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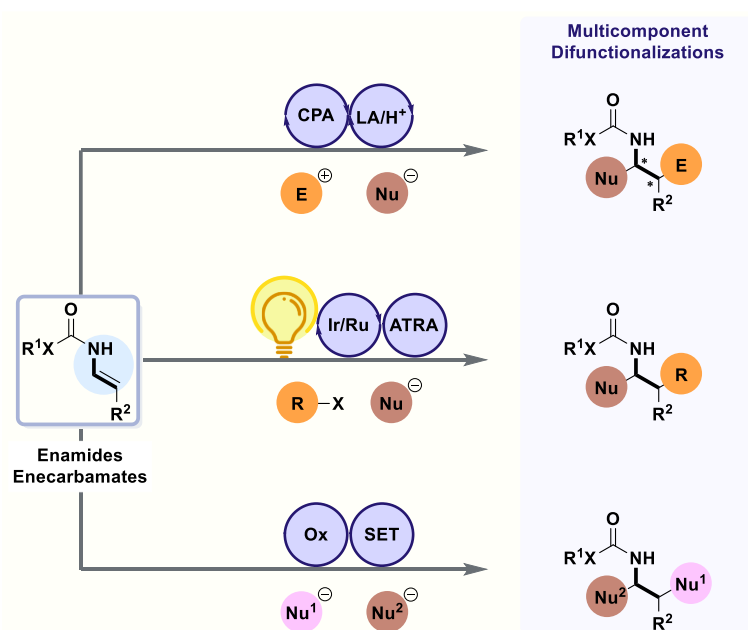
Strategies Toward the Difunctionalizations of Enamide Derivatives for Synthesizing α,β -Substituted Amines

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CONSPECTUS



Enamide and enecarbamate derivatives containing a nucleophilic center at the β -position from their nitrogen atom as well as a latent electrophilic site at its α -position are interesting motifs in organic chemistry. This dual reactivity—analogue that of the enamines—enables double functionalization and increased structural complexity. Furthermore, a stabilizing electron-withdrawing group on nitrogen drastically increases their stability. In that respect, enamides and enecarbamates are excellent partners for multicomponent transformations, and our research primarily focuses on these compounds in particular.

Difunctionalization generally occurs through the nucleophilic addition of the enecarbamate on an electrophile to form iminium, which can subsequently react with a nucleophilic species. Although potent, such an approach is highly challenging due to the low stability of the intermediate iminium, leading to undesired hydrolysis or oligomerizations. Epimerization, competitiveness, and compatibility issues between the reaction partners are additional hindrances to developing these methodologies. To overcome these limitations, we described many complementary strategies.

To control the enantioselectivity of these transformations, chiral phosphoric acids were found to be particularly well-suited to activate multiple reactants due to the formation of a hydrogen bonds network, allowing for an organized transition state in a chiral pocket. Interestingly, when deprotonated as phosphates, they can also play the role of ligands for Lewis acidic metals.

To avoid iminium oligomerization, we successfully used stabilized α -arylated enamides. However, this approach was restricted to a simple nucleophilic addition at the β -position. To achieve the difunctionalizations of α -unsubstituted derivatives, we explored reversibly linked nucleophile and electrophile to address their compatibility problem. Alternatively, we devised a sequential methodology for resolving the stability issue of the *N*-acyl iminium based on its intermediate trapping using a temporary nucleophile (alcohol or thiol). Interestingly, the trapping agent could further be displaced by the desired final α -substituent under Lewis acidic

or photocatalytic activation. This led us to design new chiral and bifunctional phosphoric acid catalysts bearing chromophores to merge asymmetric organocatalysis and photochemistry.

These photocatalysis studies incited us to focus on radical processes to manage original functionalizations that would not be feasible otherwise. β -alkylation and β -trifluoromethylation of enecarbamates *via* visible light-promoted atom transfer radical additions were successfully performed. As β -allylations remained unattainable with the precedent methods, we eventually turned our attention to cerium(IV)-mediated oxidative single electron transfers. It allowed for singly occupied molecular orbital activation of these substrates to elicit their umpolung reactivity.

Thus, the functionalization of enecarbamate derivatives appears as a valid synthetic strategy for obtaining important building blocks for agrochemical, pharmaceutical, and cosmetic industries, including diamines, haloamines, aminotryptamines, and less accessible trifluoromethylated or allylic compounds.

KEY REFERENCES

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- Alix, A.; Lalli, C.; Retailleau, P.; Masson, G. Highly Enantioselective Electrophilic α -Bromination of Enecarbamates: Chiral Phosphoric Acid and Calcium Phosphate Salt Catalysts. *J. Am. Chem. Soc.* **2012**, *134*, 10389–10392.² Enecarbamate

difunctionalization requires the combined use of an electrophile and a nucleophile, which were reversibly linked in this methodology to ensure their compatibility, while a catalyst switch enabled enantiodivergence.

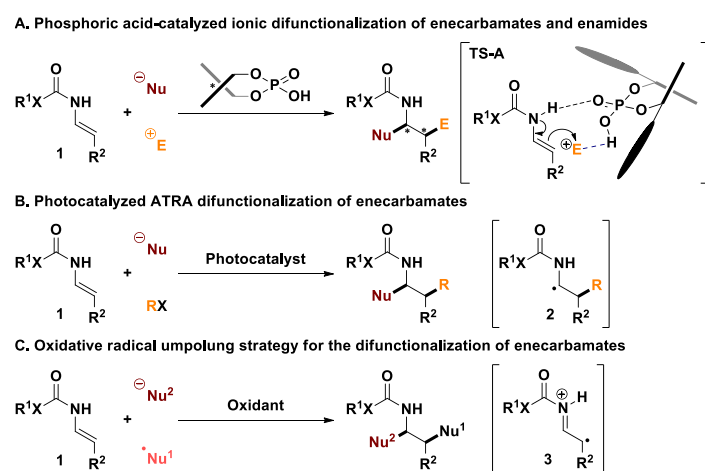
- Bekkaye, M.; Masson, G. Cerium(IV) Ammonium Nitrate Mediated Three-Component α -Allylation of Imine Surrogates. *Org. Lett.* **2014**, *16*, 1510–1513.³ This publication proposed to harness an umpolung approach *via* CAN-mediated SOMO activation of enecarbamates to promote their challenging β -allylation.
- Lyu, J.; Claraz, A.; Vitale, M. R.; Allain, C.; Masson, G. Preparation of Chiral Photosensitive Organocatalysts and Their Application for the Enantioselective Synthesis of 1,2-Diamines. *J. Org. Chem.* **2020**, *85*, 12843–12855.⁴ In this study, the strength of bifunctional catalyst design is illustrated with the development of a novel chiral phosphoric acid substituted with thioxanthone motif, which enabled the one-pot difunctionalization of enecarbamates through tandem asymmetric organocatalysis and photocatalysis.

1. INTRODUCTION

Enecarbamates and enamides **1** are highly valuable synthetic building blocks for constructing diverse nitrogen-containing molecules.⁵ Unlike standard alkenes, their carbon–carbon double bond is polarized using a nitrogen atom. Therefore, the carbon at the β -position is nucleophilic and can react with electrophiles to form iminiums. In contrast, the electron-depleted carbon at the α -position is a latent electrophilic site. These enamine analogs are more stable due to the presence of an electron-withdrawing group on the nitrogen: they can be isolated and are easy to handle. Therefore, they have previously been used as prochiral substrates in enantioselective

hydrogenation reactions.^{5c,6} However, they remain reactive enough for multicomponent difunctionalizations, enabling efficient constructions of α,β -substituted amines to increase chemical diversity. This projected strategy is relatively challenging due to the potential compatibility issues between the reactants. In the last decade, our group has developed novel selective strategies under mild conditions to address this problem. In particular, we focused on phosphoric acid-catalyzed asymmetric activation of enamides and enecarbamates for accessing highly enantioenriched amines (Scheme 1A). To complete these asymmetric methods, the photocatalyzed atom transfer radical additions (ATRA) (Scheme 1B) enabled the achiral α,β -substitutions of enecarbamates to introduce more challenging moieties on the β -carbon, like alkyl or trifluoromethyl groups, which cannot be incorporated otherwise. Alternatively, using an oxidant to generate a radical cation of type **3** (Scheme 1C) led to the reversal of their reactivity, making their β -position electrophilic (radicophilic) to allow original β -allylations.

