

Review

Beyond Cooperative Catalysis: Directly Light-Activated Chiral Phosphoric Acids in Stereoselective Photochemical Transformations

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Abstract

The combination of photochemistry with stereoselective catalysis has emerged as an effective strategy to achieve stereocontrol in light-driven transformations. Chiral phosphoric acids (CPAs) have recently attracted attention in this context due to their ability to activate substrates while providing a defined chiral environment. This minireview highlights recent developments in CPA-enabled asymmetric photochemical transformations, focusing on systems in which CPAs incorporate a chromophore on the chiral backbone or form light-absorbing CPA-substrate complexes that enable photoactivation without the presence of an external photocatalyst. The main catalytic strategies, mechanistic features, and current limitations are discussed.

Keywords: chiral phosphoric acids; photochemistry; bifunctional catalysts; organocatalysis; photoredox catalysis; radical reactions

1. Introduction

The combination of stereoselective catalysis and photochemistry has recently proven to be a powerful strategy for addressing one of the most persistent challenges in synthetic chemistry: achieving precise stereocontrol in highly reactive, photoinduced processes. Coupling light-driven generation of transient intermediates with catalytic systems capable of transferring stereochemical information enables the formation of enantioenriched products under conditions traditionally dominated by radical pathways and poor selectivity [1–8]. This great reactivity is generally achieved through the synergistic cooperation of two distinct catalytic cycles. A photoredox catalyst, such as a transition-metal complex or an organic sensitizer, initially generates reactive intermediates through a dedicated photoredox catalytic cycle. These transient species subsequently engage with a chiral organocatalyst operating within a complementary organocatalytic cycle, thereby enabling the stereocontrolled formation of a new chemical bond through cooperative catalysis.

Since the seminal publication by MacMillan and co-workers [9], this dual-catalytic strategy has proven to be highly effective for the synthesis of high functionalized molecules in a stereoselective manner, and many contributions have been reported so far. In this context, chiral phosphoric acids (CPAs), a well-established class of Brønsted acid catalysts widely employed in stereoselective transformations [10–18] and in the synthesis of

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biological products [11,19], naturally emerged as ideal organocatalysts for combination with photoredox catalysis (Scheme 1A) [20–23].

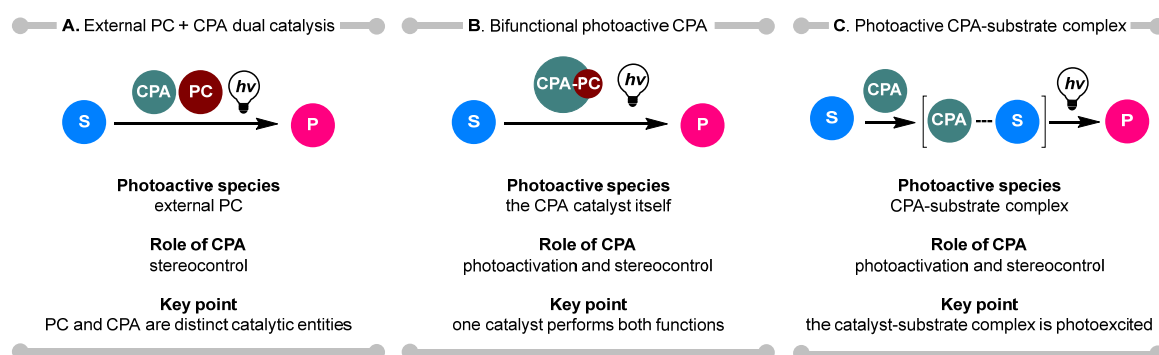
The first example of a photochemical transformation through dual photoredox–chiral phosphoric acid catalysis was reported in 2009 from Knowles and co-workers, who developed a highly enantioselective intramolecular reductive pinacol coupling of ketones and hydrazones promoted by $\text{Ir}(\text{ppy})_2(\text{dtbpy})\text{PF}_6$ as a photocatalyst and 2,2'-binaphthol-based chiral phosphoric acid in the presence of Hantzsch ester under blue LED irradiation [24].

Taking inspiration from this example, many additional transformations exploiting cooperative photoredox-CPA catalysis have been disclosed [14,25,26]. Recent examples include enantioselective Minisci-type additions [27,28], stereoselective radical couplings [29,30], deoxygenative functionalizations of amides [31], olefin isomerizations [32], atroposelective heteroarene synthesis [33], and a variety of visible-light-driven cycloadditions and dearomative photocycloadditions [34–36], while hybrid catalyst design has further broadened the synthetic potential of these systems [37,38].

In a further evolution of this approach, the functional role of CPAs in light-driven transformations has extended far beyond their classical role as a source of stereochemical information, leading to the development of two distinct but conceptually related strategies that constitute the focus of this minireview.

In the first one, bifunctional chiral phosphoric acids bearing a photoactive moiety covalently linked to the chiral backbone were developed, enabling the design of single-component catalysts in which photoactivation and enantioselective control are integrated within the same molecular structure (Scheme 1B). In the second one, the presence of an external photocatalyst is no longer required; upon coordination with the chiral phosphoric acid, the substrate undergoes a modulation of its electronic structure that lowers its LUMO energy, thereby enabling direct photoexcitation. Under light irradiation, this activated complex can be directly excited, while the phosphoric acid is also responsible for the transfer of the stereogenic information (Scheme 1C). In both cases, the CPA operates not only as a simple chiral catalyst, but as an active contributor to the photoactivation event, whether by functioning as a sensitizer, by forming a photoactive complex, or by modulating the photophysical properties of the substrate.

These advances have paved the way for the next generation of CPA-enabled asymmetric photochemical strategies. Recent progress in this area, covering the period 2020–2026, is summarized in this minireview, with a particular focus on the main advantages and limitations of each strategy.



Scheme 1. Roles of chiral phosphoric acids (CPAs) in photocatalysis. S = substrate, PC = photocatalyst, P = product.

2. Bifunctional Photoactive Chiral Brønsted Acids

In contrast to dual catalytic approaches in which a chiral phosphoric acid is combined with a separate photocatalyst, bifunctional photoactive CPAs operate as single-

component systems in which the chromophoric unit is covalently integrated into the chiral scaffold, making the CPA itself the photoactive species. Upon light excitation, these catalysts can generate reactive excited intermediates through single-electron transfer (SET), energy transfer (EnT) or proton-coupled electron transfer (PCET) processes. These newly generated species remain confined within a well-defined chiral environment, which ensures effective transfer of stereochemical information to the coordinated reaction partners.

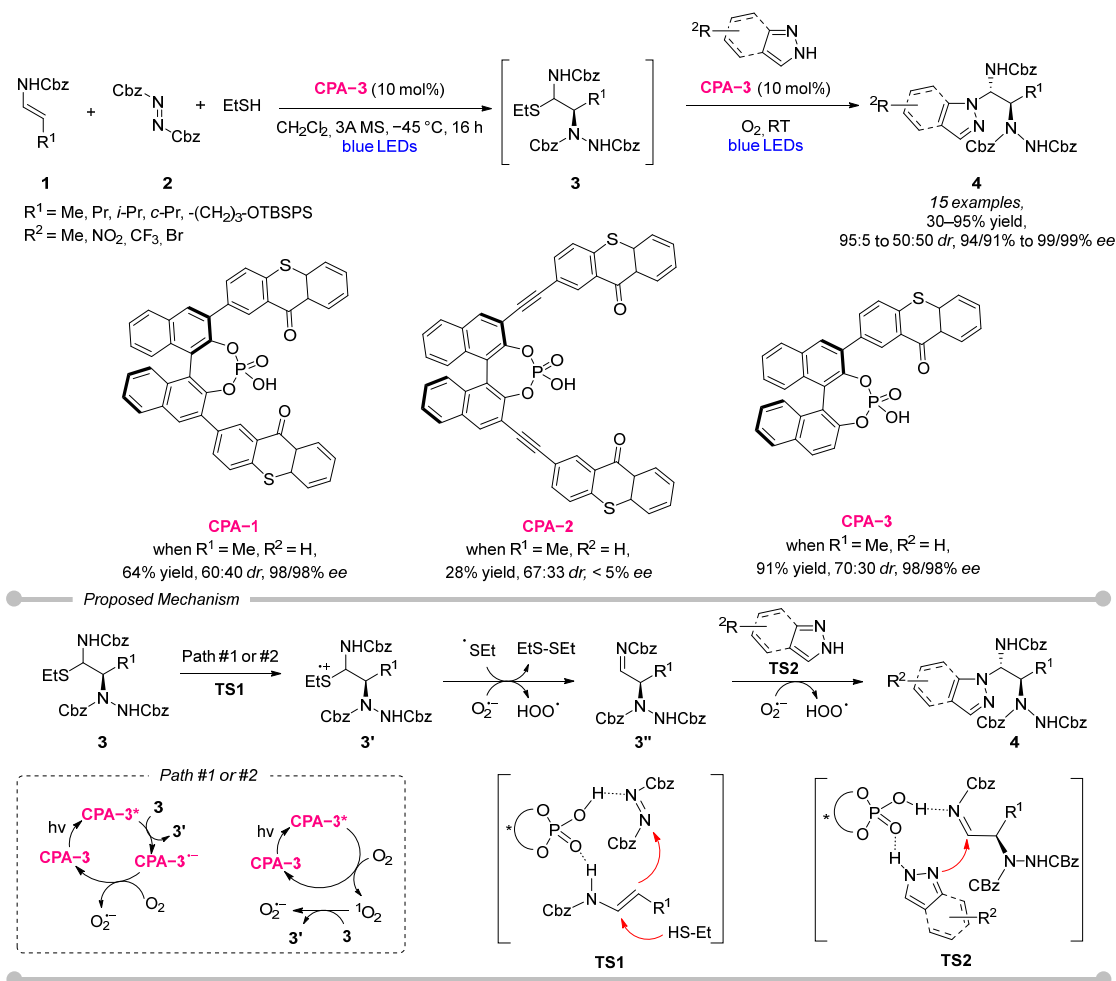
The development of bifunctional organic photocatalysts has demonstrated that the synergistic integration of a sensitizing unit and a chiral control element within a single molecular scaffold constitutes a powerful and versatile strategy for promoting stereoselective photocatalytic transformations [39,40]. These applications can be broadly divided into two main areas: stereoselective bond-forming transformations, discussed in Section 2.1, and photocatalytic deracemization and related stereochemical control processes, covered in Section 2.2.

2.1. Photocatalytic Stereoselective Bond-Forming Transformations

The earliest and most extensively developed applications of bifunctional chiral phosphoric acids have involved enantioselective photocatalyzed bond-forming reactions, in which the photoactive CPA promotes substrate activation while simultaneously controlling the stereochemical outcome through non-covalent interactions. One of the first examples in which this approach has been implemented was reported by Masson and co-workers, who developed a new class of photoactive organocatalysts based on BINOL-phosphoric acid backbone bearing one or two thioxanthone chromophores [41,42] in 3,3' position for the synthesis of chiral 1,2-diamines [43].

