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The Activation of Carboxylic Acids via Self-Assembly Asymmetric Organocatalysis: A Combined Experimental and Computational Investigation

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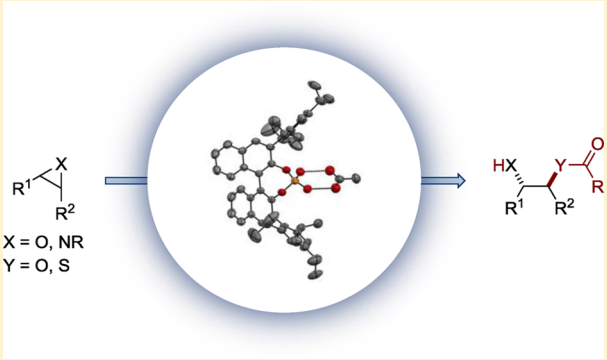
Supporting Information

ABSTRACT: The heterodimerizing self-assembly between a phosphoric acid catalyst and a carboxylic acid has recently been established as a new activation mode in Brønsted acid catalysis. In this article, we present a comprehensive mechanistic investigation on this activation principle, which eventually led to its elucidation. Detailed studies are reported, including computational investigations on the supramolecular heterodimer, kinetic studies on the catalytic cycle, and a thorough analysis of transition states by DFT calculations for the rationalization of the catalyst structure–selectivity relationship. On the basis of these investigations, we developed a kinetic resolution of racemic epoxides, which proceeds with high selectivity (up to s = 93), giving the unreacted epoxides and the corresponding protected 1,2-diols in high enantiopurity. Moreover, this approach could be advanced to an unprecedented stereodivergent resolution of racemic α-chiral carboxylic acids, thus providing access to a variety of enantiopure nonsteroidal anti-inflammatory drugs and to α-amino acid derivatives.



INTRODUCTION

Since its birth as a field at the turn of the last millennium, enantioselective organocatalysis has become a cornerstone of asymmetric synthesis.[1] The progressive development of this field has been extraordinary, and nowadays organocatalysis constitutes a solid complement to metal catalysis and biocatalysis.[2] The main reason for this success relies on the establishment of a platform of different generic activation modes, which facilitate a predictive understanding.[3] The frontier molecular orbitals of the reacting species are significantly affected by a well-defined association with the catalyst, and the stereochemical information held in the chiral microenvironment enables enantioselective catalysis.[4] For example, Brønsted acid catalysis generally relies on hydrogen-bond-assisted ion-pairing interactions between the catalyst anion and the protonated electrophilic reaction partner, leading to the activation of substrates via LUMO lowering.[5]

Despite the broad success of previously established catalytic modes, the introduction of novel activation strategies is fundamental for the exploitation of functional groups that are still elusive to asymmetric organocatalysis. For example, carboxylic acids have essentially been neglected in this research field.[6] However, considerable relevance is generally given to their synthesis and transformations because carboxylic moieties are widely occurring bioactive substructures of natural products and medicinally relevant compounds. Therefore, broadening their utilization in organocatalysis is desirable. Recently, our group has introduced a novel approach toward this goal based on the heterodimerizing self-assembly of carboxylic acids with hindered phosphoric acid catalysts (Scheme 1).[7a] The physicochemical characterization of this supramolecular interaction in early 2012 set the ground for the development of a variety of enantioselective organocatalytic ring openings of epoxides and aziridines with carboxylic acids.[7] Notably, the obtained esters are easily converted into the corresponding alcohols, and thus these methodologies can also be considered as intriguing alternatives to asymmetric hydrolysis reactions.[7a,b] Furthermore, we have recently demonstrated that the same activation strategy can be used for thiocarboxylic acids and thioamides, providing access to 1,2-thioalcohols and to enantiopure thiiranes.[7c,d]

This novel catalytic system exhibits unique features, which have previously not been observed in the realm of enantioselective Brønsted acid catalysis. Instead of proceeding via the common direct interaction between the phosphoric acid catalyst and the electrophile, the new methodologies exploit a preliminary interaction between the catalyst and the nucleophile. This unusual reaction mode allows the use of certain electrophiles, which have previously been neglected in organocatalysis. Various highly reactive electrophiles have proven to be incompatible with phosphoric acid catalysis,

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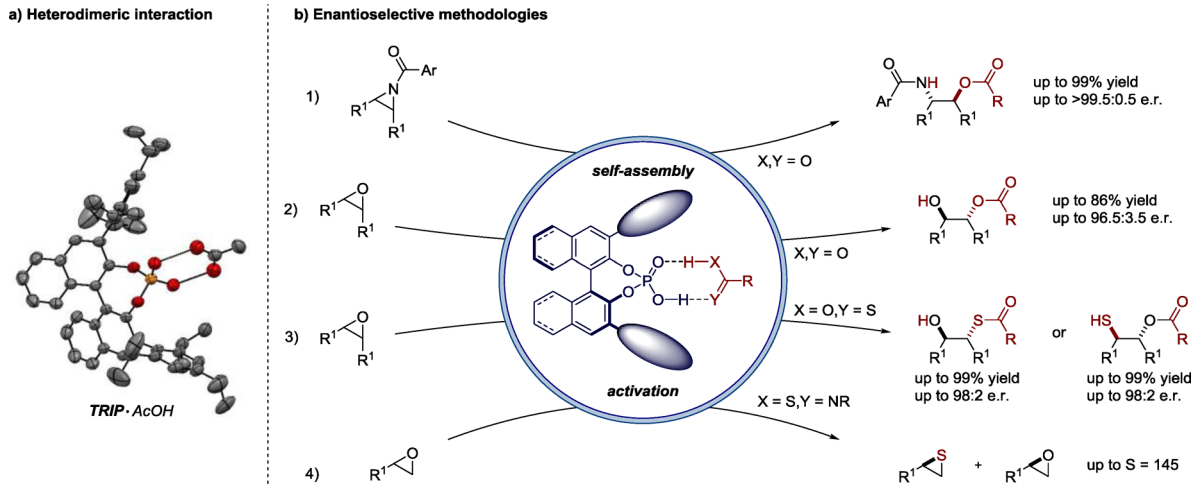
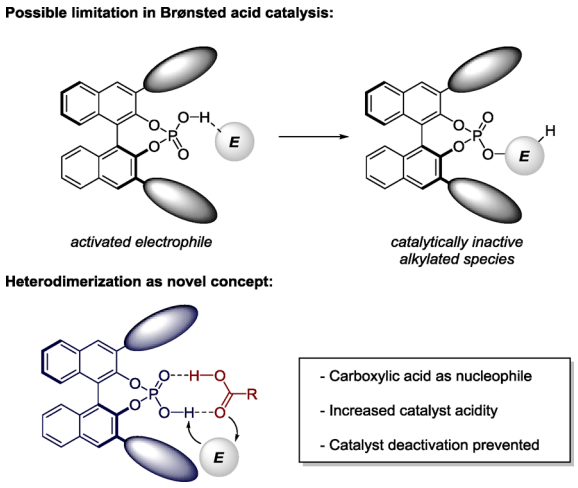
Scheme 1. Activation of Carboxylic Acids in Organocatalysis



presumably due to their tendency to engage the catalyst in an undesired nucleophilic attack, delivering an alkylated, catalytically inactive species.[8] This decomposition pathway is commonly observed when employing "hard" electrophiles such as protonated epoxides, aziridines, and nonstabilized carbocations (Scheme 2).[9]