Scheme 1. Strategies to achieve MCR difunctionalizations of enamides and enecarbamates

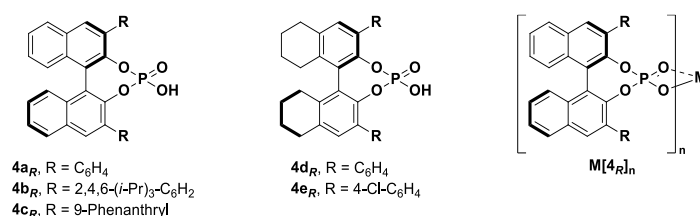


2. CHIRAL PHOSPHORIC ACID-CATALYZED ASYMMETRIC MONO- AND DIFUNCTIONALIZATIONS OF ENAMIDE DERIVATIVES

2.1 Electrophilic amination

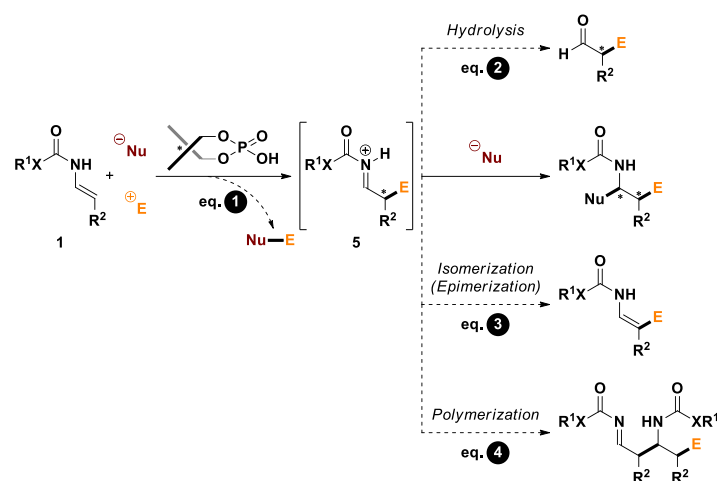
Since the reporting of Kobayashi's seminal copper-catalyzed methodology in 2004,^{5a,7} the use of secondary enecarbamate derivatives in asymmetric nucleophilic additions has acquired considerable momentum.⁵ Terada *et al.* consequently highlighted that this metal could be replaced in such a reaction using chiral phosphoric acids (Figure 1)⁸ developed by his group and Akiyama's in 2004.⁹ The bifunctional nature of these organocatalysts, which allows the synergistic activation of electrophile and nucleophile, makes them effective. They activate enamides by forming a hydrogen bond with the proton on their nitrogen, enabling their highly enantioselective difunctionalization.^{5c,d,f}

Figure 1. Chiral phosphoric acids and phosphate salts used as catalysts



However, such reactions require the simultaneous presence of two nucleophiles (the enamide derivative itself and a second one (**Nu**)) with one electrophile (**E**), leading to several issues, as depicted in Scheme 2. First, the obvious competing reaction between the electrophile **E** and the second nucleophile **Nu** (eq. 1) must be circumvented. Despite its conceptual simplicity, such a strategy lacks the high diversity and modularity offered by multicomponent reactions (MCRs).¹⁰ Other problems, such as hydrolysis (eq. 2), isomerization (eq. 3), or additional nucleophilic attack of **1** on the *N*-acyliminium ion **5**, leading to side polymerization (eq. 4), must be considered. Therefore, the choice of reaction partners is crucial for the success of these MCRs. Hereafter, we will detail the approaches we developed to address those challenges.

Scheme 2. Competitive pathways and challenges in the ionic difunctionalization of enamides

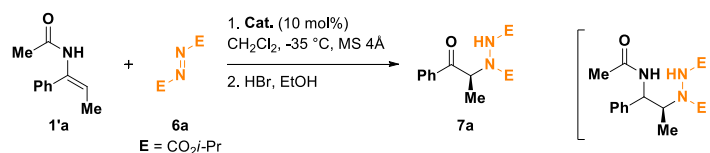


To avert the aforementioned competitive reactions, our first approach involved enecarbamates derivatives bearing aryl (Ar) substituents at the α -position of nitrogen (Table 1). We assumed that the corresponding intermediate iminiums would be stabilized and, consequently, less prone to hydrolysis. In addition, we believed that the steric hindrance created by the aromatic moiety would prevent multiple additions of the enecarbamate derivative on successive *N*-acyliminium intermediates, reducing the risk of polymerization.

Kobayashi *et al.*^{5a,7,11} reported the first asymmetric amination of (*E*)-enecarbamates and azodicarboxylates using chiral diamines–Cu(OTf)₂ complexes. This methodology was further extended by Guo, Gong *et al.* to (*Z*)-enecarbamates by the mean of chiral *N,N*-dioxide-Cu(OTf)₂ catalysis.¹² Based on these studies, we aimed at developing a new organocatalytic enantioselective version of such an electrophilic amination. Unfortunately, it appeared that enecarbamates were unsuitable substrates for this reaction, and we switched them for enamides **1'** featuring an enhanced reactivity. Their addition to diisopropylazodicarboxylate **6a**, followed by the hydrolysis of the resulting ketimines, would provide α -keto-amines. Based on our previous studies on enantioselective cycloaddition with enecarbamates,^{5f,13} we speculated that chiral phosphoric acids could induce enantioselectivity in such reactions due to the dual activation of both partners through hydrogen bonding (Scheme 1, **TS-A**).¹⁴ Upon optimization (Table 1), the corresponding 1,2-hydrazinoketone **7a** was obtained in good yield. However,

despite screening a large number of (*R*)-BINOL-derived phosphoric acids, the enantioselectivity remained below 90% (entry 1). Ishihara and List groups had demonstrated that variable portions of alkali- or alkaline-earth metal-phosphate complexes are formed during the purification of the catalyst on silica gel.¹⁵ Therefore, we inferred that these salts could be responsible for the low stereoselectivity. For reprotonating the phosphates, catalyst **4a_R** was washed with HCl after flash chromatography (entry 2). Surprisingly, the resulting phosphoric acid led to decreased enantioselectivity. Based on this observation, we reasoned that phosphate salt impurities might define a better chiral environment. This hypothesis was consistent with the findings of Ishihara *et al.*, who highlighted the catalytic efficiency of such species in enantioselective Mannich reactions with β -dicarbonylated compounds.^{9a,15a,16} In this context, we evaluated their catalytic activity in our electrophilic amination. After extensive optimization, it was found that the chiral calcium phosphate salt, **Ca[4a_R]_n**, was the best catalyst, furnishing compound **7a** in 82% yield and 95% *ee* (entry 3).¹⁴

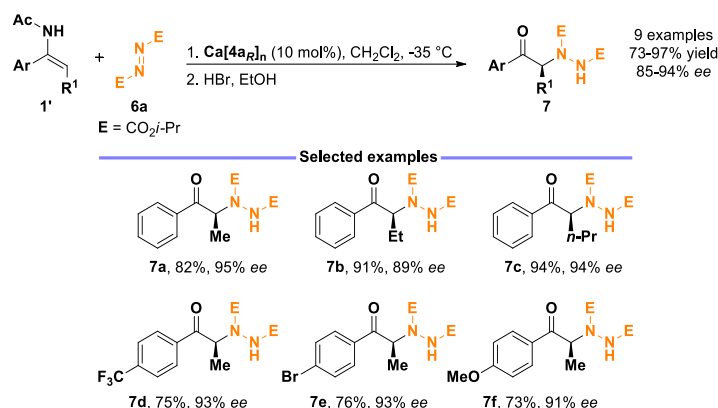
Table 1. Comparison of the reactivity of different chiral phosphoric acids and phosphate salt catalysts



Entry	3	Cat.	Yield 7a (%)	<i>ee</i> 7a (%)
1	(<i>E</i>)- 3a	4a_R	99	89
2	(<i>E</i>)- 3a	4a_R	92	85
3	(<i>E</i>)- 3a	Ca[4a_R]_n	82	95

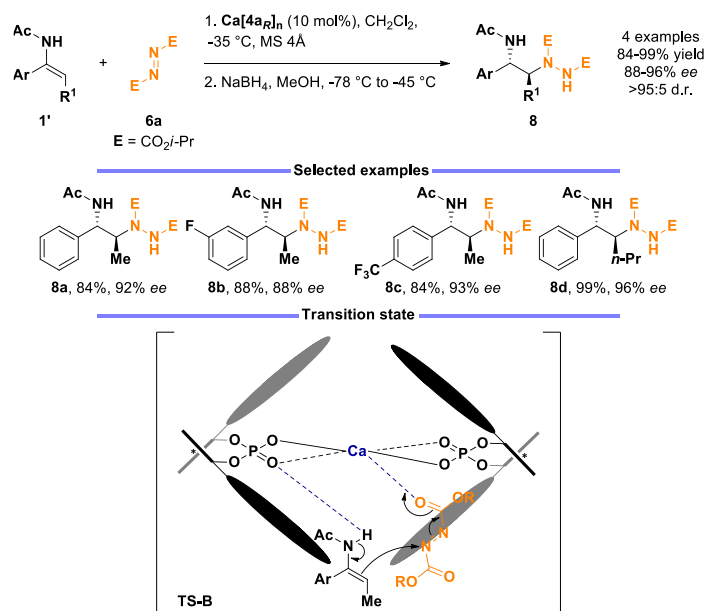
The scope investigation (Scheme 3) revealed that enamides bearing electron-poor, -neutral, and -rich aromatic substituents at the α -position react smoothly with diisopropylazodicarboxylate **6a**. (*E*)-enamides with longer linear alkyl chains at the β -position were equally well accommodated, delivering the corresponding α -keto-amines with similar enantioselectivities.¹⁴

Scheme 3. Synthesis of enantioenriched 1,2-hydrazinoketones



As the next step, we were interested in trapping the iminium intermediate with hydride to access chiral diamines, which are essential motifs in bioactive natural products, pharmaceutical compounds, and chiral ligands, as described by Kobayashi and Guo's groups.¹⁷ An asymmetric one-pot sequential amination/reduction process using NaBH₄ was developed (Scheme 4), and a wide range of *syn*-1,2-diamines **8** was obtained in excellent yields with high enantio- and diastereoselectivities (>95:5 d.r.).¹⁸

Scheme 4. Synthesis of enantioenriched 1,2-diamines



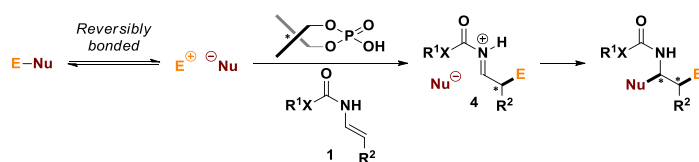
Extensive mechanistic studies were conducted to elucidate the nature of the active catalytic species.¹⁸ First, MALDI-TOF mass spectrometry analysis of Ca[4aR]_n revealed its oligomeric nature by detecting monometallic Ca[4aR]₂, bimetallic Ca₂[4aR]₃, and trimetallic Ca₃[4aR]₅

complexes. This was further supported by a strong negative nonlinear effect between calcium catalyst enantiopurity and 2-hydrazinoketone **7** enantioselectivity. Subsequently, density functional theory calculations suggested that Lewis acidic calcium-bis(phosphate) salt $\text{Ca}[\mathbf{4a}_R]_2$ would be the active species. As shown in the transition state model proposed in Scheme 4, $\text{Ca}[\mathbf{4a}_R]_2$ acts as a bifunctional catalyst, activating the enamide and azodicarboxylate *via* hydrogen bonding and calcium coordination. The *Re* face of **6a** is shielded by the calcium-bis(phosphate) complex, ensuring an excellent asymmetric induction.

