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Review

Advancements in organocatalysis for radical-mediated asymmetric synthesis: A recent perspective

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SUMMARY

Radical-mediated organic synthesis has arisen as a potent technique for forming carbon-carbon and carbon-heteroatom bonds, displaying remarkable compatibility with diverse functional groups and superior chemoselectivity. Integrating radical transformations with asymmetric organocatalysis offers a valuable approach to accessing enantio-enriched molecules through unique pathways that differ from those facilitated by transition metal catalysis. Nevertheless, this combination continues to pose challenges due to the involvement of highly reactive intermediates, which may result in undesired background reactions and struggles in controlling stereochemistry. Recent advances in this field have led to the emergence of sophisticated strategies encompassing chemical, photochemical, and electrochemical methods. This review aims to provide a thorough overview of the mechanistic insights underlying these innovative reactions, including both catalytic activation patterns and bond formation processes. Furthermore, this review will delve into their synthetic applications, limitations, and the progress achieved between 2018 and 2023.

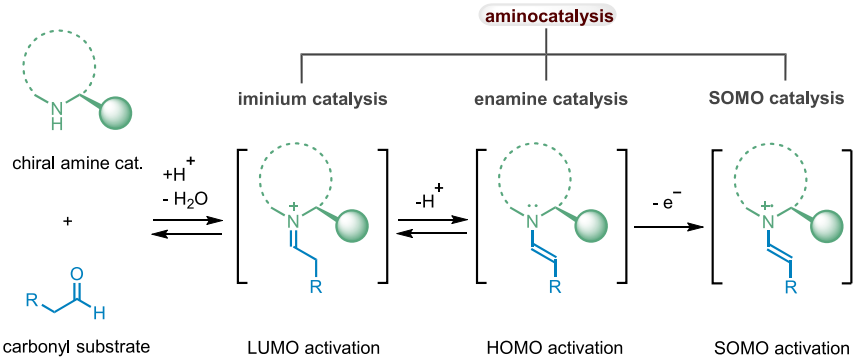
INTRODUCTION

Asymmetric organocatalysis, in collaboration with transition metal catalysis and enzyme catalysis, is widely recognized as one of the three primary strategies in asymmetric catalysis.[1] This technique not only exhibits remarkable efficacy in an extensive array of vital enantioselective transformations but also boasts advantageous characteristics such as air stability, recoverability, scalability, and economic accessibility. By aligning with the fundamental principles of green chemistry, asymmetric organocatalysis has gained growing significance in the realm of organic chemistry.[2,3]

Radical-mediated processes have emerged as powerful and indispensable tools in synthetic chemistry.[4,5] Their remarkable ability to forge carbon-carbon and carbon-heteroatom bonds across various functional groups with high chemoselectivity has rendered them highly coveted.[6–8] The integration of radical transformations with asymmetric catalysis, known as radical-mediated asymmetric catalysis, presents a valuable approach for accessing enantio-enriched molecules through distinct pathways that diverge from more common ionic reactions.[9,10] Consequently, it has become a dynamic research area in organic synthesis. The development of radical-mediated asymmetric catalysis faces several inherent challenges, such as dealing with highly reactive intermediates, eliminating undesired background reactions, and achieving precise regio- and stereodiscrimination. In response to these challenges, transition metal catalysis has showcased impressive versatility. These

THE BIGGER PICTURE

Radical-mediated asymmetric organocatalysis represents a powerful tool for constructing enantio-enriched molecules through unique reaction pathways. However, achieving high levels of stereocontrol remains a challenging task due to undesired background reactions stemming from the formation of highly reactive radicals and compatibility issues with organocatalysts in radical transformations. Recent advances in this field have led to the development of sophisticated strategies that incorporate chemical, photochemical, and electrochemical methods. This comprehensive review aims to provide insight into the mechanisms underlying these innovative reactions and their synthetic applications and limitations. This review will also systematically discuss the progress made in this field from 2018 to 2023. These significant contributions are expected to propel the advancement of asymmetric organocatalysis, radical chemistry, and pharmaceutical chemistry.



Scheme 1. Typical activation modes of asymmetric aminocatalysis

reactions can proceed through outer-sphere mechanisms, involving the activation and stereocontrol of acceptors for radical addition or coupling. Alternatively, radicals can interact with metals, leading to organometallic pathways.[11]

Although significant advances have been made in transition metal catalysis, the progression of asymmetric organocatalytic radical reactions has been relatively constrained. In recent years, however, innovative strategies and novel techniques have been developed and implemented in this field, leading to the opening of uncharted research frontiers. For instance, Beeson et al.[12] introduced the concept of singly occupied molecular orbital (SOMO) catalysis, thereby paving the way for exploring new possibilities of asymmetric radical chemistry. Furthermore, the rapid strides in photochemistry and electrochemistry have rejuvenated radical chemistry, bringing forth more sophisticated and refined strategies. The combination of organocatalysis with photocatalysis or electrocatalysis has created exciting opportunities to uncover fresh mechanistic insights and expand the scope of asymmetric radical chemistry.

This review aims to provide an up-to-date overview of the recent breakthroughs (2018–2023) in organocatalytic asymmetric radical transformations. It particularly emphasizes dissecting the mechanistic insights of these cutting-edge reactions, as well as exploring their synthetic applications and limitations. In order to enhance comprehension, the discussed reactions will be divided into three distinct categories: conventional chemical methods, photochemical strategies, and electrochemical approaches. Each subgroup will be discussed separately, providing a detailed analysis of the strategies used and their corresponding outcomes. It is worth noting that this review will not cover examples involving photo-induced energy transfer catalysis, as they have already been addressed in recent literatures.[13]

CHEMICAL APPROACHES FOR RADICAL-MEDIATED ORGANOCATALYTIC ASYMMETRIC TRANSFORMATIONS

Chiral aminocatalysis has emerged as a powerful tool in asymmetric synthesis, revolutionizing the field of organocatalysis and enabling the creation of diverse enantiopure scaffolds. These methods typically involve raising the highest occupied molecular orbital (HOMO) of aldehydes through enamines or lowering the lowest unoccupied molecular orbital (LUMO) of enals via iminium ions in chiral amine-catalyzed organic transformations.[14–16] The efficacy of these approaches has been extensively demonstrated in numerous studies. In 2007, Beeson et al.[12] introduced the concept of SOMO catalysis, which further expanded the applications of chiral aminocatalysis in asymmetric organocatalysis, particularly in radical-involved processes (Scheme 1). By harnessing the unique properties and reactivity of radicals

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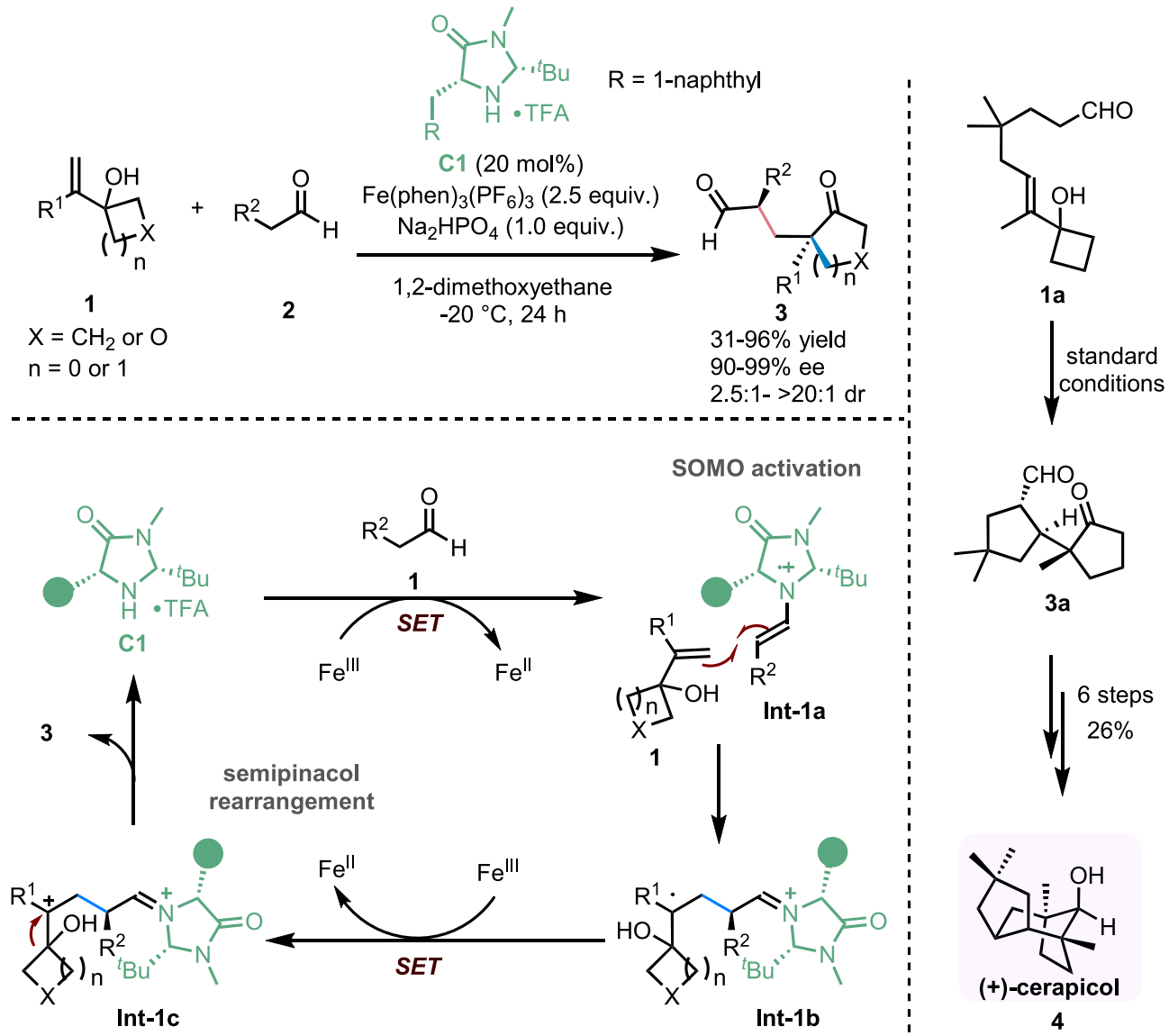
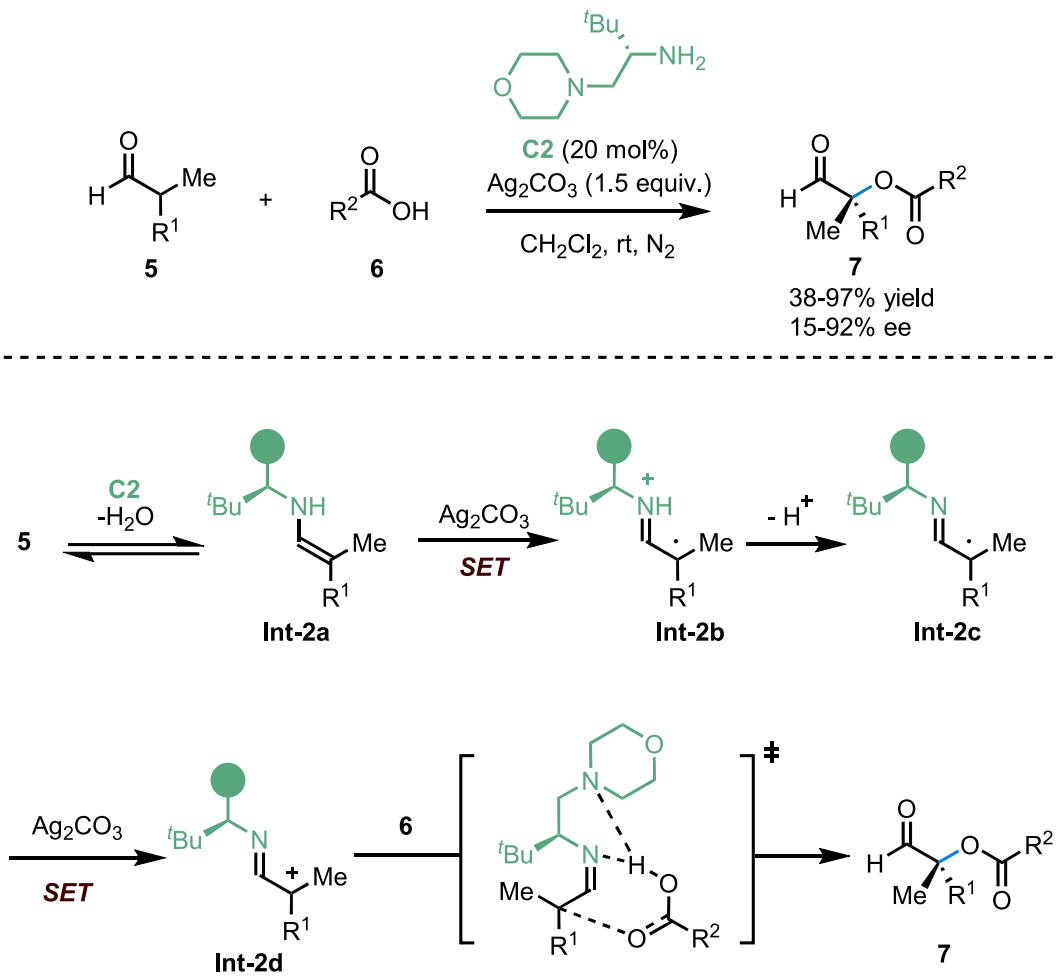


Scheme 2. Enantioselective aldehyde α-alkylation/semipinacol rearrangement by chiral aminocatalysis

and precisely designing chiral amine catalysts, researchers have been able to achieve remarkable selectivity and efficiency in various radical-mediated processes.[17]

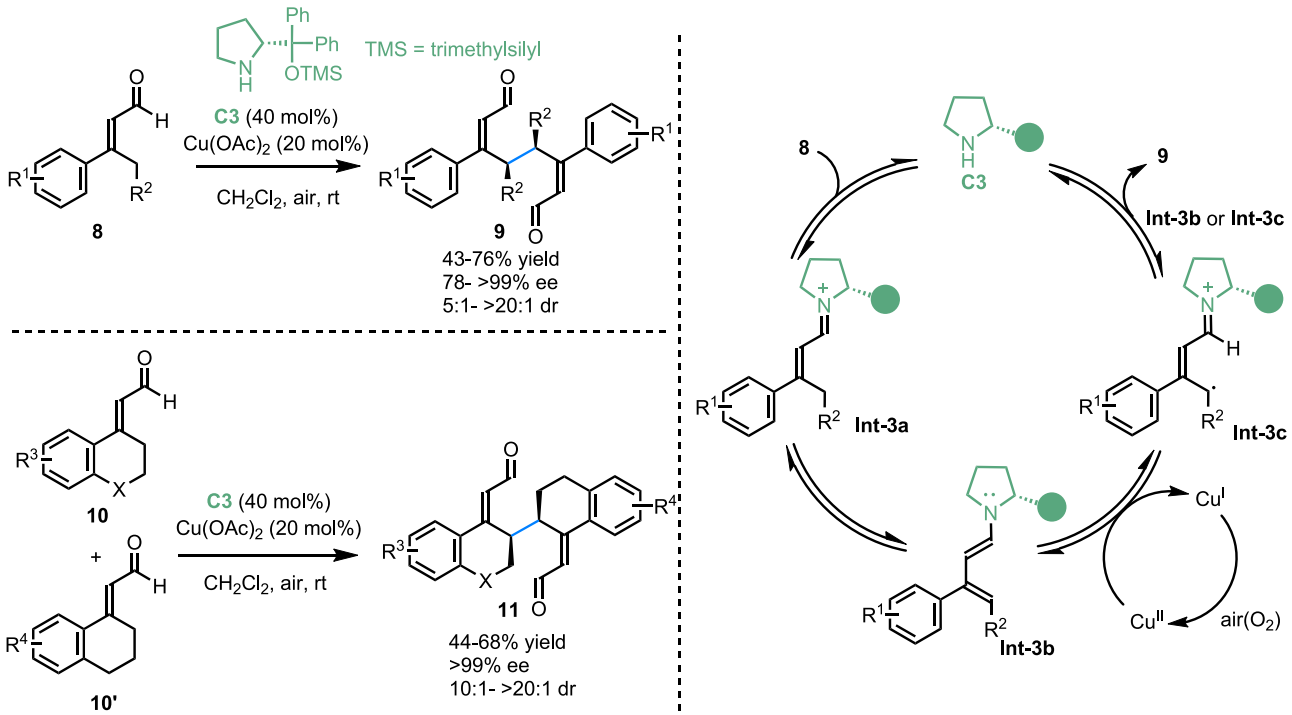
In 2020, Yang et al.[18] reported an enantioselective aldehyde α-alkylation/semipinacol rearrangement through organo-SOMO catalysis (Scheme 2). This approach used a chiral primary amine (**C1**) as the organocatalyst and a stoichiometric amount of $Fe(phen)_3(PF_6)_3$ as the oxidant. Under mild conditions, the reaction between allylic alcohols (**1**) and simple aldehydes (**2**) proceeded smoothly, delivering enantio-enriched α-quaternary-δ-carbonyl cycloketones with yields ranging from 31% to 96% and enantioselectivity of 90%–99%. The mechanism underlying this transformation involves the condensation of the amine catalyst (**C1**) with the aldehyde (**2**), generating an enamine radical cation (**Int-1a**). Subsequently, this intermediate undergoes single electronic oxidation by $Fe(phen)_3(PF_6)_3$. The activation of the substrate



Scheme 3. Asymmetric nucleophilic cross-coupling between α-branched aldehydes and carboxylic acids by chiral aminocatalysis

through SOMO enables a stereoselective reaction with the allylic alcohol (**1**), resulting in the formation of a radical intermediate (**Int-1b**). A second round of single-electronic oxidation of **Int-1b** generates a cation intermediate (**Int-1c**). Finally, through semipinacol rearrangement, the desired product (**3**) is obtained, accompanied by the regeneration of the amine catalyst. This cascade reaction showcases its versatility by successfully facilitating the total synthesis of (+)-cerapicol (**4**), a natural product of great interest. These findings not only highlight the synthetic utility of the organo-SOMO strategy, but also open up new opportunities for constructing complex chiral molecules with high control over stereochemistry.

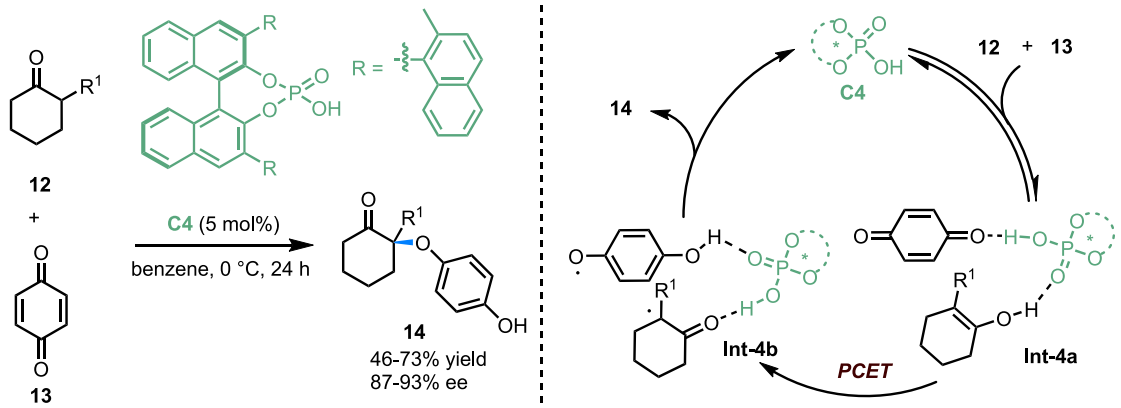
The cross-coupling of two nucleophiles poses a considerable challenge in organic synthesis due to their contrasting electronic properties and the difficulty of achieving desirable chemo- and regio-selectivity. In this context, Jørgensen and colleagues have devised an innovative organocatalyzed umpolung strategy to enable nucleophilic cross-coupling reactions.[19–23] Building upon these principles, they extended their methodology to achieve enantioselective nucleophile coupling between α-branched aldehydes (**5**) and carboxylic acids (**6**) (Scheme 3).[19] By using a chiral primary amine (**C2**) as the organocatalyst and a stoichiometric amount of Ag_2CO_3 as the oxidant, they successfully obtained α-branched chiral aldehydes (**7**) with yields reaching up to 97% and enantioselectivity up to 92%. Experimental studies and



Scheme 4. Asymmetric oxidative γ-coupling of α,β-unsaturated aldehydes by aminocatalysis

density functional theory (DFT) calculations revealed that the reaction proceeded through several single-electron oxidation steps. Specifically, the condensation of the amine catalyst (**C2**) with the aldehyde (**5**) gives rise to an enamine intermediate (**Int-2a**). Subsequently, these neutral intermediates are single-electronically oxidized by the silver oxidant (Ag_2CO_3), yielding a radical cation (**Int-2b**). This is followed by deprotonation and a second single-electron oxidation step, generating a chiral cation intermediate (**Int-2d**). In the final step, hydrogen bonding interactions between the chiral amino moiety and the carboxylic acid (**6**) facilitate a stereoselective nucleophilic addition, resulting in the formation of the desired chiral *tert*-alkyl carboxylate (**7**). The methodology exhibits broad applicability to both aromatic and aliphatic carboxylic acids, offering access to synthetically valuable *tert*-alkyl carboxylates with high yields and, in most cases, high enantioselectivities.