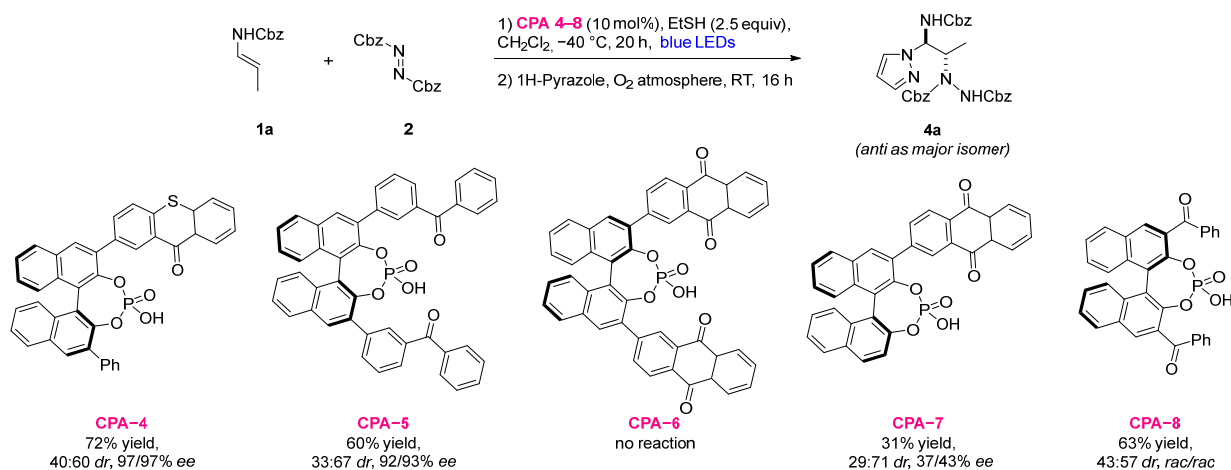
Catalysts **CPA-1**, **CPA-2** and **CPA-3** exhibited absorption in the visible region up to 440 nm, with reduction peaks at -1.55 , -1.46 , and -1.53 V vs SCE, respectively. However, only the C₁-symmetric catalyst **CPA-3**, upon blue LEDs irradiation (7.2 W, 420–510 nm) was able to promote the one-pot, three-component electrophilic amination reaction followed by a photoinduced nucleophilic addition of various azoles and dibenzyl azodicarboxylate **2** in good yield and high level of diastereo- and enantioselectivity (Scheme 2).

Upon the coordination of **CPA-3**, $\odot$ -unsubstituted enecarbamate **1** reacts with dibenzyl azodicarboxylate **2** in the presence of EtSH, which acts as a transient nucleophile to trap the imine intermediate formed after the electrophilic amination step and the presence of O₂ for the oxidative regeneration of the catalyst. This thiol-mediated interception prevents both the undesired direct addition of the azole to the azodicarboxylate and the polymerization pathway arising from further reaction of the enecarbamate with the imine intermediate. Subsequent photoinduced C-S bond cleavage of compound **3'** regenerates the imine **3''** under controlled conditions, enabling the stereoselective nucleophilic addition of the azole ring leading to the formation of the desired product **4**. The protocol tolerates a broad range of pyrazoles bearing either electron-donating or electron-withdrawing substituents, providing the desired substituted 1,2-diamine derivatives with consistently high enantioselectivities.



Scheme 2. Representation of the key intermediates involved in the photocatalytic electrophilic amination-photoinduced nucleophilic addition sequence.

Based on these results, the same group subsequently developed a small library of BINOL-derived phosphoric acid photocatalysts bearing alternative aromatic ketone-based chromophores, including thioxanthone, benzophenone and anthraquinone derivatives [44]. Their spectroscopic and electrochemical properties were investigated, and their catalytic activity was evaluated in the same asymmetric tandem electrophilic amination of enecarbamates previously reported for thioxanthone-based systems (Scheme 3).



Scheme 3. BINOL-derived chiral phosphoric acid photocatalysts bearing ketone-based chromophores evaluated in the asymmetric electrophilic amination of enecarbamates.

The photocatalytic activity of catalysts **CPAs 4–8** was evaluated in the stereoselective tandem electrophilic amination of enecarbamates previously developed by the group.

In comparison to the earlier protocol, the reaction was performed under slightly modified conditions, employing longer reaction times and a larger excess of EtSH (2.5 equiv) in the electrophilic amination step to ensure efficient trapping of the imine intermediate. Under these conditions, **CPA-4**, a C₁-symmetric thioxanthone catalyst obtained by modification of **CPA-3** through the introduction of an additional phenyl substituent at the 3' position afforded the desired product **4a** in 72% yield, with a 40:60 diastereomeric ratio and 97% *ee* for both diastereomers. Compared with **CPA-3**, only marginal differences were observed, indicating that substitution at the 3' position of the thioxanthone scaffold has a limited influence on the overall catalytic performance.

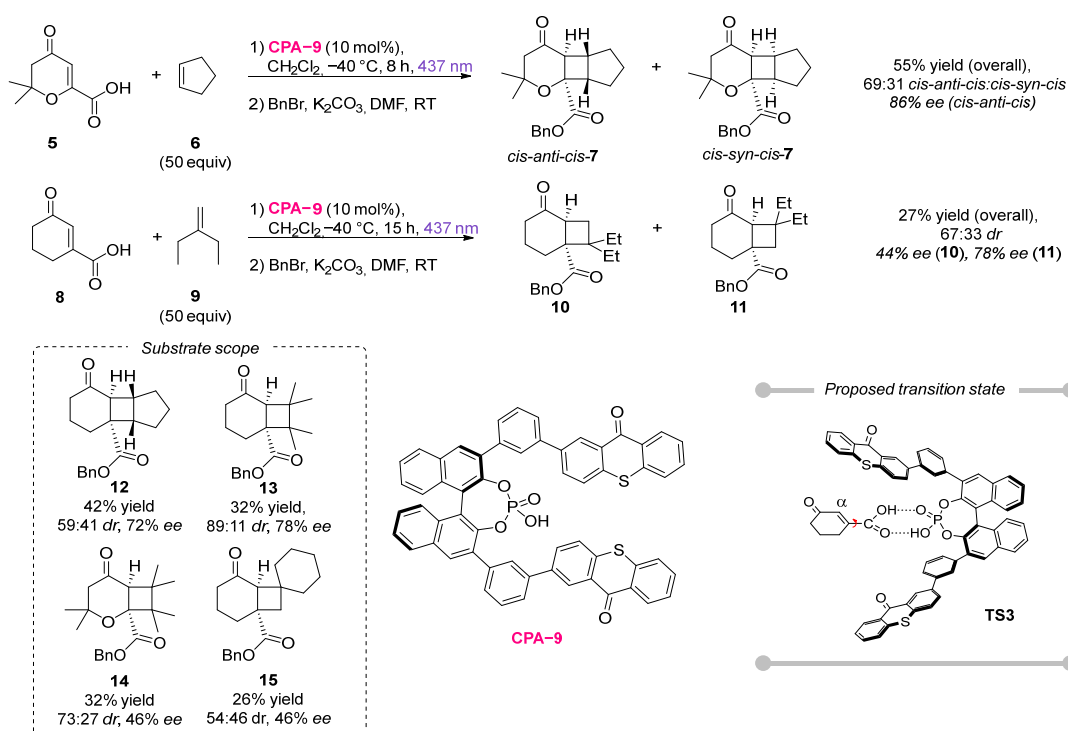
In contrast, the bis-anthraquinone catalyst **CPA-6** displayed no reactivity, whereas the mono-anthraquinone derivative **CPA-7** enabled the formation of the desired 1,2-diamine in moderate yield and enantioselectivity. Benzophenone-derived catalyst **CPA-5** provided the product with good enantioselectivity, whereas catalyst **CPA-8** led to the formation of the product in racemic form.

Overall, these results indicate that although alternative ketone-based chromophores can be successfully incorporated into the catalytic scaffold, the highest catalytic efficiency for this transformation is still achieved with the thioxanthone-derived catalyst **CPA-3**.

2,2'-binaphthol-based chiral phosphoric acids functionalized with a thioxanthone units have found applications also in different visible-light-mediated cycloadditions. In 2020, Bach and co-worker reported an intermolecular [2 + 2] photocycloaddition of α -carboxyl-substituted cyclic enones with cyclopentene or 2-ethyl-1-butene catalyzed by **CPA-9** [45]. This sensitizing chiral phosphoric acid displays two C₂-symmetrically positioned thioxanthone chromophores, which capture long wavelength light (λ_{max} = 394 nm) and promote an energy transfer (triplet energy ET = 235 kJ mol⁻¹, 77 K, CH₂Cl₂).

Although only a few substrate examples were reported and more than a stoichiometric amount of the dienophile was required, enantioenriched cyclic products were obtained in moderate yields and enantioselectivities. When 3,4-dihydro-2,2-dimethyl-4-oxo-2H-pyran-6-carboxylic acid **5** reacted with cyclopentene **6** in the presence of **CPA-13** under irradiation at 437 nm, the *cis-anti-cis* cyclic diastereoisomer **7** was preferentially formed over the corresponding *cis-syn-cis* isomer and was obtained with an enantiomeric excess of 86%, after functionalization to the corresponding benzyl ester (Scheme 2). Interestingly, the use of catalyst **CPA-1** did not induce any enantioselectivity in the same cyclization.

Under the same reaction conditions, the [2 + 2] cycloaddition of cyclohex-2-enone-3-carboxylic acid **8** with 2-ethyl-1-butene **9** afforded regioisomeric products **10** and **11** in a 67:33 diastereomeric ratio, with enantioselectivities of 44% and 78% *ee*, respectively (Scheme 4).

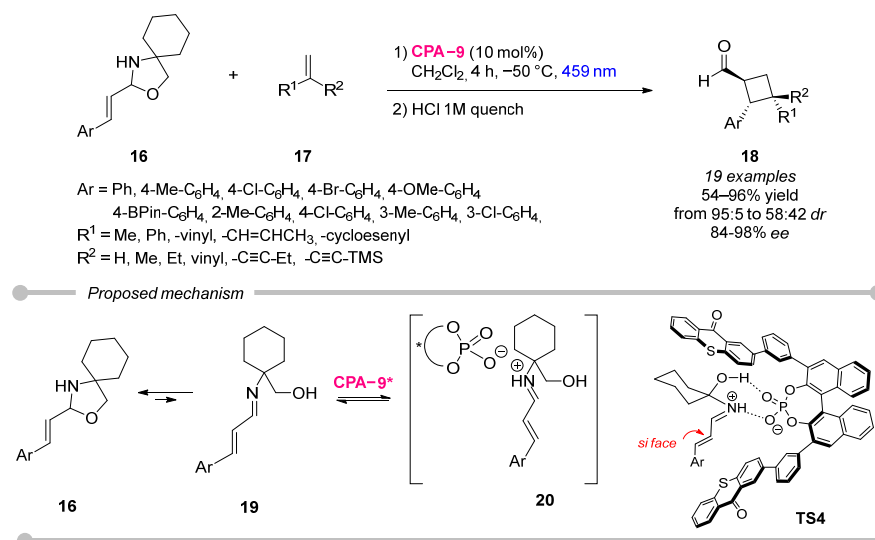


Scheme 4. Enantioselective visible-light-mediated [2 + 2] photocycloadditions of β -carboxyl-substituted cyclic enones catalyzed by a thioxanthone-functionalized **CPA-9**.