2.1 Electrophilic halogenation

Encouraged by these results, we investigated the enantioselective difunctionalization of α -unsubstituted enecarbamates, wherein the second nucleophile and electrophile would be compatible, as depicted in Scheme 5. In this regard, *N*-halosuccinimides, which possess electrophilic halogen atoms loosely bonded to a nucleophilic succinimide, were deemed promising reaction partners.¹⁹ We surmised that the phosphoric acid catalyst⁸ might control the formation of the two new bonds in an organized transition state.²

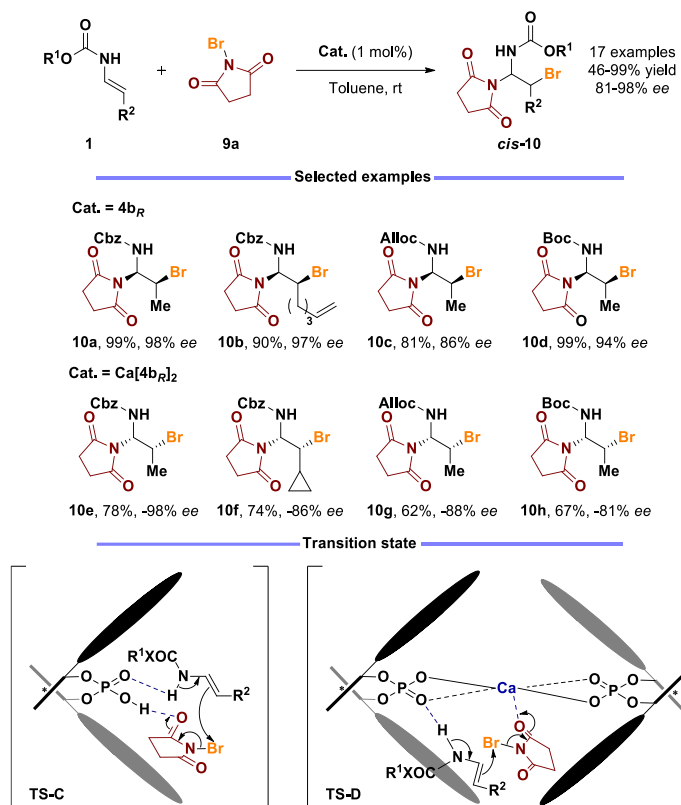
Scheme 5. Strategy relying on a reversible link between the nucleophile and electrophile



We first examined the reaction of (*E*)-enecarbamate (*E*) **1a** ($R^1 = \text{Bn}$ and $R^2 = \text{Me}$) with NBS **9a** catalyzed by 1.0 mol% of (*R*)-TRIP (**4b_R**).² The desired brominated product, **10a**, was obtained in 99% yield and 98% *ee* as the *cis*-isomer (>95:5 d.r.). The (*Z*)-isomer (*Z*)-**1a** gave the same enantiomer of **10a** as the major product (>95:5 d.r.), albeit with a moderate yield (67%) and lower *ee* (86%). To our surprise, when the catalyst was changed from **4b_R** to its corresponding calcium salt $\text{Ca}[\mathbf{4b}_R]_2$, we observed a reversal of the enantioselectivity. The

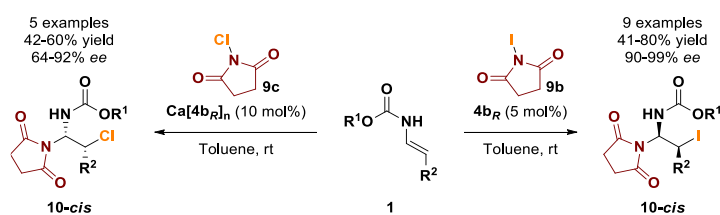
bromination afforded **10e** in 78% yield with excellent *ee* (98%) and d.r. values (>95:5). The reaction proceeded smoothly with a range of β -substituted (*E*)-enecarbamates bearing either linear or branched alkyl groups furnishing products **10** in high yields and excellent stereoselectivities (Scheme 6).

Scheme 6. Enantioselective bromoamination of enecarbamates



This transformation was further extended in later work to *N*-iodosuccinimide (NIS, **9b**) and *N*-chlorosuccinimide (NCS, **9c**) (Scheme 7).²⁰ The enantioselective iodoamination was made difficult by the partial degradation of enecarbamates due to the generation of iodine during the reaction. Yields could be improved by augmenting the catalyst loading of **4b_R** and reducing the temperature to 0 °C. Diastereo- and enantioselectivities of the resulting products were excellent. The asymmetric chloroamination provided the corresponding products in reduced yields and good enantioselectivities due to the lower reactivity of NCS compared to NBS and NIS.

Scheme 7. Enantioselective iodo- and chloroamination of enecarbamates



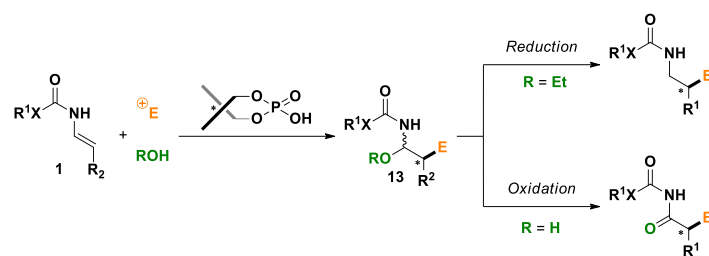
Two different transition state models—**TS-C** and **TS-D**—were proposed to account for the inversion of selectivity observed while changing the catalyst (Scheme 6).^{2,20} Phosphoric acid **4b_R** bearing bulky 2,4,6-triisopropylphenyl groups efficiently hinders the *Re* face of NBS, directing the enecarbamate attack on its *Si* face to afford the (*S*)-iminium intermediate. In contrast, the *Re* face is fully accessible with calcium-bis(phosphate) complex **Ca[4b_R]₂**, leading to the (*R*)-isomer.

3. CHIRAL PHOSPHORIC ACID-CATALYZED ASYMMETRIC THREE-COMPONENT DIFUNCTIONALIZATIONS OF ENAMIDE DERIVATIVES

3.1 Mannich reaction

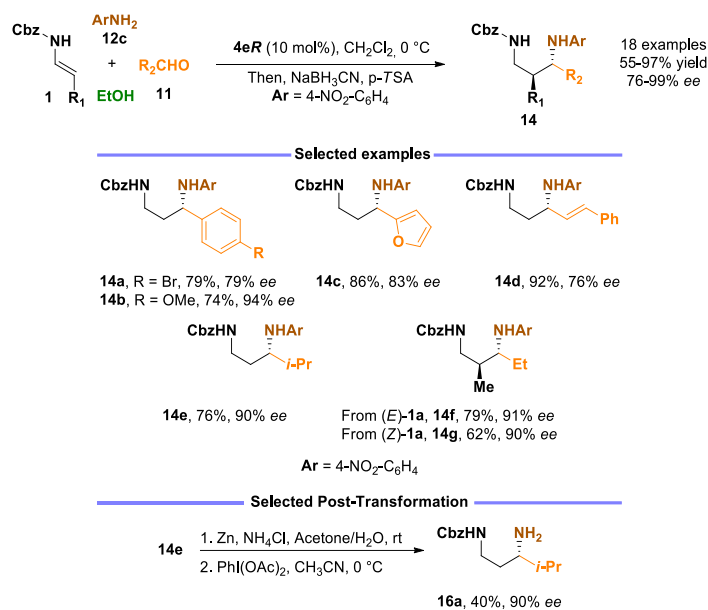
Though very efficient, this second strategy remained limited to specific cases wherein the nucleophile and the electrophile are reversibly linked. To develop a more general approach, we decided to use a weaker second nucleophile, compatible with the electrophile, that would chemoselectively attack on the iminium intermediate. Alcohols were suitable for trapping and stabilizing the highly reactive α -unsubstituted *N*-acyliminium. The resulting hemiaminal could be either reduced or oxidized (Scheme 8). However, alcohols possess acidic protons, which might disrupt transition states relying on hydrogen-bond networks between the phosphoric acid catalyst, enecarbamate, and electrophile, making enantiocontrol more challenging.

