization of steroids by ketosteroid isomerase[45]

Enol catalysis is reminiscent of *enamine* catalysis, a time proven and broadly applicable concept for the direct α-functionalization of diverse carbonyl compounds.[46] As a logical consequence, we named this novel activation mode 'enol catalysis'.[10,47] Despite its versatility, enamine catalysis suffers from steric hindrance and in particular, when branched ketones are employed, only limited reactivity is

generally observed. Furthermore, except in rare cases,[48] quaternary stereocenters cannot be accessed as enamine catalysis preferentially functionalizes the least substituted α-carbon (Scheme 11).

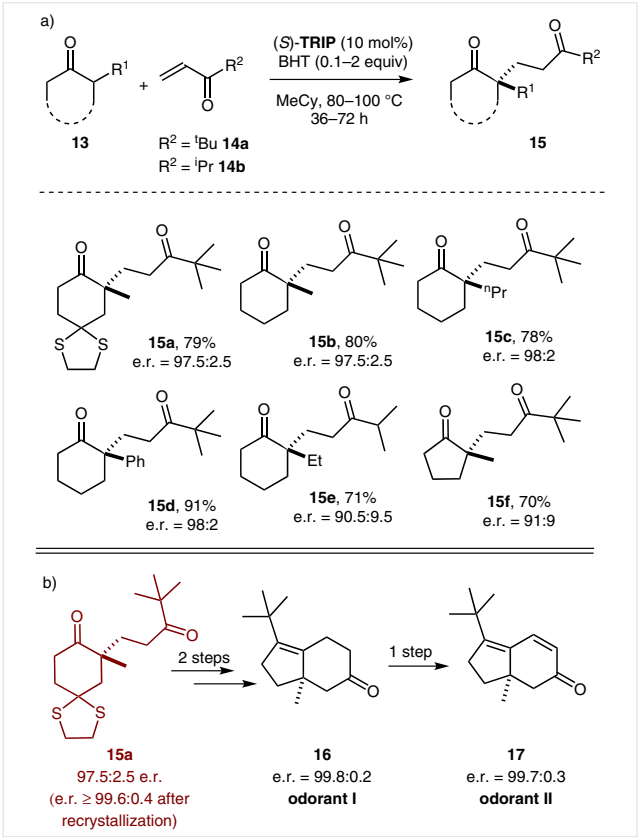


Scheme 11 Shifting from aminocatalysis to enol catalysis

We envisioned that shifting from enamine to enol catalysis would allow us to functionalize challenging branched ketones. Indeed, this concept proved to be successful as, (i) the most substituted enol was preferentially formed (or preferentially reacts), enabling access to synthetically challenging quaternary stereocenters, and (ii) the highly tunable chiral environment of the phosphoric acid would give a direct access to α-functionalized ketones in high enantiopurity.

5.1 Asymmetric Michael Addition

We reported the concept and first application of enol catalysis in 2015, and by employing enones as electrophiles, we disclosed the first chiral Brønsted acid catalyzed Michael addition of branched ketones to α,β-unsaturated ketones (Scheme 12a).[10a] This transformation perfectly illustrates the potential of enol catalysis as both the electrophile and nucleophile are unactivated and sterically hindered. The scope of this methodology with regard to the ketone nucleophile proved to be broad and both α-alkyl and α-aryl groups were tolerated. This feature suggests that reactivity does not seem to be directly related to the acidity of α-protons, thus underlining the intrinsic preference of the phosphoric acid for the functionalization of the most substituted position. As shown in Scheme 12a, different substitutions are tolerated and both five- and six-membered rings react smoothly to afford the desired products in good yields and very high enantioselectivities (up to 98:2), even at rather high temperatures (80–100 °C). Interestingly, highly unpolar aliphatic solvents, such as methylcyclohexane (MeCy), proved to be superior both for reactivity and enantioselectivity. Our method was also successfully employed as the key step in the total synthesis of novel designed odorants (Scheme 12b).