To eliminate the need for stoichiometric amounts of chemical oxidants in nucleophilic coupling reactions, Næsborg et al.[24] introduced an innovative approach that combines asymmetric aminocatalysis with a catalytic single-electron transfer (SET) reagent capable of regeneration by air. This strategy enabled the enantioselective oxidative γ-coupling of α,β-unsaturated aldehydes (Scheme 4). By using 20 mol % copper(II) salt as the SET reagent, air as the terminal oxidant, and a chiral aminocatalyst (**C3**), the homo-γ-coupling of α,β-unsaturated aldehydes (**8**) was achieved, delivering corresponding chiral products (**9**) in yields ranging from 43% to 76% and with enantioselectivities of 78% to >99%. Remarkably, most examples exhibited extremely high diastereoselectivity (>20:1 dr). Mechanistically, the reaction proceeds through several key steps. The condensation of chiral aminocatalyst **C3** with α,β-unsaturated aldehyde **8** generates a chiral iminium intermediate (**Int-3a**), which can undergo tautomerization to form a dienamine (**Int-3b**). Finally, the stereoselective radical coupling of two molecules of **Int-3c** or the combination of **Int-3c** with the more electron-rich dienamine (**Int-3b**) leads to the formation of the

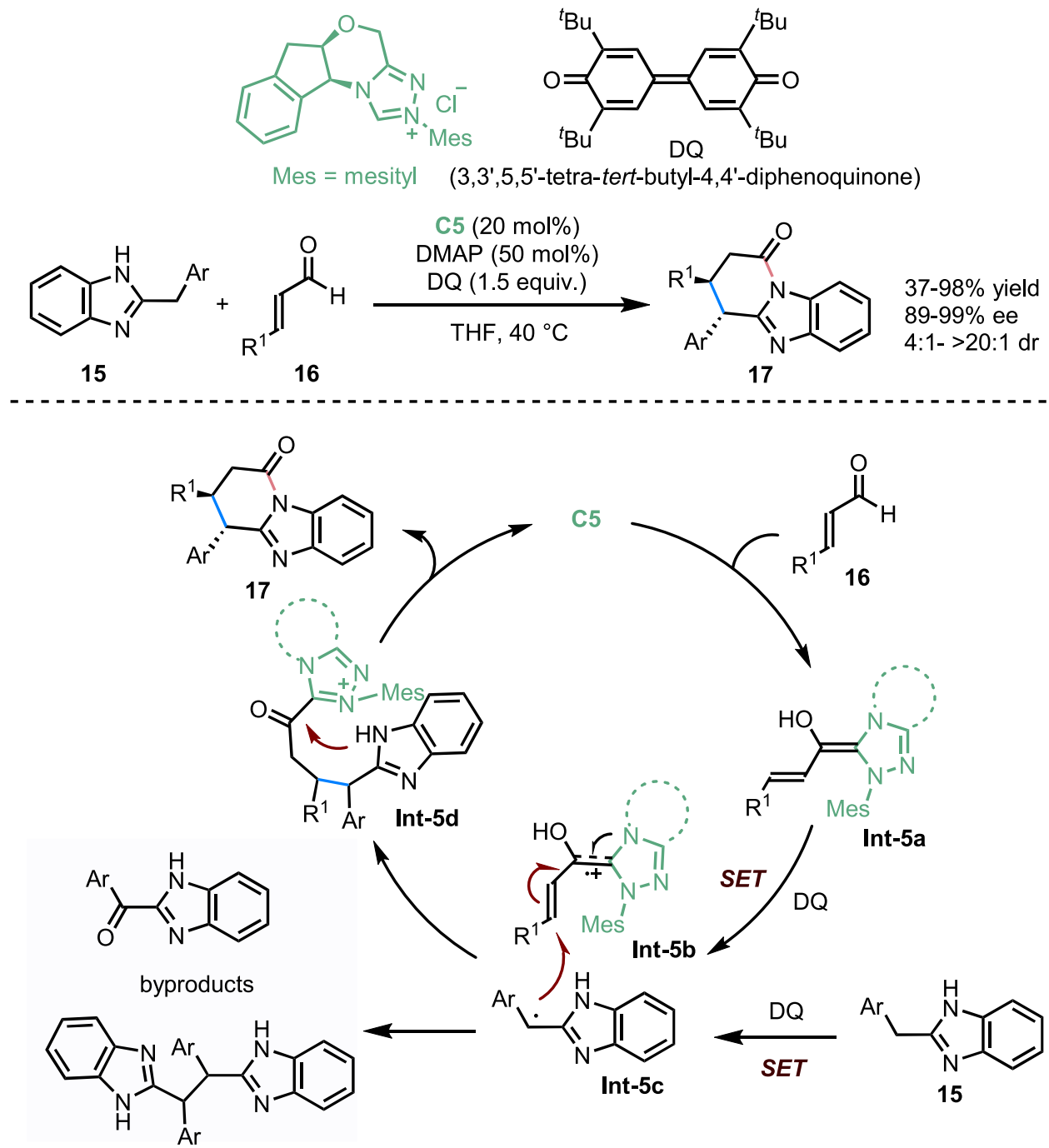


Scheme 5. CPA-catalyzed asymmetric 1,6-aryloxylation of cyclic α-branched ketones

product (**9**) and regeneration of catalyst **C3**. Meanwhile, the Cu(II) reagent can be re-generated by the oxidation of the resulting Cu(I) species using air. This methodology proved to be successful in achieving enantioselective hetero-γ-coupling of two different cyclic α,β-unsaturated aldehydes (**10** and **10′**). The hetero-coupling reactions resulted in the desired products (**11**) with yields ranging from 44% to 68% and showed excellent stereoselectivity of 10:1 to >20:1 dr and >99% ee in all examples. Additionally, the enantioselective α-coupling of aldehydes was reported by the same group.[25]

Chiral phosphoric acids (CPAs) represent one of the most important classes of organocatalysts, making significant contributions to the development of efficient protocols for asymmetric reactions over the past two decades.[26] Traditionally, CPA-enabled asymmetric transformations involve non-covalent interactions, such as electrophile protonation followed by nucleophilic attack in a stereospecific manner. The adaptable interaction modes, tunable nature, and remarkable stability of CPAs against hydrolysis and oxidation make them ideal candidates for synergistic association with transition metal catalysts. This association can occur either as ligands, influencing the coordination sphere, or as co-catalysts. In 2018, Shevchenko et al.[27] reported an unexpected α-oxidation of cyclic ketones (**12**) with 1,4-benzoquinones (**13**) facilitated by a CPA catalyst (**C4**) (Scheme 5). Although 1,4-benzoquinones typically undergo 1,4-addition reactions with various nucleophiles, this reaction yielded chiral products with 1,6-addition selectivity ranging from 46% to 73% and high enantioselectivity of 87%–93% ee. Mechanistically, the reaction begins with the CPA-catalyzed enolization of the ketone substrate (**12**). This is followed by the formation of a ternary complex (**Int-4a**) through hydrogen bonding with the quinone derivative (**13**), which then undergoes a proton-coupled electron transfer (PCET) to form a diradical complex (**Int-4b**). The final step involves radical combination, leading to the stereoselective production of the 1,6-adduct (**14**). This method represents a unique approach for the asymmetric α-aryloxylation of cyclic ketones via a PCET process. It expands the scope of enol catalysis and serves as inspiration for various other enantioselective transformations involving enol-derived radical intermediates.

Chiral *N*-heterocyclic carbenes (NHCs) are recognized as efficient Lewis basic catalysts for the umpolung of various polarized unsaturated compounds usually including aldehydes, imines, acyl chlorides, and activated esters, enabling a wide range of enantioselective reactions involving polarity inversion. In 2018, the Chi group reported a chiral NHC-catalyzed direct oxidative coupling of di(hetero)



Scheme 6. NHC-catalyzed enantioselective oxidative coupling of di(hetero)arylmethanes and α,β-unsaturated aldehydes

arylmethanes (**15**) and α,β-unsaturated aldehydes (**16**) (Scheme 6).[28] By using a chiral NHC catalyst (**C5**), enantio-enriched benzimidazole-fused lactams (**17**) were obtained under mild conditions with yields ranging from 37% to 98%, enantiomeric excesses of 89%–99% ee, and diastereoselectivity ratios of 4:1 to >20:1. Detailed experimental studies suggested that the reaction proceeds through a radical pathway. Specifically, an Breslow intermediate (**Int-5a**), derived from the reaction between the catalyst (**C5**) and the α,β-unsaturated aldehydes (**16**), undergoes

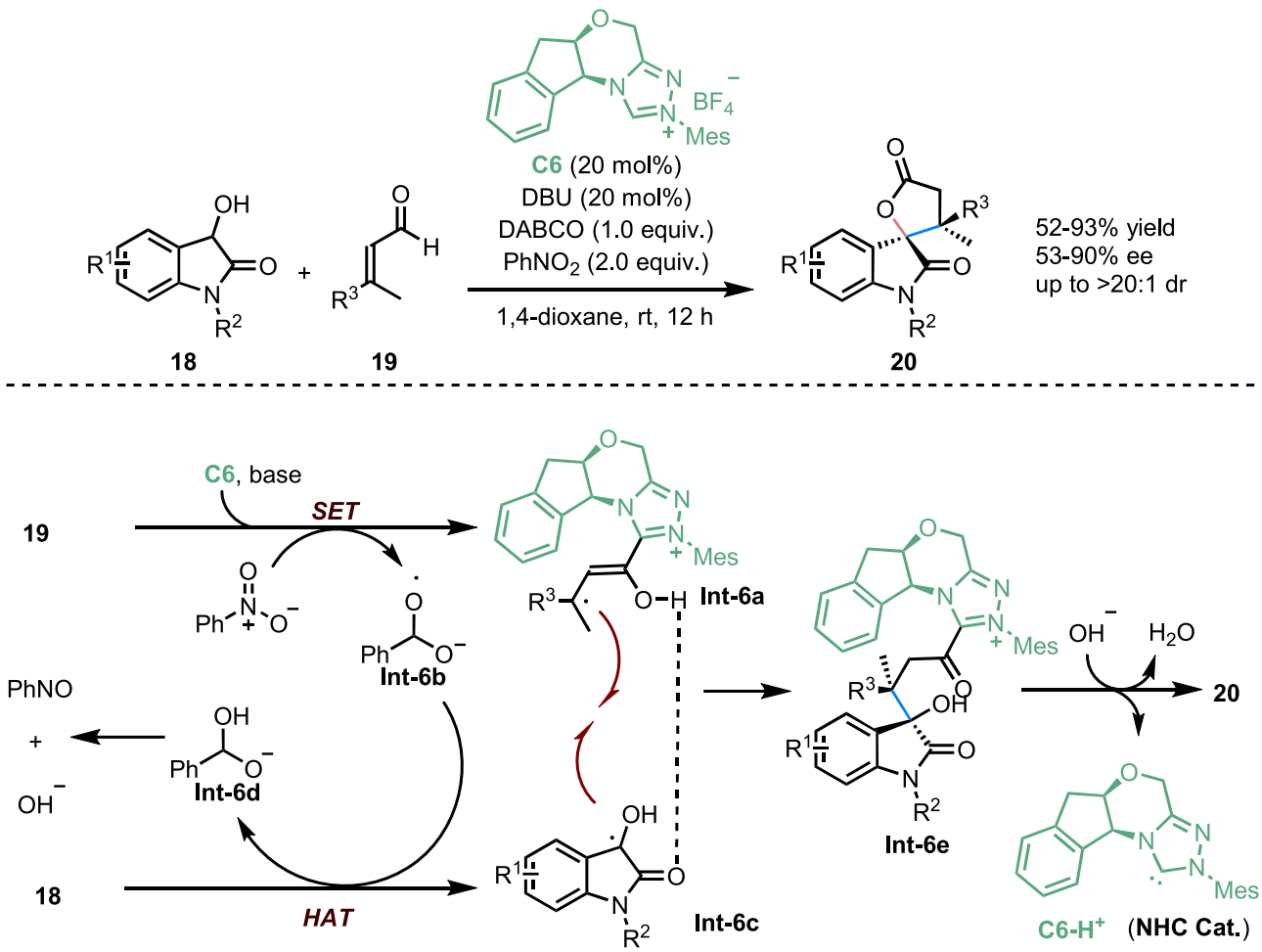
single-electron oxidation by 3,3′,5,5′-tetra-*tert*-butyl-4,4′-diphenoquinone (DQ), resulting in the formation of a radical cation (**Int-5b**). Simultaneously, the diarylmethane bearing a benzimidazole moiety (**15**) exhibits an increasing tendency to convert into a benzyl radical (**Int-5c**) via SET oxidation by DQ. The cross-coupling of these two radical intermediates leads to the formation of intermediate **Int-5d**, ultimately yielding the desired chiral product (**17**). The presence of byproducts such as diaryl ketones and homo-coupling dimers in nearly all examples strongly suggests the involvement of the radical intermediate (**Int-5c**). The enantioselective C(sp^3)-H functionalization of di(hetero)arylmethane poses a considerable challenge in organic synthesis due to the inert nature of robust aliphatic C–H bonds and the lack of enantiofacial discrimination between two sterically similar aryl substituents. However, this method offers a practical and effective solution to tackle this enduring synthetic challenge. It enables the highly enantioselective conversion of diaryl methanes into benzimidazole-fused lactams, which possess considerable synthetic and biological significance.

In 2018, Song et al.[29] reported a diastereo- and enantioselective [3+2] annulation of dioxindoles (**18**) and β,β-disubstituted enals (**19**) by NHC catalysis. This methodology enables the synthesis of chiral spirooxindoles (**20**) (Scheme 7). By using 20 mol % of the L-pyroglutamic acid-derived pre-NHC catalyst (**C6**), nitrobenzene as the single-electron oxidant, and 1,5-diazabicyclo[4.3.0]non-5-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) as bases, the reaction provided satisfactory yields ranging from 52% to 93%, with high enantioselectivity (53%–90%) and excellent diastereoselectivity (>20:1) in most cases. Previous electron paramagnetic resonance (EPR) studies and control experiments supported the proposal that this reaction proceeds through radical-involved steps. Initially, the β,β-disubstituted enal (**19**) condenses with **C6** in the presence of the bases, followed by a SET process with nitrobenzene, generating a chiral homoenol radical (**Int-6a**) and a radical anion of nitrobenzene (**Int-6b**). Intermediate **Int-6b** abstracts a hydrogen atom from the benzyl C–H bond of the dioxindole substrate (**18**), leading to the formation of an enol radical (**Int-6c**). The radical-radical cross-coupling between **Int-6a** and **Int-6c** affords intermediate **Int-6e**, which undergoes lactonization under basic conditions to produce the chiral product (**20**) and regenerate the active NHC catalyst (**C6**-H^+). This study presents a convenient approach for accessing chiral spirocyclic oxindole-γ-lactones, which possess two contiguous tetra-substituted stereocenters. Furthermore, it highlights the effectiveness of chiral NHC in precisely controlling the stereochemistry within radical-mediated transformations.

PHOTOCHEMICAL APPROACHES FOR RADICAL-MEDIATED ORGANOCATALYTIC ASYMMETRIC TRANSFORMATIONS

Photocatalysis has revolutionized the field of organic synthesis by providing a versatile and environmentally friendly method for the construction of carbon-carbon and carbon-heteroatom bonds.[30] This powerful technique allows researchers to access complex molecules with high efficiency under mild reaction conditions. One particularly exciting development in this field is asymmetric photocatalysis, which combines the principles of asymmetric catalysis with the unique properties of photocatalysts.[31–33] Asymmetric photocatalysis operates through distinct mechanistic pathways, providing access to nonracemic compounds that are difficult to obtain using conventional methods.

A diverse range of asymmetric photocatalytic reactions have been developed, making use of various types of catalysts. Chiral organocatalysts, such as chiral amines,

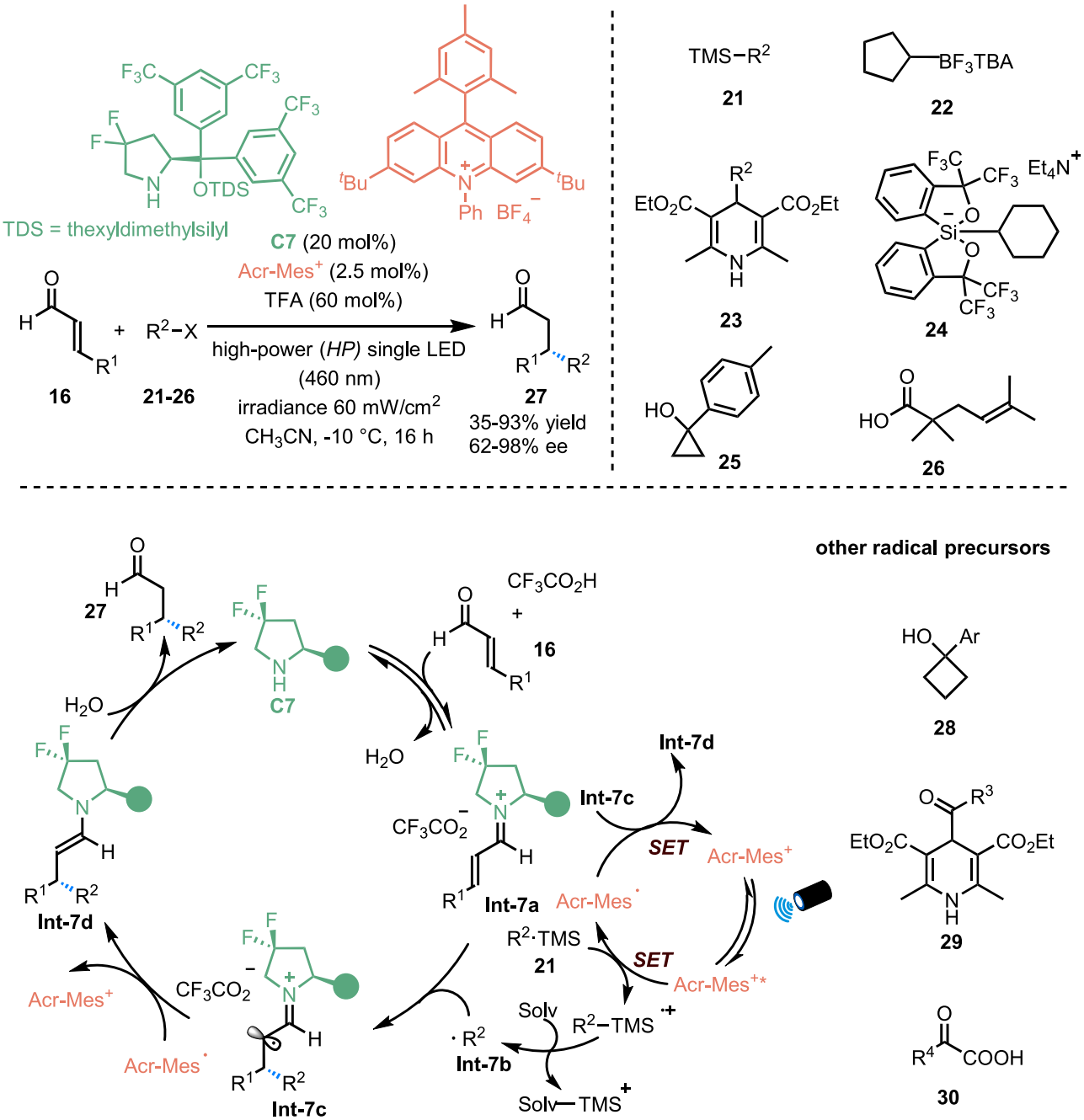


Scheme 7. NHC-catalyzed diastereo- and enantioselective oxidative [3+2] annulation of dioxindoles and β,β-disubstituted enals

NHCs, CPAs, squaramides, thioureas, ion pair catalysts like chiral phosphate salts, and chiral isothioureas, have shown tremendous potential in achieving stereodiscrimination during these transformations.[34] These catalysts play a crucial role in activating reaction partners and orchestrating precise control over the stereochemistry of the resulting products. The advantages of these approaches are manifold. First and foremost, the mild reaction conditions used in asymmetric photocatalysis minimize the formation of undesired byproducts and increase the overall efficiency of the process. Furthermore, the ability to selectively form chiral centers enables the synthesis of structurally diverse chiral molecules with high enantiomeric purity.