Scheme 8. Strategy relying on the iminium trapping by a temporary nucleophile followed by reduction or oxidation



Hence, we reported a chiral phosphoric acid-catalyzed 4-component synthesis of 1,3-diamines,²¹ a ubiquitous moiety in biologically relevant molecules.²² This enantioselective Mannich condensation involved aldehydes **11** and electron-deficient aniline **12c**, forming an electrophilic iminium and enecarbamate **1b** in the presence of a large excess of ethanol and 10 mol% of **4e**. The obtained hemiaminals **13** were then reduced *in situ* by NaBH₃CN and *p*-TSA to obtain the corresponding optically active 1,3-diamines **14** (Scheme 9). A wide range of aromatic aldehydes was tolerated, providing the corresponding 1,3-diamines in high yields and enantioselectivities. Enolizable aliphatic α - and β -substituted aldehydes worked equally well. β -substituted (*E*)-enecarbamates furnished *anti*-1,3-diamines with similar results. (*Z*)-isomer (*Z*)-**1a** also delivered the *anti*-product **14g** in good *ee*, albeit in moderate yield. Notably, the 4-nitrophenyl group was removed in two steps including the reduction of the nitro moiety followed by the oxidative cleavage of the resulting aniline.

Scheme 9. Synthesis of enantioenriched 1,3-diamines



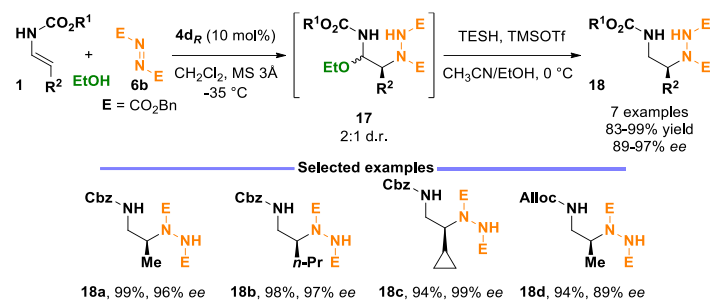
3.2 Electrophilic amination with alcohols as temporary nucleophiles

As the latter alcohol trapping strategy had proved its robustness, we thought to apply it for the direct enantioselective α -amination of α -unsubstituted enecarbamates **1** to access chiral 1,2-diamines after reduction (Scheme 10).¹ Because of the instability of the generated *N*-acyliminium intermediate, only a few asymmetric examples have been reported with moderate enantioselectivity.⁷ Contrary to the asymmetric α -amination of α -substituted arylenamides, chiral calcium phosphate salts did not provide satisfactory yields and enantiomeric excesses.¹⁴ In contrast, octahydrogenated (*R*)-H₈-3,3'-bis-phenyl-BINOL phosphoric acid **4d_R** afforded **17a** as a mixture of diastereoisomers in 99% yield and 97/95% *ee*. This time, only one equivalent of EtOH was required. The poor diastereoselectivity of the reaction was not problematic as the noncontrolled hemiaminal asymmetric carbon was lost during the following reduction step.

Conditions for the reduction were then established. An excess of triethylsilane in the presence of TMSOTf furnished the enantioenriched 1,2-diamines **18** in excellent yield (99%) with no loss of enantioselectivity (96% *ee*). Combining the two reactions in a one-pot synthesis resulted in greatly reduced yields. The two-step sequence was then applied to a small range of mainly

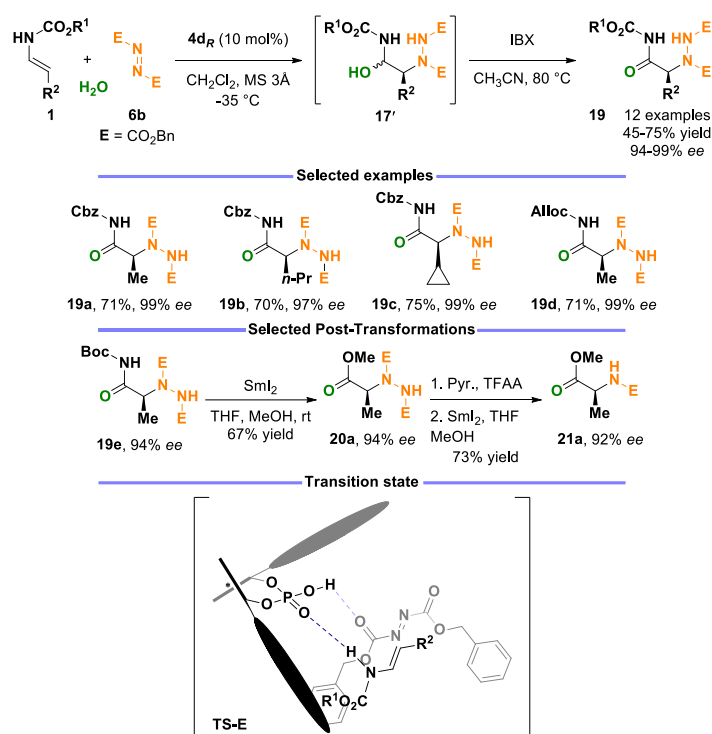
linear β -substituted (*E*)-enecarbamates, affording the desired product in high yields and enantioselectivities.¹

Scheme 10. Reductive sequence to access enantioenriched 1,2-diamines



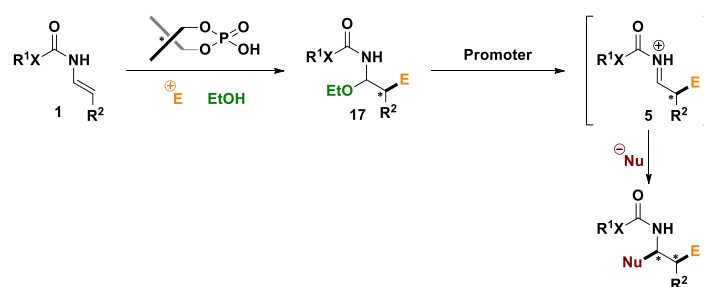
The methodology was easily extended for forming optically active α -hydrazinoamides **19** by replacing EtOH with water, followed by IBX-mediated oxidation (Scheme 11). A broad scope of linear and branched (*E*)-enecarbamates was tolerated.¹ Varying the *N*-protecting groups did not result in any erosion of either yield or *ee* except when Fmoc was used. α -Hydrazinoamides are attractive precursors of enantiomerically enriched α -amino acids. To demonstrate their usefulness, we developed a route from substrate **19e** providing nonproteogenic amino-acid **21a** in 49% yield over three steps with almost no loss in enantioselectivity. To explain the enantiocontrol of the reaction, we proposed transition state **TS-E** based on the dual activation of reactive partners by the phosphoric acid, which shields the *Re* face of DBAD (**6b**), leading to the exclusive attack of its *Si* face by enecarbamate **1**.

Scheme 11. Synthesis of enantioenriched α -hydrazinoamides



In light of previous publications from Hiemstra and Speckamp and interest in pursuing our synthetic investigation regarding amidoethers, we hypothesized that such species could regenerate the electrophilic iminium in the presence of a suitable promoter.²³ Such a process would allow a second and irreversible nucleophilic addition, opening the way for chemical divergence (Scheme 12).

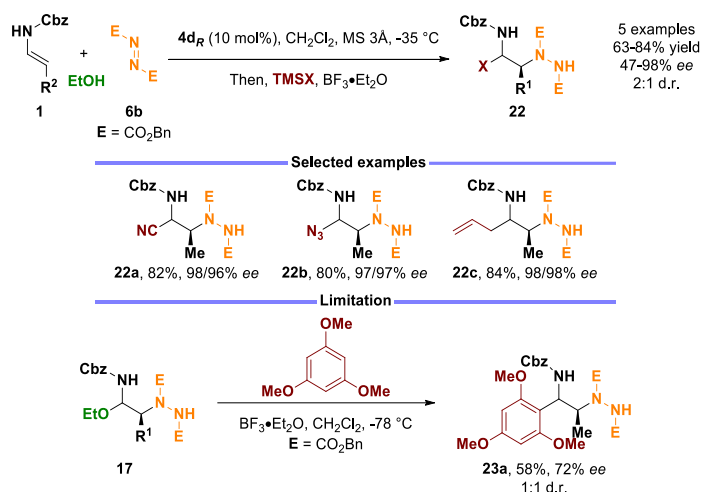
Scheme 12. Difunctionalization strategy based on the iminium regeneration from the intermediate hemiaminal



We started with the objective of introducing silylated nucleophiles. The *N*-carbamoylaminoether **17a** was synthesized, isolated, and purified based on the aforementioned procedure.²⁴ Diverse Lewis acids were then screened to regenerate *N*-acyliminium intermediate

5. Boron trifluoride etherate was found to be the best one in combination with TMSCN as a nucleophile, providing 1,2-diamine **22a** in 82% yield as a mixture of diastereoisomers (2:1 d.r.), with high *ee* (>96%) for both of them. Other silylated nucleophiles (TMSN₃ and TMS-allyl) were successfully applied, delivering the corresponding products in good yields and excellent enantioselectivities (Scheme 13).