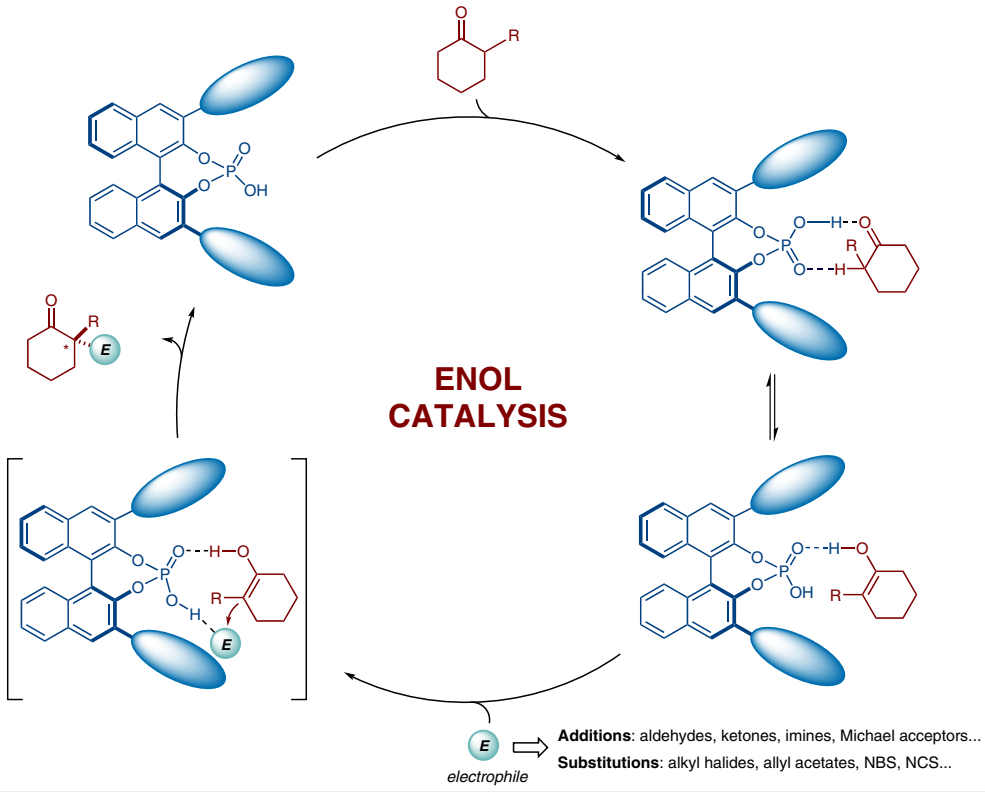


Scheme 12 (a) Selected examples for the asymmetric Michael reaction of α-branched ketones with enones. (b) Application to the total synthesis of odorants. BHT = butylated hydroxytoluene

5.2 Asymmetric α-Amination

Following our initial report, we proposed a general catalytic cycle for enol catalysis (Scheme 13).[10b] Accordingly, the chiral phosphoric acid initially interacts with the branched ketone to promote enolization. Then, the thermodynamic, most substituted enol further reacts with a generic electrophile **E** (which may or may not be activated *via* additional protonation from the catalyst). Its successive electrophilic attack on the enol affords the desired product and regenerates the catalyst.

To explore enol catalysis as a generic activation mode, we turned our attention to the α-amination of branched cyclohexanones, which, subsequent to our initial discovery of the Michael reaction, was reported both by the Toste group[49] and our group.[10b] This methodology represents an elegant access to numerous drugs bearing α-amino ketones,



Scheme 13 Proposed general catalytic cycle for enol catalysis

for example, ketamine. Additionally, 1,2-aminoalcohols, which can be readily accessed from the corresponding ketones, are widely used as pharmaceuticals, chiral ligands, catalysts, and auxiliaries in asymmetric synthesis.[24,25] Numerous methodologies for the α-amination of carbonyl compounds have been disclosed, yet until 2015, no examples involved challenging unactivated branched ketones.