NMR studies and DFT calculations suggested that the catalyst–substrate coordination occurs through the formation of two hydrogen bonds between the carboxylic acid functionality of the substrate and the phosphoric acid moiety of the catalyst (**TS3**). This coordination not only enables an enantioface differentiation but also modulates the triplet energy of the substrates. However, due to the presence of multiple freely rotating conformers of the catalyst–substrate complex, no transition state responsible for the observed stereoselectivity was computed. Although the substrate scope remains limited, this study represents an important early example demonstrating how hydrogen-bonding interactions can be exploited to control both reactivity and stereoselectivity in visible-light-mediated cycloadditions.

One year later, using the same BINOL-derived catalyst **CPA-9**, Bach and co-workers reported a further improvement, demonstrating that *N,O* acetals derived from α,α,α -unsaturated α -aryl substituted aldehydes and (1-aminocyclohexyl)methanol **18** are also suitable substrates for [2 + 2] photocycloadditions with a variety of olefins under visible light irradiation (459 nm) [46].

This acid-catalyzed [2 + 2] cycloaddition allows access to highly substituted cyclobutanecarbaldehydes with three contiguous stereocenters in good yield and high level of enantioselectivity. However, while the relative configuration between the aryl group in 2-position and the formyl group at C1 is consistently *trans*, the relative configuration between the stereogenic centers C2 and C3 varies upon the olefin used (Scheme 5).



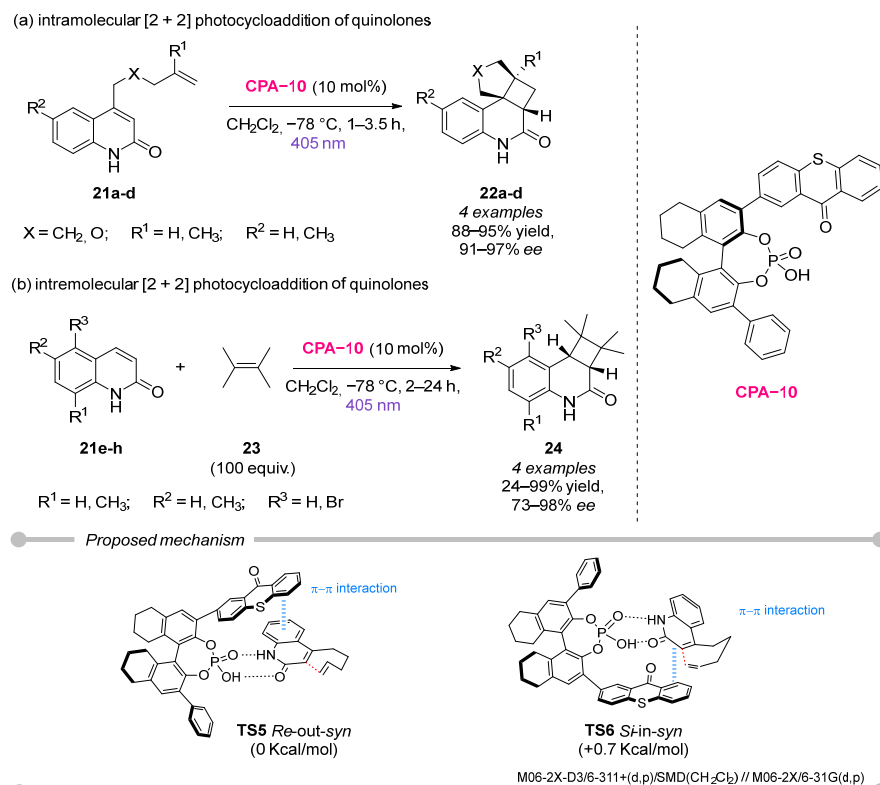
Scheme 5. Visible-light-induced [2 + 2] photocycloaddition of *N,O*-acetals with olefins via iminium ion activation mediated by CPA-9.

Mechanistic studies indicate that catalyst CPA-9 promotes protonation of the *N,O*-acetal, generating iminium ion **16**, which forms a hydrogen-bond-assisted ion pair with the chiral phosphate anion and thereby establishes a defined chiral environment. Notably, NMR studies revealed that the *N,O*-acetal exists in equilibrium between the closed acetal form and the open-chain form, with a slight preference for the closed structure (**16**:**19** ratio of 2:1). After protonation, however, the open species **20** becomes the catalytically relevant intermediate. Upon visible-light irradiation, the thioxanthone units of the catalyst act as photosensitizers, enabling triplet energy transfer and promoting the intermolecular [2 + 2] photocycloaddition with substituted olefin **17** according to a *Si face* attack. Control experiments revealed that the phosphoric acid not only activates the substrate through iminium ion formation but also mediates the energy transfer step, thereby ensuring efficient enantioface differentiation during C-C bond formation.

In 2022, Takagi and co-workers demonstrated that the H₈-BINOL-derived CPA-9, monofunctionalized with a thioxanthone moiety at the *ortho* position of the phosphoric acid unit, is capable of promoting the [2 + 2] photocycloaddition of suitably designed quinolones [47]. In this case, a series of differently substituted quinolones **21** were dissolved in CH₂Cl₂ and irradiated at 405 nm at −78 °C in the presence of CPA-10, affording both intramolecular [2 + 2] cycloadducts **22** in good to excellent yields and high enantiomeric excesses (Scheme 6a). The same transformation was also performed in the presence of 2,3-dimethyl 2-butene **23** achieving desired cycloadducts **24** in good yields and *ee*, although 100 equiv. of olefin were necessary (Scheme 6b).

NMR studies revealed that CPA-10 and compound **21a** (X = CH₂, R¹ = R² = H) form a 1:1 complex. DFT calculations of the transition states revealed that the quinolone was faced with the thioxanthone ring of the catalyst in the energetically most favorable geometry, described as *Re*-out-*syn*. In this arrangement, the substrate approaches the catalyst with its *Re face* directed toward the thioxanthone moiety (*Re*), the carbonyl group of the thioxanthone unit is oriented away from the quinolone (out), and the quinolone overlaps directly with the thioxanthone ring in a parallel fashion (*syn*), as represented in TS5. This geometry is stabilized by two key non-covalent interactions: π - π stacking between the thioxanthone chromophore and the quinolone ring, and dual hydrogen bonding between the phosphate oxygens of the catalyst and the substrate. Distortion/interaction analysis on the transition states confirmed that these non-covalent interactions are the dominant

factor in determining the stereochemical outcome, as *Re*-out-*syn* transition state is significantly lower in energy than the competing **TS6** *Si*-in-*syn* counterpart.



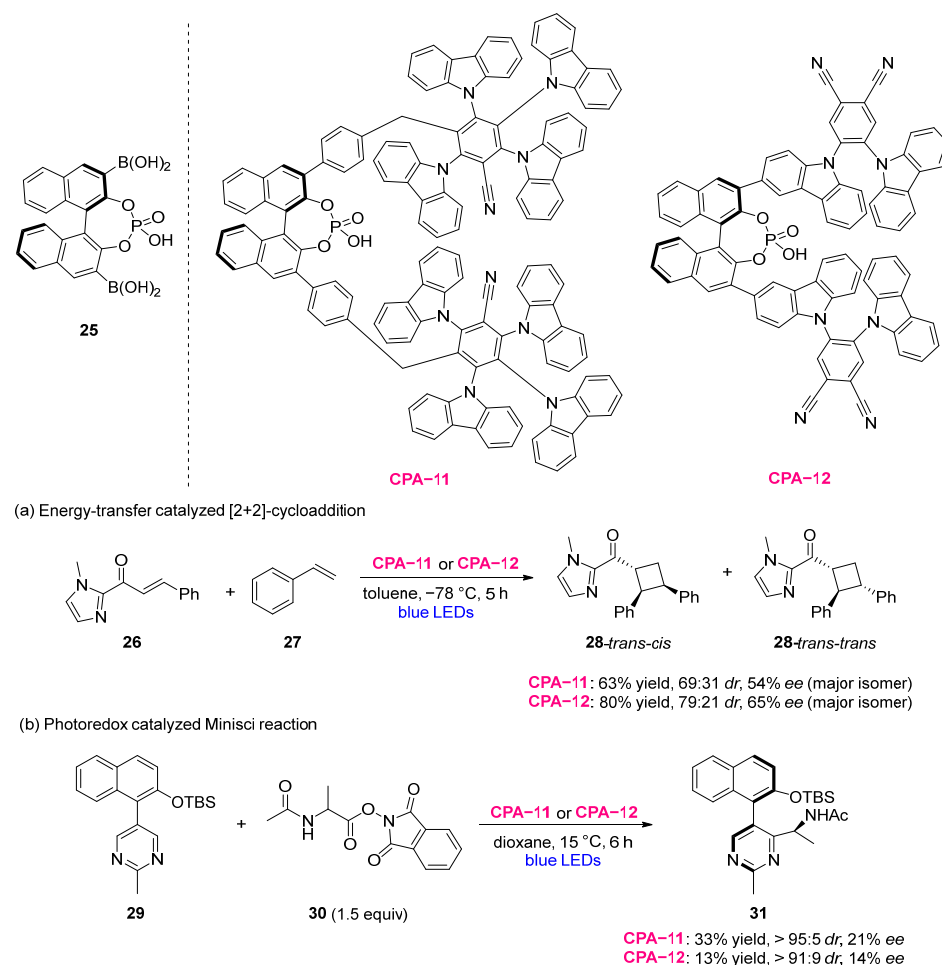
Scheme 6. Enantioselective [2 + 2] photocycloaddition of quinolones under visible-light catalysis by **CPA-10**.

In an alternative strategy aimed at overcoming the limited tunability of the thioxanthone scaffold, König and Toste, instead of modifying the chiral backbone to access bi-functional photoactive chiral Brønsted acids, replaced the thioxanthone moiety with a cyanoarene-based donor–acceptor photocatalyst [48]. To this end, they selected 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) [49,50], an organic dye originally developed for OLED research [51] that has since found widespread application in photoredox catalysis owing to its broad redox window, high photoluminescence quantum yield, and long excited-state lifetime.

CPA-11 and **CPA-12** were then synthesized in a seven-step sequences starting from a BINOL-derived boronic acid **25**, which was functionalized with the cyanoarene moiety via Suzuki cross-coupling, followed by demethylation and introduction of the phosphoric acid moiety. Notably, the ³¹P NMR spectrum of **CPA-12** displayed three distinct singlet signals (³¹P NMR: 0.56, 0.76, and 0.92 ppm in DMSO-*d*₆), which the authors attributed to conformational restrictions imposed by the more sterically congested 2CzPN-derived scaffold rather than to the presence of impurities or reaction intermediates—an assignment supported by HRMS and ¹H NMR data, and by the observation that neither high-temperature NMR studies nor alternative purification protocols altered the signal ratio.