Scheme 2. Heterodimerization as Novel Concept in Brønsted Acid Catalysis



In the presence of carboxylic acids, the direct interaction between the catalyst and the alkylating electrophile is prevented. For this reason, we postulated that in the developed methodologies, the formation of the noncovalent self-assembly has a 3-fold role: (1) it prevents the direct catalyst alkylation, (2) it enhances the nucleophilicity of the carboxylic acid, and (3) it provides additional activation to the electrophile due to its increased acidity (Scheme 2).

Here we describe details of our studies toward elucidating the catalytic principles of the unique activation mode of this type of self-assembly organocatalysis. A combined experimental and theoretical investigation allows a vivid description of the heterodimeric interaction between carboxylic acids and phosphoric acid catalysts, providing guidelines for the design of novel methodologies. Indeed, we also describe the design and development of a highly enantioselective kinetic resolution of racemic epoxides and its application to a remarkable stereodivergent resolution of carboxylic acids.

RESULTS AND DISCUSSION

Self-Assembly and Organocatalysis. The formation of homodimeric aggregates is known to significantly influence the physical and chemical properties of both carboxylic acids and phosphoric acid diesters in apolar media (boiling point, solubility, acidity, *etc.*).[10−12] Interestingly, however, mixed carboxylic-phosphoric acid dimers have not been described before our studies, and their properties were largely unknown.[13] At the onset of our explorations, when we first designed a heterodimeric self-assembly between chiral phosphoric acid catalysts and carboxylic acids, the hypotheses on the reactivity of these species were rather general and vague, and a rational prediction on the effect on the molecular orbitals of the carboxylic acid could not be made. Intriguingly, our initial findings by NMR spectroscopy revealed an *upfield* shift of the proton signals of the carboxylic acid monomer, suggesting an *increased* electronic density.[7a] In order to elucidate and further rationalize the chemical properties of the heterodimer, we first undertook a thorough theoretical analysis.

We focused on the effects of the self-assembly on both the acidity of the dimer and on the frontier molecular orbitals of its carboxylic acid moiety. The investigation on the Brønsted acidity was performed using pyridine as an indicator: the comparison of the protonation by **TRIP** and by the heterodimer **TRIP**-AcOH allowed an evaluation of the acid strength of the different species (Figure 1a). The stabilization free energy (ΔG) of the different acid−base complexes were evaluated using density functional theory (DFT) calculations, performed at the B3LYP/cc-pVTZ level. Toluene was chosen as solvent for our investigations, and the solvation effects were taken into account through a polarizable continuum model approach.

Interestingly, this analysis suggested that the trimeric species **D** is more stable than complex **C** ($\Delta G = -12.25$ kcal mol^{-1}) and also indicates that in this assembly, the proton transfer is favored, leading to the protonation of the indicator, which is present as a pyridinium ion. This is in agreement with a hydrogen-bonding heteroconjugation effect (i.e., stabilization of the conjugate base)[14] and reveals that a significant acidity enhancement takes place upon association.[15] These studies also

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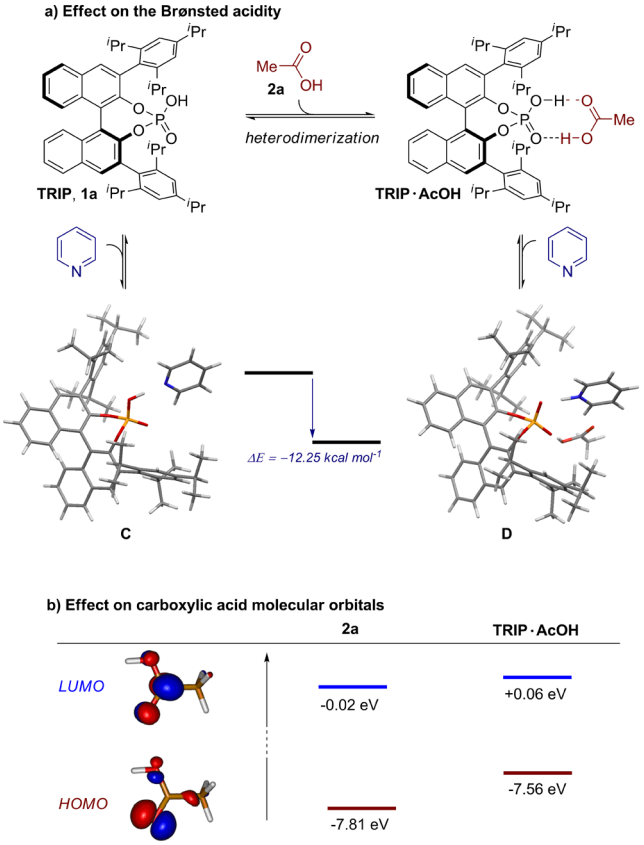

Figure 1. Synergistic activation upon heterodimerization. (a) Evaluation of acid strength using pyridine as indicator. (b) Evaluation of the effect of dimerization on frontier molecular orbital energies of acetic acid. Structures are computed at B3LYP/cc-pTVZ level. See SI for further details.

corroborate the findings by the research groups of Akiyama, Rueping, and Antilla, who reported a qualitative effect of carboxylic acid cocatalysts in different phosphoric acid-catalyzed reactions.[16]

We also investigated the effects of the dimerization process on the frontier molecular orbitals of the carboxylic acid molecule (Figure 1b). Comparing the orbital energies of an acetic acid molecule with those of the same molecule in association with **TRIP**, a HOMO raising effect was observed rather than the perhaps more intuitive LUMO lowering. Presumably, this phenomenon is due to the amphoteric nature of the two interacting monomers: the phosphoric acid catalyst is both more acidic and more basic than the carboxylic acid, and a "partial deprotonation" with concurrent HOMO raising is the result of the overall pull−push effect.[17]

These theoretical results shed new light on the reactivity of heterodimeric species and provide a rationalization of the high nucleophilic character of carboxylic acids observed in our asymmetric addition reactions to epoxides and aziridines.