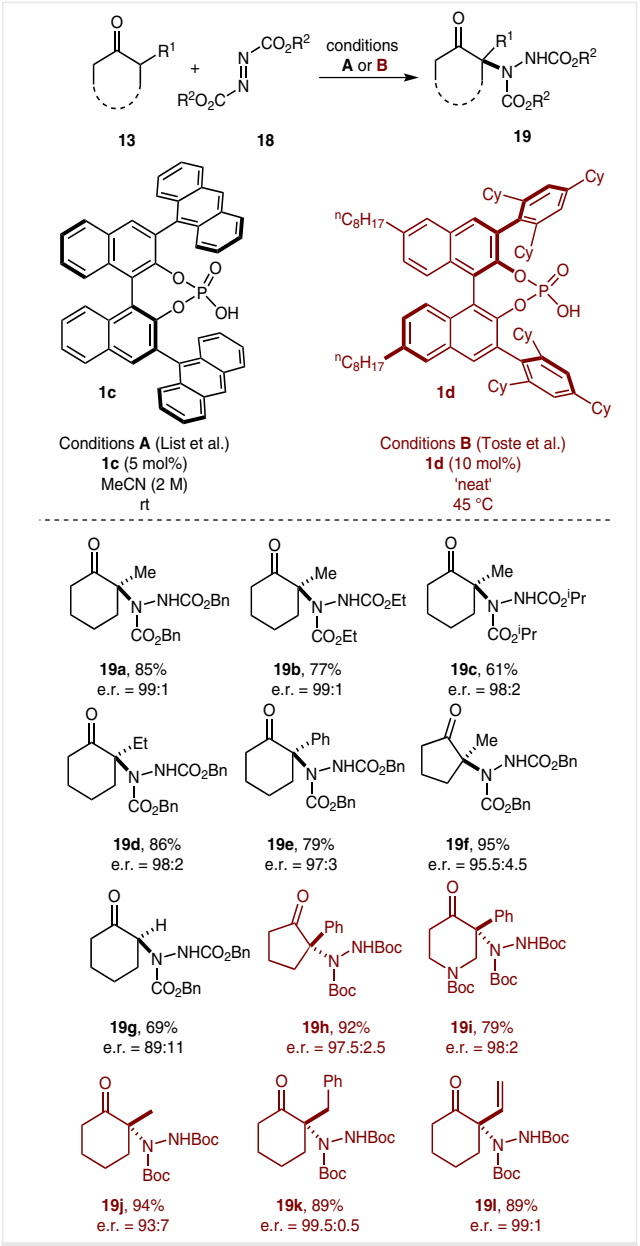
To our delight, when the ketone was treated with an excess of azodicarboxylates in the presence of a chiral phosphoric acid, the desired products were obtained in excellent yields and enantioselectivities (Scheme 14). Different ester protecting groups on the electrophiles and both α-aryl and α-alkyl five-, six- and seven-membered ring-substituted ketones reacted smoothly under the optimized reaction conditions. The only limitations proved to be both indanone/tetralone systems and seven-membered rings. The good yields and enantioselectivity of product **19g**, obtained from unsubstituted cyclohexanone, shows that enol catalysis can even be employed for the formation of tertiary stereocenters. Finally, by employing the α-amination reaction, the Toste group has also reported an efficient kinetic resolution of branched ketones.[49]

5.3 Asymmetric α-Allylation

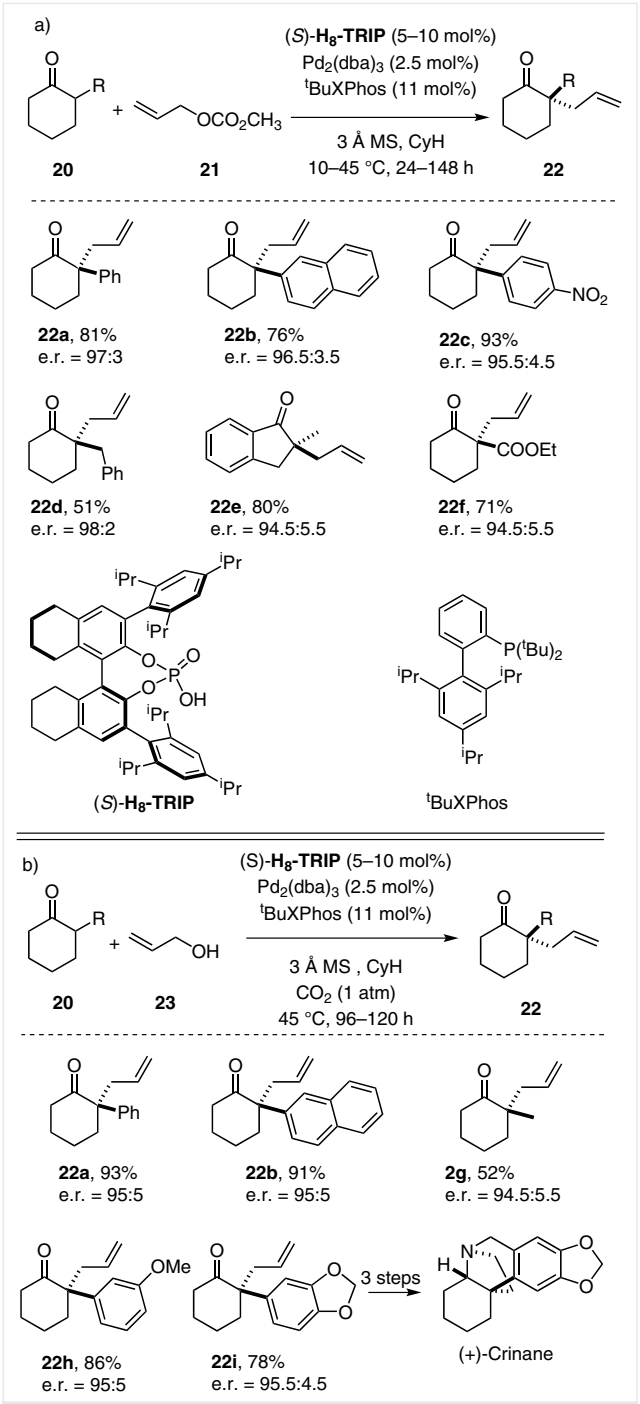
Based on our proposed general catalytic cycle, the number of transformations which can be envisioned is exceedingly broad. Among these, we turned our attention to the long-standing challenge of a direct catalytic asymmetric α-allylation of ketones. This reaction represents an elegant approach towards all-carbon quaternary stereocenters, which are common motifs in natural products and pharmaceutical drugs.[50]