Aminocatalysis

Recently, chiral amines have shown significant potential in facilitating visible light-induced asymmetric radical reactions through enamine or iminium ion catalysis.[35,36] In 2021, Le Saux et al.[37] reported a photocatalytic enantioselective β-functionalization of enals (**16**) using stable radical precursors (**21**–**26**) (Scheme 8). This method demonstrated compatibility with various radical precursors, such as α-silylamines (**21**), trifluoroborate salts (**22**), dihydropyridine derivatives (**23**), alkylsilicates (**24**), cyclopropanols (**25**), and alkenoic acids (**26**). This provided flexible routes and abundant sources of radicals for further asymmetric transformations, resulting in the formation of diverse β-alkylated products with yields ranging from 35% to 93% and



Scheme 8. Photocatalytic enantioselective β-functionalization of enals enabled by aminocatalysis

enantioselectivities ranging from 62% to 98%. According to the proposed mechanism, the condensation of enals (**16**) with the chiral amine catalyst (**C7**) leads to the formation of an electrophilic iminium ion (**Int-7a**). Simultaneously, photo-excited photocatalyst (Acr-Mes^{+}*) oxidizes the radical precursor (**21**) to generate an alkyl radical intermediate (**Int-7b**). The subsequent radical addition of **Int-7b** to **Int-7a** forms a radical cation intermediate (**Int-7c**), where the stereochemistry is controlled by the chiral iminium fragment. Finally, the desired enantioselective aldehyde (**27**) is obtained through subsequent SET reduction and hydrolysis, accompanied by the

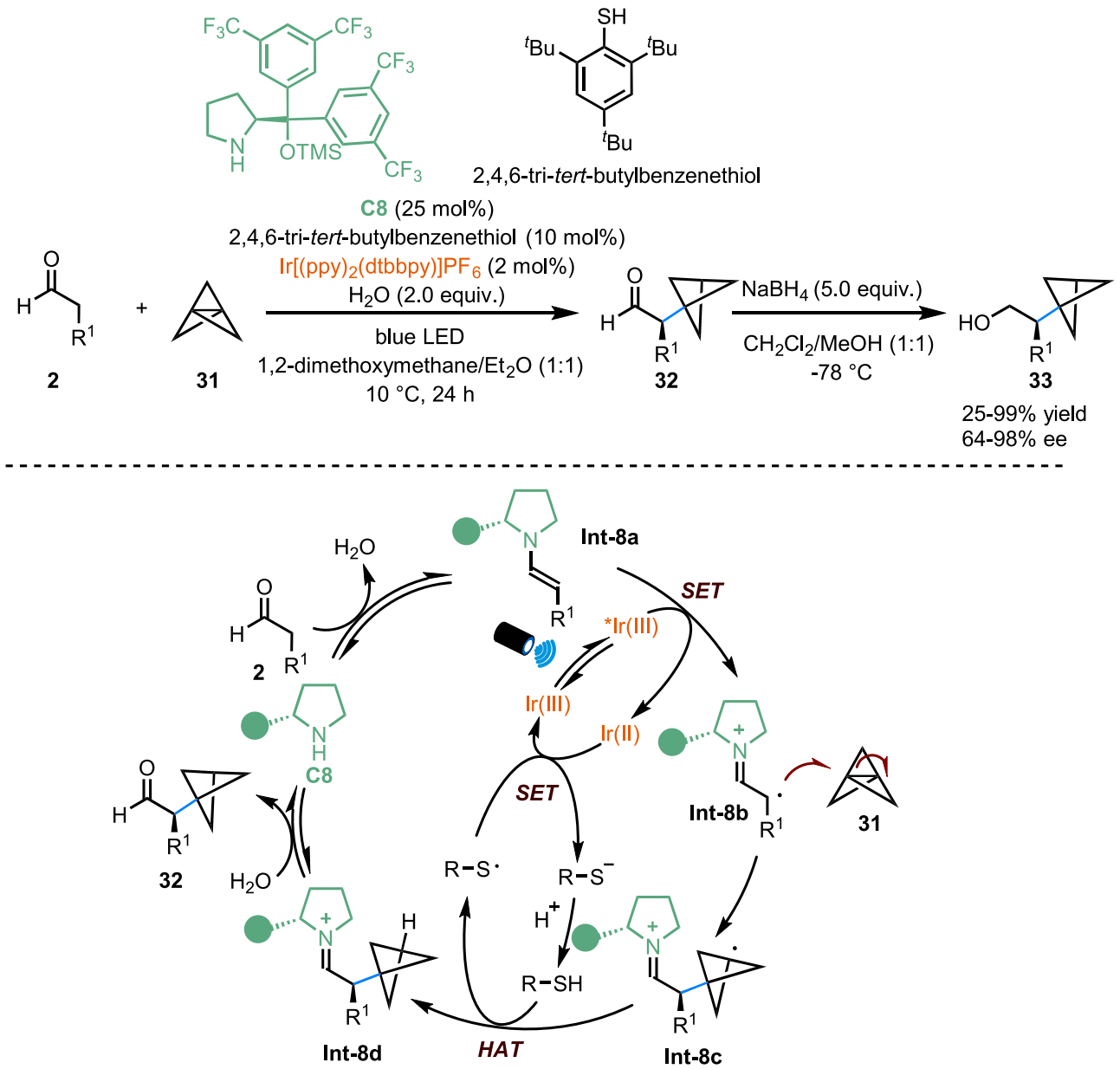
regeneration of the chiral catalyst and photocatalyst. This protocol has successfully been applied in designing asymmetric radical intermolecular cascade reactions.

Later, they also extended the strategy based on radical addition to iminium ion for achieving enantioselective β-functionalization of enals with other radical precursors, such as cyclobutanols (**28**), 4-alkyl-1,4-dihydropyridines (**23**), 4-acyl-1,4-dihydropyridines (**29**).[38–40] These enabled a range of photochemical asymmetric reactions and delivered various valuable products with high levels of enantioselectivity. Furthermore, Zhao et al.[41] developed an enantioselective radical hydroacylation of enals with α-ketoacids (**30**) as radical precursors, providing an efficient way to access synthetically challenging enantio-enriched 1,4-dicarbonyl compounds.

Bicyclo[1.1.1]pentanes (BCPs) play a crucial role in contemporary drug design by serving as linear spacer units that enhance the pharmacokinetic profiles of drugs. The synthesis of BCPs with adjacent stereocenters presents considerable challenges, yet it remains highly desirable given the fundamental importance of three-dimensional chemical space in medicinal chemistry.[42,43] In 2021, Wong et al.[44] reported a method for synthesizing α-chiral BCPs (**32**) through the direct and asymmetric addition of simple aldehydes to [1.1.1]propellane (**31**) (Scheme 9). This reaction involved the combination of an Ir(III) photocatalyst ($Ir[(ppy)_2(dtbbpy)]PF_6$), a chiral amine catalyst (**C8**), and a thiol-based HAT catalyst (2,4,6-tri-*tert*-butylbenzenethiol) to generate a chiral α-iminyl radical cation intermediate, simultaneously introducing a stereocenter while opening the ring of [1.1.1]propellane. As a result, this ternary catalytic system demonstrated excellent performance under mild conditions, affording high yields up to 99% and satisfactory enantioselectivity up to 98% ee.

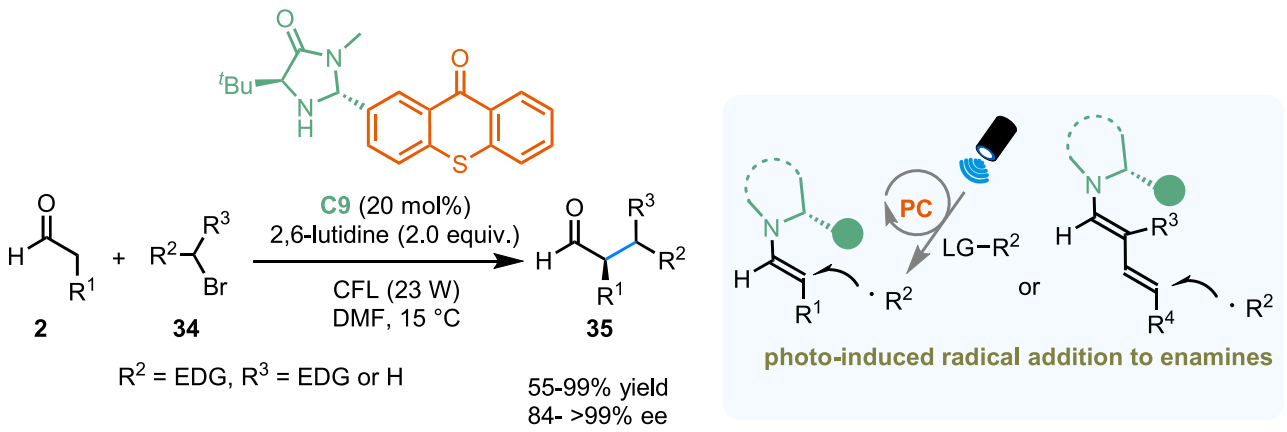
The reaction mechanism initiates with the formation of an enamine intermediate (**Int-8a**) derived from the aldehyde substrate (**2**) and the chiral catalyst (**C8**). This is followed by SET with the excited iridium photocatalyst (Ir(III)*). The resulting iminium radical (**Int-8b**) undergoes radical addition to [1.1.1]propellane (**31**), generating a ring-opening alkyl radical (**Int-8c**). Subsequently, **Int-8c** abstracts a hydrogen atom from the thiol co-catalyst, yielding an iminium intermediate (**Int-8d**) that finally converts into the chiral product (**32**) through hydrolysis, releasing **C8** in the process. Notably, the reduced photocatalyst (Ir(II)) can efficiently reduce the generated thiol radical via a SET, regenerating the thiol co-catalyst for subsequent cycles. The reaction demonstrates remarkable tolerance toward a variety of substrates, including those bearing saturated and unsaturated carbon chains, heterocyclic motifs, aryl and heteroaryl groups, as well as heteroatoms. Moreover, the resulting products can be readily diversified, enabling the synthesis of valuable chiral BCP building blocks that were previously difficult to obtain or inaccessible. These findings highlight the potential of this methodology for application in various synthetic scenarios.

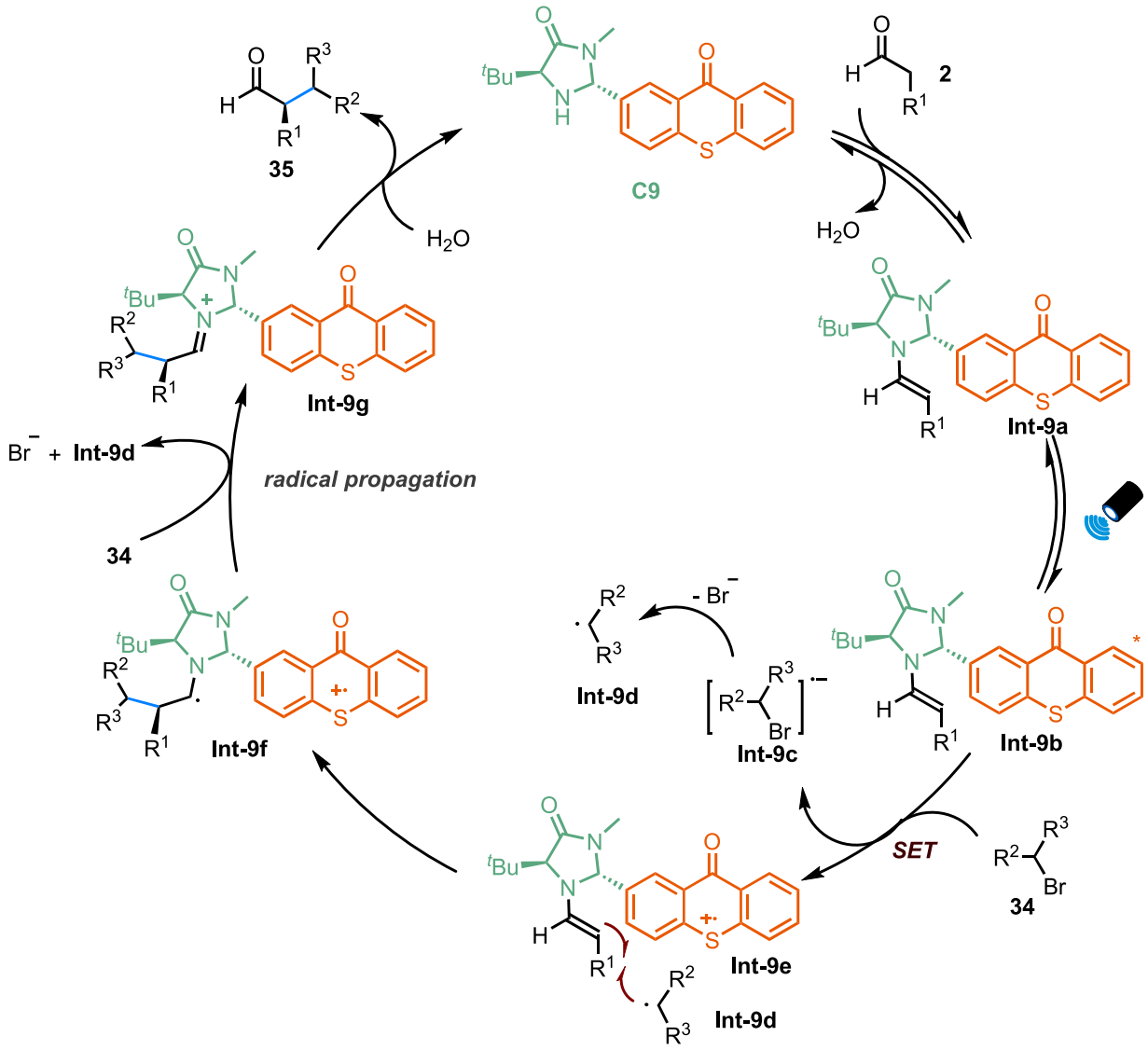
Photo-induced radical addition to *in situ* generated chiral enamine intermediates has shown considerable potential in facilitating efficient photocatalytic asymmetric synthesis. For example, in 2018, Rigotti et al.[45] reported an innovative bifunctional photoaminocatalysis approach for the enantioselective α-alkylation of aldehydes (**2**) with alkyl bromides (**34**) (Scheme 10). These reactions used a class of structurally unique bifunctional chiral photocatalysts, where a light-responsive thioxanthone moiety was incorporated into a chiral imidazolidinone scaffold. The catalysts could be easily synthesized through a two-step procedure and were subsequently applied in the photochemical α-alkylation of aliphatic aldehydes. Under visible light conditions and in the presence of 2,6-lutidine as the base, the reactions proceeded smoothly, resulting in a diverse library of chiral α-alkylated products (**35**) with yields



Scheme 9. Photocatalytic asymmetric synthesis of α-chiral bicyclo[1.1.1]pentanes by a ternary catalytic system

ranging from 55% to 99% and enantiomeric excess ranging from 84% to >99%. Regarding the reaction mechanism, the condensation of the aldehyde (**2**) and the catalyst (**C9**) generates a chiral enamine intermediate (**Int-9a**), which absorbs photons and transitions to its excited state (**Int-9b**) upon CFL (compact fluorescent light) irradiation. This is followed by a SET process with the alkyl bromide (**34**), leading to the formation of a radical anion (**Int-9c**) and a chiral radical cation of the enamine (**Int-9e**). Dehalogenation of **Int-9c** results in the formation of an alkyl radical (**Int-9d**). Subsequently, **Int-9d** adds to the enamine fragment of **Int-9e**, yielding an α-amino radical (**Int-9f**). Finally, the desired product (**35**) is obtained through radical chain propagation and hydrolysis. In the realm of organocatalysis, the simultaneous activation of reagents by a bifunctional organocatalyst holds significant significance and has spurred the advancement of innovative transformations. Most of the





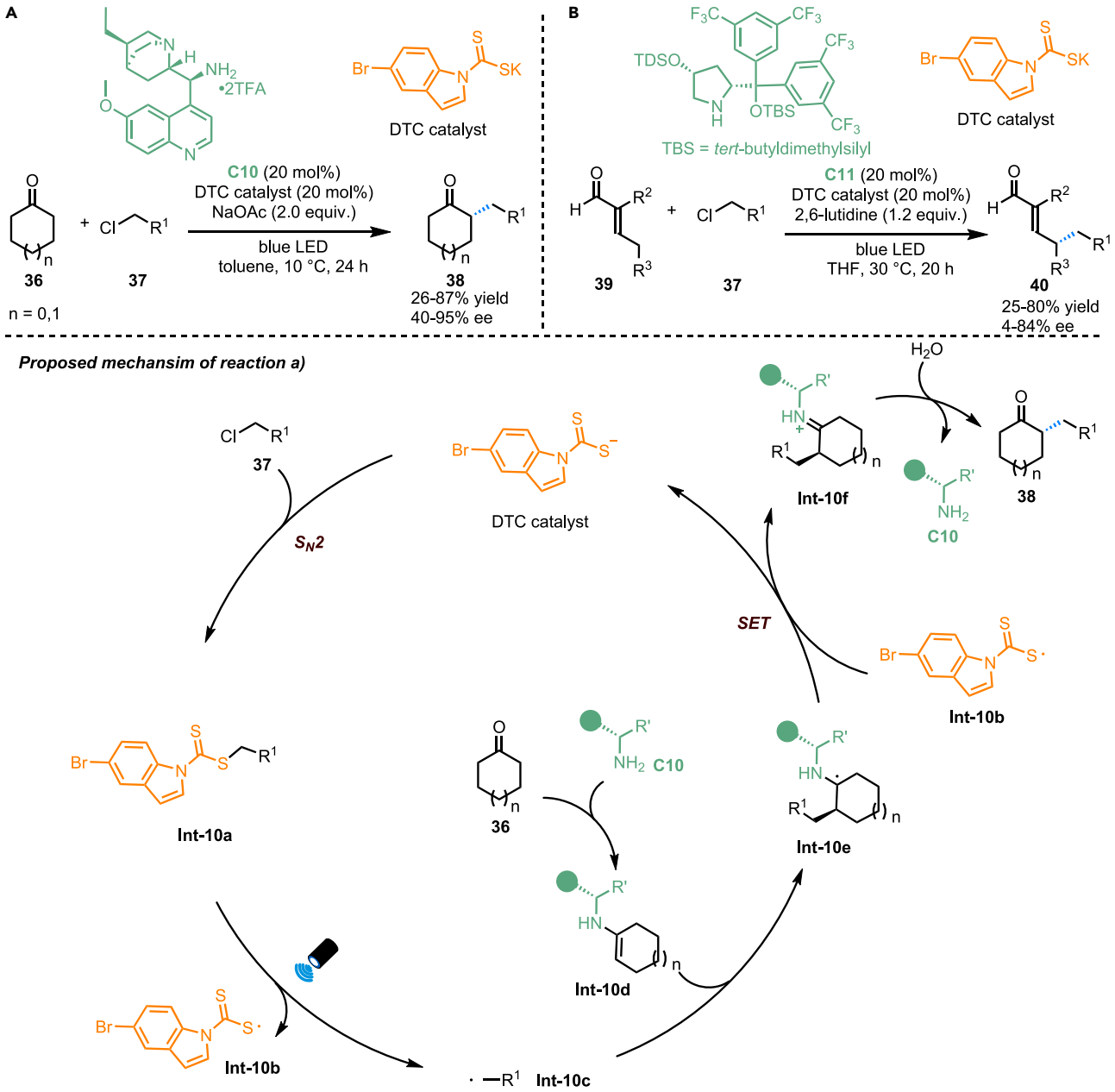
Scheme 10. Chiral amine-catalyzed enantioselective alkylation via photo-induced radical addition to chiral enamine intermediates

previously reported bifunctional catalysts are composed of a combination of a Lewis base and a Lewis acid moiety. However, this study presents a remarkable fusion of a photosensitizer and a chiral organocatalyst within a single bifunctional catalyst, introducing fresh perspectives for catalyst design.