Both catalysts were evaluated in proof-of-concept reactions previously reported in the literature using separate photocatalyst/chiral acid dual catalytic systems. As an energy transfer process, the intermolecular [2 + 2] cycloaddition between C-cinnamoyl imidazoles **26** and styrene **27**, originally developed in racemic form by Yoon and co-workers [52], was selected as a benchmark transformation. When operating at −78 °C under blue light irradiation, **CPA-12** proved to be the superior catalyst, delivering cycloadduct **28** in 80% yield

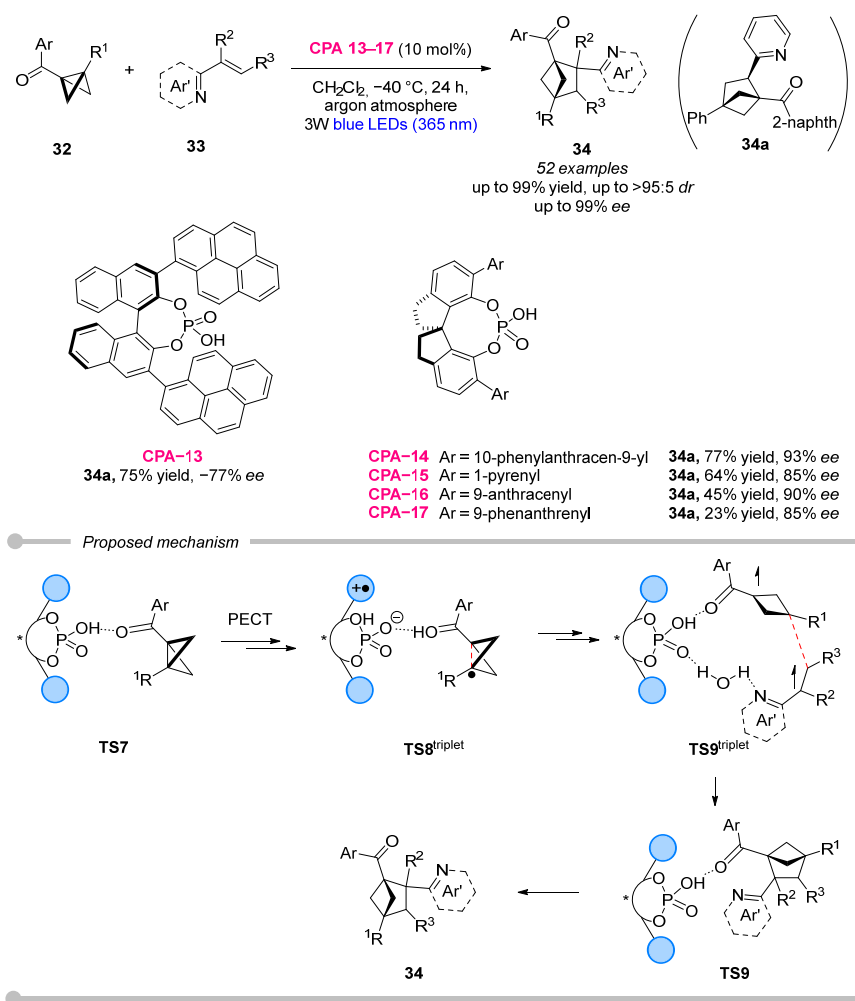
and 65% *ee*, while **CPA-11** performed considerably worse, affording the same product in lower yield and enantioselectivity (63% yield, 54% *ee*) (Scheme 7a).



Scheme 7. Application of cyanoarene-based bifunctional chiral phosphoric acid photocatalysts **CPA-11** and **CPA-12** in enantioselective energy transfer and photoredox catalysis.

As second application, CzipN-based chiral phosphoric acids were employed in the photoredox-catalyzed Minisci-type reaction of compounds **29** and **30** for the construction of axially chiral heterobiaryl scaffolds **31**, originally reported by Xiao and co-workers [53]. In this context, **CPA-11** afforded the product in 33% yield, >95:5 *dr* and 21% *ee* (Scheme 6b). Although only moderate enantioselectivities were achieved, these preliminary results demonstrate that **CPA-11** and **CPA-12** can operate as bifunctional catalysts in two distinct photochemical activation modes. Moreover, their modular architecture offers ample opportunities for further structural optimization. On the other hand, their high molecular weight (exceeding 2000 amu for **CPA-11**) represents a practical drawback, since catalyst loadings as high as 5 mol% correspond to relatively large amounts of catalyst per reaction.

In 2024, Wang, Lv, Jiang and co-workers reported that a SPINOL-based chiral phosphoric acid **CPA 13–17**, and specifically **CPA-14** functionalized at the 6,6'-positions with a 10-phenylanthracen-9-yl chromophore, enables enantioselective $[2\pi + 2\sigma]$ photocycloadditions between bicyclo[1.1.0]butanes **32** and vinylazaarenes **33**. This methodology affords pharmaceutically relevant bicyclo[2.1.1]hexanes **34** in high yields and with high enantioselectivities under irradiation at 365 nm at -40°C for 24 h (Scheme 8) [54].



Scheme 8. Enantioselective [2 + 2] photocycloadditions of bicyclo[1.0.0]butanes with vinylazaarenes.

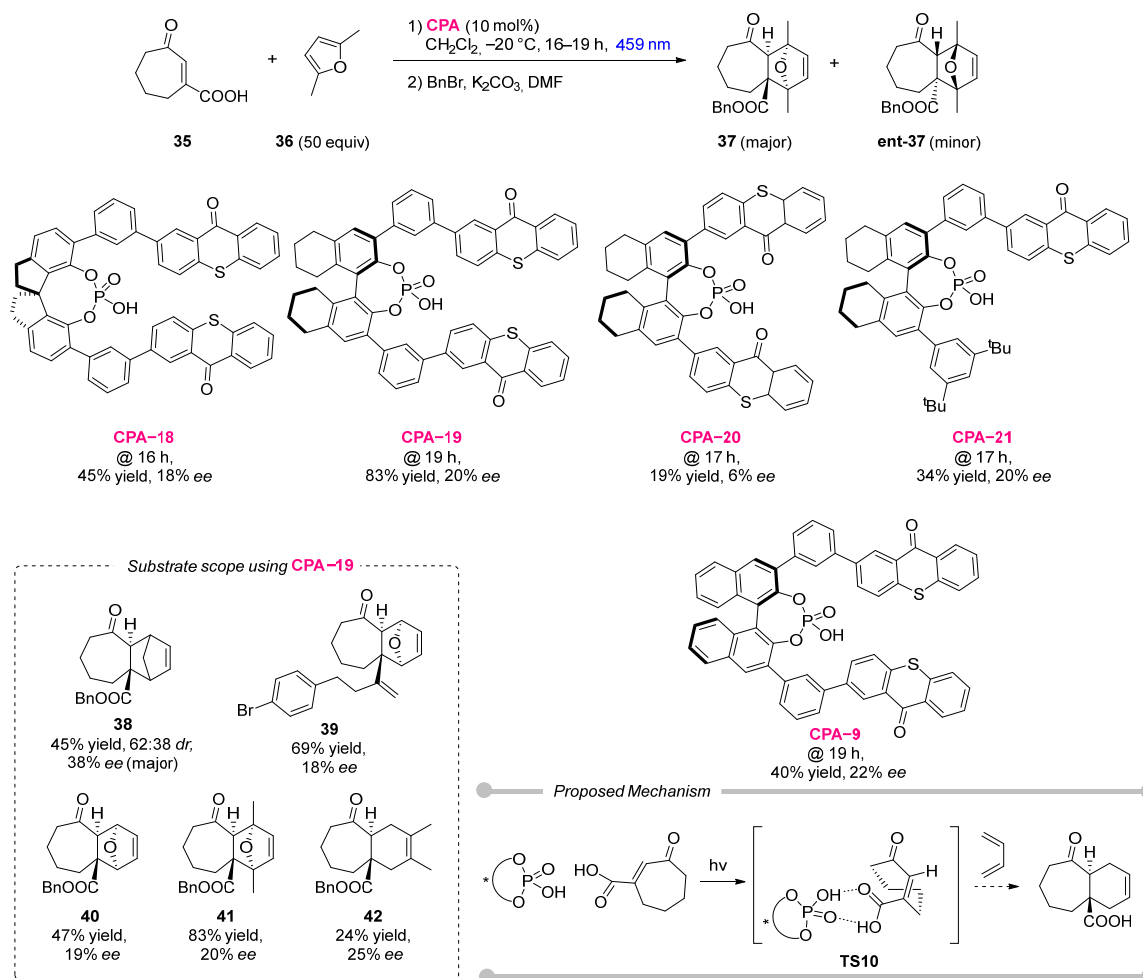
A broad range of 1-ketocarbonyl-3-substituted bicyclo[1.1.0]butanes bearing both electron-withdrawing and electron-donating groups, as well as heteroaryl substituents, were well tolerated, highlighting the broad functional-group compatibility at the ketone moiety. Moreover, both α -substituted vinylazaarenes (**33**, R³ = H) and β -substituted vinylazaarenes (**33**, R² = H) were successfully employed: $\odot$ -substituted vinylazaarenes afforded products bearing a quaternary stereocenter, while $\ominus$ -substituted vinylazaarenes led to the formation of two adjacent tertiary stereocenters, with the *E*-olefin configuration proving more reactive in the [2 + 2] photocycloaddition than the corresponding *Z* isomer.

Across 52 examples, a wide range of substituted bicyclo[2.1.1]hexanes **34** were obtained with broad structural diversity and consistently high levels of reactivity and enantiocontrol. Mechanistic studies, supported by Stern–Volmer quenching experiments, cyclic voltammetry measurements, and DFT calculations, indicate that the reaction proceeds through a proton-coupled electron transfer between the photoexcited triplet state of the chiral phosphoric acid **CPA-14** and the bicyclobutane substrate. This process generates a neutral ketyl radical as an H-bonded adduct of the chiral phosphate (TS8^{triplet}), which undergoes ring opening and subsequent radical addition to the vinylazaarene (TS9^{triplet}) before a final triplet-to-singlet spin crossing (TS10) delivers the desired cycloaddition product **34**. It must be noted that the reaction needs to be conducted under an inert argon atmosphere, as exposure to air completely suppresses product formation, consistent with the known quenching of triplet excited states and radical intermediates by molecular oxygen.

In 2025, chiral phosphoric acids functionalized with a thioxanthone photosensitizer found a novel application in the photochemical isomerization of *cis* cyclohept-2-enone-3-carboxylic acid **35** to its transient *trans* isomer. Stierle, Bach, and co-workers reported that upon triplet energy transfer from the catalyst, the resulting short-lived chiral *trans* intermediate (lifetime ca. 130 μ s in CH₂Cl₂ at room temperature) can be generated enantioselectively and subsequently trapped by 2,5-dimethylfuran **36** in a Diels–Alder reaction to form corresponding tricyclic lactones **37** in an enantioselective manner (Scheme 9) [55,56].

Among the five thioxanthone-based CPAs evaluated, catalyst **CPA-19** shows better chemical and stereochemical efficiency, and was applied across the substrate scope affording tricyclic lactones **38–42** in yields up to 83% and enantioselectivities of up to 38% *ee* under blue light irradiation (459 nm) at -20°C . A comprehensive mechanistic model based on DFT calculations revealed that enantioselectivity originates from a conformational constrain imposed by the catalyst prior to the photoisomerization event (**TS10**). This preorganization dictates the direction of the one-bond flip, favoring the formation of one enantiomer of the transient *trans*-isomer.