Investigations on the Catalytic Cycle. The remarkable thermodynamic stability of the noncovalent self-assembly is another key feature of the mode of action of the catalytic system ($K_{a(\mathbf{TRIP}\text{-AcOH})}$ = 1948 M^{-1}; $K_{a(\mathbf{TRIP}\text{-BzOH})}$ = 3981 M^{-1} in dichloromethane). Presumably, the phosphate moiety is saturated under reaction conditions, and this prevents the above-mentioned alkylative deactivation of the catalyst with reactive epoxides and aziridines (Scheme 2). Aiming toward an elucidation of the mechanism of this multifaceted reaction mode, we focused on the analysis of the kinetic reaction profile. Assuming that all the reported transformations proceed according to a common catalytic cycle, we investigated the asymmetric carboxylysis of epoxides as model reaction.

The carboxylysis of epoxide **3a** with benzoic acid **2b** (*vide infra*) was found to be suitable for the evaluation of the reaction progress by *in situ* ^{1}H NMR measurements (Figure 2).

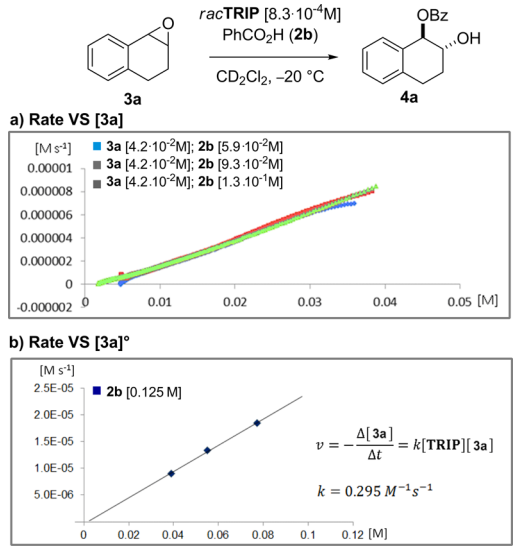

Figure 2. Kinetic studies on the ring opening of epoxides. The experiments were followed by ^{1}H NMR spectroscopy (see SI for further details).

Following the analytical method described by Blackmond, different experiments were performed to determine the kinetic rate law.[18] The consumption of epoxide **3a** was monitored during time, and a numerical fitting process was used to manipulate the data (Figure 2a).

A linear relationship was observed between the reaction rate and the concentration of the starting epoxide, thus suggesting a first-order reaction. Employing different amounts of benzoic acid, three independent experiments were performed, and an almost perfect overlay of the reaction profiles was obtained. This result suggests that the carboxylic acid concentration does not influence the rate of the ring-opening reaction at least in the concentration range investigated. Next, using the method of the initial rates, we explored the role of the epoxide in the kinetic law.[19] The linear plot obtained in this experiment accounts for a first-order dependence of the reaction rate with respect to the concentration of substrate **3a** (Figure 1b). From this analysis we derived both the carboxylysis reaction rate equation and the observed kinetic constant (K_{obs} = 0.295 M^{-1} s^{-1}).

Aiming toward a more complete understanding of the system, we also investigated the deactivation pathway of the phosphoric acid catalyst in the absence of carboxylic acid. In this case, we used ^{31}P NMR analysis to follow the alkylation of **TRIP** with epoxide **3b** (Figure 3). The reaction was performed employing an excess (10 equiv) of the epoxide for two reasons: (1) to mimic catalytic conditions for the phosphoric acid compound and (2) to ensure pseudo-zero-order dependence with respect to that substrate.

As shown in Figure 3, a linear relationship was observed between the decomposition rate and the concentration of **TRIP**, thus indicating a bimolecular reaction in which only one

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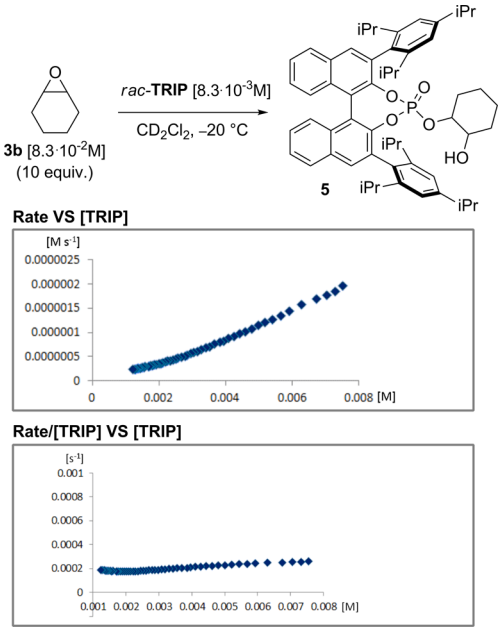


Figure 3. Studies on the catalyst deactivation reaction. The experiment was followed by ^{31}P NMR spectroscopy (see SI for further details).

molecule of the phosphoric acid is involved in the reaction pathway.

According to this kinetic analysis, a reaction mechanism can be proposed (Scheme 3). The interaction between catalyst **1** and epoxide **3** leads to the direct alkylation of the catalyst. Conversely, upon heterodimerization with carboxylic acids, this undesired pathway is effectively prevented. The heterodimer then engages in the asymmetric carboxylysis reaction due to the observed increased acidity and nucleophilicity, delivering the product **4** and regenerating the "free" catalyst which is immediately associated again with another molecule of carboxylic acid. The resting state of the catalytic cycle is proposed to be the heterodimeric species (due to the observed zeroth order dependence on the carboxylic acid), while the ring-opening reaction is the rate-determining step (first-order with respect to the epoxide).

The catalytic cycle was also investigated by DFT calculations at the B3LYP/cc-pVTZ level, following the sequence of the different intermediates by computing the corresponding free energy profile (Figure 4).