Recently, Spinnato et al.[46] developed a sophisticated strategy that relies on the use of a nucleophilic dithiocarbonyl (DTC) anion organocatalyst to generate radicals through S_N2-based activation of alkyl halides, followed by photo-induced homolysis. This strategy was successfully applied to achieve dienamine-involved enantioselective α-alkylation of ketones (**36**) (Scheme 11A). By combining the DTC catalyst with a cinchona-based primary amine catalyst (**C10**), blue light irradiation of a mixture of ketones (**36**) and alkyl chlorides (**37**) yielded enantio-enriched α-alkylated products (**38**) with enantioselectivity ranging from 40% to 95% ee. Mechanistically, the nucleophilic DTC catalyst undergoes an S_N2 attack on the alkyl chloride (**37**), resulting in the formation of an intermediate (**Int-10a**). When photons are absorbed, **Int-10a** is homolytically cleaved, generating a pair of radicals (**Int-10b**, **Int-10c**). A chiral enamine intermediate (**Int-10d**), formed by the condensation of compound **36** and **C10**, captures the *C*-centered radical (**Int-10c**), leading to the production of an *N*-α radical (**Int-10e**). Subsequently, a SET between **Int-10e** and the *S*-centered radical (**Int-10b**) leads to the formation of a cation intermediate (**Int-10f**) and regeneration of the DTC catalyst. **Int-10f** can easily undergo hydrolysis to yield the final product (**38**) while regenerating **C10**. This reaction showcases mild conditions and excellent functional group tolerance, allowing the formation of α-stereocenters in ketones. Such moieties are typically incompatible with traditional anionic processes. Furthermore, this approach was successfully extended to the γ-alkylation of α,β-unsaturated aldehydes (**39**), providing corresponding products (**40**) with exclusive γ-selectivity and good stereocontrol (Scheme 11B).[47]

Linear α,β-unsaturated aldehydes exhibit a pronounced preference for nucleophilic cyanide addition at the aldehyde functionality rather than the β-carbon (1,2- versus 1,4-chemoselectivity), which can be attributed to both electronic and steric factors and has been observed since early studies. The achievement of chemoselective and stereoselective conjugate cyanation of linear enals has posed a significant challenge in organic synthesis. In 2023, Berger et al.[48] reported a photochemical organocatalytic method for achieving exclusive 1,4-cyanation of α,β-unsaturated aldehydes (Scheme 12). This innovative approach used the synergistic combination of an organophotocatalyst, specifically, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4-CzIPN), along with a secondary amine featuring bulky perfluoro-isopropyl groups on the arene scaffold (**C12**). By using trifluoroacetic acid (TFA) as the co-catalyst, Hantzsch ester (**42a**) as the reductant, and H_2O as the additive, this reaction achieved remarkable efficiency, exclusive chemoselectivity and a high level of asymmetric induction. Detailed mechanistic studies provided valuable insights, suggesting that the key to the success of this reaction lay in the *in situ* formation of nucleophilic chiral 5π-electron β-enaminyl radicals, which effectively intercepted the electrophilic TsCN to enable conjugated 1,4-cyanation.

Specifically, the condensation of the chiral catalyst (**C12**) with the α,β-unsaturated aldehyde (**16**) initiates the formation of a chiral iminium ion (**Int-11a**). This is followed by an umpolung process, where the electron-deficient iminium ion (**Int-11a**) undergoes single-electronic reduction, facilitated by the reduced photocatalyst ($4CzIPN^{\bullet-}$), transforming it into a nucleophilic 5π-electron β-enaminyl radical (**Int-11b**). The steric moiety present in **Int-11b** plays a crucial role in governing the interception of TsCN, resulting in an exceptional level of stereoselectivity and β-site selectivity. After controlled nitrile

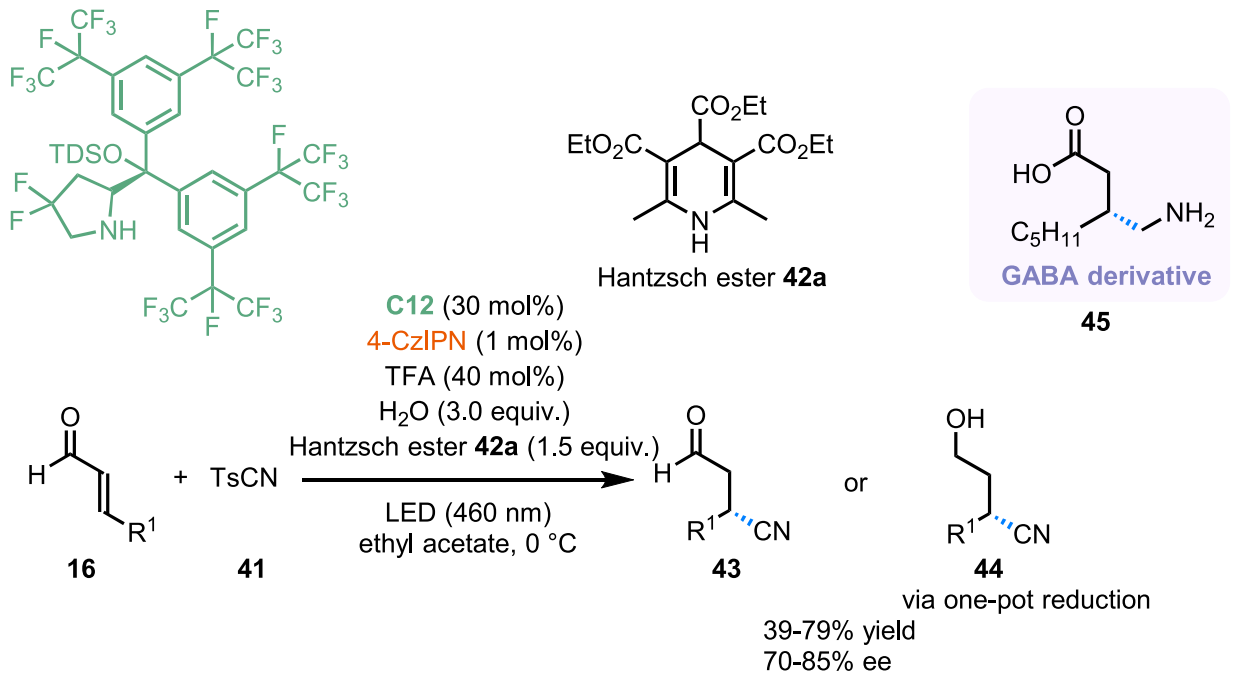


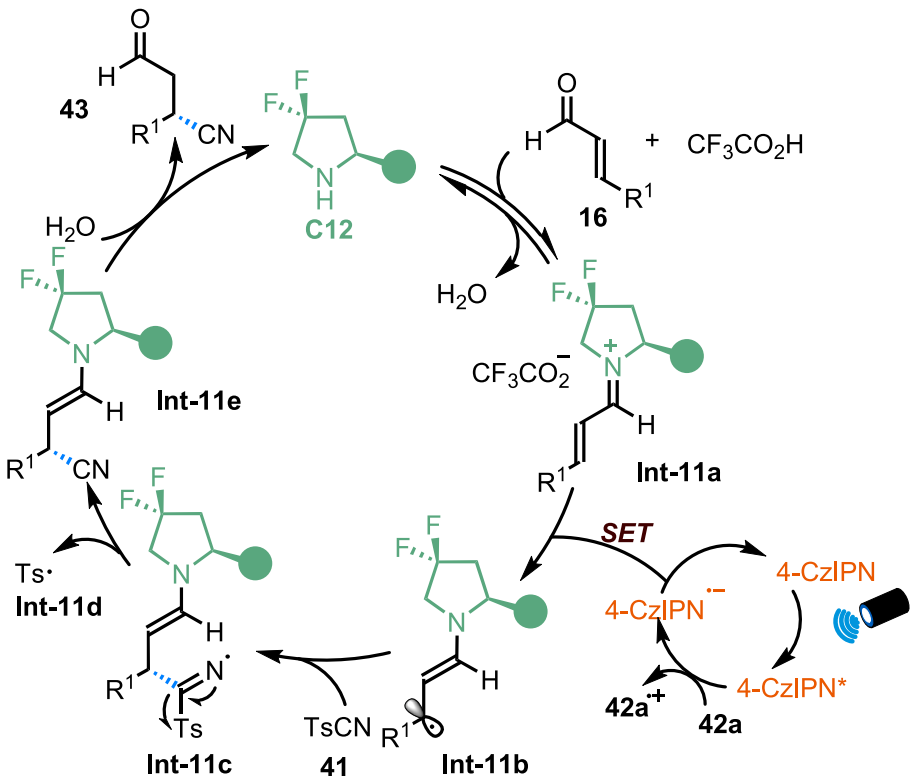
Scheme 11. Combination of nucleophilic catalysis with enamine catalysis for photochemical enantioselective alkylation reactions

(A) Photochemical enantioselective α-alkylation.

(B) Photochemical enantioselective γ-alkylation.

transfer, the resulting radical **Int-11c** undergoes β-fragmentation, generating enamine **Int-11e** while simultaneously releasing a tosyl radical (**Int-11d**). Subsequent hydrolysis of **Int-11e** not only yields the desired chiral product (**43**) but also regenerates the organocatalyst (**C12**). One of the products can be easily converted into a biologically valuable derivative of γ-aminobutyric acid (GABA) (**45**), highlighting the synthetic utility of this approach. Overall, this photo-induced polarity umpolung strategy offers a solution to a long-standing challenge in asymmetric synthesis by providing a convenient means of achieving enantioselective conjugate cyanation of α,β-unsaturated aldehydes.





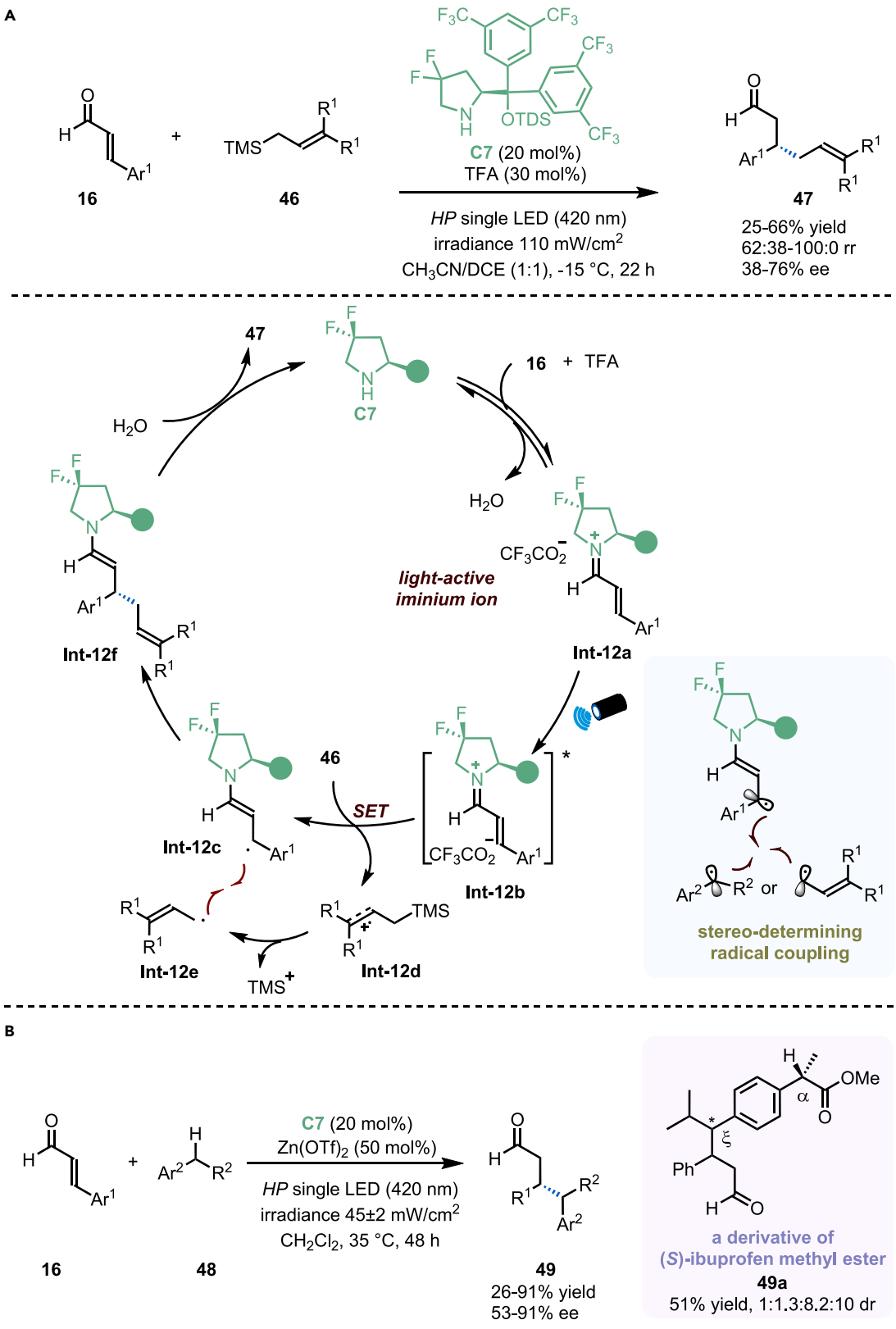
Scheme 12. Enantioselective 1,4-cyanation of linear α,β-unsaturated aldehydes by combining aminocatalysis and photoredox catalysis

Recently, photosensitizer- and transition metal-free organic transformations have garnered significant attention from the green synthetic chemistry community. This interest stems from their remarkable ability to facilitate the formation of new chemical bonds under simplified conditions and operations. These methods primarily rely on

the light response exhibited by substrates, key intermediates, or products, thereby eliminating the need for external photosensitizers.[49] In 2021, Berger et al.[50] presented an organocatalytic regio- and enantioselective conjugate addition of α,β-unsaturated aldehydes (**16**) with allyl silanes (**46**) (Scheme 13A). This transformation was achieved through the visible light-induced excitation of chiral iminium intermediates. In their proposed reaction mechanism, the crucial imine intermediate (**Int-12a**) is generated through the condensation of a secondary amine catalyst (**C7**) with the β-aryl α,β-unsaturated aldehyde (**16**). Upon absorption of photons, **Int-12a** undergoes conversion into an excited state (**Int-12b**). A subsequent SET process between **Int-12b** and the allyl silane (**46**) leads to the formation of a 5π-electron β-enaminyl radical (**Int-12c**) and an allyl silane radical cation (**Int-12d**). Intermediate **Int-12d** then transforms into an allyl radical (**Int-12e**) through rapid solvent-assisted desilylation. Finally, a cross-coupling between these two radical species (**Int-12c** and **Int-12e**), followed by hydrolysis, facilitates product formation and catalyst regeneration. This study represents the first example of catalytic enantioselective conjugate addition of allyl groups to enals. It also highlights the potential of photo-excited iminium ions in visible light-triggered photochemical synthesis. Building on this success, they further developed a photochemical asymmetric radical coupling of toluene derivatives (**48**) with α,β-unsaturated aldehydes (**16**), again without the need for external photosensitizers (Scheme 13B).[51] Notably, a pharmaceutically relevant compound, namely (*S*)-ibuprofen methyl ester (**49a**), could be obtained with a moderate yield of 51% and diastereoselectivity of 1:1.38:2:10 dr through regio- and stereoselective ζ-alkylation.

Asymmetric cascade reactions offer powerful strategies for rapidly enhancing structural and stereochemical complexity while enabling the synthesis of intricate chiral molecules in a single step. Remarkable progress has been achieved in this research field over the past decades.[52] However, the implementation of catalytic asymmetric variants in radical-mediated cascade processes remains a significant challenge. Recently, Melchiorre and colleagues successfully extended their exploration of excited-state chemistry involving chiral iminium ions to encompass various enantioselective radical cascade reactions. These reactions involved the interaction of β-aryl α,β-unsaturated aldehydes (**16**) with diverse substrates with multiple reactive sites, including cyclopropanols (**50**), alkenoic acids (**51**), and allenes (**52**) (Scheme 14).[53–55] For example, when α,β-unsaturated aldehydes (**16**) and cyclopropanols (**50**) were irradiated in CH_3CN with a single high-power (HP) LED (λ_{max} = 415 nm), along with 20 mol % of the secondary amine catalyst (**C7**), 30 mol % of TFA co-catalyst, and 1.0 equivalent of 1,1′-biphenyl (BP) as a redox mediator, chiral cyclopentane derivatives (**53**) were obtained in yields ranging from 43% to 89%. These reactions exhibited a high level of stereoselectivity, with enantiomeric excesses ranging from 90% to 99% and diastereomeric ratios of 8:1 to >20:1.). Under similar reaction conditions, the photochemical reaction of **16** with alkenoic acids (**51**) resulted in the formation of enantio-enriched lactones with low diastereoselectivity (1:1–1.3:1 dr) but with high enantioselectivity (89%–97% ee). On the other hand, when **16** reacted with allenes (**52**), it led to the production of chiral bicyclic compounds (**55**) with moderate enantioselectivity (57%–83% ee) and satisfactory diastereoselectivity (88:12-19:1 dr). In the latter case, the catalyst combination involved a secondary amine bearing bulky perfluoro-isopropyl groups on the arene scaffold (**C12**) and a Lewis acid co-catalyst ($Zn(OTf)_2$).

In terms of the mechanism, these protocols follow similar reaction pathways. They begin with the formation of an iminium ion, which is then excited to its excited state by photoexcitation (**Int-13a**). This excited state undergoes SET with the respective reaction partner (**50**, **51**, or **52**), affording a,β-enaminyl radical (**Int-13c**) and the

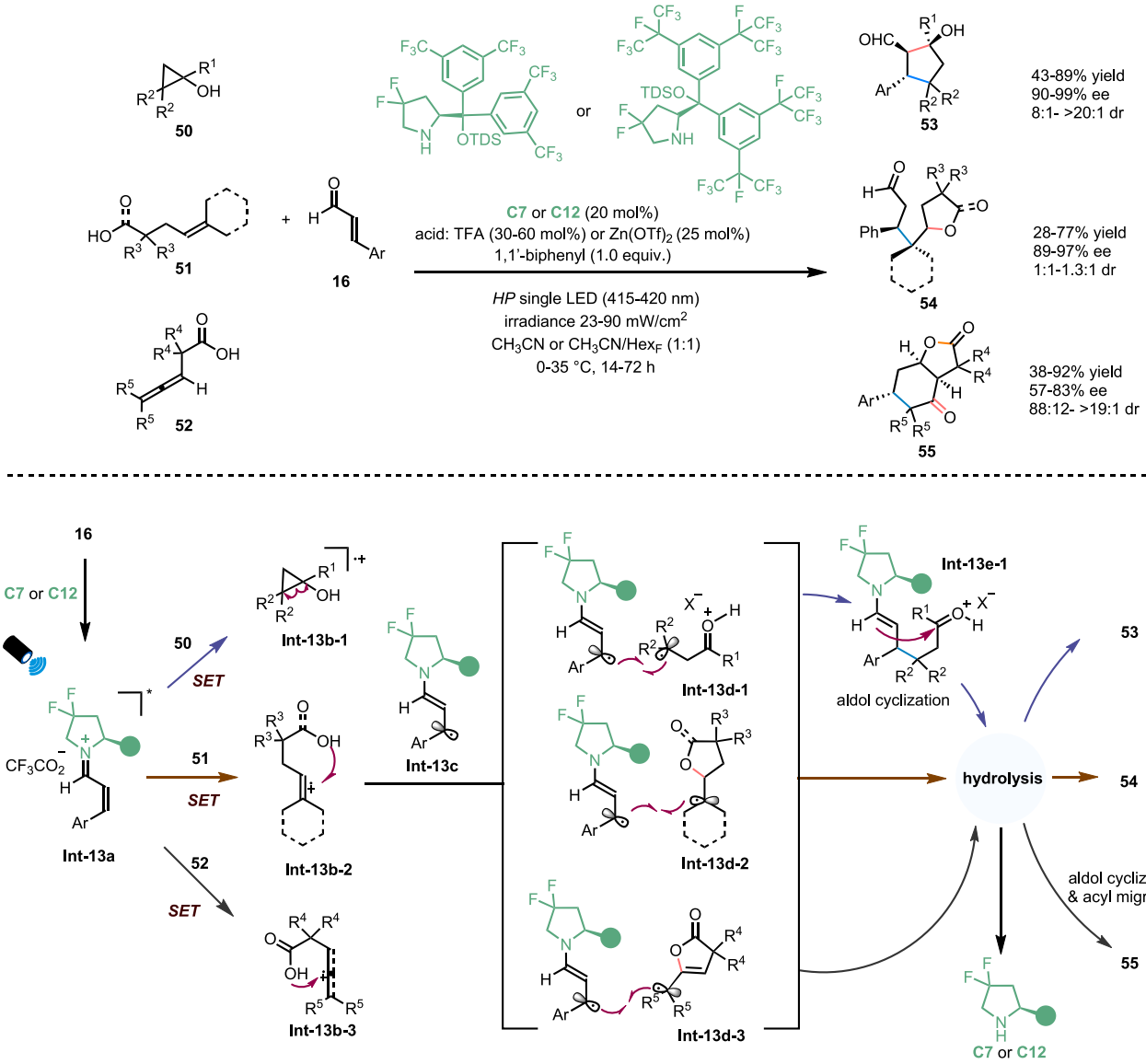

A
16
46
C7 (20 mol%)
TFA (30 mol%)
HP single LED (420 nm)
irradiance 110 mW/cm2
CH3CN/DCE (1:1), -15 °C, 22 h
47
25-66% yield
62:38-100:0 rr
38-76% ee
C7
16 + TFA
H2O
47
light-active
iminium ion
Int-12a
Int-12b
Int-12c
Int-12d
Int-12e
Int-12f
SET
46
TMS+
stereo-determining
radical coupling
B
16
48
C7 (20 mol%)
Zn(OTf)2 (50 mol%)
HP single LED (420 nm)
irradiance 45±2 mW/cm2
CH2Cl2, 35 °C, 48 h
49
26-91% yield
53-91% ee
a derivative of
(S)-ibuprofen methyl ester
49a
51% yield, 1:1.3:8.2:10 dr