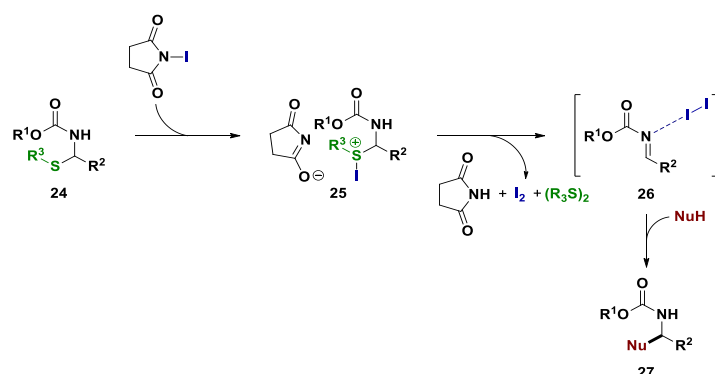
Scheme 13. Synthesis of α -substituted enantioenriched 1,2-diamines



3.2 Electrophilic amination with thiols as temporally nucleophiles

We next expanded the reactivity to aromatic and heteroaromatic nucleophiles, which are key building blocks for agrochemical, pharmaceutical, and cosmetic industries.²⁵ However, using electron-rich trimethoxybenzene with the same conditions furnished the corresponding product **23a** in only moderate yield (58%) and *ee* (72%) with no diastereoselectivity. This observation was attributed to the partial epimerization of the imine intermediate due to the slower addition of the aryl partner compared to silylated nucleophiles. Therefore, we looked for milder conditions to prevent this side reaction. We efficiently generated *N*-acylimines **26** using NIS-mediated catalytic activation of α -amidosulfides **24** through the formation of cationic amidoiodosulfonium intermediates **25** (Scheme 14).²⁶

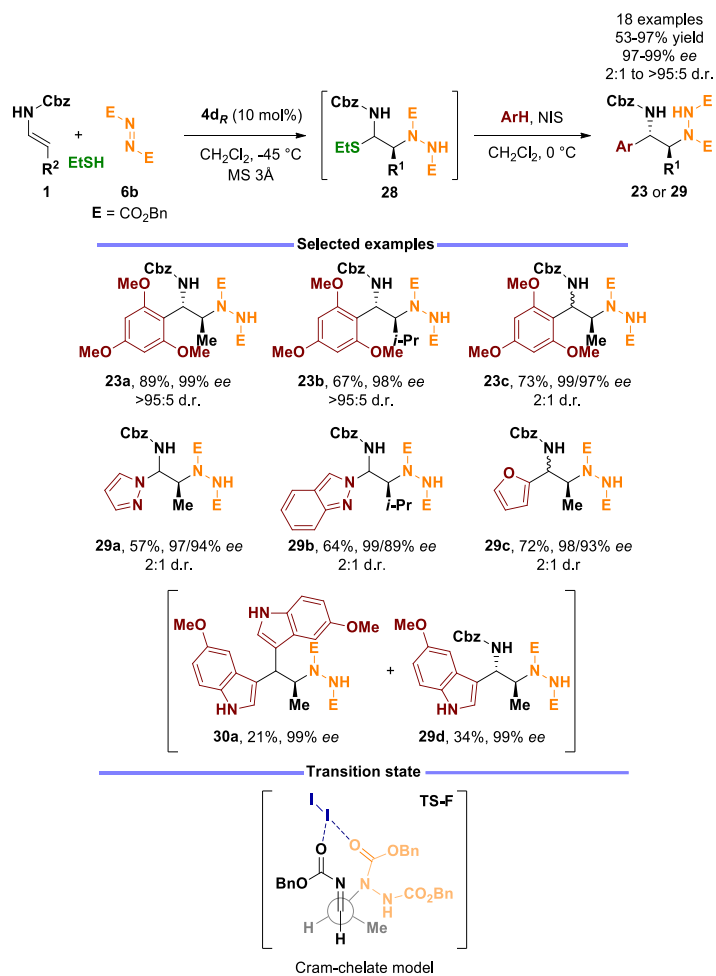
Scheme 14. NIS-mediated aza-Friedel–Crafts reaction



Hence, we replaced alcohol with thiol to produce the corresponding α -amidosulfide ($R^1 = \text{Bn}$ and $R^2 = \text{Me}$) **28a**. Despite being more acidic than ethanol, ethanethiol did not disrupt hydrogen-bond interactions between the substrates and the catalyst.²⁴ To our delight, **28a** was isolated in 99% yield and excellent *ee* for each diastereomer (1:19 d.r.). This purified intermediate was reacted with trimethoxybenzene (1.1 equiv.) in the presence of NIS (30 or 50 mol%). The desired product **23a** was obtained in 89% yield and 99% *ee*. Unexpectedly, an almost complete *syn*-diastereoselectivity was observed. The iodine generated *in situ* could function as a Lewis acid in a Cram-chelate model (Scheme 15, **TS-F**).²⁴

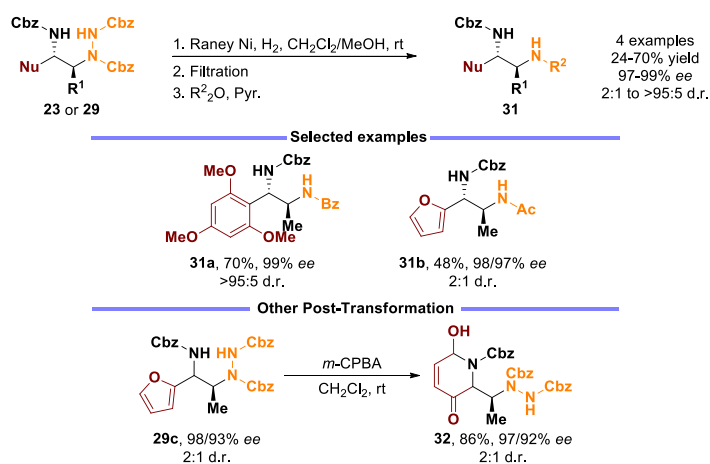
The reactions worked smoothly with a range of electron-rich arenes and heteroarenes, furnishing the *syn*-products **23** and **29**, respectively, in good yields, high *ee* and modest diastereoselectivity (2:1 d.r.), probably due to their smaller size. Surprisingly, electron-neutral and electron-poor indoles led to double aza-Friedel–Crafts reactions, yielding bis-indoles **30** in good to high yields and excellent enantioselectivities. Similarly, electron-rich indoles provided a mixture of mono- and double-addition products (Scheme 15).²⁴

Scheme 15. Synthesis of enantioenriched 1,2-diamines substituted with arenes and heteroarenes



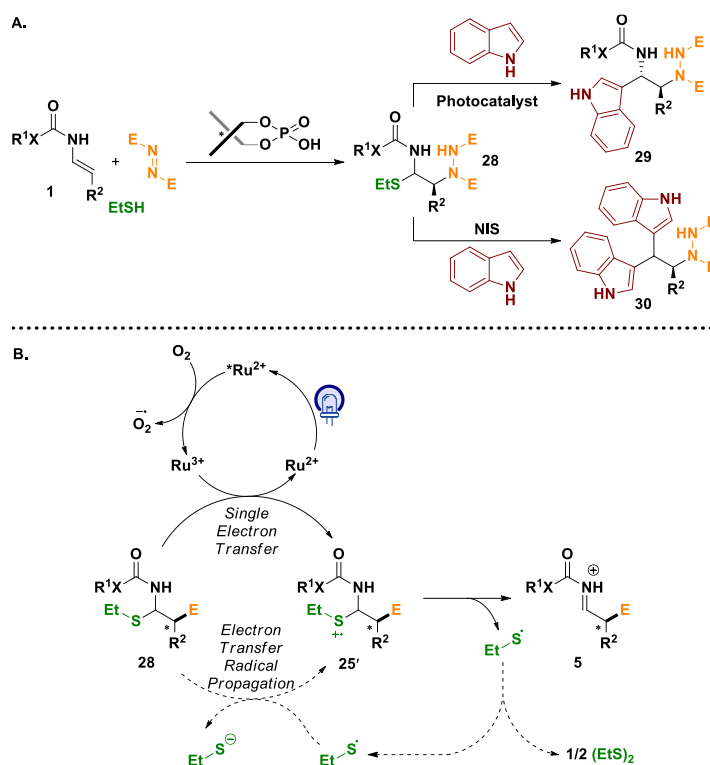
α -Hydrazinoamides **23** or **29** were converted to the corresponding chiral 1,2-diamines **31** through Raney nickel-catalyzed hydrogenolysis of the hydrazine functionality without epimerization of the stereogenic centers. Finally, aza-Achmatowicz oxidation of **29c** (2:1 d.r.) provided enantioenriched dihydropyridone **32** in 95% yield without any erosion of enantioselectivity (Scheme 16).²⁴

Scheme 16. Derivatizations of arene-substituted 1,2-diamines



To avert such double addition and favor the formation of monoarylated compounds, we focused on neutral and Lewis acid-free conditions for the iminium regeneration, as iodine was promoting the second attack of the indole on product **29**. Visible light photoredox catalysis seemed to be a potential solution.²⁷ Indeed, we had previously reported the monoaddition of various heteroarenes to *N*-carbamoylimine derived from α -amidosulfides, leading to an effective synthesis of functionalized heteroarylamines.²⁸ As an extension of these works, we envisioned merging this methodology with the phosphoric acid-catalyzed formation of α -carbamoylsulfides **28**, which could give access to enantioenriched arylated amines (Scheme 17A). After its excitation by blue light, a ruthenium(II) photocatalyst reacts with oxygen to form a strongly oxidizing ruthenium(III) complex. This species can abstract an electron from α -amidosulfide **28** leading to radical cation **25'**. The latter undergoes a fragmentation regenerating iminium **5**. Therefore, radical-chain propagation cannot be ruled out for this mechanism (Scheme 17B).^{28a}

Scheme 17. Chiral phosphoric acid/photoredox dual catalysis for the 1,2-difunctionalization of enecarbamates