Although this photoisomerization step is intrinsically enantioselective, a competing ground-state selectivity in the subsequent Diels–Alder reaction partially erodes the overall enantioselectivity. Specifically, **CPA-19** favors cycloaddition of the minor enantiomer **ent-37**, thereby accounting for the reduced enantiomeric excess observed across different diene partners.



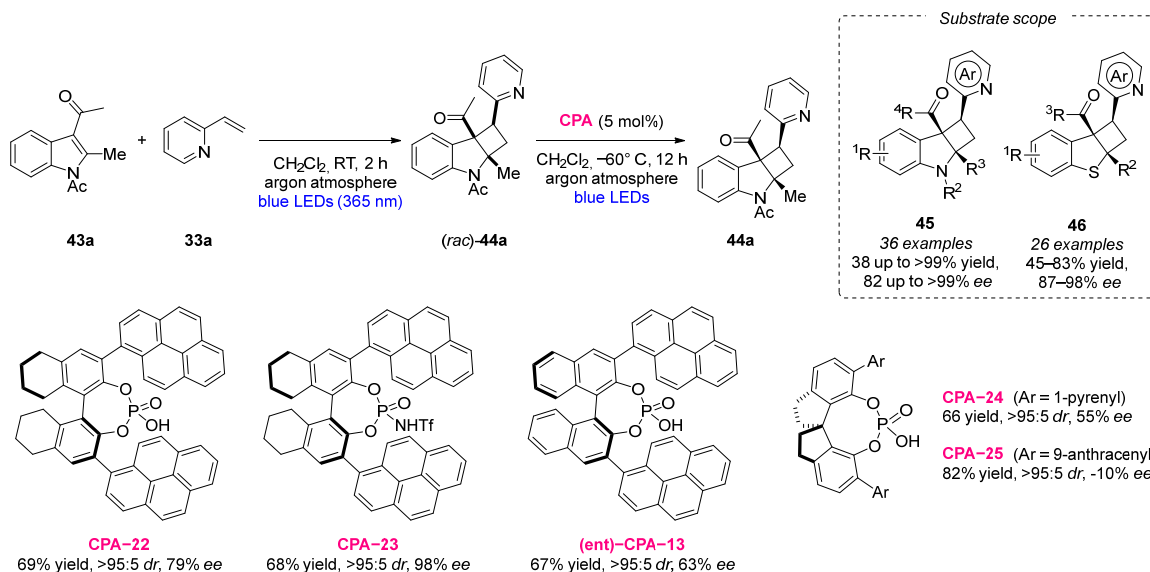
Scheme 9. CPA-mediated enantioselective photoisomerization of cyclohept-2-enone-3-carboxylic acids to a chiral *trans*-intermediate and subsequent Diels–Alder trapping.

Altogether, these examples highlight the broad synthetic potential of bifunctional photoactive CPAs in photocatalytic stereoselective bond-forming transformations and demonstrate how covalent integration of the chromophore into the chiral backbone scaffold enables efficient coupling of photoactivation and stereoselectivity.

2.2. Photocatalytic Deracemization Processes

Beyond bond-forming processes, bifunctional photoactive CPAs have also been applied to photochemical deracemization and related transformations, in which the bifunctional catalyst does not perform the construction of new bonds, but instead controls the stereochemical outcome of photoinduced interconversion processes. According to this approach, Jang and co-workers reported a “de novo deracemization” strategy based on vinylazaarenes as partners in [2 + 2] photocycloadditions, in which the initial photocycloaddition furnishes racemic cyclobutanes, and enantioselectivity is achieved during the photocycloreversion step under the control of a chiral phosphoric acid (Scheme 10) [57].

The process is defined as de novo deracemization because enantioenriched products are generated directly from simple, achiral starting materials, without the need of using preformed racemic substrates, through a sequence of reversible photocycloaddition and enantioselective photocycloreversion steps. In this approach, benzoyl indoles or benzo[b]thiophenes reacts with vinylazaarenes **33** in an initial [2 + 2] photocycloaddition to give the corresponding racemic cyclobutanes **45** or **46**, which then undergo reversible photocycloreversion under the control of the chiral catalyst, leading to the selective formation of the corresponding single enantiomer.



Scheme 10. De novo deracemization of cyclobutanes *via* reversible [2 + 2] photocycloaddition/photocycloreversion.

Although the chiral phosphoric acid is present throughout the reaction, the initial photocycloaddition proceeds with little stereocontrol, whereas enantioselectivity is established during the photocycloreversion step. In this step, differences in catalyst/substrate interactions and in the excitation properties of the diastereomeric complexes enable selective cleavage of one enantiomer, driving the system toward an enantioenriched product.

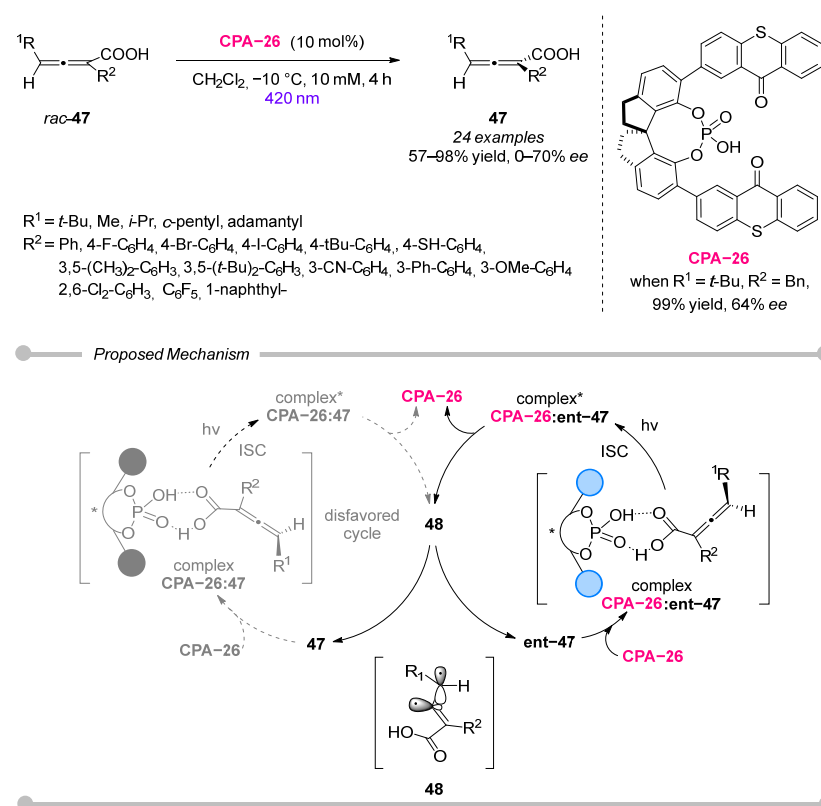
The transformation requires irradiation at 365 nm and proceeds efficiently in the presence of chiral phosphoric acids; even if better results have been obtained using chromophore-substituted *N*-triflylphosphoramidate **CPA-23**. For instance, cyclobutane **44a** is obtained in 69% yield with 79% ee when **CPA-22** was employed, but in general a broad

range of derivatives are accessible in 38–99% yield with up to >99% *ee*. This approach shows a broad substrate scope across various indoles and vinylazaarenes; however, the overall efficiency is influenced by the balance between photocycloaddition and photocycloreversion, which in some cases leads to moderate yields for less reactive substrates.

Alongside this *de novo* approach, Bach and co-workers further demonstrated that bifunctional chiral phosphoric acids bearing a thioxanthone chromophore can also promote direct photochemical deracemization of 2,3-allenoic acids (Scheme 11) [58].

Different CPAs based on different chiral scaffolds were investigated, but only the SPINOL-derived catalyst **CPA-26** functionalized with two thioxanthone units proved to be effective for the deracemization of 2,4-disubstituted allenoic acids **47**. Under irradiation at 420 nm for 4 h at −10 °C, **CPA-26** afforded the enantioenriched acid **47** in high yields (57–98%) and moderate enantioselectivities (up to 70% *ee*), with preferential formation of **47** enantiomer over the **ent-47** counterpart. The methodology shows good tolerance toward various substituted benzyl groups, although enantioselectivity is sensitive to steric effects at both termini of the allene.

Mechanistic studies revealed that, upon photoexcitation, **CPA-26** populates its triplet excited state and subsequently transfers energy to the allene substrate, which is associated with the catalyst through hydrogen bonding to the COOH group, leading to the formation of the achiral diradical intermediate **48**, which dissociates from the phosphoric acid and forms either one of the two enantiomers **47** or **ent-47** of the allenoic acid. Because the efficiency of the energy transfer process is highly distance-dependent, the two diastereomeric catalyst/substrate complexes are processed at different rates, leading to the accumulation of the more slowly excited enantiomer at the photostationary state.



Scheme 11. Photochemical deracemization of 2,3-allenoic acids mediated by the SPINOL-derived catalyst **CPA-26**.

This mechanistic proposal is supported by control experiments and Boltzmann-weighted DFT calculations, which reveal a greater van der Waals overlap between the

thioxanthone chromophore of the catalyst and the allene moiety of the substrate in one diastereomeric complex, consistent with its faster energy transfer and the observed enantioselectivity. While this work represents an elegant demonstration of a bifunctional CPA operating as a single-component photocatalyst for substrates previously inaccessible by this approach, the enantioselectivities remain moderate. This limitation is attributed to the conformational flexibility of both the catalyst and the substrate, which reduces the efficiency of enantiomer discrimination during the energy transfer step.

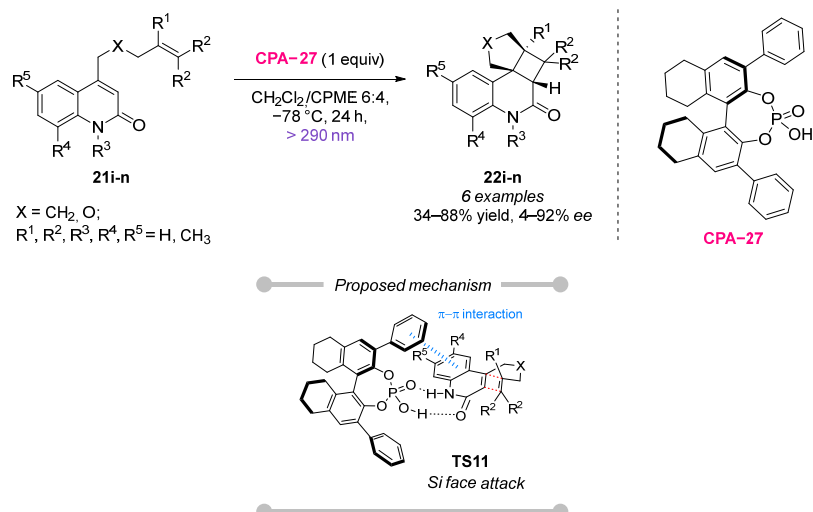
Overall, these studies highlight the remarkable versatility of bifunctional photoactive chiral phosphoric acids as single-component photocatalysts capable of promoting a wide range of stereoselective photochemical transformations. By covalently integrating a photoactive unit within the chiral scaffold, CPAs can operate through different activation modes while maintaining a well-defined chiral pocket suitable for performing enantioselective catalysis as well as deracemization and photoisomerization of transient intermediates. The thioxanthone moiety has emerged as the privileged chromophore, although cyanoarene- and anthracene-based systems have also shown potential in expanding the scope of accessible transformations and tuning the photophysical properties of these catalysts. Despite these advances, several limitations remain, including moderate enantioselectivities in some systems, restricted substrate scope in certain transformations, and the need for precise tuning of catalyst/substrate interaction to achieve efficient stereocontrol. Addressing this challenge, the development of more rigid catalyst architectures [59,60], improved substrate preorganization, or data-driven catalyst design strategies [61–63] will be crucial for advancing this approach and will likely define the next developments in the field.