Scheme 13. Enantioselective radical coupling of enals with allyl C–H precursors or toluene derivatives via visible light excitation of chiral iminium intermediates

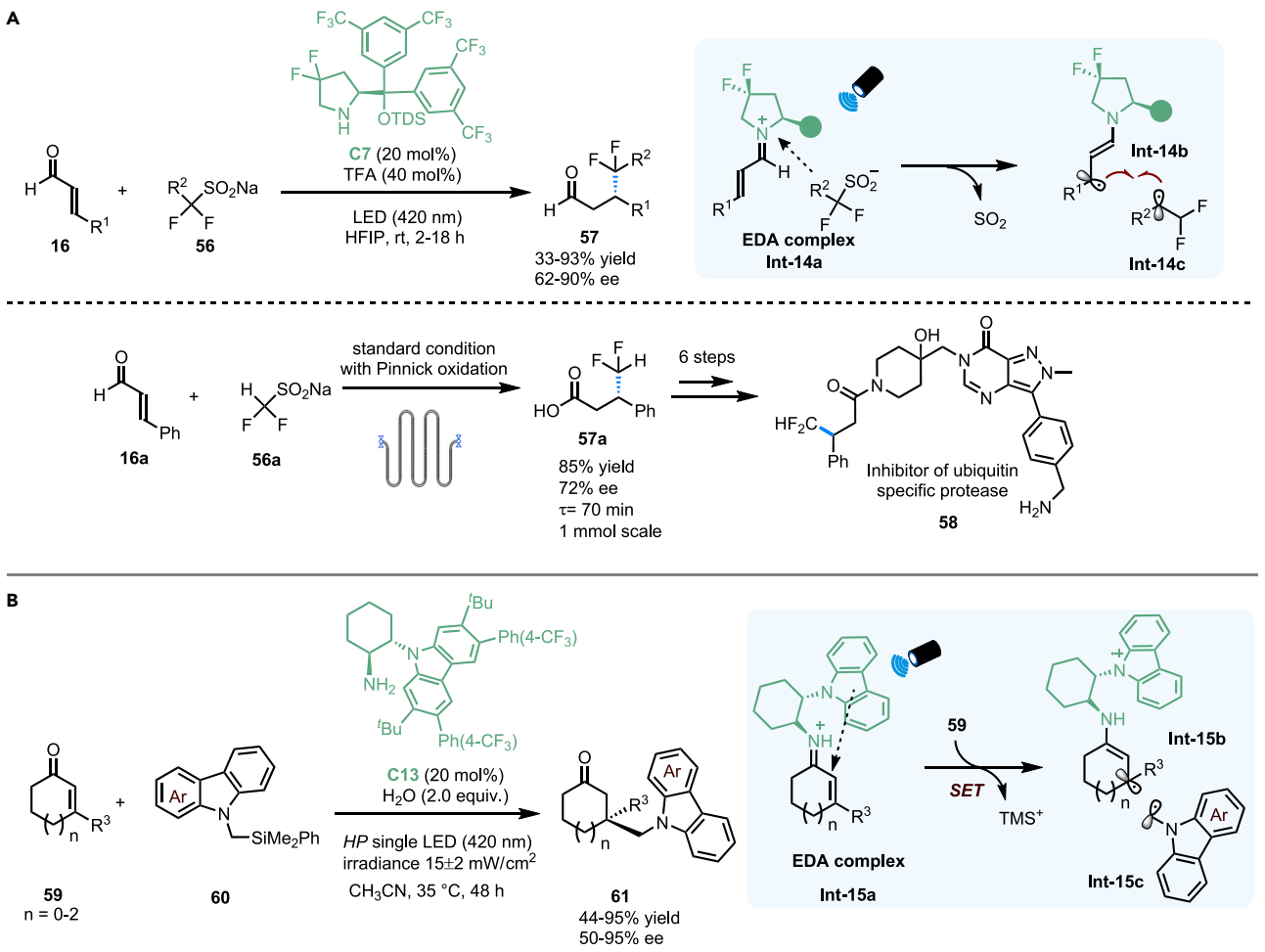
(A) Allyl C–H precursors.

(B) Toluene derivatives.

corresponding radical cation intermediate (**Int-13b-1**, **Int-13b-2**, or **Int-13b-3**). Among them, **Int-13b-1** can undergo a ring-opening process to generate a,β-keto radical cation (**Int-13d-1**), while **Int-13b-2** or **Int-13b-3** prefers an intramolecular nucleophilic attack, leading to the formation of a cyclized radical species (**Int-13d-2** or **Int-13d-3**). The final step involves the stereoselective combination of radicals, followed by hydrolysis, resulting in product formation and catalyst regeneration. Notably, in reactions involving **50** or **52**, aldol cyclization and acyl migration processes may be involved. These transformations showcase the potential to successfully combine a stereocontrolled radical pattern with a classical ionic process in a cascade sequence. They also



Scheme 14. Enantioselective radical cascade reactions via visible light excitation of chiral iminium intermediates



Scheme 15. Photochemical enantioselective reactions enabled by iminium-ion-based EDA complexes

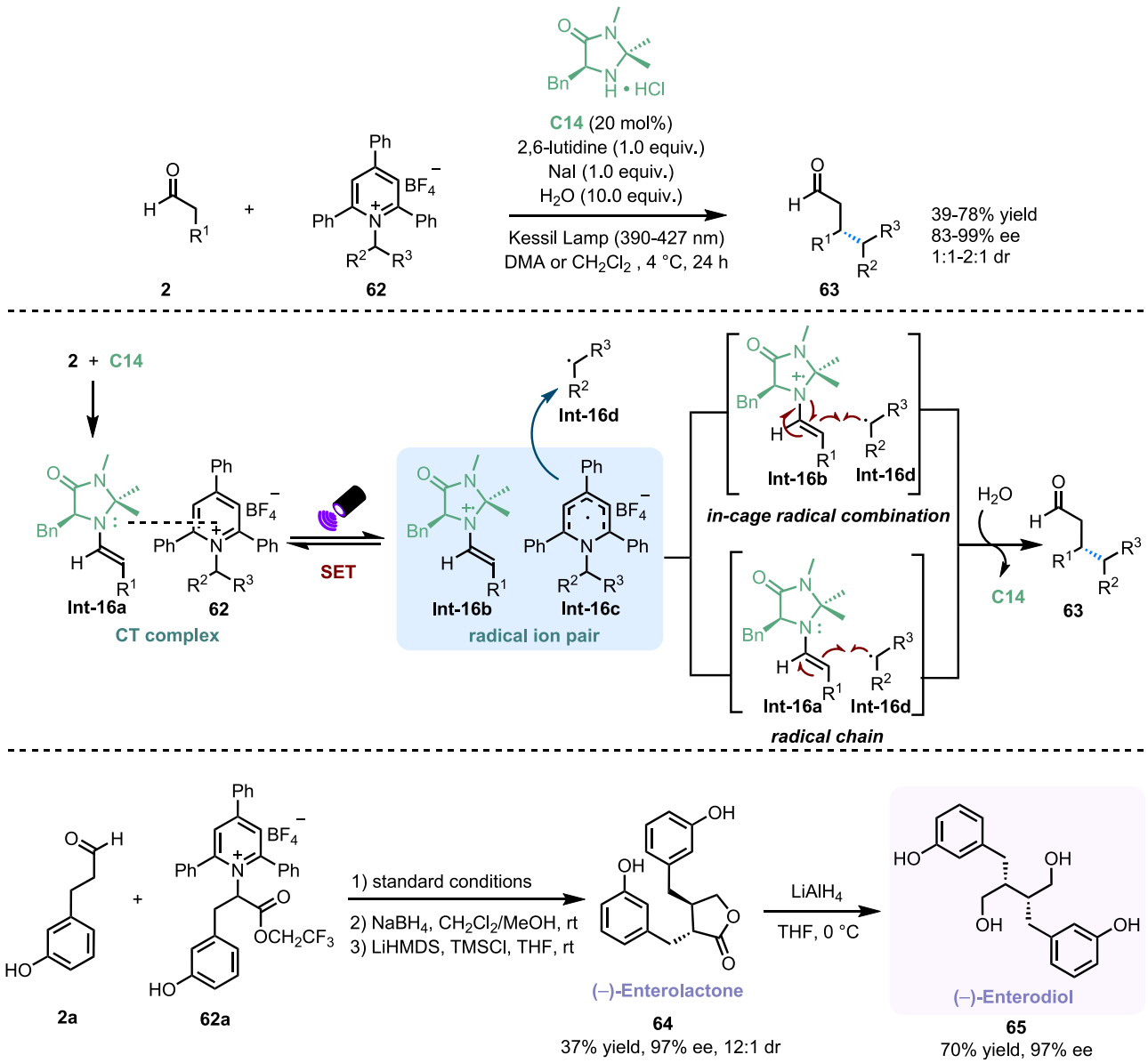
(A) Intermolecular iminium-ion-based EDA complexes.

(B) Intramolecular iminium-ion-based EDA complexes.

highlight the effectiveness of using excited-state chemistry of chiral iminium ions as a strategy to generate complexity in chemical reactions.

Electron donor-acceptor (EDA) complexes are one class of useful intermediates in organic reactions, which are formed through the association between electron-rich substrates and electron-poor substrates. They can trigger a light-induced electron or energy transfer process, leading to the generation of highly reactive intermediates without the requirement for external photocatalysts.[56]

In 2022, Rodríguez et al.[57] reported the first example of a photochemical stereocontrolled insertion of gem-difluoro derivatives into unsaturated aldehydes (Scheme 15A). The reaction used **C7** as the secondary amine catalyst, TFA as the co-catalyst, and sodium difluoalkyl sulfinates (**56**) as reaction partners. This approach resulted in the successful synthesis of various gem-difluoroalkylated products (**57**), with yields ranging from 33% to 93% and enantioselectivity between 62% and 90%. The reaction mechanism revolves around an EDA complex (**Int-14a**), formed by the *in situ* generated iminium and the difluoalkyl sulfonate. This complex plays a crucial role in the process, absorbing photons and undergoing a SET process. This leads to



Scheme 16. Photochemical enantioselective α-alkylation of aldehydes enabled by photoactive CT complexes

the formation of a,β-enaminyl radical (**Int-14b**) and a corresponding alkyl radical (**Int-14c**). Subsequently, through a radical coupling process, the enantioselective construction of a C–C bond is achieved. Notably, the use of flow techniques enabled the scale-up synthesis of compound **57a**, which can be easily converted to an inhibitor of ubiquitin-specific protease (**58**) in a single step.

Moreover, Melchiorre and colleagues developed visible light-triggered radical conjugate additions involving photoactive intramolecular iminium-ion-based EDA complexes, which exhibit the ability to selectively activate distinct bond formations (Scheme 15B).[58,59] The effective use of EDA complexes has paved the way for more sustainable and efficient synthetic routes, reducing the reliance on harsh reagents or high temperatures.

In 2023, Yetra et al.[60] reported a catalytic photochemical enantioselective α-alkylation of aldehydes through the formation of donor-acceptor complex intermediates, also known as light-activated charge-transfer (CT) complexes (Scheme 16). In this reaction, pyridinium salts derived from amino acids (**62**), which belong to a class of stable compounds resistant to air and moisture, were used as alkyl radical precursors. A chiral secondary amine (**C14**) developed by MacMillan and colleagues served as the organocatalyst.[2] Irradiation of a mixture containing alkyl aldehydes (**2**), pyridinium salts (**62**), the amine catalyst (**C14**), and additives (NaI, H_2O) in CH_2Cl_2 with purple light (390 nm) resulted in the production of various enantio-enriched α-alkylated aldehydes (**63**) with yields ranging from 39% to 78% and high enantioselectivity of 83%–99% ee, while exhibiting low diastereoselectivity of 1:1–2:1 dr.

Regarding the reaction mechanism, a chiral enamine intermediate (**Int-16a**), derived from the condensation of **2** and **C14**, forms a CT complex with the pyridinium salt (**62**). This CT complex then undergoes SET, resulting in the generation of a radical ion pair consisting of **Int-16b** and **Int-16c**. The subsequent radical addition step is considered to be the stereo-determining step, which can occur through an in-cage radical combination between the resulting alkyl radical (**Int-16d**) and **Int-16b**, and/or a radical chain reaction involving **Int-16d** and **Int-16a**. Finally, the desired product (**63**) is formed via hydrolysis, accompanied by the regeneration of **C14**.

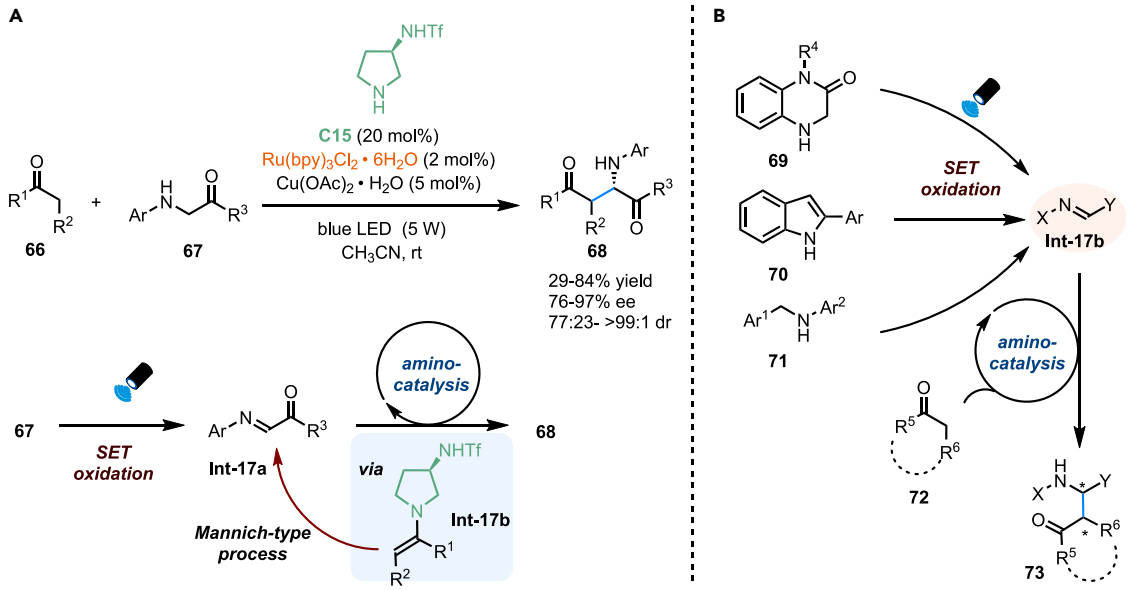
Notably, the addition of NaI had a significant impact on the equilibrium of enamine formation, potentially by modifying the equilibrium of the CT complex. The mild reaction conditions are compatible with a wide range of functional groups, allowing the enantioselective synthesis of lignan natural products including (−)-enterolactone (**64**) and (−)-enterodiol (**65**). Furthermore, Alemán and colleagues used the concept of photoactive CT complexes to advance aminocatalytic radical [2+2] cycloaddition reactions.[61,62]

By using cooperative photoredox catalysis and aminocatalysis, Yang et al.[63] reported in 2020 an enantioselective aerobic oxidative cross-dehydrogenative coupling of carbonyl compounds (**66**) with glycine derivatives (**67**) (Scheme 17A). Various unnatural α-alkyl α-amino acid derivatives were obtained with yields of 29%–84%, diastereoselectivity ranging from 77:23 to >99:1 dr, and enantioselectivity of 76%–97% ee. Mechanistically, the reaction proceeds through a photo-induced single-electron oxidation of the glycine substrate (**67**) to form an imine intermediate (**Int-17a**). This is followed by a highly selective Mannich-type reaction involving a chiral enamine intermediate (**Int-17b**) formed via the condensation of the carbonyl substrate (**66**) with the chiral amine catalyst (**C15**). This gentle protocol enables the direct formation of a C–C bond while simultaneously introducing two new stereocenters, without the need for wasteful removal of functional groups.

The strategy of photo-induced single-electron oxidation/asymmetric organocatalysis circumvents the need to isolate unstable imine intermediates, which was also successfully used to modify *N*-α positions of other substrates, such as dihydroquinoxalinones (**69**),[64] phenylindoles (**70**)[65] and benzylic secondary amines (**71**)[66] in a stereoselective manner (Scheme 17B).

NHC catalysis

The integration of photoredox catalysis with chiral NHC catalysis was initially reported by the Rovis group in 2012, paving the way for a new pathway in photochemical asymmetric synthesis.[67] However, the progress of this approach has been slow over the years, possibly due to the challenge of identifying compatible dual catalytic



Scheme 17. Photochemical enantioselective oxidative cross-dehydrogenative coupling via oxidation/chiral aminocatalysis

(A) Coupling with glycine derivatives.

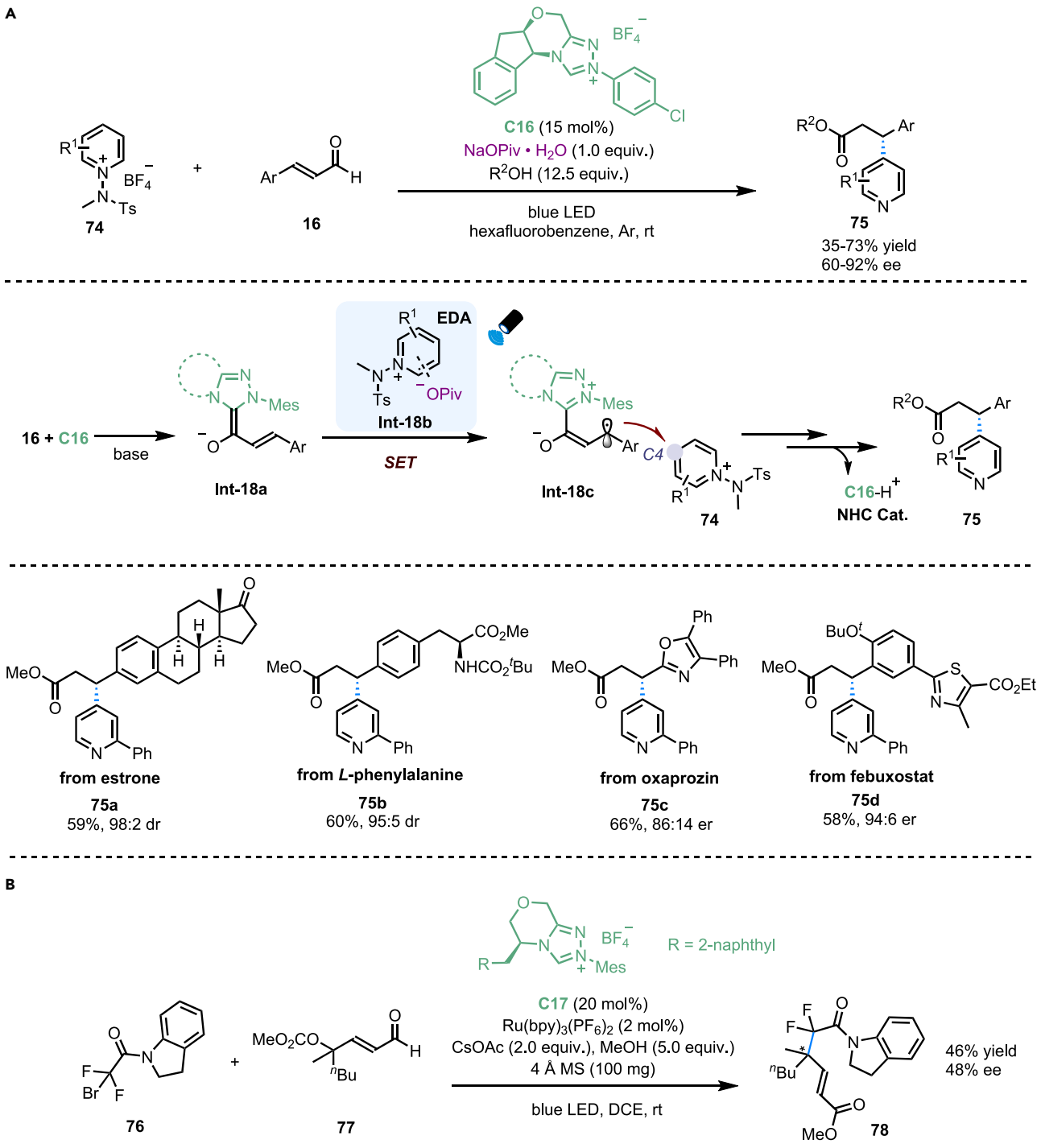
(B) Coupling with dihydroquinoxalinones, phenylindoles, or benzylic secondary amines.

systems that can effectively facilitate such transformations while ensuring high asymmetric induction during the radical processes with suitable NHC catalysts.