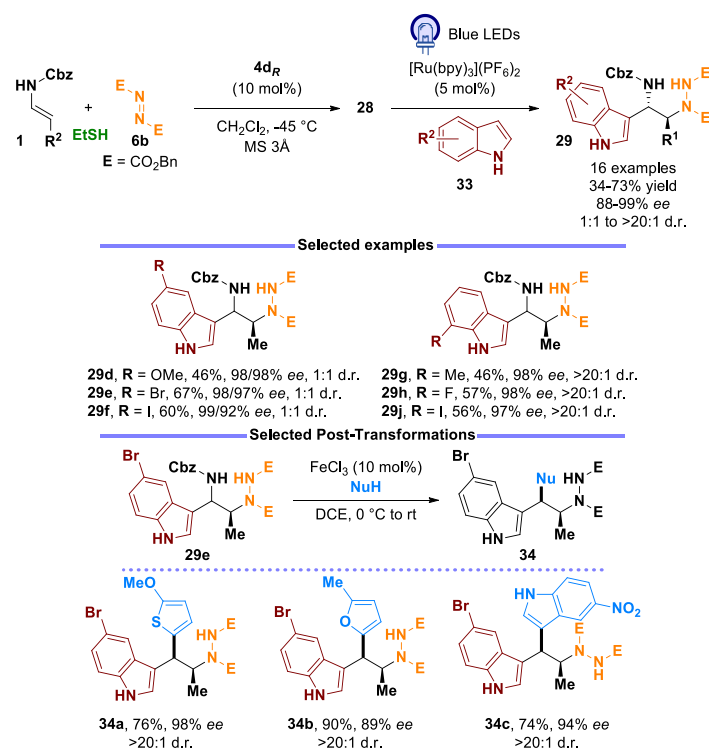


α -Carbamoylsulfide **29a** was prepared from (*E*)-enecarbamate **1a**, DBAD (**6b**) and ethanethiol in the presence of **4d_R**, following the procedure previously described.²⁹ This purified intermediate was then subjected to the photocatalyzed arylation using indole **33a** (3.0 equiv.) and 5 mol% of [Ru(bpy)₃](PF₆)₂ under blue LEDs irradiation (465 nm) in acetonitrile. Desired monoarylated 1,2-diamine **29a** was obtained as a single product in high *ee* but moderate yield without diastereoselectivity. Unfortunately, any change to these conditions failed to improve the two latter parameters. Similarly, running the reaction in a one-pot process, without isolation of intermediate **28**, resulted in a complex mixture and gave much lower yields. Electron-rich and electron-poor 5- and 6-substituted indoles furnished corresponding products in moderate to good yields and excellent enantioselectivities but consistently moderate d.r. However, 7-substituted indoles unexpectedly led to excellent diastereoselectivities (>20:1 d.r.).²⁹

The synthesized 1,2-diamines were further derivatized *via* the selective nucleophilic displacement of the *N*-carboxybenzyle group promoted by FeCl₃ Lewis acid. It gave access to optically active substituted tryptamines, a motif extensively found in psychoactive molecules.³⁰

Diverse heteroaromatic nucleophiles were employed, affording β -substituted tryptamines **34** in good yields with no loss of diastereo- or enantioselectivity (Scheme 18).

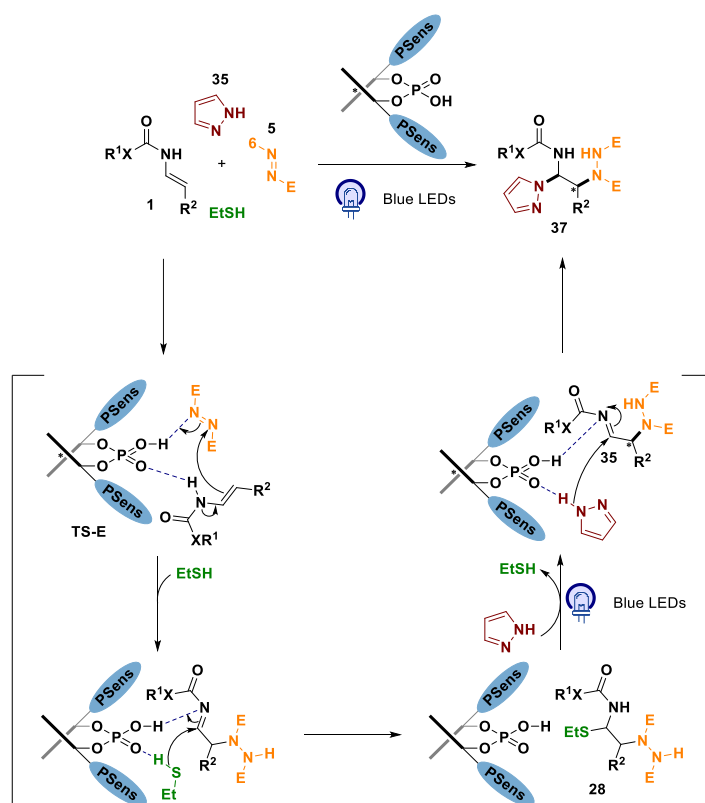
Scheme 18. Enantioselective synthesis of α,β -substituted tryptamines



We were interested in developing a one-pot sequence from this chiral α -hydrazinoamines synthesis. Unfortunately, the simultaneous use of phosphoric acid and photocatalyst is not possible due to solvent mismatch. The ruthenium-mediated Friedel–Crafts reaction is indeed ineffective in DCM, whereas the electrophilic amination proceeds with only moderate enantioselectivities and yields in acetonitrile. Moreover, modest *ee* was observed with less nucleophilic pyrazoles **35**, possibly due to partial racemization of the intermediary imine **36**. Interestingly, Bach *et al.*, in 2005, disclosed a powerful combination of photocatalysis with enantioselective organocatalysis by merging, in the same congested tricyclic structure, a hydrogen-bond donor/acceptor with a photosensitizer.^{31,32} We decided to transpose this approach to chiral phosphoric acids by substituting their 3- and 3'-positions with photosensitizers. We assumed that the resulting polyfunctional species could catalyze the three

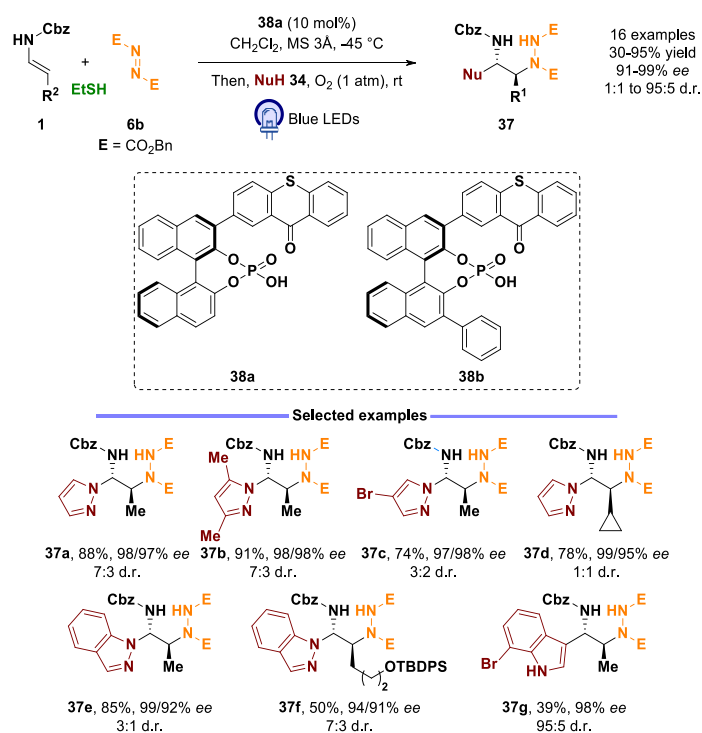
steps of our sequence.⁴ These steps are: (1) a highly enantioselective electrophilic amination *via* the well-organized transition state **TS-E** to form α -carbamoylsulfide **28**, (2) photocatalyzed imine **36** regeneration, and (3) final *N*-arylation to access **37** without undesired racemization (Scheme 19). Hence, we developed several new BINOL-derived organophotocatalysts bearing thioxanthenes photosensitizers, the best being *C*₁-symmetric photocatalyst **38a**.⁴ In parallel, independent reports by Bach *et al.* demonstrated that a thioxanthone-functionalized *C*₂-symmetric chiral phosphoric acid was competent in (2+2)-cycloadditions.³³

Scheme 19. Use of a chiral organophotocatalyst derived from phosphoric acid for the enantioselective difunctionalization of enecarbamates



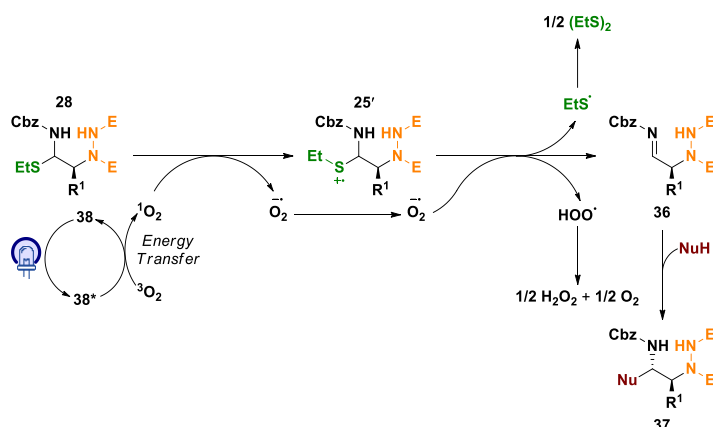
The desired product ($R^1 = \text{Bn}$ and $R^2 = \text{Me}$) **37a** was isolated in 73% yield, moderate diastereoselectivity (7:3 d.r), and 98% *ee* for both diastereomers. The reaction was applied to a series of electron-rich and electron-poor substituted pyrazoles as well as indazoles, producing **37a-g** in good yields, excellent *ee*, and modest diastereoselectivities (Scheme 20).