3. Photoactive CPA–Substrate Complexes

In a conceptually different approach, chiral phosphoric acids have been used to promote the formation of photoresponsive catalyst/substrate complexes, rather than to act as photoactive catalysts themselves. Upon coordination through hydrogen bonding or ion pairing, the electronic properties of the substrate are modified, enabling direct excitation under light irradiation in the absence of an external photocatalyst. In this way, the CPA simultaneously controls the substrate activation and the stereochemical outcome of the reaction. This strategy provides a particularly elegant platform for stereoselective photochemical synthetic methodologies, as it merges molecular recognition, photoactivation, and enantiocontrol within a single catalyst/substrate assembly. In many other light-driven transformations, however, the role of the chiral phosphoric acid follows a classical pathway: rather than rendering the substrate itself photoactive, the CPA coordinates and stereochemically organizes reactive intermediates that are generated independently through an initial photochemical event [64–66]. Such cases fall outside the scope of the present section and will not be discussed.

3.1. Direct Excitation and Activation of CPA/Substrate Complexes.

Studies on chiral Lewis acid-mediated photochemical reactions have shown that substrate binding can modulate photophysical properties and enable stereocontrolled excitation [67,68]. A first representative example in this field involving chiral phosphoric acids was reported in 2020 by Takagi and Tabuchi, who developed an enantioselective intramolecular [2 + 2] photocycloaddition of substituted 4-bishomoallyl-2-quinolones **22i-n** using stoichiometric amounts of chiral phosphoric acid **CPA-25** as a template for direct excitation of the CPA/substrate complex in CH₂Cl₂/CPME mixture at –78 °C for 78 h [69]. Upon these reaction conditions, desired cycloadducts **22i-n** were formed in good yields and up to 92% ee (Scheme 12).



Scheme 12. Enantioselective intramolecular [2 + 2] photocycloaddition of quinolinones promoted by phosphoric acids.

Mechanistic studies based on ^1H and ^{31}P NMR measurements supported the formation of a 1:1 complex between **CPA-27** and quinolones **21**. As observed in the analogous transformation promoted by the thioxanthone-functionalized H_8 -BINOL-derived catalyst **CPA-10** (Scheme 6), the stereochemical outcome of the process was found to be primarily determined by $\pi-\pi$ interactions between the 3,3' substituent of the chiral phosphoric acid and the quinolinone substrate (**TS11**). Structural variation in substrate **21** further highlighted the importance of dual hydrogen bonding, as *N*-methylation or the introduction of competing hydrogen-bonding sites led to a marked decrease or complete loss of enantioselectivity.

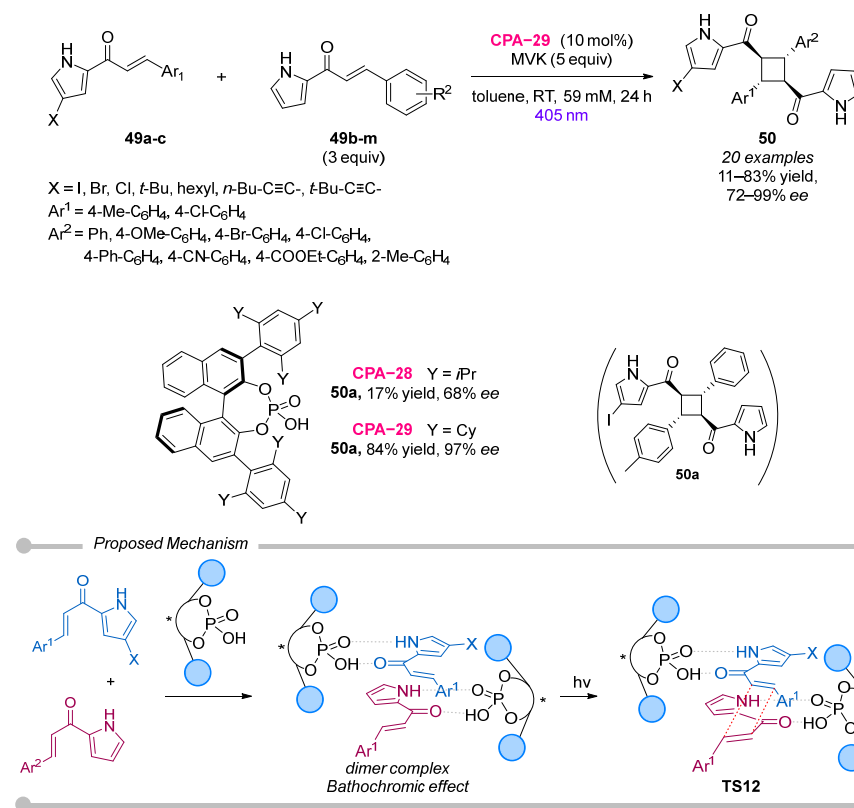
Although this methodology can be considered more as a template-controlled direct excitation process rather than a photoactive CPA/substrate complex, it nevertheless represents an important early precedent showing that phosphoric acid can preorganize substrates for stereocontrolled photochemical activation. Catalytic variants of enantioselective [2 + 2] photocycloadditions were subsequently developed, although the optimal systems involved BINOL-derived chiral phosphoramides rather than classical chiral phosphoric acids [70–72].

The first enantioselective [2 + 2] photocyclization specifically promoted by CPAs was reported in 2023 by Akiyama and co-workers. They developed an intermolecular [2 + 2] photocyclization of alkenyl 2-pyrrolyl ketones **49** using catalysts **CPAs 28–29** to afford cyclobutanes **50**. Among these catalysts, only the bathochromic shift induced by the chiral phosphoric acid **CPA-29** enabled the synthesis of cyclobutanes with enantioselectivities in up to 99% *ee* (Scheme 13) [73].

It was found that mixing alkenyl 2-pyrrolyl ketones **51** with chiral phosphoric acid **CPA-29** induced a bathochromic absorption shift, allowing the resulting complex to be excited upon violet LED irradiation at 405 nm. This excitation allows the formation of cyclobutane products in up to 85% yield and 98% *ee*. A broad substrate scope was demonstrated, including halo-, alkyl-, alkynyl-, and aryl-substituted enones, although yields and enantioselectivities are quite influenced by the electronic characteristics of the substituents.

Studies on the related mechanism suggested that the reaction proceeds through direct excitation of the CPA/substrate complex from the singlet excited state, rather than through a triplet pathway. A positive nonlinear effect further indicated that more than one phosphoric acid molecule is involved in the stereodetermining transition state. On this basis, the authors proposed transition state **TS-12** composed of two molecules of **CPA-**

28 and two molecules of substrate **49**. DFT calculations supported this hypothesis, revealing that this dimeric complex is further stabilized by π - π stacking interactions between the pyrrole moieties.

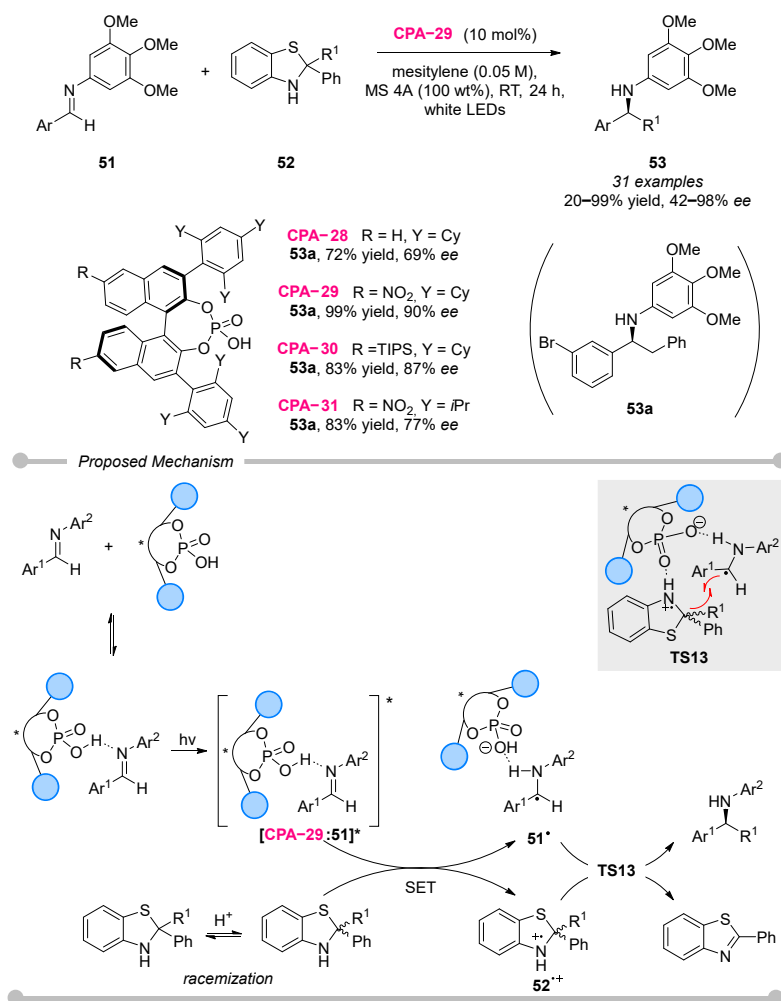


Scheme 13. CPA-mediated enantioselective [2 + 2] photocycloaddition of alkenyl 2-pyrrolyl ketones.

With a similar approach, the same research group also reported a visible-light-driven enantioselective radical addition to imines enabled by direct excitation of a chiral phosphoric acid–imine complex (Scheme 14) [74].