In 2021, Choi et al.[68] devised a highly efficient approach for the enantioselective β-heteroarylation of enals (**16**) with pyridinium salts (**74**), using chiral NHC catalysis to achieve remarkable control over both enantioselectivity and pyridyl C4-selectivity (Scheme 18A). This method eliminates the need for external photosensitizers, as the *in situ* formation of an EDA complex between the pyridinium salt (**74**) and the sodium pivalate additive (NaOPiv·H_2O) is thought to act as the photo-responsive component. Under blue LED irradiation, a wide range of β-pyridinated products with diverse functionality (**75**) were synthesized with moderate yields ranging from 35% to 73%, accompanied by high enantioselectivity of 60%–92% ee. Notably, unlike previous studies that reported radical addition at C2-positions of pyridine derivatives,[69] this reaction exhibited exclusive C4-selectivity.

Several control experiments and spectroscopic analyses provided evidence for a reaction pathway involving the photoexcitation of EDA intermediates, followed by SET with chiral NHC-activated enals. Specifically, the reaction between the enal substrate (**16**) and NHC precursor (**C16**) in the presence of a base leads to the formation of the enolate form of Breslow intermediate (**Int-18a**). Simultaneously, a pyridinium-pivalate EDA complex (**Int-18b**), capable of absorbing photons, is generated. Under visible light irradiation, **Int-18b** undergoes SET with **Int-18a**, producing a homoenolate radical (**Int-18c**). The subsequent stereoselective radical addition of **Int-18c** to the C4-position of the pyridinium salt (**74**), along with chain processes and alcoholysis, facilitates product formation and regenerates the active NHC catalyst. The use of hexafluorobenzene as a solvent plays a crucial role in improving stereocontrol, potentially due to the establishment of electrostatic interactions during the radical addition process.

The protocol was effectively used for the modification of various biorelevant molecules, including estrone (product **75a**), L-phenylalanine (**75b**), oxaprozin (**75c**), and

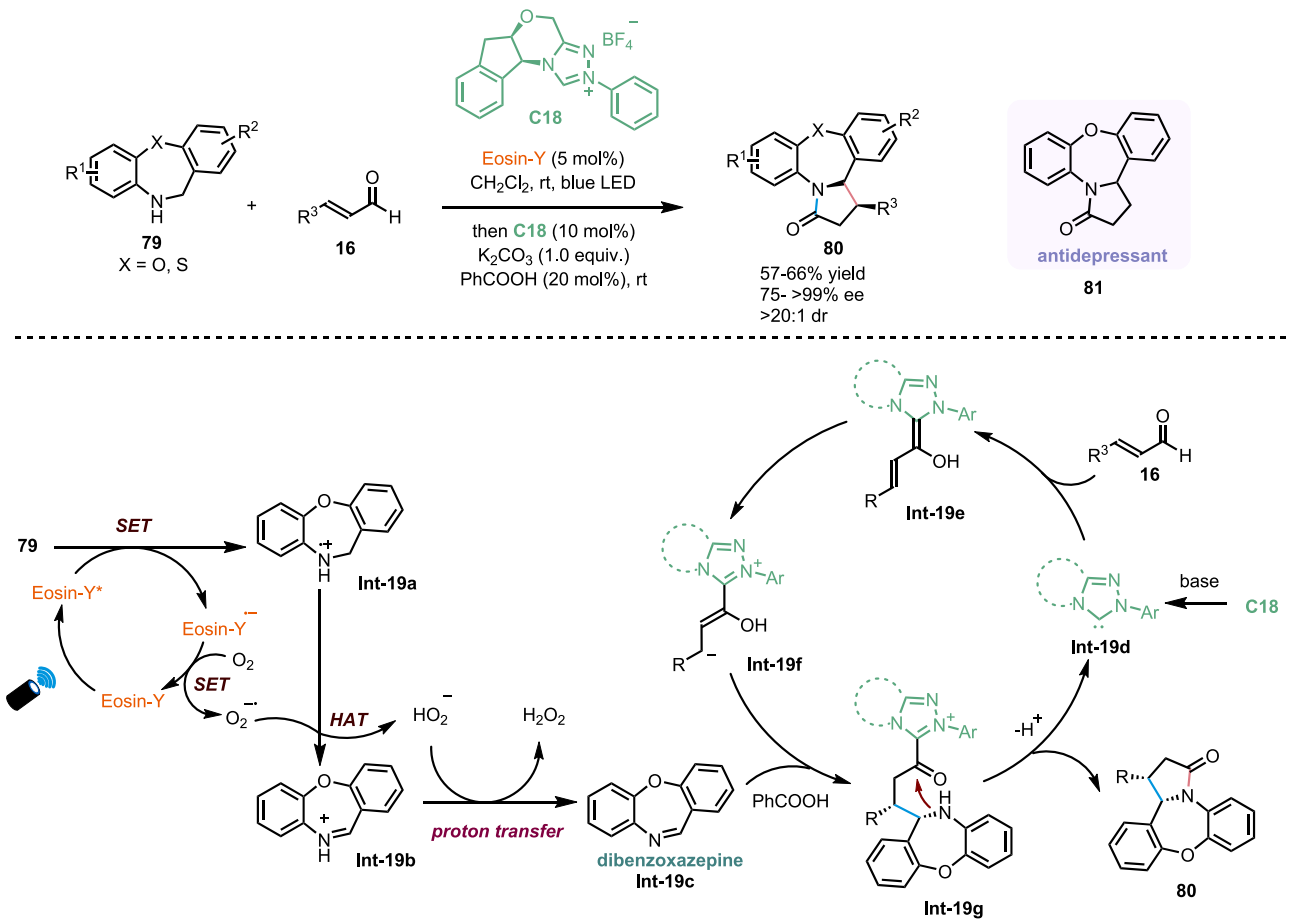


Scheme 18. Synergic photoredox and chiral NHC catalysis for enantioselective radical transformations

(A) Enantioselective β-heteroarylation of enals with pyridinium salts.

(B) Enantioselective synthesis of γ-difluoroalkyl-α,β-unsaturated esters.

febuxostat (**75d**). Additionally, Dai et al.[70] used the approach of photoredox NHC-catalyzed radical transformations to synthesize γ-difluoroalkyl-α,β-unsaturated esters. However, in its enantioselective form, only a moderate yield (46%) and selectivity (48% ee) were achieved for the chiral product (**78**) (Scheme 18B).



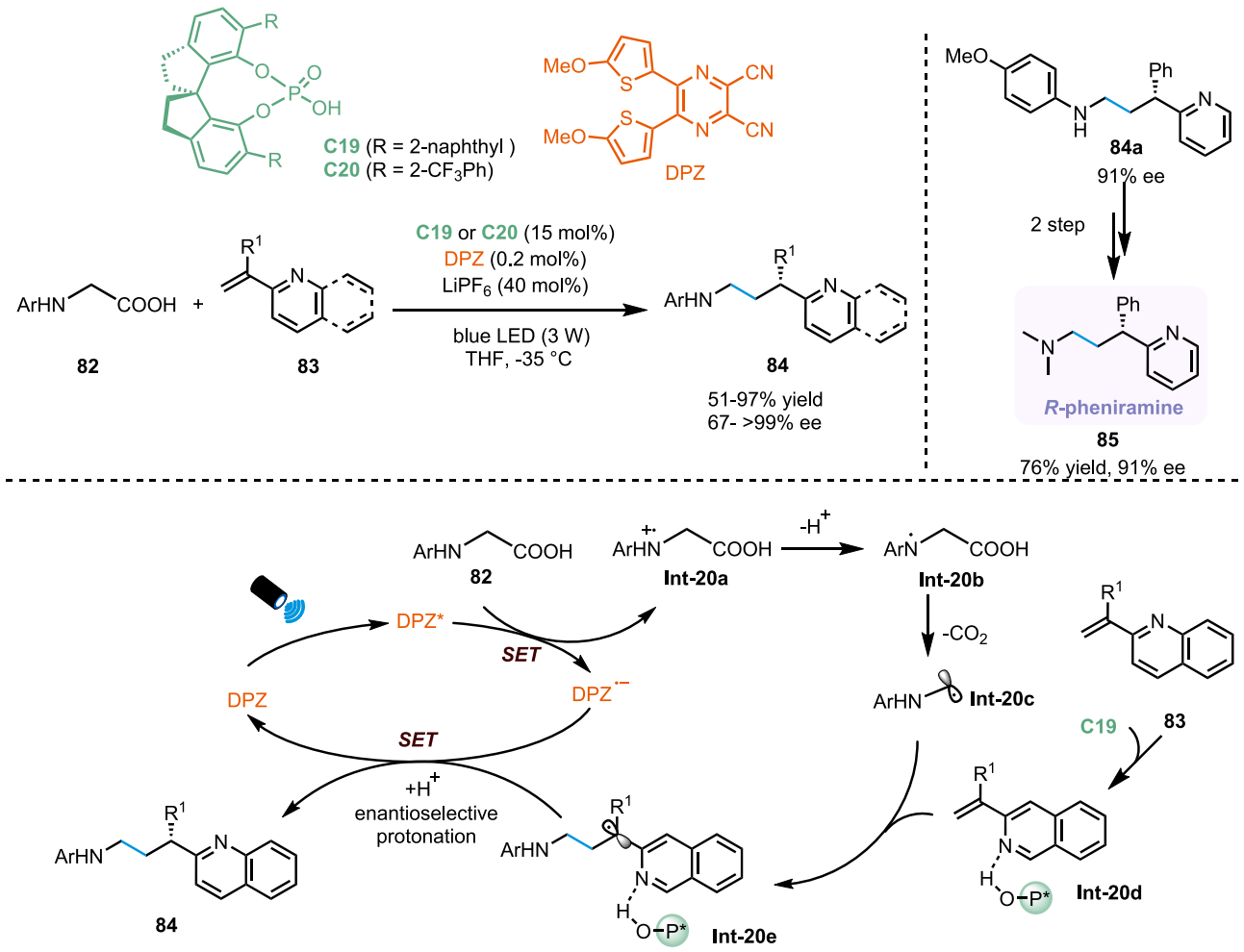
Scheme 19. Photoredox/*N*-heterocyclic carbene relay catalysis for the synthesis of biologically interesting pyrrolo[1,2-*d*][1,4]oxazepin-3(2*H*)-ones

Dibenzoxazepine, serving as a valuable synthon, has found applications in the synthesis of biologically active compounds. However, its toxic properties have restricted its use in organic synthesis. In 2023, Hussain et al.[71] reported a highly stereoselective synthesis of pyrrolo[1,2-*d*][1,4]oxazepin-3(2*H*)-ones using photoredox/NHC relay catalysis (Scheme 19). This approach enables the use of potentially safer starting materials, such as substituted dihydrodibenzoxazepine (**79**) and enals (**16**), and the production of various enantio-enriched pyrrolo[1,2-*d*][1,4]oxazepin-3(2*H*)-ones (**80**) as single diastereomers with excellent enantioselectivity of 75% to >99% ee.

In terms of the reaction mechanism, the key intermediate dibenzoxazepine (**Int-19c**) is generated *in situ* through photoredox-triggered single-electron oxidation of **79** to yield an *N*-centered radical cation (**Int-19a**), followed by a HAT and proton transfer process. This eliminates the direct use of toxic dibenzoxazepines as starting materials. Acting as an electrophilic imine, dibenzoxazepine (**Int-19c**) readily reacts with the chiral NHC-bonded enal (**Int-19f**), enabling stereoselective [3+2] annulation and facilitating the formation of the final product. This protocol offers an efficient and safe pathway for synthesizing chiral derivatives with anti-depressive activity, exemplified by product **81**.

CPA catalysis

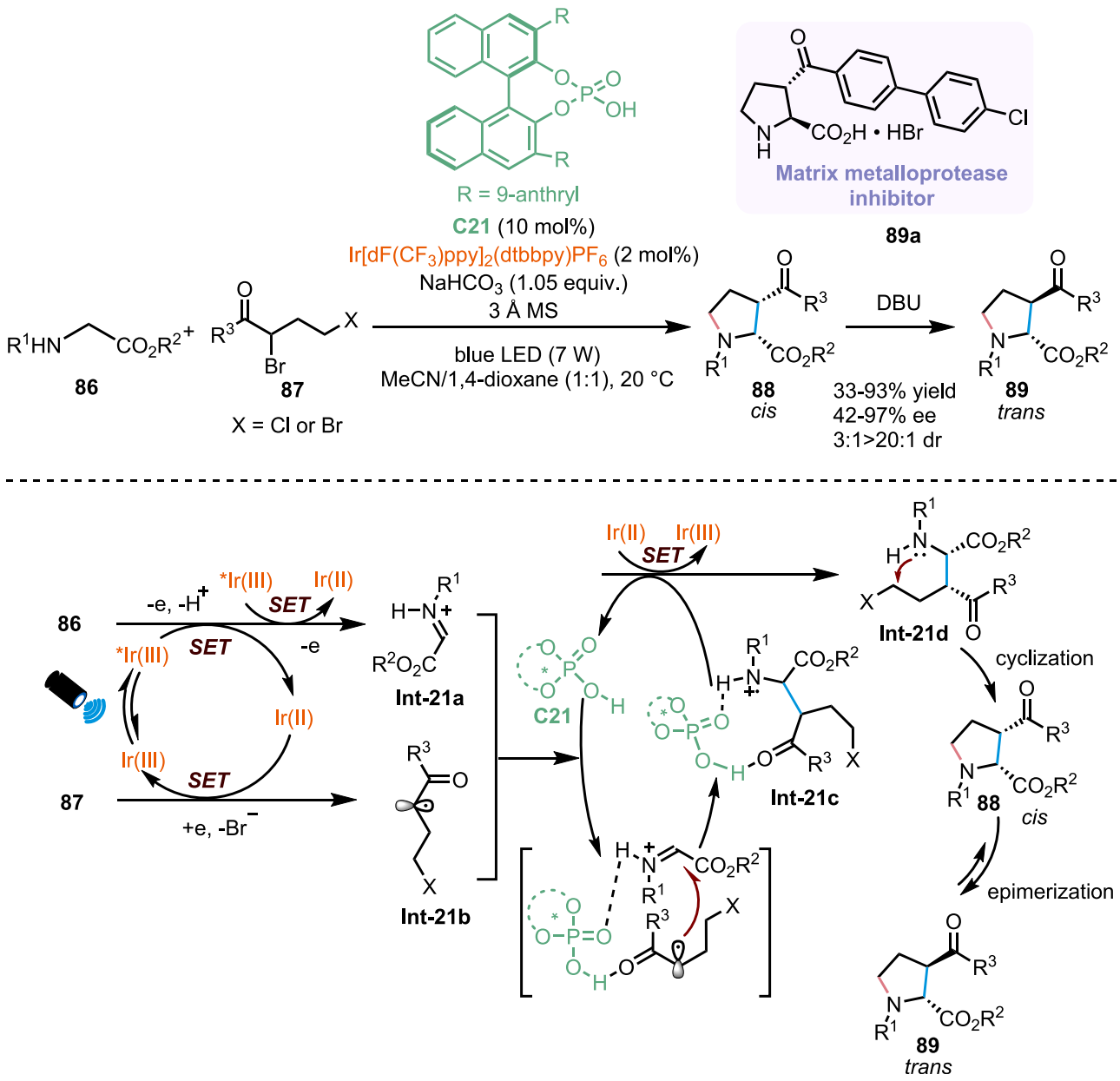
CPAs have demonstrated remarkable catalytic efficiency and selectivity, not only in numerous stereoselective transformations under thermal conditions but also in



Scheme 20. Photo-induced conjugate addition—Enantioselective protonation by dual photoredox and CPA catalysis

various photochemical asymmetric radical processes.[72–79] In 2018, Yin et al.[73] introduced a novel conjugate addition/enantioselective protonation cascade, made possible by the synergistic combination of photoredox and CPA catalysis (Scheme 20). By using a dicyanopyrazine (DPZ)-derived chromophore photosensitizer, along with a 1,1′-spirobiindane-7,7′-diol (SPINOL)-based CPA (**C19** or **C20**), and supplemented with $LiPF_6$ as an additive, the mixture of α-aryl glycines (**82**) and α-branched 2-vinylazaarene (**83**) was subjected to irradiation in THF at −35°C using a 3 W blue LED lamp. This protocol resulted in the desired adducts (**84**) with yields ranging from 51% to 97% and enantioselectivities between 67% and >99% ee.

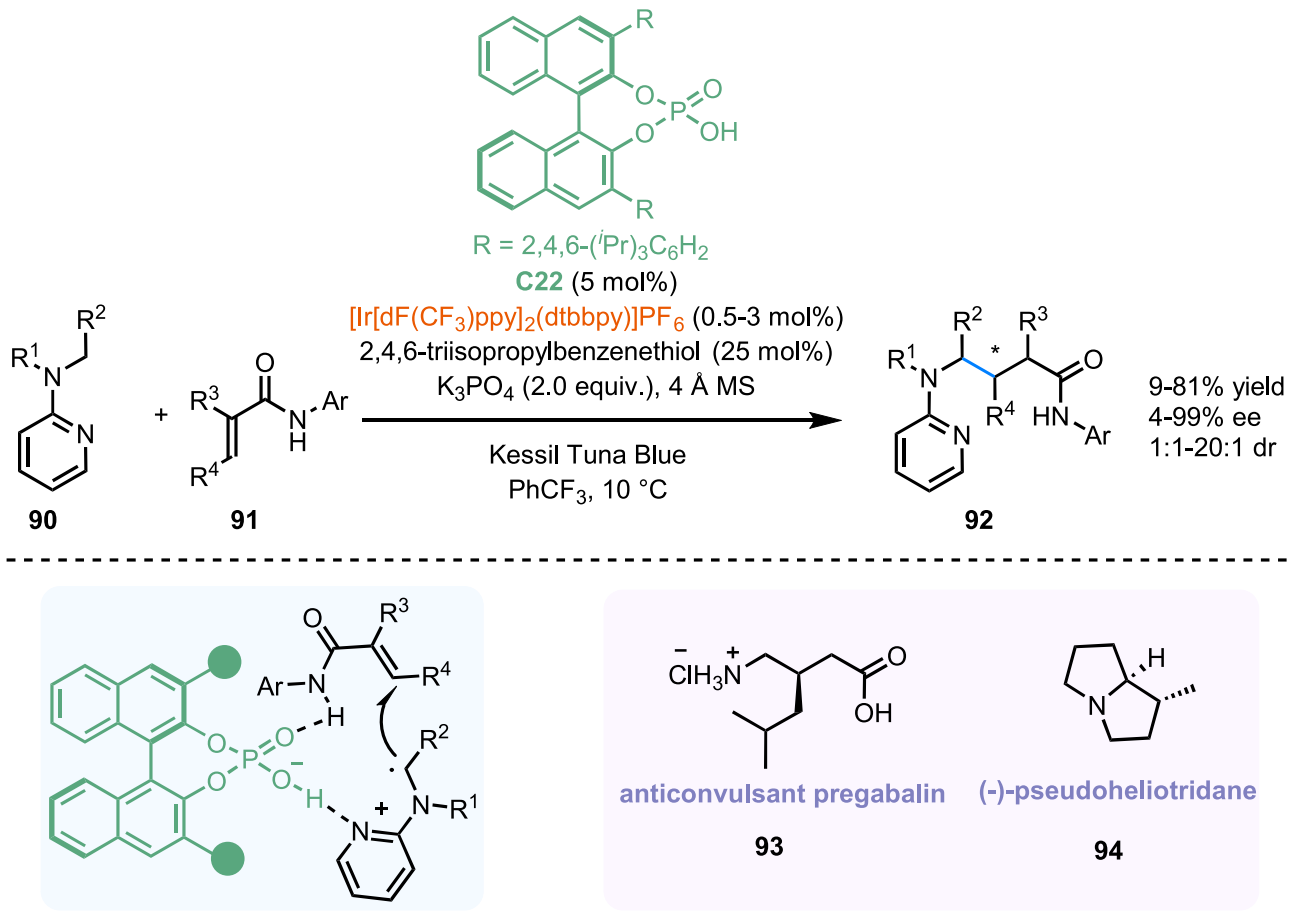
Mechanistically, the α-aryl glycine (**82**) undergoes single-electron oxidation by the excited photocatalyst (DPZ*) to generate an α-aminoalkyl radical cation (**Int-20a**). Subsequent deprotonation leads to the formation of an *N*-centered radical (**Int-20b**), while decarboxylation produces an *N*-α carbon radical. The radical addition of **Int-20c** to the CPA-activated 2-vinylazaarene (**Int-20d**) gives rise to a prochiral radical (**Int-20e**). This prochiral radical then participates in a SET process with the reduced photocatalyst ($DPZ^{\bullet-}$) to generate a prochiral carbanion. The enantioselective protonation is controlled through hydrogen bonding induction from the CPA catalyst, ultimately yielding the desired chiral product (**84**). This study exemplifies



Scheme 21. Enantioselective *de novo* construction of 3-substituted proline derivatives via CPA-enabled enantioselective radical addition to iminium ions

an innovative application of enantioselective protonation, paving the way for new opportunities in synthesizing chiral α-tertiary azaarenes. Notably, the antihistamine drug (*R*)-pheniramine (Avil) (**85**) was successfully synthesized using this approach, yielding 76% and exhibiting an impressive enantioselectivity of 91% ee.