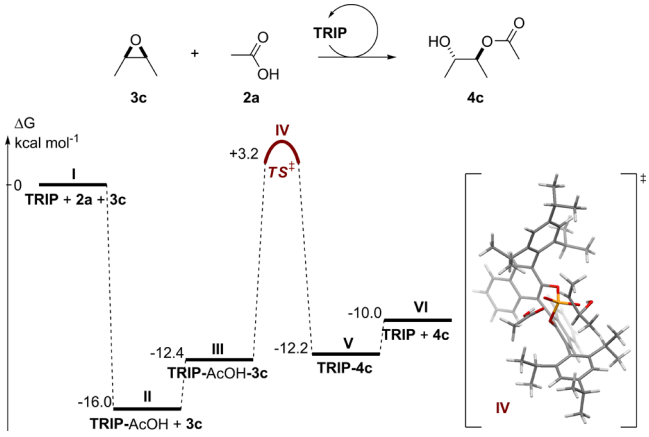


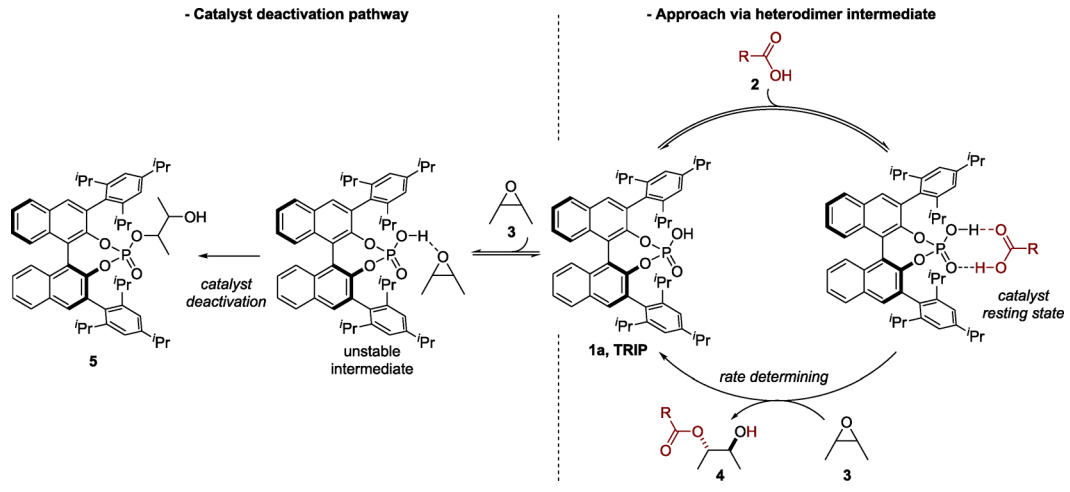
Figure 4. DFT analysis of the intermediates of the catalytic cycle. Structures are computed at the B3LYP/cc-pTVZ level (see SI for further details).

We propose that the heterodimer resting state (**II**) is intercepted by the epoxide resulting in the formation of a trimolecular complex (**III**) in a reversible fashion (Scheme 3). Next the S_N2 ring-opening reaction occurs via a bifunctional transition state (**IV**) delivering a catalyst-product complex (**V**) that gets eventually dissociated, and the product will be replaced by "fresh" carboxylic acid. The overall exothermicity of the reaction is in accordance with the release of the epoxide ring strain.

According to this analysis, the heterodimeric association plays a crucial role in the reaction, which is based on the inherent dichotomy between stability and reactivity. The apparent change of the polarity of the mechanism, in which the phosphoric acid catalyst primarily establishes an interaction with the nucleophile rather than with the electrophile, is somewhat peculiar. This type of "umpolung" strategy represents a core feature of our approach to carboxylic acid activation.

Origin of Enantioselectivity. Having established the catalytic cycle and the structure of the transition state, an investigation on the catalyst structure-selectivity relationship

Scheme 3. Proposed Catalytic Cycle



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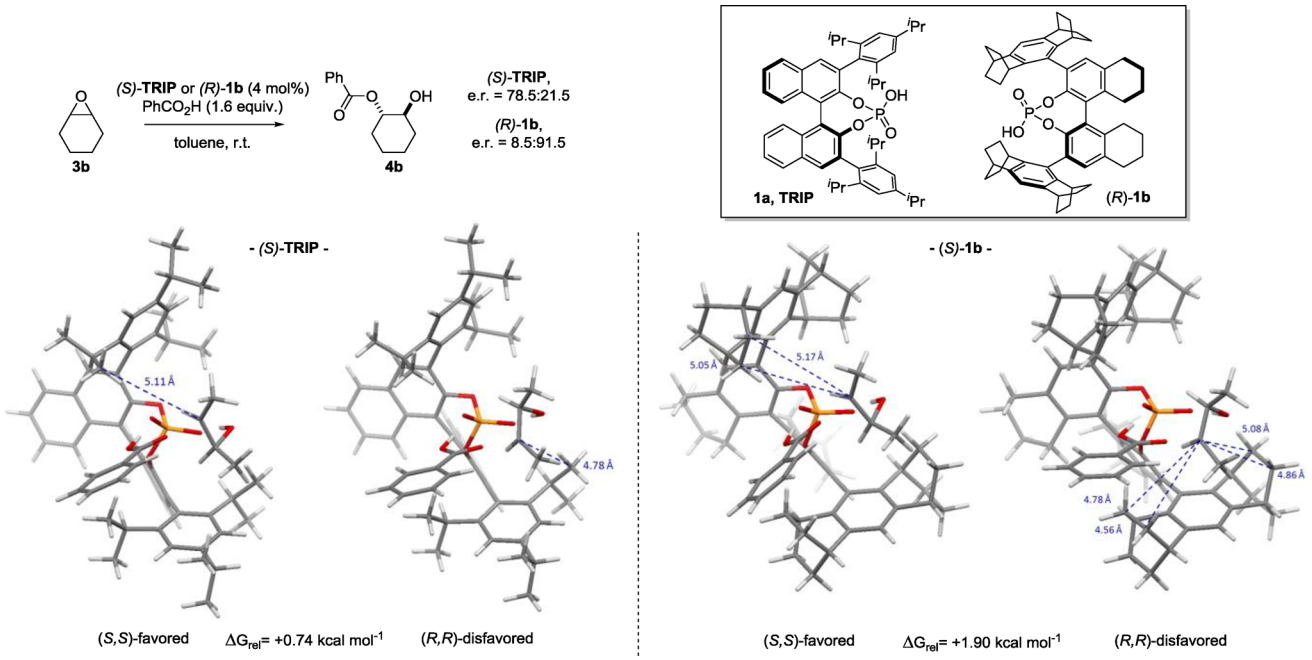

Figure 5. Transition states analysis. Structures computed at the B3LYP/6-31G* level. Key substrate−catalyst distances indicated in blue. See SI for further details.

was performed. In particular, we aimed at understanding the pronounced influence of the 3,3′-substituents of BINOL-derived phosphoric acid catalysts on the reaction outcome. In fact, in all the asymmetric transformations which exploit this activation mode, sterically demanding catalysts usually outperform less bulky ones with significant influence on both reactivity and enantioselectivity.[7] This simple experimental observation was realized while investigating the carboxylysis of aziridines and turned out to be crucial for the optimization of the reaction on the epoxide system.[7b] In this transformation, a moderate selectivity was obtained with **TRIP**, while the more congested catalyst **1b**, bearing rigid polycyclic substituents, was found to be optimal for the transformation. This interesting outcome was consistently confirmed in the reactions with thiocarboxylic acids.[7c] Intrigued by this finding, we investigated the transition states for the ring opening of *meso*-epoxides using DFT calculations both with (*S*)-**TRIP** and with catalyst (*S*)-**1b** (Figure 5). The studies were performed using different functionals (B3LYP, BH&H), empirical dispersion corrections, and basis sets (further details are provided in the SI).