Scheme 20. Bifunctional photoredox catalysis for the asymmetric difunctionalization of enecarbamates



Based on our previous studies,^{28,29} we proposed a plausible reaction pathway for the photochemical C–S bond cleavage relying on a direct energy transfer (Scheme 21). We believe these bifunctional catalysts have a great potential to mediate reactions involving both RedOx process and hydrogen-bond activation.

Scheme 21. Mechanistic hypothesis for the photoredox imine regeneration and the Friedel–Crafts reaction



For increasing our efforts in catalyst design, we recently synthesized a new chiral phosphoric acid–based photocatalyst to study the impact of photosensitive substituents.³⁴ Thioxanthenes-

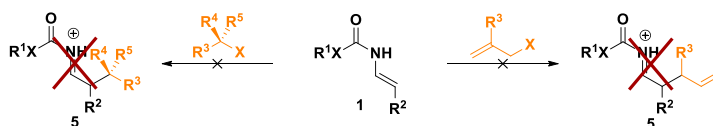
bearing phosphoric acids were found to be more efficient than their ketones-substituted analogs. We also tried to functionalize **38a** with a phenyl at the 3'-position leading to **38b**, which improved diastereoselectivity moderately.

4. THREE-COMPONENT DIFUNCTIONALIZATIONS OF ENECARBAMATES VIA RADICAL PATHWAYS

4.1 Photocatalyzed ATRA difunctionalization of enecarbamates

Although useful, aforementioned carbon–carbon double bond functionalizations of enecarbamates and enamides did not encompass allylations and alkylations, representing significant limitations (Scheme 22). Indeed, every strategy we have described up to that point relied on ionic pathways and required strongly electrophilic partners, such as imines, azidocarboxylates, or halosuccinimides, for the initial nucleophilic attack to proceed. Consequently, the comparatively low electrophilicity of alkyl and allyl halides rendered this first step ineffective, meaning an alternative way to include such substrates was required.

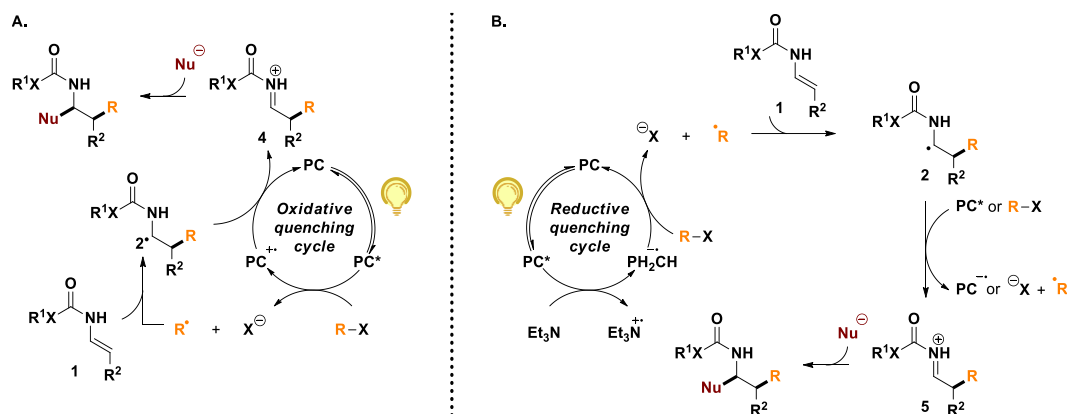
Scheme 22. Limitations of enecarbamate derivatives for nucleophilic additions *via* ionic strategies



We then turned our attention to radical pathways³⁵ and more specifically photoredox processes as a clean method to generate electrophilic radicals from halide derivatives.³⁶ Such intermediates might react with enecarbamate **1** to produce α -amidoalkyl radical **2**, subsequently oxidized by the photocatalyst.²⁷ The resulting *N*-acyliminium cation **5** can eventually be trapped by a nucleophile (Scheme 23A). Alternatively, the excited photocatalyst can react with an amine, increasing its reduction potential (Scheme 23B). In such a pathway, intermediate **2** can

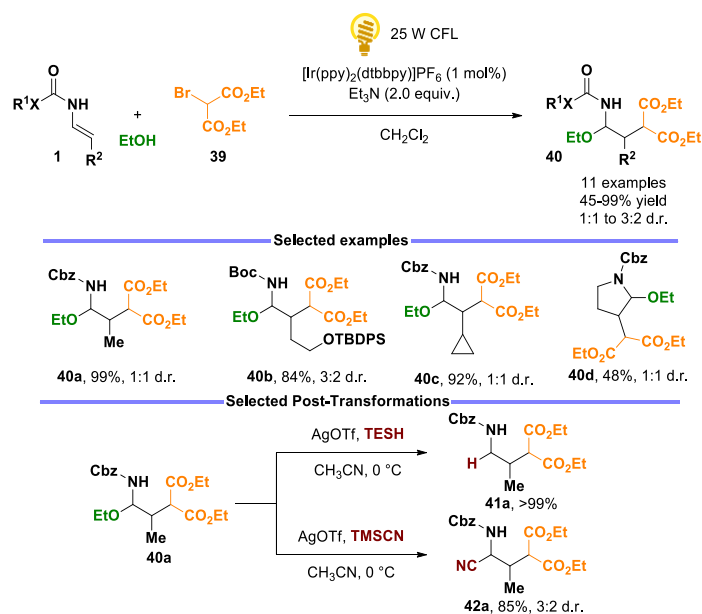
be oxidized either by the photoactivated catalyst or halogen derivatives in a chain propagation process.

Scheme 23. Photocatalyzed difunctionalization of enamides



As a starting point, we reacted enecarbamate (*E*)-**1a**, diethyl bromomalonate (**39**), and ethanol in acetonitrile in the presence of Et₃N (2.0 equiv.), [Ru(bpy)₃]Cl₂ (1.5 mol%), and light from a 25 W CFL bulb.³⁷ Though the desired 3-component adduct **40a** was obtained as a 3:2 mixture of diastereoisomers (60% yield), the reaction was not clean due to the partial oligomerization of the enecarbamate. A change to [Ir(ppy)₂(dtbbpy)]PF₆ photocatalyst improved the yield (79%), whereas reducing the quantity of Et₃N was nefarious for this parameter. Finally, running the reaction in DCM quantitatively afforded **40a** within 3 h. β -Substituted enecarbamates with linear, branched, and functionalized moieties were generally well tolerated, whereas the change of *N*-protecting groups (Alloc, Boc, cyclic-enamide) resulted in moderately lower yields. We eventually regenerated the *N*-acyliminium ions **5** from amidoether **40a** through AgOTf or phosphoric acid activation to incorporate diverse secondary nucleophiles such as hydride (triethylsilane) leading to **41a** or TMSCN to afford **42a** as an adaptation of our sequential strategy (Scheme 24).³⁷

Scheme 24. Photocatalyzed α -alkylation of enecarbamates

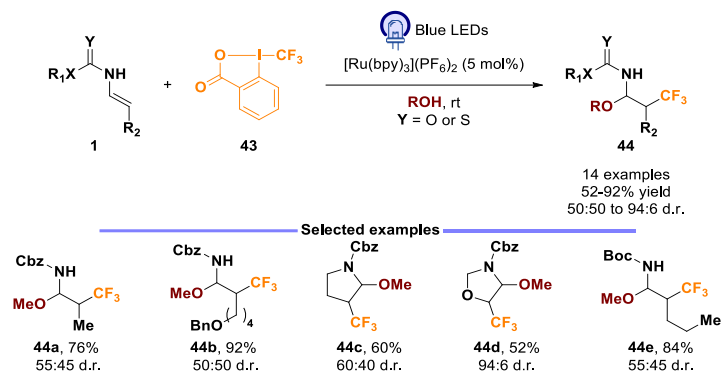


The radical character of the mechanism was easily established thanks to control experiments without photocatalyst, in the absence of light, or in the presence of a radical quencher such as TEMPO. The need for two equivalents of a tertiary amine suggests that Et₃N plays the role of a reductive quencher (*vide supra*, Scheme 24B). In addition, a radical-chain propagation process cannot be excluded entirely here.

Photoredox trifluoromethylation of alkenes has attracted considerable attention with successful applications to various unsaturated substrates driven by the attractivity of CF₃ moiety in drug discovery.³⁸ Hence, we investigated again the photocatalytic strategy by developing the first β -trifluoromethylation of enecarbamates to access *N*-protected precursors of β -trifluoromethyl amines.³⁹ We first focused on the ruthenium-promoted trifluoromethylation of β -unsubstituted vinylcarbamate (R¹ = Bn, X = O and R² = H) **1b**. A quick screening of trifluoromethyl radical sources showed that the Togni reagent (**43**) smoothly afforded **44a** in 76% yield (Scheme 25). Further optimizations proved that 1 mol% of [Ru(bpy)₃](PF₆)₂ was sufficient to maintain high reactivity, whereas methanol could be replaced by EtOH, *i*-PrOH, or even water. The reaction accommodated diverse β -substituted enecarbamates with varied *N*-protecting groups (including Boc, thiocarbamate, or thiourea). The transformation worked

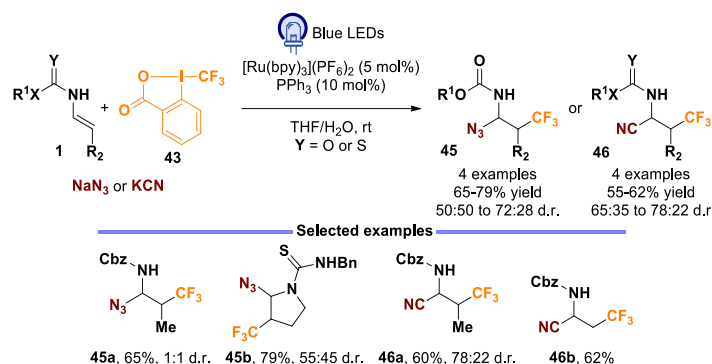
equally well with cyclic enecarbamates giving access to trifluoromethylated pyrrolidine **44c** and oxazolidine derivative **44d** in good yields.