In 2020, Che et al.[80] reported an enantio- and diastereoselective *de novo* synthesis of 3-substituted proline derivatives through the use of cooperative photoredox/CPA catalysis and epimerization (Scheme 21). A variety of enantioenriched 3-*cis*-substituted (**88**) and 3-*trans*-substituted (**89**) prolines were successfully obtained through the photochemical reaction of glycine esters (**86**) and α,γ-halo ketones (**87**), which proceeded via an unprecedented radical addition/cyclization cascade.

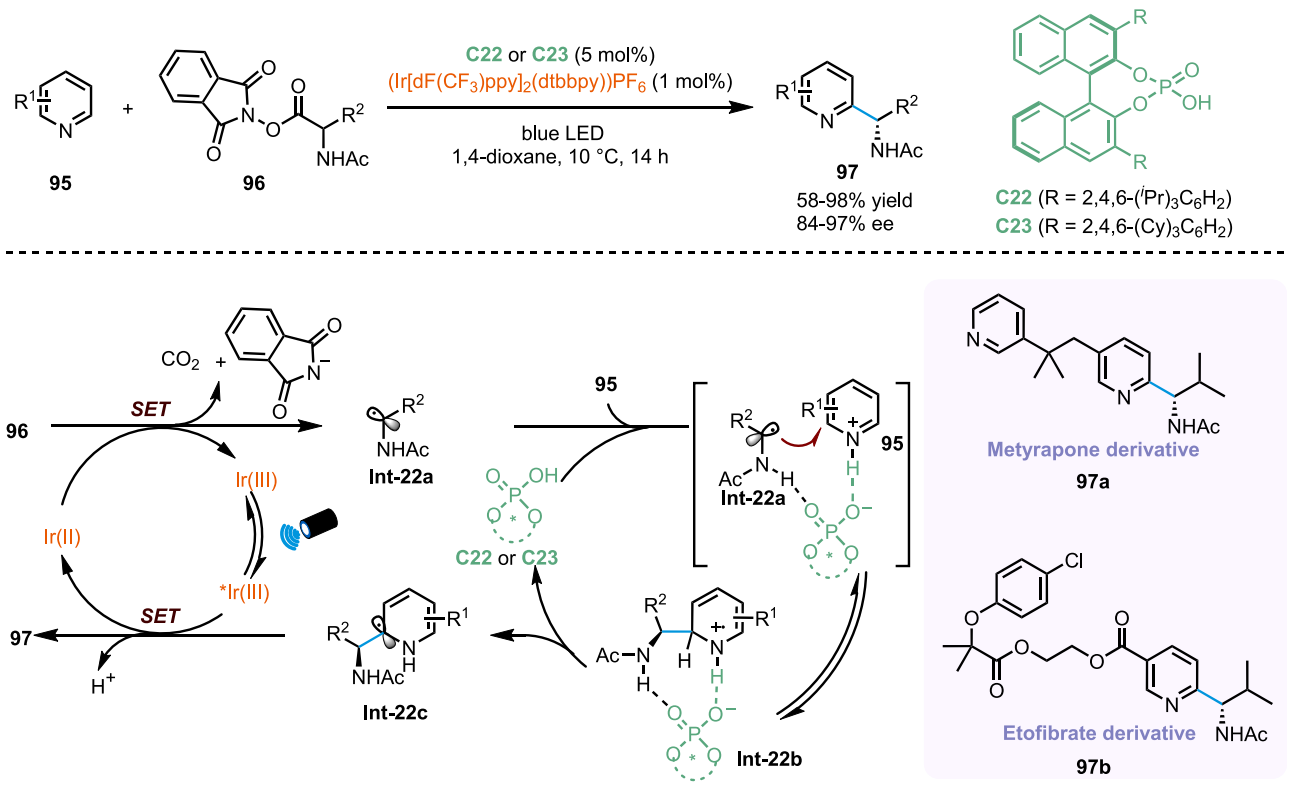


Scheme 22. Photochemical enantioselective Giese addition via the formation of ion pairs

In the proposed mechanism, the glycine ester (**86**) undergoes photochemical oxidation to form an iminium ion (**Int-21a**), while the α,γ-halo ketone (**87**) is simultaneously reduced to produce an α-carbonyl radical. These two radical species then interact with the CPA catalyst (**C21**) through hydrogen bonding interactions, resulting in enantioselective radical addition and the formation of a chiral radical cation (**Int-21c**). Following the SET reduction of **Int-21c** by the Ir(II) species, an intermediate **Int-21d** is generated, thereby completing the photocatalytic cycle and liberating the CPA catalyst. The formation of 3-*cis*-substituted proline (**88**) occurs through an intramolecular cyclization process. Moreover, in the presence of DBU, compound **88** can undergo epimerization to convert into its *trans*-isomer (**89**). This reaction exemplifies a remarkable instance of achieving access to all four stereoisomers of 3-substituted prolines from scratch.

Additionally, building upon the analogous approach involving CPA-facilitated enantioselective radical addition to iminium ions, Dai et al.[81] accomplished first asymmetric [3+2] photocycloadditions of cyclopropylamines through the combined implementation of dual photoredox and CPA catalysis.

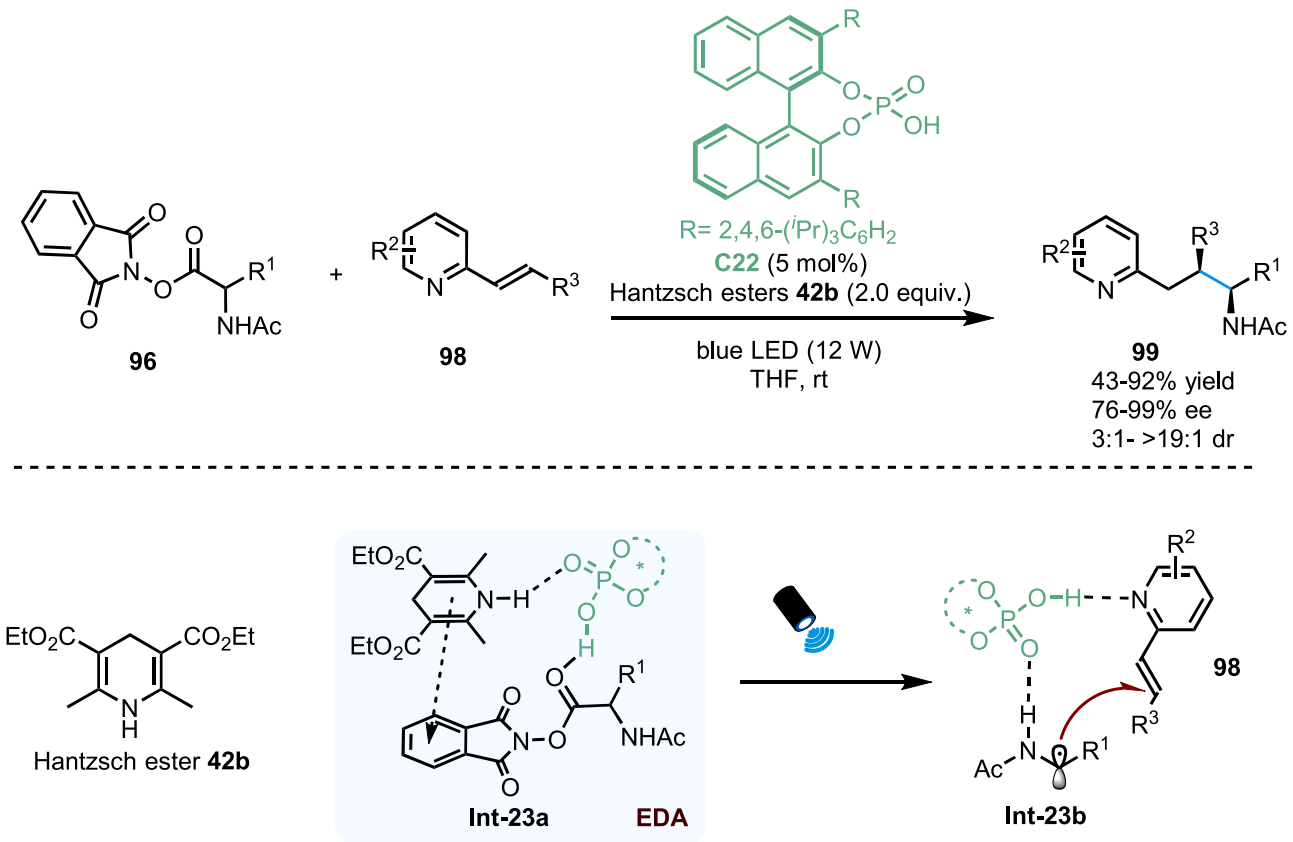
The formation of ion pairs between the substance or active intermediate and CPA plays a crucial role in ensuring precise control over high enantioselectivity during the radical addition process.[82–91] The development of catalytic asymmetric reactions that generate a novel α-amino stereocenter via prochiral α-amino radicals



Scheme 23. Photochemical enantioselective Minisci-type reaction via synergetic photoredox and CPA catalysis

remains limited. The Giese addition of α-amino radicals to electron-deficient alkenes provides an efficient approach for achieving enantioselectivity. However, the occurrence of a new stereocenter originating from a prochiral α-amino radical in an enantioselective Giese reaction is exceedingly rare. In 2022, Lahdenperä et al.[90] made a significant contribution by reporting on the photochemical enantioselective Giese additions of prochiral α-amino radicals that bear a heteroarene group to unsaturated carbonyls. Notably, this groundbreaking study also demonstrated successful diastereocontrol (Scheme 22). By using an iridium-based photosensitizer ([Ir(dF(CF$_3$)ppy]$_2$(dtbbpy)]PF$_6$) and a BINOL-derived CPA catalyst (**C22**), the reaction involving pyrrolidine-derived amines (**90**) and *N*-arylacrylamides (**91**) successfully yielded chiral products (**92**) with high stereoselectivity (up to 99% ee, up to 20:1 dr). During the crucial stereo-determining step, the steric-bulky CPA catalyst selectively interacts with both the acrylamide (**91**) and a pivotal *N*-α radical intermediate. This interaction ultimately facilitates the diastereo- and enantioselective addition of radicals. Building upon this methodology, the formal synthesis of some important compounds such as the anticonvulsant pregabalin (**93**) and the pyrrolizidine alkaloid (−)-pseudoheliotridane (**94**).

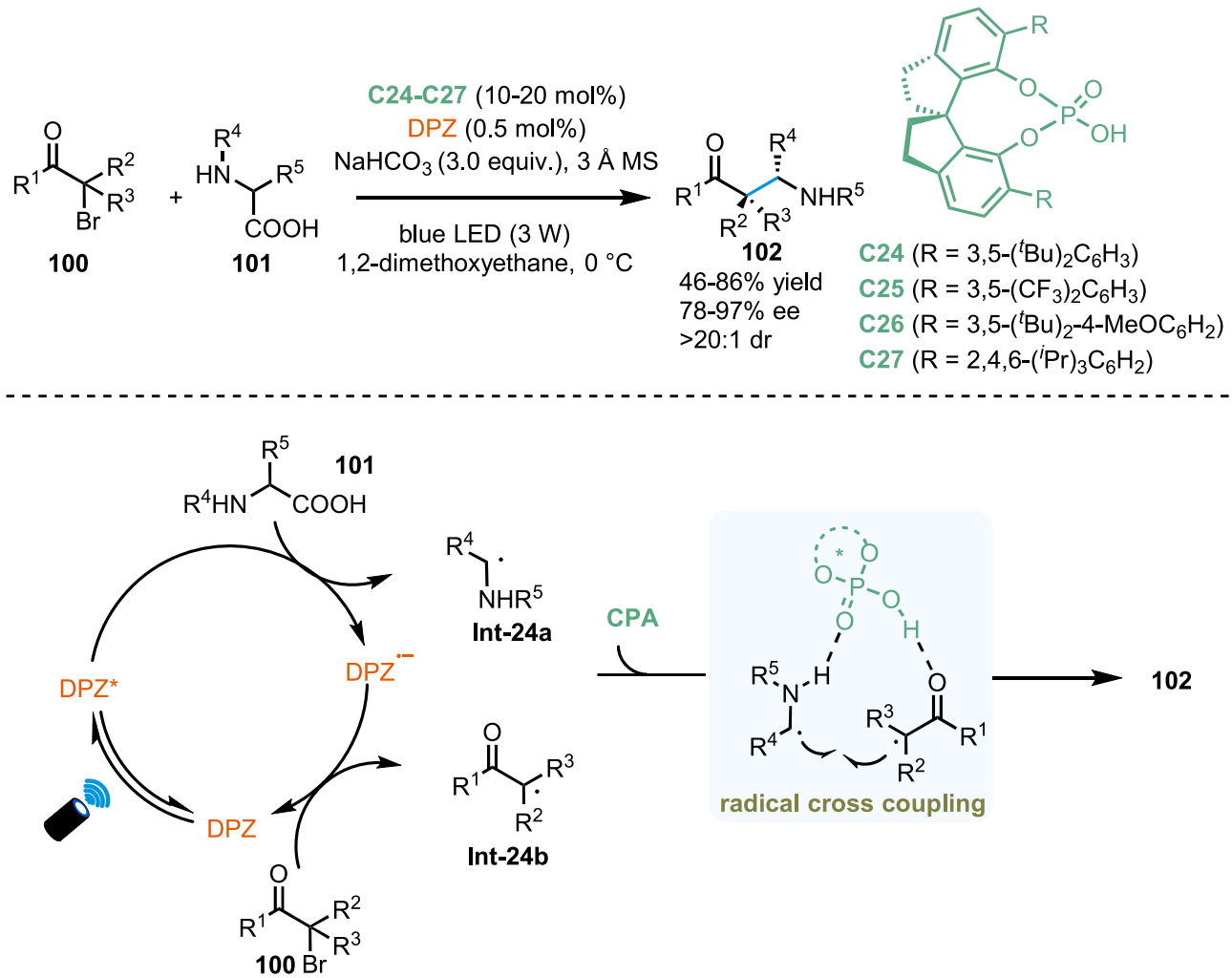
The Minisci-type reaction represents a highly efficient approach for constructing pharmaceuticals and bioactive basic heterocycles. In 2018, Proctor et al.[92] introduced an enantioselective Minisci-type reaction, using a synergistic combination of CPA catalysis and photoredox catalysis (Scheme 23). Using an iridium photoredox catalyst ((Ir[dF(CF$_3$)ppy]$_2$(dtbbpy))PF$_6$) in combination with the CPA catalyst (**C22** or **C23**), a series of chiral α-heterocyclic amine derivatives (**97**) were obtained with high enantioselectivity of 84%–97% starting from heteroarenes (**95**) and amino acid-derived esters (**96**). The reaction mechanism initiates with the single-electron



Scheme 24. CPA-catalyzed enantioselective radical addition enabled EDA complexes

reduction of **96**, which is then followed by decarboxylation to generate an α-aminoalkyl radical (**Int-22a**). Subsequently, the CPA catalyst (**C22**) facilitates the interaction between the radical (**Int-22a**) and the heteroarene substrate (**94**) within a distinctive steric environment through hydrogen bonding interactions. This unique interaction enables enantioselective radical addition, resulting in the formation of a C2-addition radical cation (**Int-22b**). Finally, a second SET process, coupled with deprotonation, leads to the formation of the desired product (**97**). This protocol was effectively used for the functionalization of pharmaceutical compounds such as metyrapone (**98a**) and etofibrate (**98b**). By providing a chiral Brønsted acid catalysis/photocatalysis model, this method enables the efficient synthesis of diverse chiral small-molecule compounds containing basic heterocycles. Furthermore, it serves as an inspiration for organic researchers to explore and develop numerous enantioselective Minisci-type reactions using different combinations of reaction partners and catalysts.[93–98]

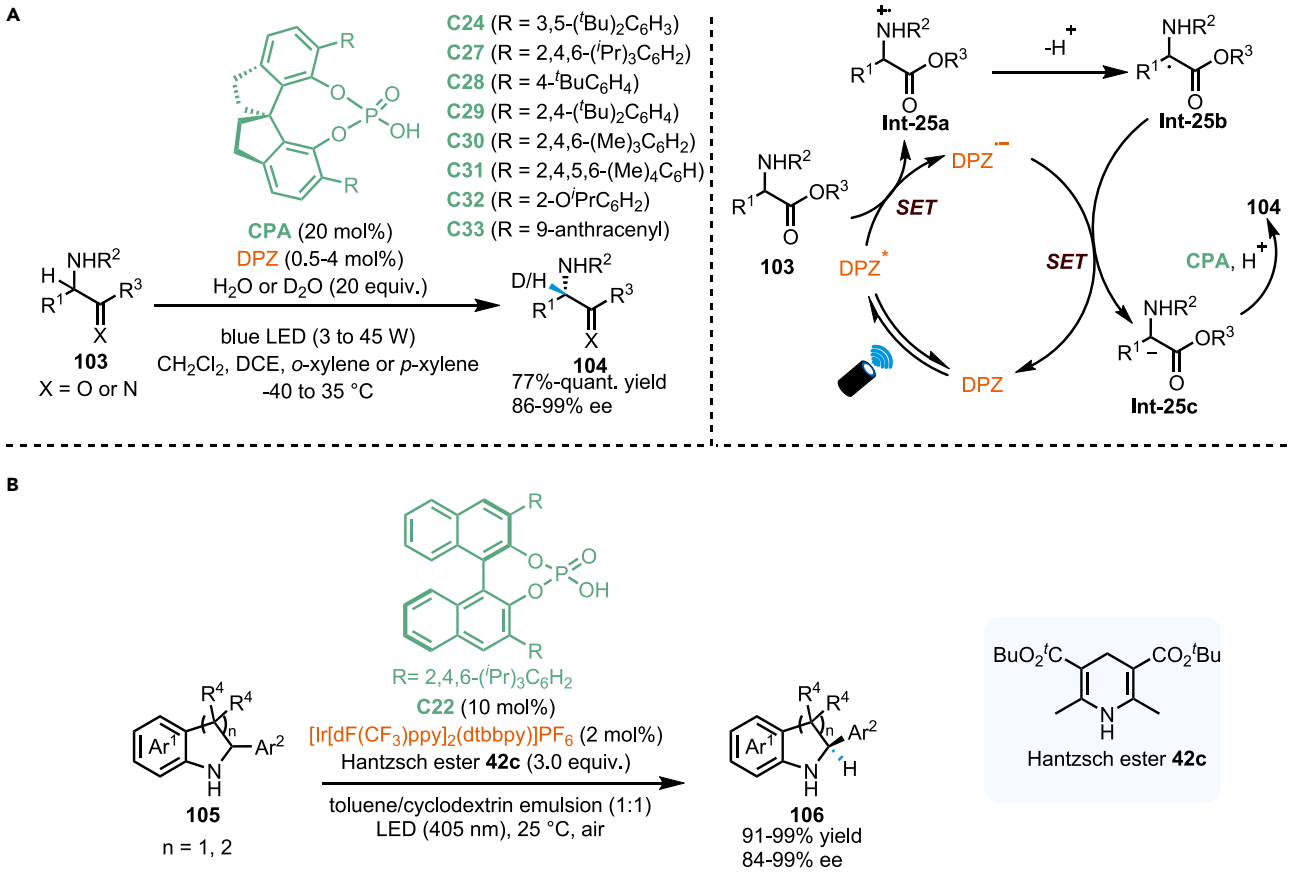
In 2022, Guo et al.[99] reported a significant advancement in the development of a CPA-catalyzed enantioselective hydroalkylation of alkenylpyridines using EDA complexes (Scheme 24). This innovative reaction involves the formation of a light-active EDA complex (**Int-23a**) through a synergistic interaction between the electron-rich Hantzsch ester (**42b**), the electron-poor redox-active ester (**96**), and the CPA catalyst (**C22**). This interaction is facilitated by hydrogen bonding interactions and π-π stacking, ultimately leading to the desired enantioselective transformation. Upon exposure to light, **Int-23a** absorbs photons and undergoes SET as well as radical fragmentation. This process leads to the formation of an α-aminoalkyl radical (**Int-23b**). The resultant radical species then undergoes a radical addition reaction with the pyridyl



Scheme 25. Photochemical asymmetric radical coupling via dual photoredox and CPA catalysis

alkene bonded to CPA, enabling the stereoselective formation of C–C bonds. In this way, the CPA catalyst serves dual roles in the transformation: facilitating the formation of EDA complex intermediates and governing the stereochemistry during the radical addition process. Building upon this methodology, a diverse range of chiral pyridines featuring vicinal tertiary stereocenters at the β,γ-positions (**99**) were successfully synthesized with remarkable levels of diastereo- and enantioselectivity. The obtained products exhibited diastereoselectivity ratios ranging from 3:1 to 19:1 dr, accompanied by high ee values between 76% and 99%.