The analysis performed at the B3LYP/6-31G* level is in good agreement with the experimental observations, and the calculated structures of the transition states for the reaction catalyzed by **TRIP** phosphoric acid show a lower energy for the transition state leading to the (*S*,*S*)-product (ΔG = 0.74 kcal mol^{-1}). The two structures are characterized by a different spatial orientation of the trimolecular complexes: The carbon reacting center is significantly closer to the catalyst scaffold in the energetically disfavored pathway rather than in the favored one (4.78 vs 5.11 Å).

The analysis of the transition states for the reaction catalyzed by **1b** reveals a higher energy difference (ΔG = 1.90 kcal mol^{-1}), thus being in accordance with the high enantioselectivity of the transformation. It is noteworthy that in the disfavored transition state (leading to *R*,*R*-product), the reacting epoxide is mainly surrounded by aliphatic portions of the polycyclic substituent, which will presumably not provide any significant stabilization to the polar, partially charged reaction center, which is indeed placed almost equidistant to the four aliphatic groups. Notably, the methylene group closest to the epoxide center is in the *meta*-position of the aryl substituent (4.58 Å), confirming the importance of the *ortho*−*meta* substitution pattern in our designed class of catalysts.

Very recently, in a broad and comprehensive computational study on a related transformation, the Wheeler group has proposed an attractive electrostatic interaction between the electron-rich phosphoryl oxygen and the partially positively charged C−H moiety of the epoxide, which undergoes the nucleophilic attack.[20] This interaction was found to contribute to the lowering of the transition state. Our computational investigations fully support this hypothesis. The analysis of the electrostatic potential iso-surfaces reveals that the Coulombic interaction is significantly larger in the (*S*,*S*)-transition state, thus correlating with its stabilization and therefore with its thermodynamic favor (Figure 6).

Based on these studies, we suggest that the origin of the enantioselectivity in this reaction is ascribable to the spatial orientation of the substrates in the catalyst active pocket. The relative energy of the transition states reflects the influence of two different parameters: a destabilizing steric interaction and an attractive electrostatic interaction. The constrained nature of catalyst **1b**, bearing a polycyclic rigid scaffold, allows an optimal modulation of these two effects, thus leading to enhanced enantiomeric excess with respect to **TRIP**. These results corroborate the importance of confined catalysts in asymmetric Brønsted acid catalysis, and we thus believe that **1b** will serve as an effective catalyst for the development of other highly selective transformations.[21]

Kinetic Resolution of Racemic Epoxides. Having obtained a clear description of a novel organocatalytic reaction mode, we focused on broadening the applicability of this activation mode for challenging methodologies. Although chiral epoxides are generally recognized as important building blocks in stereoselective synthesis, the development of highly

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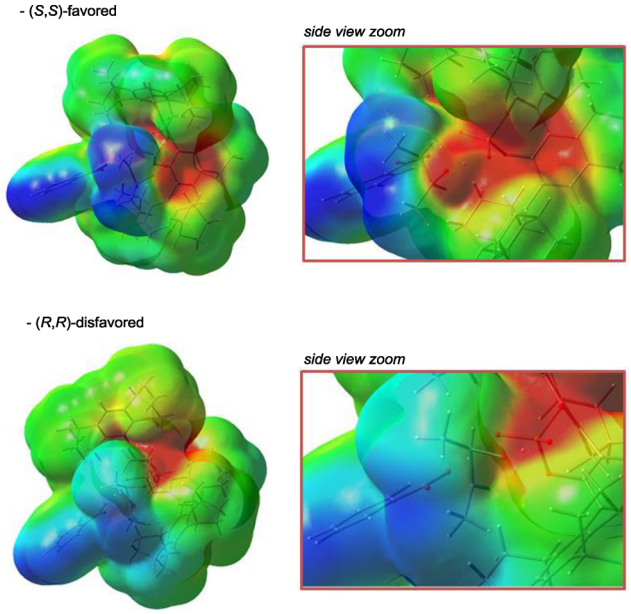

Figure 6. Electrostatic surfaces of the transition states for catalyst (*S*)-**1b**. Electrostatic potentials (blue, $+3 \times 10^{-1}$ au; red, -2×10^{-1} au) mapped onto the electron density isosurface (ρ = 0.002 e/au^3). Structures computed at the B3LYP/6-31G* level.

enantioselective epoxidation reactions of unactivated olefins is still in need.[22] However, racemic epoxides are inexpensively derived from the corresponding alkenes, and thus the development of efficient resolution strategies can be practically useful. In this context, the leading methodology is the hydrolytic kinetic resolution developed by Jacobsen et al. in the field of metal-based catalysis.[23] Promoted by an enantiopure Co-salen catalyst, the transformation proceeds with remarkable selectivity and, due to its high efficiency, it is also applied on an industrial scale.[24]

In contrast, metal-free asymmetric resolutions of epoxides are rare. Very recently, we used the heterodimeric activation of a thioamide to achieve the first highly enantioselective thiirane synthesis, which proceeds via the kinetic resolution of racemic epoxides.[7d] However, the use of inexpensive carboxylic acids as *O*-nucleophiles could be highly desirable for applications on a large scale. Therefore, given the excellent results observed in the desymmetrizing carboxylysis of aziridines and *meso*-epoxides, we set out to perform an investigation toward the identification of suitable conditions for the kinetic resolution of racemic epoxides.

We began the exploration by employing styrene oxide **3d** as model substrate and **TRIP** as catalyst, and we could indeed verify that a highly selective kinetic resolution to *O*-benzoylated phenyl ethylene glycol **4d** was occurring. Remarkably, the ring-opening reaction selectively occurs on the most substituted carbon center, and no regioisomer could be detected in the reaction mixture. Furthermore, the optimization of the reaction conditions confirmed the superior selectivity of confined catalyst **1b** and revealed that a substoichiometric amount of carboxylic acid could be used in this case to facilitate the control of the reaction progress (see SI). Under cryogenic conditions and by using toluene as the solvent, the desired transformation was found to smoothly proceed with very high enantioselectivity (s = 44, entry 1, Table 1).