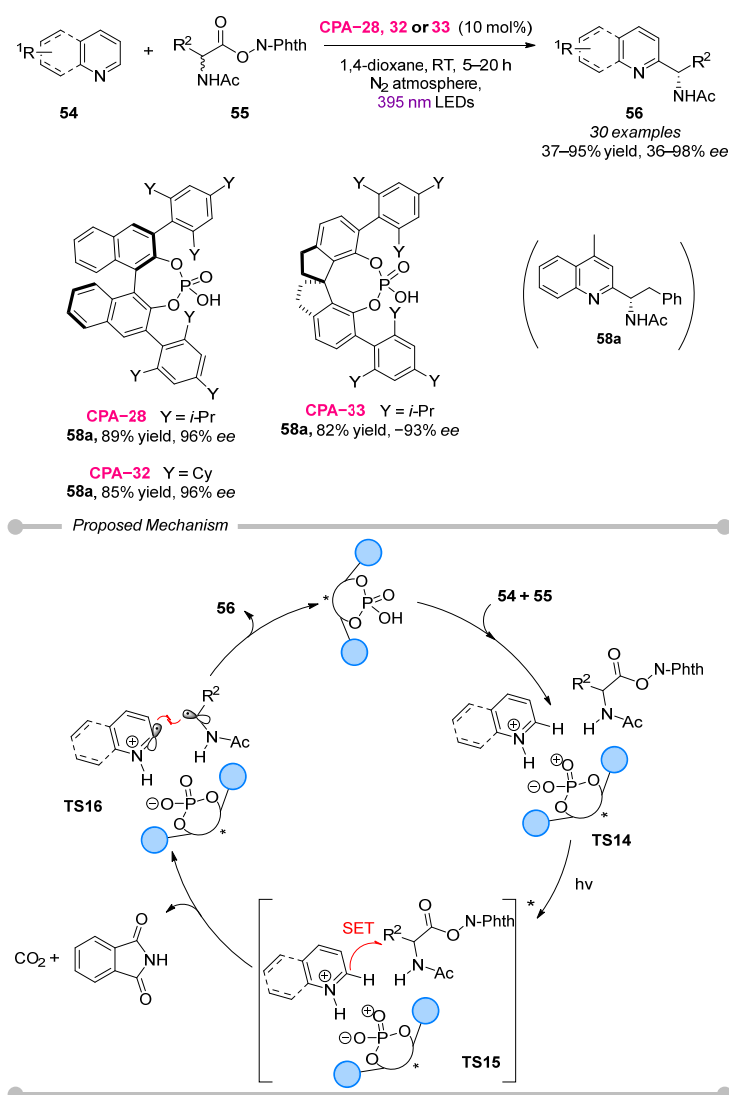
The reaction between *N*-3,4,5-trimethoxyphenyl substituted aldimines **51** and benzothiazolines **52** was carried out in mesitylene in the presence of the BINOL-derived chiral phosphoric acid **CPA-29** bearing two nitro groups at the 6,6'-positions, under white LED irradiation, leading to the formation of chiral amines **53** in high yields and with enantioselectivities of up to 98% *ee*. Control experiments showed that the presence of **CPA-29** and light is necessary, while the reaction was completely suppressed under air. The substrate scope included a broad range of aromatic and aliphatic imines, although aliphatic imines proved to be less reactive than their aromatic counterparts.

Mechanistic studies supported an alkyl radical pathway: visible-light excitation of the protonated imine generates a highly oxidizing chiral phosphoric acid–imine complex [CPA-29:51]*, which promotes single-electron transfer to benzothiazoline **52**, affording the amino radical **51**[•] and the benzothiazoline radical cation **51**^{•+}. Their interaction with the chiral phosphate anion enables enantioselective radical transfer to give the desired enantiopure amine **53** and benzothiazole, while in situ racemization of benzothiazoline ensures selective reaction of the matched enantiomer.



Scheme 14. Enantioselective radical addition to imines enabled by a photoactive CPA-imine complex under visible light.

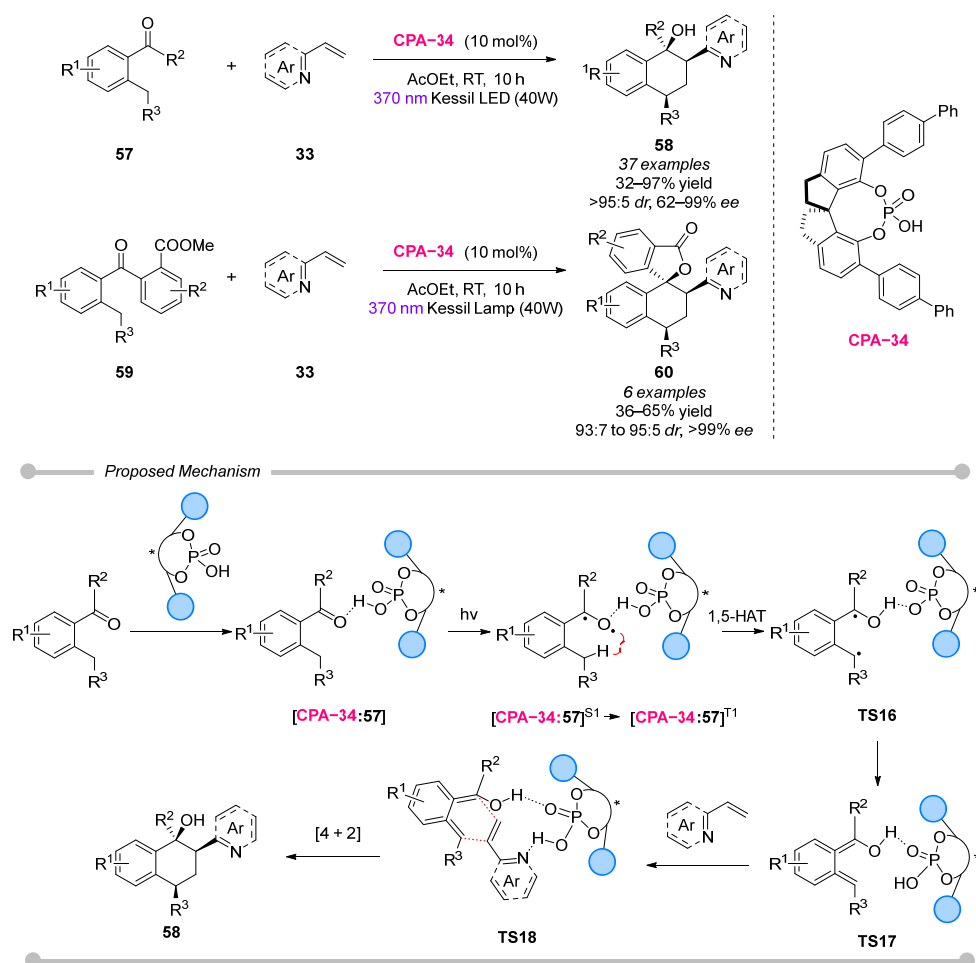
A further relevant contribution in this field was reported by Zheng and co-workers, with the development of an enantioselective Minisci-type alkylation of *N*-heteroarenes catalyzed by chiral phosphoric acids under 395 nm irradiation without the need for metals, photocatalysts, or other additives (Scheme 15) [75]. It was found that quinoline-, isoquinoline-, and pyridine-type substrates reacts with α -aminoalkyl radicals derived from redox-active esters, affording chiral aminoalkylated *N*-heteroarenes **54** in high yields and with enantioselectivities of up to 98% *ee* when irradiated at 395 nm in the presence of a chiral phosphoric acid (Scheme 14). Optimization studies identified the bulky BINOL-derived CPA-28 and CPA-32 as the most effective catalysts, although good results were also obtained with the spiro-phosphoric acid CPA-33. Notably, the addition of a conventional iridium-based photoredox catalyst did not improve the reaction outcome, supporting the hypothesis that the transformation does not rely on an external photocatalyst.



Scheme 15. Photocatalyst-free enantioselective Minisci-type alkylation of *N*-heteroarenes promoted by CPAs.

Mechanistic studies confirm the presence of radical intermediates, and ruled out both *N*-oxide intermediates and a simple EDA complex between the *N*-heteroarene and the redox-active ester. Irradiation at 395 nm of the hydrogen-bonded CPA/substrate complex TS14 generates the excited species TS15, which promotes intermolecular single-electron transfer to the redox-active ester. Subsequent chiral phosphoric acid-assisted enantioselective radical coupling (TS16) affords the aminoalkylated product 56 with high enantioselectivity.

A further recent extension of the capability of chiral phosphoric acid to generate a photosensible complex was disclosed by Chen, Xiao and co-workers in an enantioselective photoenolization/Diels–Alder (PEDA) reaction between aryl ketones 57 and 59 and 2-vinyl-pyridine 33 [76]. In this study, different BINOL- and SPINOL-derived chiral phosphoric acid were found to be effective in promoting highly stereoselective [4 + 2] cycloadditions between aryl ketones and vinylazaarenes under near-UV irradiation (370 nm) at room temperature, leading to the formation of azaarene-containing carbocyclic products 58 and spiro lactones 60 in good yields and excellent levels of enantio- and diastereoselectivity (Scheme 16).



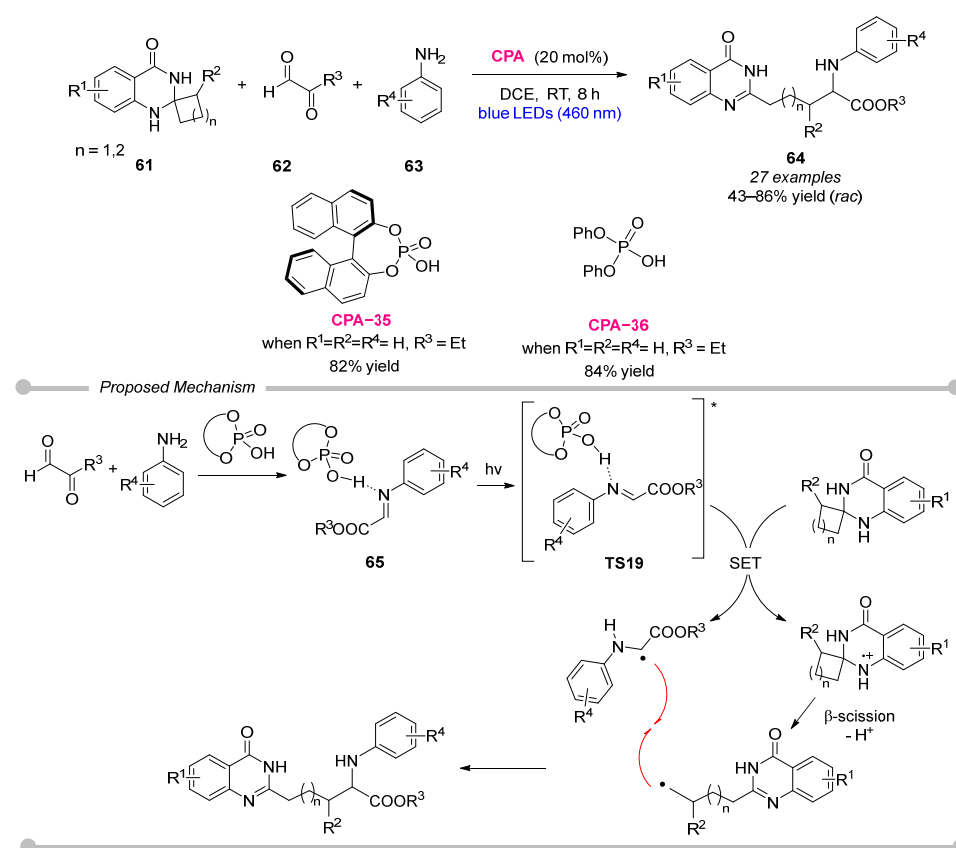
Scheme 16. Enantioselective photoenolization/Diels–Alder reaction catalyzed by CPAs.

Since UV-Vis analysis confirmed that **[CPA-34:57]** complex is the predominant light-absorbing species, the proposed mechanism involves initial hydrogen-bonding association of aryl ketone **57** with CPA-34. The complex formed acts as the photoactive species and upon excitation, it reaches singlet state **[CPA-34:57]^{S1}**, then undergoes intersystem crossing to **[CPA-34:57]^{T1}**, with the consequent formation of diradical **TS16** through 1,5-HAT. This radical evolves in the corresponding CPA-stabilized photoenol **TS17**, which undergoes enantioselective Diels–Alder cycloaddition with the vinylazaarene through **TS18**, delivering the final adduct **58** in enantioenriched form.