Numerous reports have circumvented this problem by employing indirect approaches involving preformed enolates[51] or decarboxylative allylic alkylation conditions.[52] These protocols are intrinsically less atom-economic and often require additional synthetic steps for the preparation of the starting materials. Recently, we reported a solution to this problem and disclosed a highly atom-economic Tsuji–Trost type α-allylation of ketones by exploiting enol catalysis.[53]

We initially employed allylic carbonates (Scheme 15a) and later proved that simple allylic alcohols, upon *in situ* activation by CO_2, were also suitable electrophiles (Scheme 15b). The desired compounds **22a–h** were obtained in good to excellent yields and regio-/enantioselectivities. Additionally, this approach generates water as sole by-product. The methodology relies on a triple catalytic cycle in which the



Scheme 14 Selected examples of the Brønsted acid catalyzed α-amination reaction with azodicarboxylates as reported by Toste et al.[49] and our group[10b]



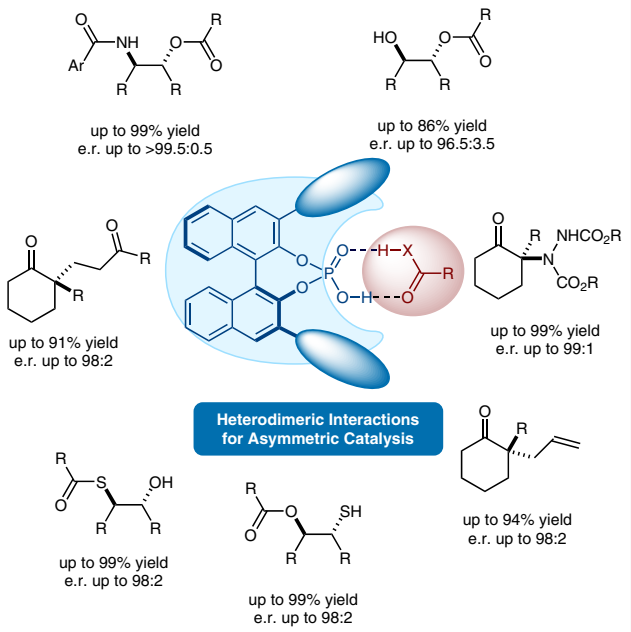
Scheme 15 Selected examples for the asymmetric α-allylation of branched ketones with (a) allylic carbonate and (b) allylic alcohol activated by CO_2

chiral phosphoric acid (**H_8-TRIP**) promotes enolization, a palladium catalyst bearing an achiral phosphine ligand (^{t}BuXPhos) generates the active π-allyl system from the corresponding precursor, and formally catalytic amounts of CO_2 activate the electrophile. Under air or argon atmosphere, allylic alcohol only afforded limited conversions (>15%), yet when the reaction was run under a CO_2 atmosphere, a putative allyl carbonic acid ester[54] was formed, thus acting as a highly reactive π-allyl precursor. To underline the potential of enol catalysis in natural product synthesis, the methodology was later applied to the shortest formal total synthesis of the Amaryllidaceae alkaloid (+)-crinane (Scheme 15b).