Having identified optimal conditions for the desired kinetic resolution, we tested the transformation on a variety of unsymmetrical epoxides, and the results are collected in Table 1. The reaction proceeds with excellent selectivity (s from 29 to 93) and different substitution patterns on the phenyl ring of the starting epoxides are well tolerated. It is worth noticing that the reactivity of the different substrates is found to be related to the electronic properties and the position of the substituents. Rate acceleration due to the presence of electron-donating groups is observed, and a qualitative correlation with the Hammett sigma constants was possible.[25] For example, styrene oxide **3d** reacted at −20 °C (σ = 0.00; s = 44), its *para-tert*-butyl-substituted congener **3i** was found to be reactive even at −40 °C (σ = −0.20; s = 73), while for the reaction of *meta*-methoxy styrene oxide **3k**, the temperature had to be raised to +4 °C (σ = +0.12; s = 29).[26] Presumably, this general trend is on account of the localized positive charge developed at the reacting carbon center of the epoxide in the ring-opening transition state, which is also in agreement with the perfect regiospecificity of the transformation (*vide infra*). Nevertheless, an influence of the steric features of the epoxide is also observed. Presumably due to the geometrically constrained structure, epoxides **3a** and **3l** exhibited the highest reactivity and were resolved with outstanding selectivities (s = 93 and 87) at −50 °C with reduced catalyst loading (2 mol %, entries 9−10, Table 1).

Although the regiospecificity of the transformation was in accordance with our previous computational investigation on the desymmetrization of *meso*-epoxides, we were intrigued by the remarkable rate acceleration observed for electron-rich substrates. Therefore, we carried out an experimental investigation on the nature of the nucleophilic substitution to exclude the possibility of a S_N1 pathway with a carbocationic intermediate. Enantiopure (*R*)-styrene oxide was subjected to the carboxylysis reaction with both enantiomers of the **TRIP** catalyst, and the same enantiomer of the product was formed in both reactions, albeit at different rates (Scheme 4). This outcome is consistent with an asynchronous S_N2 pathway, which proceeds with inversion of configuration at the chiral center.[27]

We next turned our attention to the kinetic resolution of the more challenging aliphatic epoxides. As expected, these compounds showed reduced reactivity presumably due to the lower tendency to stabilize a partial empty p orbital in the transition state. In particular, the reaction with 1-octene oxide **3m** gave almost no conversion under cryogenic conditions, while poor regio- and stereoselectivity were observed at elevated temperature. Nevertheless, we discovered that the use of highly acidic carboxylic acids leads to a beneficial effect on the reaction rate. Presumably, the overall acidity of the heterodimeric species is finely tuned by the carboxylate monomer. In particular, when employing 2,6-dichlorobenzoic acid **2c** as the nucleophile and **TRIP** as the catalyst, the ring-opening reaction occurred at 0 °C and with restored regiocontrol (see SI). Interestingly, catalyst **1b** was unreactive under similar reaction conditions, probably due to the increased steric demand of the nucleophile. Finally, as shown in eqs 1 and 2, epoxides **3m** and **3n** smoothly underwent the reaction, yielding the desired glycol products and the unreacted epoxides with excellent selectivity factors (respectively s = 40 and 35).

Stereodivergent Resolution of Carboxylic Acids. The structural analysis of the computed transition states for the carboxylytic kinetic resolution of racemic epoxides gave interesting insights. DFT calculations on the ring opening of styrene oxide confirmed that the interactions between the catalyst and the electrophile provide different thermodynamic

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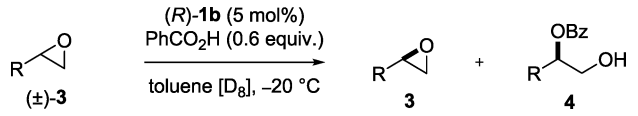
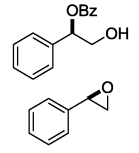
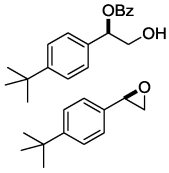
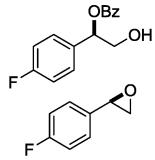
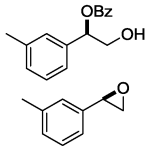
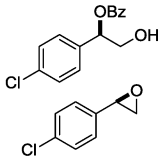
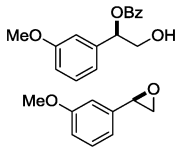
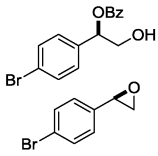
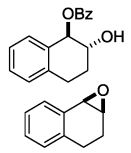
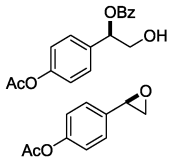
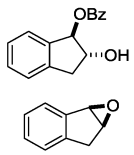
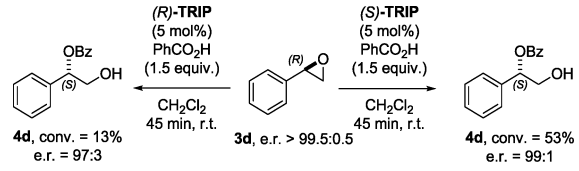
Table 1. Kinetic Resolution of Racemic Epoxides[a]

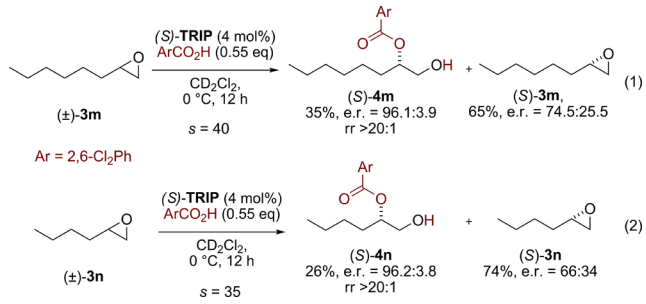


Entry	Products	Yield[b]	e.r.[c]	s[d]	Entry	Products	Yield[b]	e.r.[c]	s[d]
1	 (*R*)-**4d**	40%	95.7:4.3	44	6[e]	 (*R*)-**4i**	50%	95.3:4.7	73
	(*R*)-**3d**	55%	82.6:17.4			(*R*)-**3i**	47%	97.2:2.8	
2	 (*R*)-**4e**	50%	93.3:6.7	48	7	 (*R*)-**4j**	47%	94.3:5.7	61
	(R)-**3e**	46%	96.7:3.3			(*R*)-**3j**	44%	97.5:2.5	
3	 (*R*)-**4f**	30%	96.9:3.1	50	8[f]	 (*R*)-**4k**	48%	91.2:8.8	29
	(*R*)-**3f**	61%	73.5:26.5			(*R*)-**3k**	45%	93.2:6.8	
4	 (*R*)-**4g**	28%	97:3	49	9[g]	 (*R,R*)-**4a**	45%	98:2	93
	(*R*)-**3g**	51%	71:29			(*R,S*)-**3a**	55%	81.2:18.8	
5	 (*R*)-**4h**	46%	93.4:6.6	46	10[g]	 (*R,R*)-**4l**	53%	94.1:5.9	87
	(*R*)-**3h**	45%	95.8:4.2			(*R,S*)-**3l**	44%	99.6:0.4	