As shown, these studies demonstrate that hydrogen-bonding association between a chiral phosphoric acid and the substrate can substantially modulate its photophysical properties, opening reaction pathways that would otherwise remain inaccessible without the presence of an external photocatalyst. Although only a limited number of synthetic applications have been developed so far, these studies clearly show that chiral phosphoric acids fulfill a dual and inseparable function: by engaging the substrate through hydrogen bonding or ion pairing, they simultaneously lower the LUMO energy of the resulting complex and create a well-defined chiral environment that controls the stereochemical outcome of the subsequent photochemical process. However, despite the remarkable enantioselectivities achieved in some cases, significant limitations are still present, which limit functional-group compatibility and restrict the broader generality of the methodology. For that reason, further progress will require both rational catalyst design and a deeper understanding of the CPA/substrate interactions that govern these transformations.

3.2. Multicomponent and Supramolecular Systems in CPA-Mediated Photoactivation

More recent developments have demonstrated that direct substrate photoactivation by phosphoric acid binding is not limited to simple CPA/substrate complexes, but can also be extended to multicomponent and supramolecular systems. In these more elaborate cases, the photoactive assembly is embedded within a broader network of non-covalent interactions, enabling radical generation and stereocontrol in structurally and mechanistically more complex settings. A representative example of this evolution was reported by Guo and co-workers, in a visible-light-driven three-component deconstructive aminoalkylation of spirodihydroquinazolones, in which the photoactive species is not a pre-formed binary CPA/substrate complex, but an in situ generated phosphoric acid/aldimine assembly operating within a multicomponent reaction system (Scheme 17) [77].



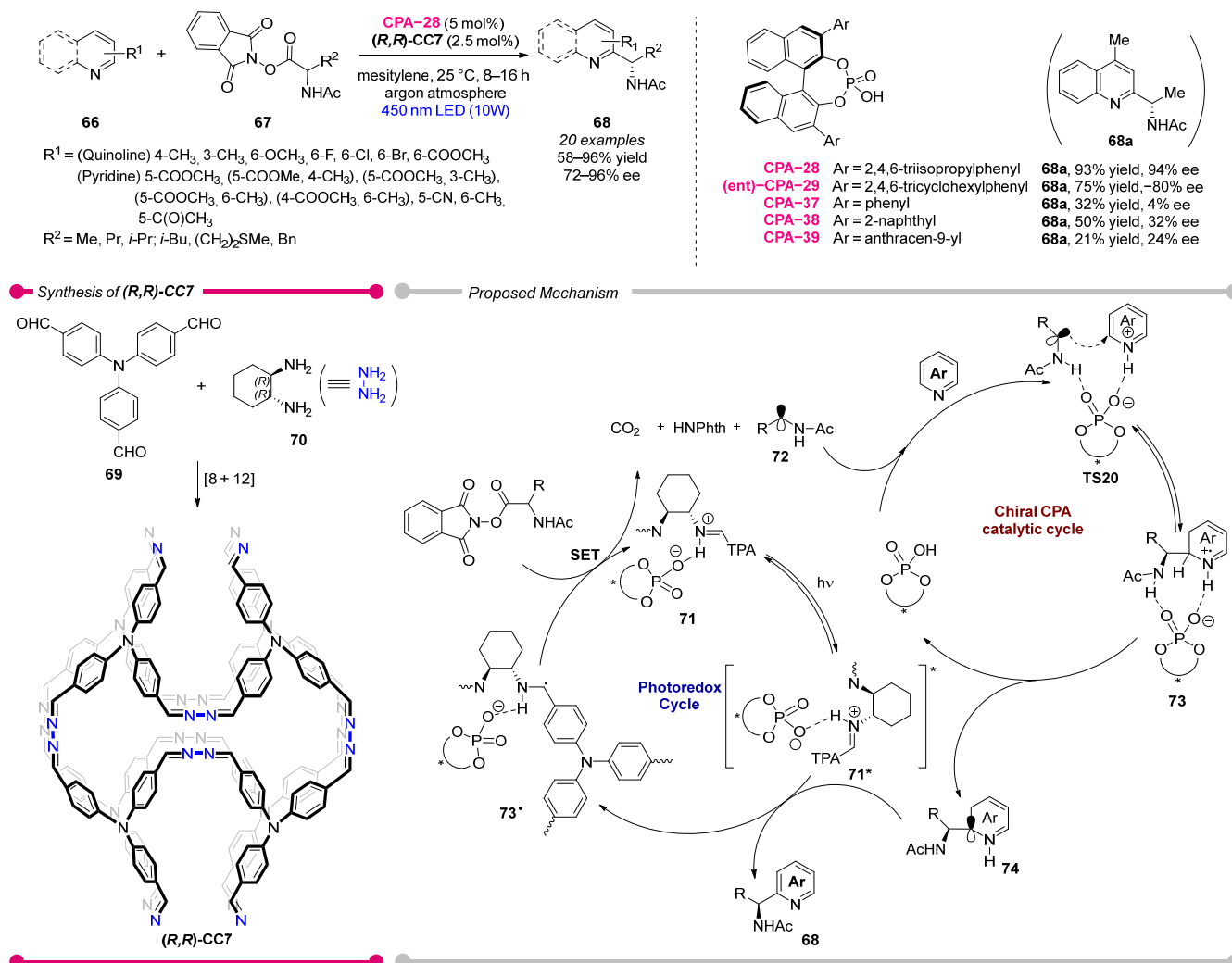
Scheme 17. Deconstructive aminoalkylation for α -functionalized unnatural amino acids.

Spiro-dihydroquinazolinones **61**, substituted glyoxylates **62**, and aromatic amines **63** were reacted in dichloroethane (DCE) under 10 W blue LED irradiation (460 nm) at room temperature for 8 h, affording the corresponding unnatural N -aryl α -amino esters **64** containing a quinazolin-4(3H)-one fragment in up to 86% yield and with broad functional-group tolerance.

Although this transformation lacks in enantioselectivity (the radical is generated on the final stereogenic center), the importance of this study arises from the fact that an in situ generated acid/imine complex can act as a photoresponsive intermediate involved within a multicomponent radical cascade. According to the proposed mechanism, the phosphoric acid first promotes condensation between the aromatic amine and alkyl glyoxylate to form aldimine **65** in situ, and the resulting phosphoric acid/aldimine complex then acts as the key photoactive redox species under blue light irradiation.

In another very recent contribution, Liu and co-workers reported a supramolecular extension of CPA-mediated photoactivation through an organic imine cage-mediated

enantioselective Minisci addition of *N*-heteroarenes, in which a phosphoric acid/imine cage assembly acts as the photoactive species responsible for radical generation, while an additional chiral phosphoric acid molecule controls the stereoselective addition step [78]. (*R,R*)-CC7 cage was synthesized through an [8 + 12] imine condensation reaction between tris(4-formylphenyl)amine **69** and (*R,R*)-1,2-cyclohexanediamine **70** (Scheme 18).



Scheme 18. Supramolecular cage-enabled enantioselective Minisci addition of *N*-heteroarenes through CPA-mediated photoactivation.

Used in combination with **CPA-28**, this supramolecular system enabled the photocatalytic enantioselective Minisci reaction between *N*-heteroarenes **66** (quinolines, isoquinolines, pyridines) and redox-active esters **67** in mesitylene under 450 nm LED irradiation at 25 °C for 8–16 h, affording the corresponding chiral heteroarene derivatives **68** in high yields and enantioselectivities.

Mechanistic studies and control experiments support a radical reaction pathway involving the in situ formation of a CPA/imine adduct, in which the organic imine cage acts as a supramolecular scaffold that binds the phosphoric acid and provides the photoactive assembly responsible for radical generation under light irradiation.

Two distinct but cooperative catalytic cycles involving **CPA-28** were hypothesized, in which the chiral phosphoric acid serves a dual function. One molecule of the catalyst interacts with the cage to form the CPA/imine complex responsible for the initial photocatalytic step, whereas a second molecule of **CPA-28**, not bound to the cage, mediates the enantioselective transformation.

In the photoredox cycle, one molecule of **CPA-28** binds to the imine units of the (*R,R*)-**CC7** cage through hydrogen bonding, generating the CPA/imine adduct **71**, which upon light irradiation is excited to **71*** which evolves into the reduced CPA/imine radical adduct **71•**. The resulting excited complex transfers an electron to the redox-active ester via SET process, ultimately leading to decarboxylation and formation of the α -aminoalkyl radical **72**. The photoredox cycle is then completed by the regeneration of the ground-state CPA/imine complex **71**, which allows catalyst turnover in the subsequent cycle. In the enantioselective cycle, a second molecule of **CPA-28** protonates the *N*-heteroarene and organizes both reaction partners through hydrogen-bonding interactions, enabling enantioselective radical addition from the α -aminoalkylradical to the substrate through a **TS20**. The resulting radical cation **73** then undergoes deprotonation to give intermediate **74**, which is further oxidized and deprotonated to give the final enantioenriched product **68**.

Although examples of multicomponent and supramolecular systems in CPA-mediated photoactivation are still relatively few, these studies clearly demonstrate that this activation mode is not confined to simple binary catalyst/substrate complexes, but can also be extended to systems of substantially greater structural and mechanistic complexity. In such cases, the phosphoric acid does not simply interact with an individual substrate, but instead contributes to the formation of photoresponsive assemblies capable of generating reactive intermediates under light irradiation. These findings point to new opportunities for the future development of asymmetric photochemical catalysis.

4. Conclusions

The examples discussed herein illustrate that the role of chiral phosphoric acids is under continuous evolution; from classical Brønsted acid catalysts to photoactive components capable of both promoting and controlling stereoselective transformations under light irradiation. Depending on catalyst design and substrate class, they can operate as photosensitizers, photoredox-active catalysts, hydrogen-bonding templates, or components of photoactive supramolecular assemblies, while maintaining a defined chiral environment around highly reactive excited-state intermediates. In this context, CPA catalysis emerges as a powerful solution to one of the key challenges of photochemical synthesis: combining the high reactivity of excited-state intermediates with effective stereochemical control. The results gathered so far demonstrate that this strategy can be successfully extended to carbon–carbon bond-forming reactions, photocycloadditions, radical additions, deracemization processes, and more complex multicomponent transformations.

At the same time, however, several challenges in both approaches are still present. In bifunctional photoactive catalysts, further progress will depend on more precise tuning of the relationship between chromophore, catalyst geometry, and substrate recognition. In the case of photoactive CPA/substrate complexes, the main limitations arise from the strongly substrate-dependent nature of complex formation and from the often modest photophysical perturbation induced by acid binding, which can restrict generality and functional-group compatibility.

Future advances in this area will likely require a combination of rational catalyst design, improved substrate preorganization, and deeper mechanistic understanding of excited-state catalyst/substrate assemblies. In particular, greater insight into how catalyst structure influences absorption properties, excited-state lifetimes, intersystem crossing, energy- and electron transfer events should provide a more predictive basis for reaction development. If these challenges can be addressed, directly light-activated chiral phosphoric acids may evolve from a collection of elegant and mechanistically intriguing case studies into a broadly applicable strategy for asymmetric photochemical synthesis.

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