This methodology shows for the first time that enol catalysis can be successfully combined with metal catalysis, thus further expanding the library of novel reactions which can be envisioned for the near future.

6 Concluding Remarks

The establishment of novel activation modes in organocatalysis ideally provides access to a variety of transformations which were previously elusive.[55] In this regard, by fully exploiting the bifunctionality of phosphoric acids, we discovered heterodimeric interactions with small organic molecules and disclosed unprecedented methodologies for the activation of carboxylic acids and thiocarboxylic acids. This dual interaction then led us to expand this concept to the activation of ketones and the development of enol catalysis, which enables unprecedented direct, regioselective, and enantioselective α-functionalizations of branched ketones (Scheme 16).

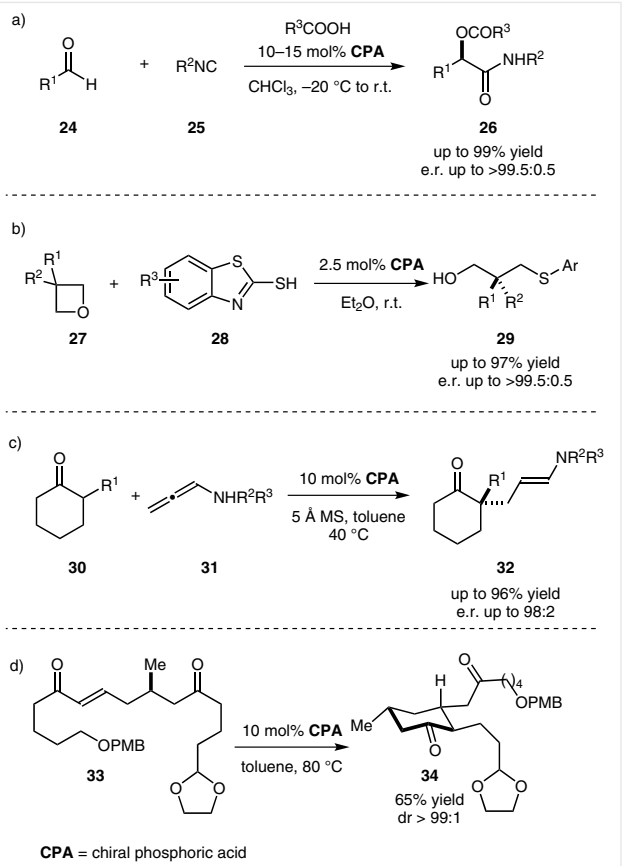


Scheme 16 Summary of the methodologies exploiting heterodimeric interactions

Our findings immediately imply diverse and multifold applications in asymmetric catalysis. In fact, after the disclosure of the concepts described above, the scientific community has already begun picking up on these principles. For example, an elegant asymmetric variant of the Passerini reaction has recently been disclosed by Liu, Tan and coworkers, thus providing an easy access to a valuable class of chiral α-hydroxylated amides (Scheme 17a).[56] Furthermore, the Sun group has recently disclosed a related catalytic mode for mercaptobenzothiazoles, which exploits a related and interesting heterodimeric activation (Scheme 17b).[57]

Finally, it appears as if we have just scratched the surface of enol catalysis. Nonetheless, there have already been some interesting expansions and applications of this concept from other groups. In particular, in 2016, the Toste group reported the phosphoric acid catalyzed addition of branched ketones to allenamides as acetaldehyde surrogates (Scheme 17c).[58] Furthermore, a Brønsted acid catalyzed intramolecular Michael reaction of ketones to enones was recently employed to elegantly build the cyclohexanone core of the *Lycopodium* alkaloid, lycoposerramine-Z (Scheme 17d).[59]

Numerous other classes of compounds, which have traditionally been activated by bases, may in the future be activated as nucleophiles by Brønsted acids (e.g., linear ketones, amides, esters). Exciting discoveries can be expected in this new area.



Scheme 17 Recently published examples exploiting chiral phosphate-based heterodimeric interactions. (a) Asymmetric Passerini reaction. (b) Oxetane ring opening with 2-mercaptobenzothiazoles. (c) Phosphoric acid catalyzed addition of α-branched ketones to allenamides. (d) Intramolecular Michael reaction *via* enol catalysis

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