[a]Unless otherwise indicated, all reactions were carried out on 0.1 mmol scale in 0.016 M solution. [b]Determined by NMR analysis with internal standard (see SI). [c]Determined by HPLC on chiral stationary phase. [d]Determined by Kagan's equation.[30] [e]Reaction performed at −40 °C. [f]Reaction performed at +4 °C. [g]Reaction performed at −50 °C with 2 mol % catalyst loading.

Scheme 4. Stereoselectivity Study





stability to the diastereoisomeric transition states (ΔG = 0.99 kcal mol^{-1}). Surprisingly, however, we noticed that while the epoxide is constrained in the confined pocket of the catalyst, the carboxylic acid backbone lies instead in a relatively open space (Figure 7a). This led to the hypothesis that, despite being highly selective for the epoxide substrate, our catalytic system might instead be "promiscuous" with regard to the nucleophile structure.

This observation suggested that the asymmetric carboxylysis of epoxides could be effectively applied to an unprecedented stereodivergent parallel kinetic resolution of racemic α-chiral carboxylates, since the catalyst would dictate the configuration of newly formed stereogenic centers, regardless of the extant stereochemistry of the substrate.[28,21c] We speculated that the enantiomers of an α-chiral carboxylic acid could be reacted with only minimal difference in the relative reaction rate (Figure 7b). Therefore, the transformation would yield an equimolar mixture of highly enantioenriched diastereoisomeric ester products. Chromatographic separation and hydrolysis under mild conditions would eventually provide an easy access to enantiopure carboxylic acids.

Chiral carboxylic acids are important molecules in medicine.[29] For instance, a large family of nonsteroidal anti-inflammatory drugs (NSAIDs) is represented by α-aryl

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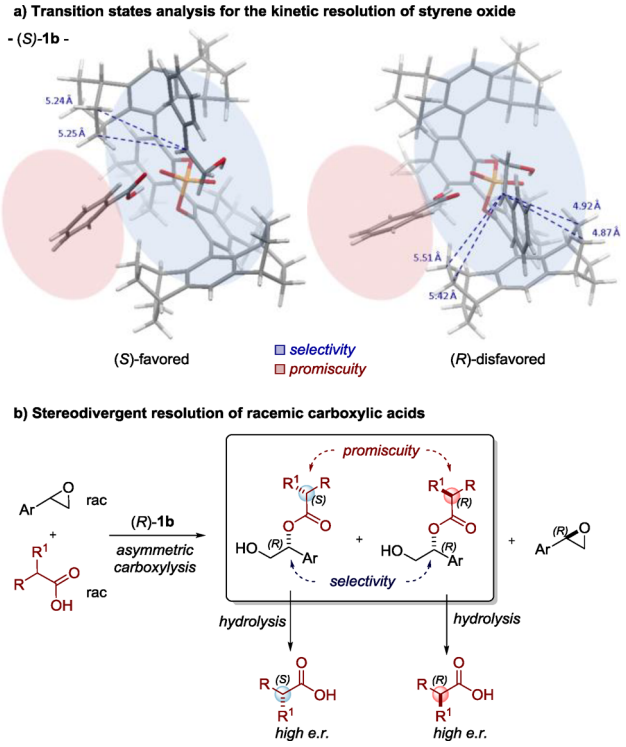


Figure 7. Design of a diastereodivergent resolution of carboxylic acids. Structures computed at the B3LYP/6-31G* level. Key substrate-catalyst distances indicated in blue. See SI for further details.

propionic acid derivatives, and it is well accepted that chirality influences both the pharmacokinetics and the pharmacodynamics of these compounds.[30] Ibuprofen, ketoprofen, fenoprofen, and flurbiprofen, to name just a few, are marketed drugs and are industrially produced in their racemic form (Figure 8).[31] Therefore, the development of simple methodologies to achieve effective resolutions may be valuable.

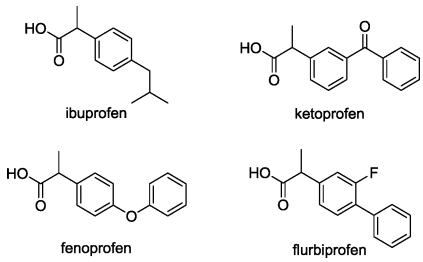
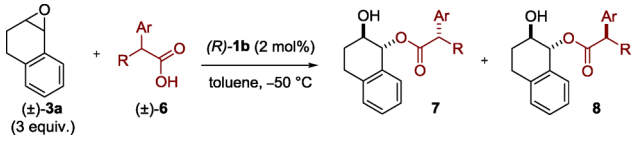
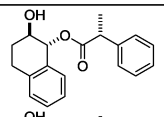
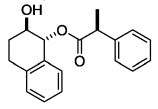
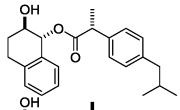
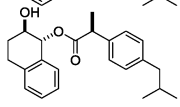
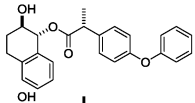
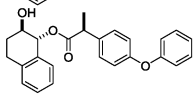
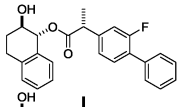
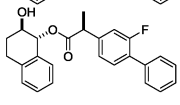
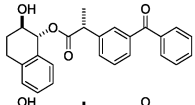
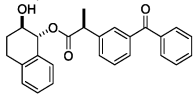
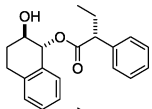
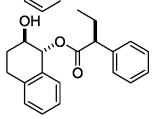
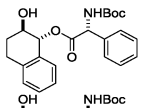
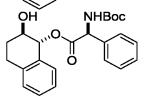


Figure 8. Chiral carboxylic acids as NSAIDs.