Scheme 25. Photocatalyzed oxytrifluoromethylation of enecarbamates derivatives



This reactivity was further expanded to challenging intermolecular amino- and carbotrifluoromethylations.³⁹ Using enecarbamate ($R^1 = \text{Bn}$, $X = \text{O}$ and $R^2 = \text{Me}$) (*E*)-**1a**, Togni reagent (**43**, 1.2 equiv.), and an excess of NaN_3 with $[\text{Ru}(\text{bpy})_3](\text{PF}_6)_2$ as a catalyst, the desired product **45a** could be isolated. However, the yield was moderate (45%) due to iodine generation from **43**, leading to the formation of the corresponding β -iodo derivative.⁴⁰ The yield could be improved to 65% by adding 10 mol% of PPh_3 for circumventing the iodination side reaction. Under these conditions, a small range of cyclic and acyclic enecarbamates provided azides **45** in decent yields. It was even possible to replace NaN_3 with KCN to form cyano-substituted products **46** (Scheme 26).

Scheme 26. Amino- and carbotrifluoromethylation of enecarbamates derivatives



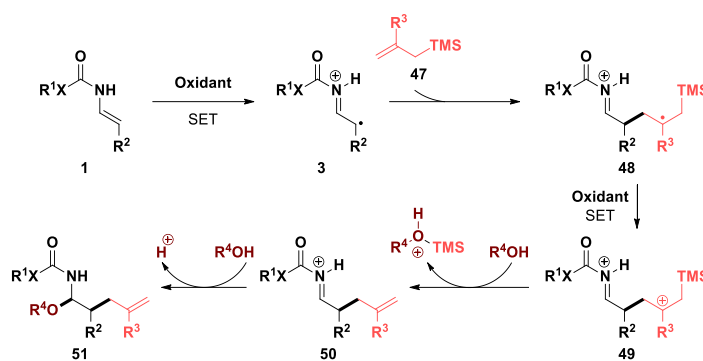
Finally, usual control experiments (absence of light or photocatalyst, addition of TEMPO) supported an oxidative quenching mechanism as depicted in Scheme 23A with NaN_3 or KCN playing the role of the final nucleophile. Despite their interest, these synthetic methods remain racemic. Hence, further investigations, involving catalyst design based on our previous results with chiral phosphoric acids bearing photosensitizers, are currently underway for developing enantioselective ATRA reactions.

4.2 Umpolung difunctionalization of enecarbamates: Access to complementary β -allylations

If the photocatalyzed generation of radical species enabled us to access alkylated products, we needed an alternative strategy to achieve β -allylation of enecarbamates. In every example presented until this point, the latter substrates behaved as nucleophilic species. In this context, we thought about reversing the primal reactivity of enecarbamates to make their β -carbon electrophilic, solving the issue of the weak reactivity of allyl halides

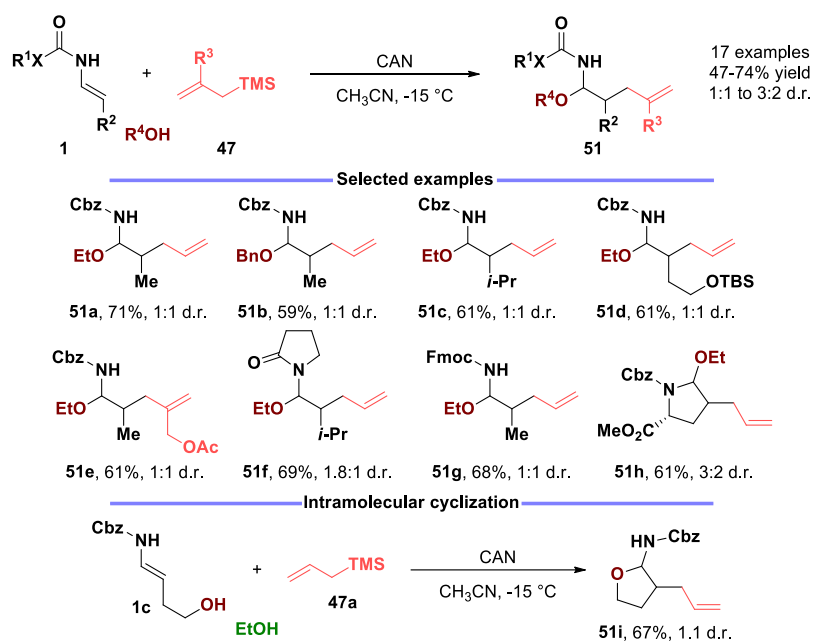
We took inspiration from the singly occupied molecular orbital (SOMO) catalysis developed by MacMillan *et al.*⁴¹ They reported single electron transfer (SET) oxidation of catalytically generated chiral enamines. Such a step was promoted with ceric ammonium nitrate (CAN), and resulting intermediates further reacted with allylsilanes. We envisioned transposing such an approach to enecarbamate **1**, leading to the electron-deficient radical cation **3**. The latter intermediate would easily attack on radicophilic allyl silane **47**, enabling the functionalization of its β -position and providing radical species **48**. A CAN-mediated oxidation/TMS-elimination sequence would lead to iminium **50**, and the mechanism could be concluded by its polar trapping with nucleophilic alcohol – an inert species with regards to the radical pathway involved in this transformation (Scheme 27).

Scheme 27. SOMO activation for the β -allylation of enamides



Based on previous works of our group⁴² and others,⁴³ we initially examined the reaction of (*E*)-**1a**, allyltrimethylsilane **47a**, and ethanol with $FeCl_3$ as the oxidant. However, no reaction occurred even when an excess of this reagent was used. No improvements were obtained in the presence of $NaNO_2$ and O_2 .^{42,43b} Therefore, we switched to CAN as cerium(IV) has a higher oxidation potential than iron(III).³ Its mere addition was unsuccessful, resulting in direct degradation, polymerization, and isomerization of **1a**, which suggested that CAN behaved more like a Lewis acid than an oxidant. The slow addition of **1a** to a solution containing allylsilane, EtOH, and CAN at a low temperature led to the formation of the desired β -allylated product **51a** in 71% yield. It should be noted that the role of EtOH is not limited to the trapping of the iminium intermediate. However, it is also necessary to increase the solubility of the oxidant through the formation of an ate complex. Diverse linear or cyclic β -substituted enecarbamates, with several *N*-protecting groups, were productively engaged in the reaction, resulting in β -allyl α -carbamoylethers **51** with good yields. β -branched allylsilane also reacted well to furnish the corresponding products. Alcohol-functionalized enecarbamate **1c** underwent the β -allylation with a concomitant cyclization in good yield, offering easy access to β -allyl α -aminotetrahydrofuran **51i** (Scheme 28).

Scheme 28. CAN-mediated β -allylation of enecarbamates derivatives



5. CONCLUSION

Difunctionalizations of enecarbamate derivatives through MCRs are formidable strategies for constructing highly functionalized nitrogen-containing building blocks, including 1,2-diamines, 1,3-diamines, 1,2-haloamines, β -trifluoromethylated amines, and 2-aminotryptamines, among other synthons. Our group, alongside others, has developed several strategies to harness such syntheses *via* chiral phosphoric acid organocatalysis. Our synthetic toolbox encompasses the use of (1) stable α -substituted substrates, (2) temporarily linked nucleophile/electrophile reactants, and (3) the addition of transient nucleophiles such as alcohols or thiols, which are easily oxidized, reduced, or irreversibly displaced by a second nucleophilic partner in a consecutive step. The latter option enables a significant chemical divergence.

Complementary reactivities are also accessible through radical pathways for achieving challenging β -allylations, β -alkylations, and β -trifluoromethylations. They comprise an umpolung radical oxidative addition based on the nucleophilicity reversal of the enecarbamate

β -position to obtain a radicophilic center and electrophilic attacks from photogenerated radicals on their double bond. Finally, we aim to actively investigate dual photoredox/hydrogen-bond donor/acceptor catalysis with the design and evaluation of new chiral phosphoric acids functionalized with chromophores. We are convinced that such species will promote new reactivities to push further the boundaries of the enantioselective difunctionalizations of enamides and enecarbamates.

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Notes

The authors declare no competing financial interests.

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BIOGRAPHIES

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Damien Bouchet obtained his Master's degree in engineering from ESPCI Paris in 2019, followed by an M.Sc. degree in Molecular chemistry from PSL and Sorbonne Universities in 2020. During this time, he joined the team of Dr. Géraldine Masson for an internship on chiral phosphoric acid-catalyzed cycloadditions. He continued to work in this group and started his doctoral studies in 2020, focusing on organocatalysis and photocatalysis.

Géraldine Masson received her Ph.D. in 2003 from Joseph Fourier University under the supervision of Dr. Sandrine Py and Prof. Yannick Vallée. From 2003 to 2005, she was a Marie Curie postdoctoral research fellow in Prof. Jan van Maarseveen and Prof. Henk Hiemstra's team at the University of Amsterdam. In 2005, she was appointed "Chargée de Recherche" by the CNRS at ICSN/Paris-Saclay University. She was promoted to Research Director DR2 in 2014 and then Research Director DR1 in 2020. Her research focuses on enantioselective organocatalysis, photoredox catalysis, and electrochemical syntheses.

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