We initially decided to probe our design using α-phenyl propionic acid **6a** as the model substrate, and we selected epoxide **3a** as the electrophile in order to exploit the inherently superior reactivity that we had previously observed (entry 9, Table 1). Under the optimal conditions described above for the kinetic resolution, we could demonstrate the potential of our novel approach. Using catalyst **1b** in toluene under cryogenic conditions (−50 °C), the two diastereoisomers **7a** and **8a** were obtained in excellent yield and enantiomeric ratio and could be effectively separated by standard chromatography on silica gel (**7a**: 49%, er = 97:3; **8a**: 46%, er = 98.5:1.5; entry 1, Table 2). It is worth mentioning that the small difference in the enantiomeric excess of the two products is presumably due to a residual enantiodiscrimination of the stereogenic center of the carboxylic acid substrate.

Table 2. Stereodivergent Resolution of Carboxylic Acids[a]



Entry	Products		Yield (%)	e.r.[b]
1		**7a**	49	97:3
		**8a**	46	98.5:1.5
2		**7b**	50	97.5:2.5
		**8b**	48	98:2
3		**7c**	48	96:4
		**8c**	49	98.5:1.5
4		**7d**	50	97:3
		**8d**	48	98.5:1.5
5		**7e**	50	95:5
		**8e**	46	98.5:1.5
6		**7f**	48	>99.5:0.5
		**8f**	49	96:4
7[c]		**7g**	44	96:4
		**8g**	39	98:2

[a]All reactions were carried out on substrates **6** (0.5 mmol) and epoxide **3a** (1.5 mmol, 3 equiv) in 1.6 mL of toluene. [b]Determined by HPLC on chiral stationary phase. [c]Reaction performed at −30 °C.

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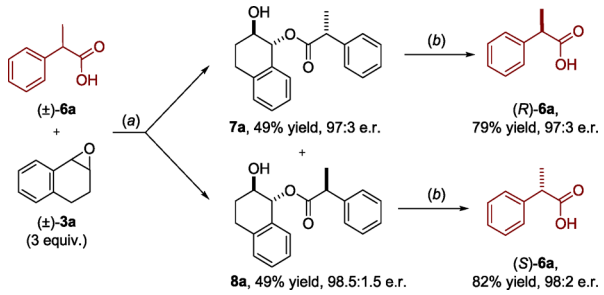
Having found optimal conditions for the stereodivergent transformation, we investigated the scope and the limitations of the methodology (Table 2). We initially explored medicinally relevant carboxylic acids, thus focusing our attention on substrates bearing a variously substituted aromatic moiety. Remarkably, further confirming our initial speculation on the promiscuity of the catalytic system, the transformation was found to be basically insensitive to the electronic and steric features of the substrates. Ibuprofen **6b**, fenoprofen **6c**, and flurbiprofen **6d** smoothly underwent the transformation delivering the corresponding ester products in high yields and enantioselectivities (entries 3−5, Table 2).

Despite the low solubility exhibited under the reaction conditions, ketoprofen **6e** was effectively reacted, maintaining high levels of enantiocontrol albeit in a longer reaction time (entry 6, Table 2). Notably, also α-phenyl butanoic acid **6f** was smoothly converted into the desired ester products, however in this reaction, the different enantiomeric ratios observed in compounds **7f** and **8f** suggest a non-negligible control over the stereocenter of the nucleophile (entries 2, Table 2).[32]

Next, the methodology was applied to protected α-amino acids. Racemic N-protected phenylglycine **6g** was successfully reacted, giving the desired products **7g** and **8g** in very high enantiomeric ratio (entry 7, Table 2). It is worth to mention that while naturally occurring amino acids are largely available in an enantiopure form, nonproteinogenic ones are often obtained via chemical resolution of racemic mixtures.[33] Therefore, we believe that the application of our methodology to this class of compounds is of particular interest.

Finally, the complete stereodivergent resolution strategy was showcased for the model substrate α-phenyl propionic acid **6a** (Scheme 5). After the enantioselective carboxylysis, the two isolated diastereoisomers were subjected to mild aqueous acidic conditions, thus giving access to the corresponding carboxylic acid enantiomers with essentially no erosion of the optical purity.[34]

Scheme 5. Stereodivergent Resolution of α-Phenyl Propionic Acid 6a[a]



[a](a) (*R*)-**1b** (1 mol %), toluene −50 °C; (b) dioxane, HCl_{aq} 10%, 50 °C.

CONCLUSIONS

We have demonstrated that the heterodimeric self-assembly with phosphoric acid catalysts serves as useful tool in the organocatalysis of nucleophilic addition reactions of carboxylic acids. The novel reaction mode has been recently applied to a variety of useful transformations, which were previously elusive in organocatalysis. Several highly enantioselective ring-opening reactions of aziridines and epoxides have been disclosed, giving access to chiral 1,2-aminoalcohols and diols.[7a,b] The concept has also been successfully expanded to include thiocarboxylic acids for the synthesis of β-hydroxythiols and more recently to thioamides, leading to the first catalytic, enantioselective thiirane synthesis.[7c,d] By combining experimental and DFT analyses, we have fully elucidated the catalytic principles of this novel activation mode. Detailed mechanistic studies provided extensive support for the proposed self-assembly organocatalysis. We show that the noncovalent supramolecular interaction leads to a 2-fold effect: increased acidity of the phosphoric acid catalyst and enhanced nucleophilicity of the carboxylic acid. The remarkable stability of this heterodimeric species in unpolar solvents was found to be crucial for the transformations, effectively overriding the undesired alkylative deactivation of phosphoric acid catalysts with aziridines and epoxides.

The rationalization of the reactivity of the heterodimeric species as well as the careful description of the catalytic cycle and the transition state analysis allowed the detailed codification of the novel activation strategy. Based on our mechanistic investigations, we designed and explored two novel asymmetric transformations. Catalyzed by a confined phosphoric acid catalyst, we demonstrated the kinetic resolution of terminal epoxides via asymmetric carboxylysis. This methodology was found to be robust and general for aromatic epoxides and, with a slight modification of the conditions, also applicable to aliphatic substrates. In addition, we disclosed a practically useful stereodivergent resolution of α-chiral carboxylic acids, thus providing an attractive alternative for the preparation of many enantiopure NSAIDs and α-amino acids.

In view of the synthetic value of the transformations and the broad applicability shown, this mode of action will be further exploited and investigated in asymmetric Brønsted acid catalysis.[35] Nonetheless, we also anticipate that the concepts described here will provide useful guidelines for the design of similar heterodimeric activation modes,[36] thus broadening asymmetric organocatalysis to several still elusive classes of substrates.[37]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09179.

Experimental part: procedures, compound characterization, NMR spectra and GC and HPLC traces for all new compounds (PDF)

Computational part: methods, detailed numerical results for energies, transition states, Cartesian coordinates of the optimized structures, and further discussion of the computational results (PDF)

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Notes

The authors declare no competing financial interest.

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