The photoredox-triggered radical coupling process mediated by CPA catalysis has emerged as a highly effective approach for achieving stereoselective C–C bond formation.[100–106] Traditional nucleophilic substitutions of alkyl halides often struggle to achieve asymmetric induction. To address this limitation, Li et al.[100] developed an effective enantioconvergent substitution of alkyl halides through catalytic asymmetric photoredox radical coupling (Scheme 25). Under transition metal-free conditions, the reaction between alkyl halides (**100**) and *N*-aryl amino acids (**101**) was successfully accomplished in the presence of a SPINOL-derived CPA catalyst (**C24-C27**) and an organophotocatalyst (DPZ). This approach yielded enantio-enriched β^2- and



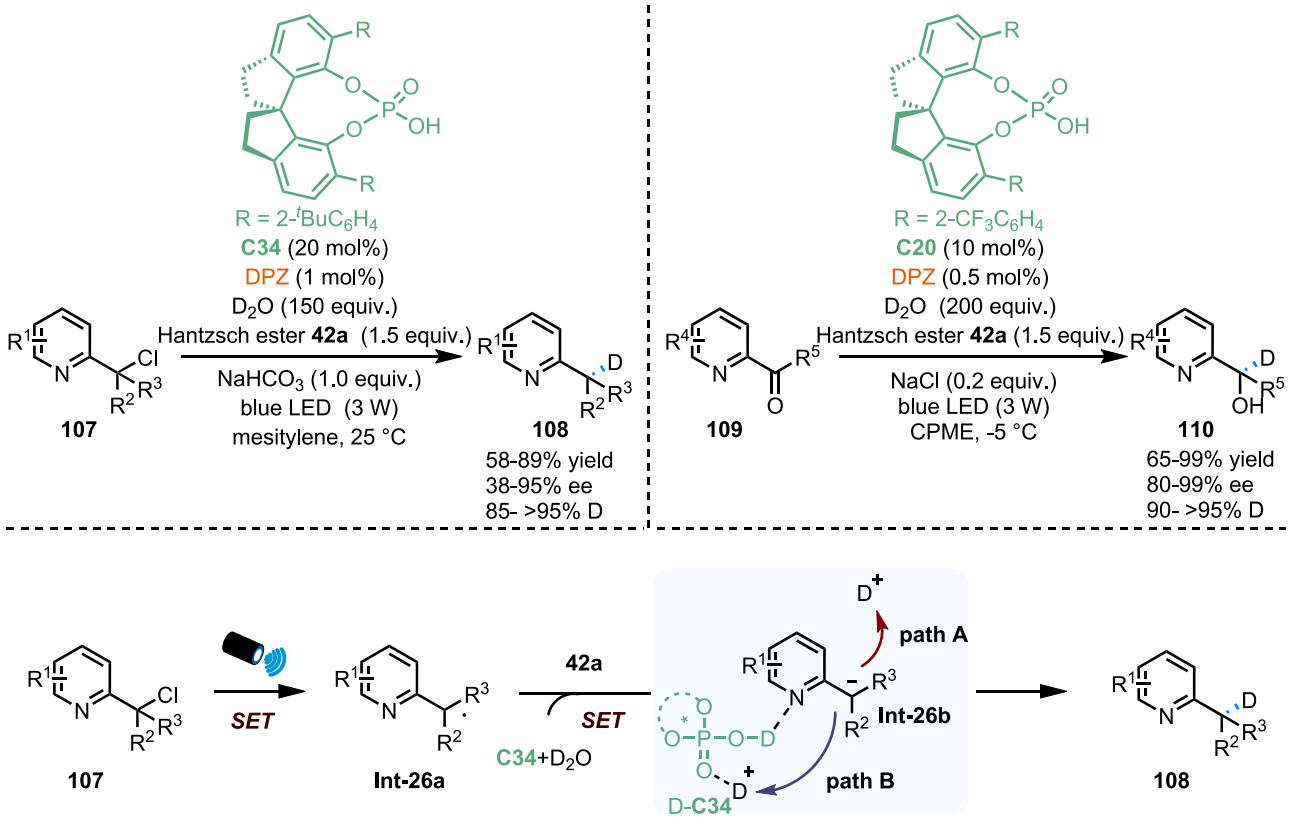
Scheme 26. Photochemical deracemization reactions using a photocatalyst coupled with a CPA catalyst

(A) Deracemization of α-amino esters.

(B) Deracemization of indolines and tetrahydroquinolines.

β^{2,2}-amino ketone products (**102**) with significant synthetic and biological value. The obtained products exhibited satisfactory yields ranging from 46% to 86%, along with remarkable levels of diastereoselectivity (>20:1 dr) and high enantioselectivity ranging from 78% to 97% ee. Regarding the reaction mechanism, under light irradiation, an excited DPZ* is generated. This species then undergoes SET with the *N*-aryl amino acid (**101**), resulting in the formation of an α-aminoalkyl radical (**Int-24a**) and the reduced form of DPZ (DPZ$^{\bullet-}$). Subsequently, a second SET process occurs between the alkyl halide (**100**) and DPZ$^{\bullet-}$, leading to the generation of an alkyl radical (**Int-24b**) and the release of DPZ. Finally, the chiral product (**102**) is formed through a radical coupling reaction between the α-aminoalkyl radical (**Int-24a**) and the alkyl radical (**Int-24b**), with the stereochemistry being induced by the CPA catalyst. This strategy introduces a novel pathway for synthesizing enantiopure molecules of high value starting from readily available alkyl halides. Significantly, this approach successfully addresses the challenge of constructing fluoro-heteroquaternary and full-carbon quaternary stereocenters, which are typically difficult to prepare.

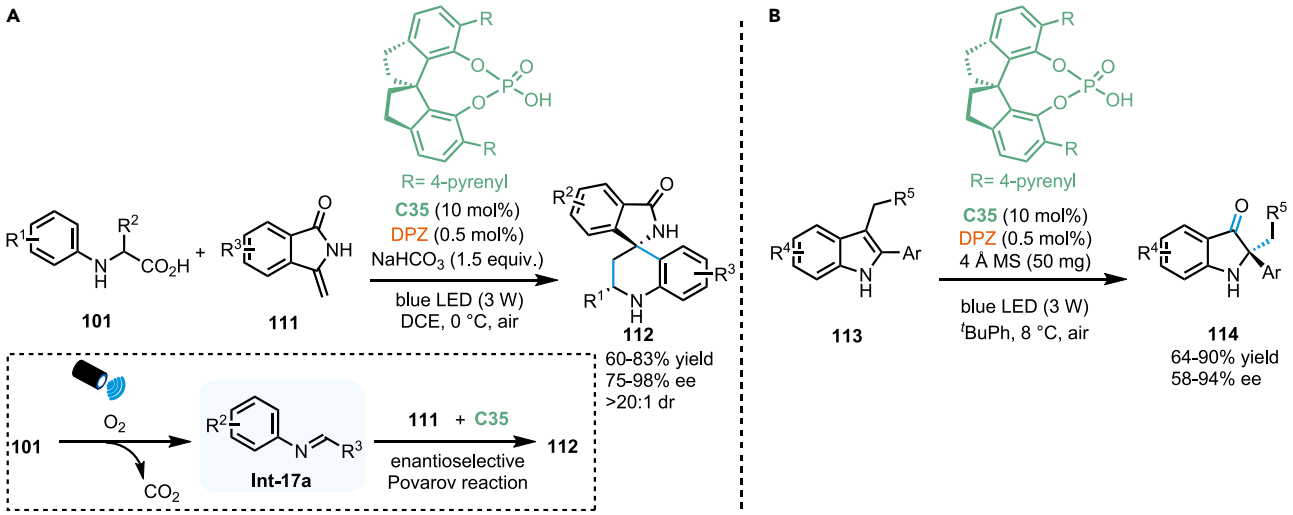
Catalytic deracemization is a highly efficient and atom-economical strategy for generating optically active molecules. In 2022, Gu et al.[107] made a significant contribution by developing a catalytic photoredox-neutral approach for achieving stoichiometric reagent-free deracemization of α-amino esters (Scheme 26A). The synergistic combination of a SPINOL-derived CPA catalyst (**C24**, **C27**-**C33**) with an



Scheme 27. Enantioselective protonation via dual photoredox and CPA catalysis

organophotocatalyst (DPZ) enabled the photochemical deracemization reaction of diverse α-amino esters and α-amino variants (**103**). This innovative approach resulted in the production of chiral α-amino ester products (**104**) with remarkable yields and enantioselectivity ranging from 86% to 99% ee. Mechanistically, the generation of a crucial prochiral ion intermediate (**Int-25c**) occurs through photoredox-induced two SET steps. This intermediate subsequently undergoes enantioselective protonation, guided by the CPA catalyst. Remarkably, this method offers an effective approach for synthesizing enantioenriched α-deuterated-α-amino esters, even in the presence of a racemic background process. Recently, Chen et al.[108] successfully accomplished the photoredox-triggered deracemization of indolines and tetrahydroquinolines (**105**) using a comparable dual catalytic system (Scheme 26B).

The synergistic combination of photoredox and CPA catalysis has also demonstrated remarkable efficiency and selectivity in other stereoselective radical transformations. For instance, Shao et al.[109] presented a photoredox-catalyzed asymmetric α-deuteration of azaarenes (**107**, **109**) using D_2O as the deuterium source and a Hantzsch ester (**42a**) as the terminal reductant (Scheme 27). Under the control of the SPINOL-derived CPA catalyst (**C20** or **C34**), this reaction yielded a range of valuable enantioenriched α-deuterated azaarenes (**108**, **110**) with yields ranging from 58% to 99%, and ee values between 38% and 99%. Notably, high levels of deuterium incorporation (90%–95%) were also accomplished. In the proposed mechanism, a prochiral radical intermediate (**Int-26a**) is initially generated through sequential SET processes. In the presence of D_2O, the CPA catalyst (**C34**) is transformed into its deuterated analog (D-**C34**), which then binds with the resulting α-pyridyl anion (**Int-26b**). Subsequent intermolecular or intramolecular D^+ transfer leads to the



Scheme 28. Photo-induced aerobic oxidation cascade reactions via CPA catalysis

(A) *N*-Aryl α-amino acids as substances.

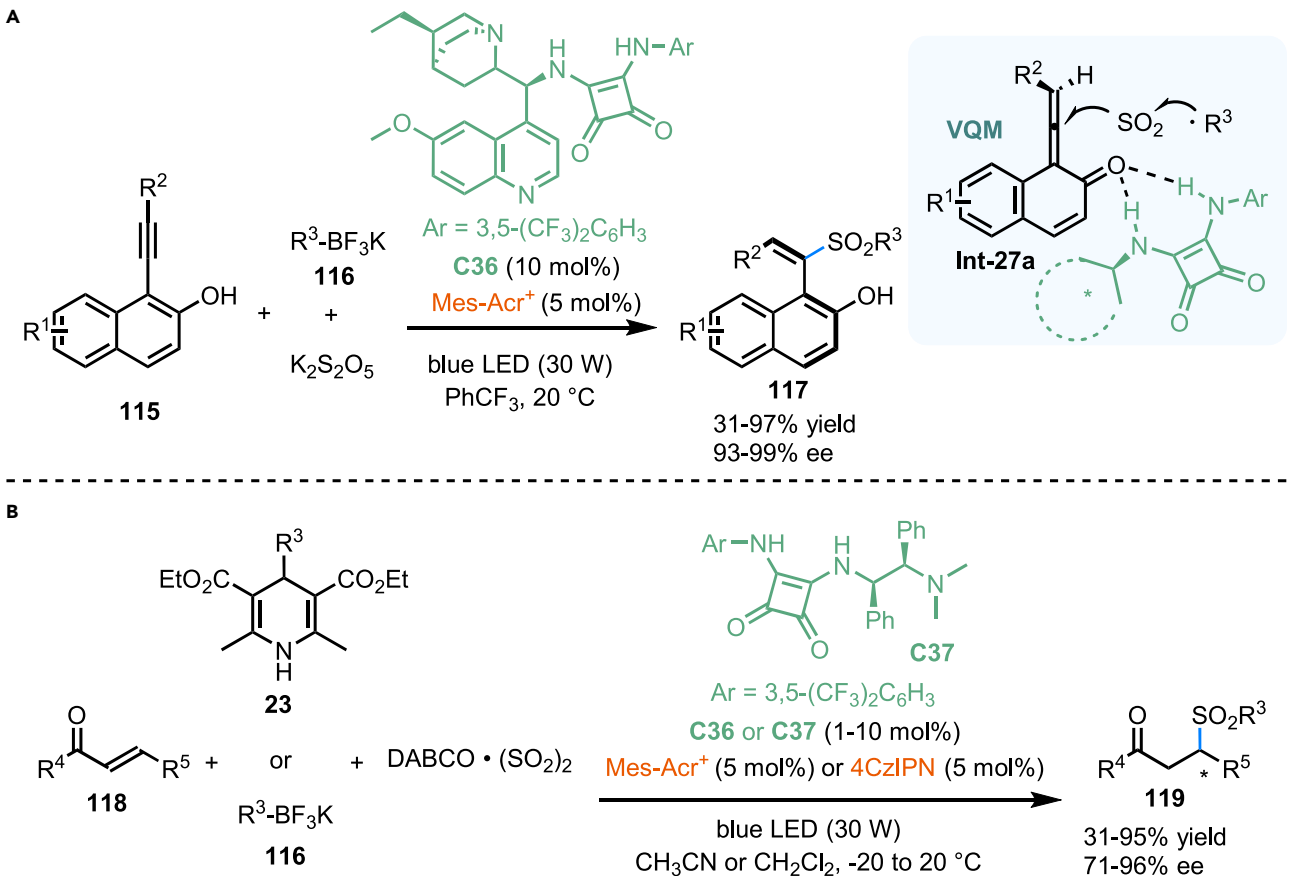
(B) 2-Aryl-3-alkyl substituted indoles as substances.

formation of the deuterated product (**108**) with enantioselectivity. This study serves as a testament to the effectiveness of these dual catalytic systems in mitigating strong racemic background processes.

In 2019, Li et al.[110] demonstrated an asymmetric aerobic decarboxylative Povarov reaction involving *N*-aryl α-amino acids (**101**) and methylenephthalimidines (**111**). This achievement was accomplished through a strategic combination of photo-induced radical oxidation and CPA catalysis (Scheme 28A). As a result, enantioenriched isoindolin-1-ones with a 3,3-spiro-tetrahydroquinoline-based stereocenter (**112**) were obtained, exhibiting an impressive up to 98% ee and all >20:1 dr. The reaction commences by generating a crucial *N*-aryl imine intermediate (**Int-17a**) through photochemical aerobic decarboxylation. Subsequently, the enantioselective Povarov process is used with methylenephthalimidine (**111**) to facilitate the formation of a spiro-six-membered ring, leading to the desired product (**112**) with stereocontrol. This study represents the first example of asymmetric catalysis synthesis of 3,3-spiro-six-membered ring for isoindolin-1-ones. Furthermore, they successfully developed a CPA-catalyzed photochemical asymmetric synthesis method for generating optically active 2,2-disubstituted indolin-3-ones (**114**) through a sequence involving aerobic oxidation and semipinacol rearrangement (Scheme 28B).[111]

Hydrogen bonding catalysis

Squaramides and thioureas have gained significant popularity as versatile catalysts for hydrogen bonding in asymmetric synthesis.[112,113] Recently, Wu and colleagues pioneered the development of photochemical three-component asymmetric radical sulfonation reactions using squaramide catalysis.[114–116] For instance, the atroposelective construction of axially chiral sulfone-containing styrenes (**117**) was successfully accomplished by using a chiral squaramide catalyst derived from cinchona alkaloid (**C36**) in combination with an organophotoredox co-catalyst (Mes-Acr$^+$). (Scheme 29A).[115] The prototropic rearrangement of 1-(phenylethynyl)naphthalen-2-ol (**115**) results in the formation of a vinylidene *o*-quinone methide (VQM) intermediate (**Int-27a**) that is activated by **C36**. The subsequent enantioselective addition of the *in situ* generated sulfonyl radical to **Int-27a** enables the synthesis of chiral sulfone-containing styrene (**117**)



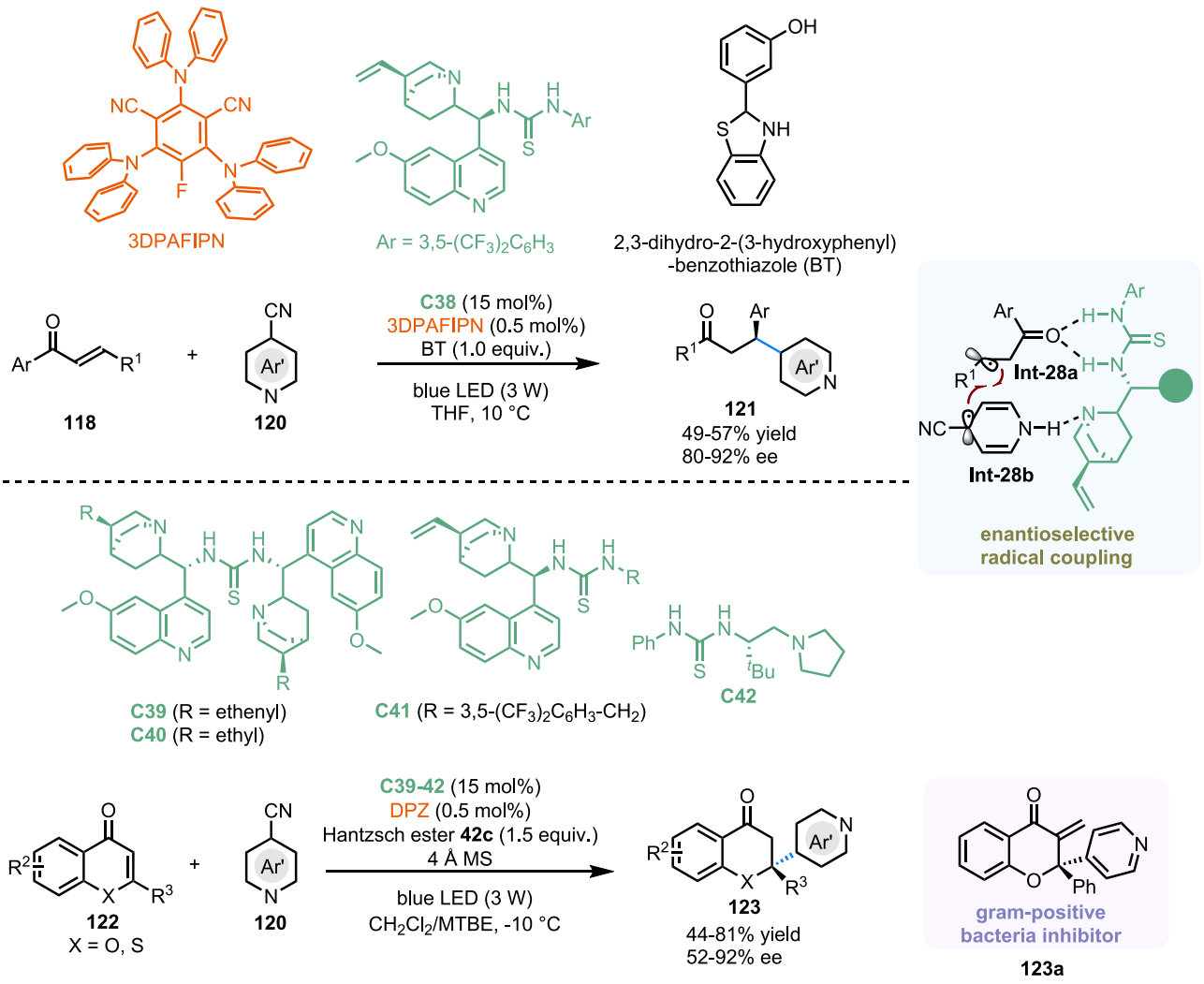
Scheme 29. Photochemical enantioselective construction of axially chiral sulfone-containing styrenes and chiral β-sulfonyl carbonyl compounds via squaramide catalysis

(A) Synthesis of axially chiral sulfone-containing styrenes.

(B) Synthesis of chiral β-sulfonyl carbonyl compounds.

with exceptional enantioselectivity (93%–99% ee). This method stands as a pioneering example of synthesizing axially chiral sulfone-containing styrene through photochemical techniques. Furthermore, Wu's group accomplished visible light-induced organocatalytic asymmetric radical sulfonations of α,β-unsaturated carbonyl compounds (**118**) using various radical precursors, including alkyl substituted Hantzsch esters (**23**) and alkyl trifluoroborates (**116**), using similar strategies. (Scheme 29B).[114,116]

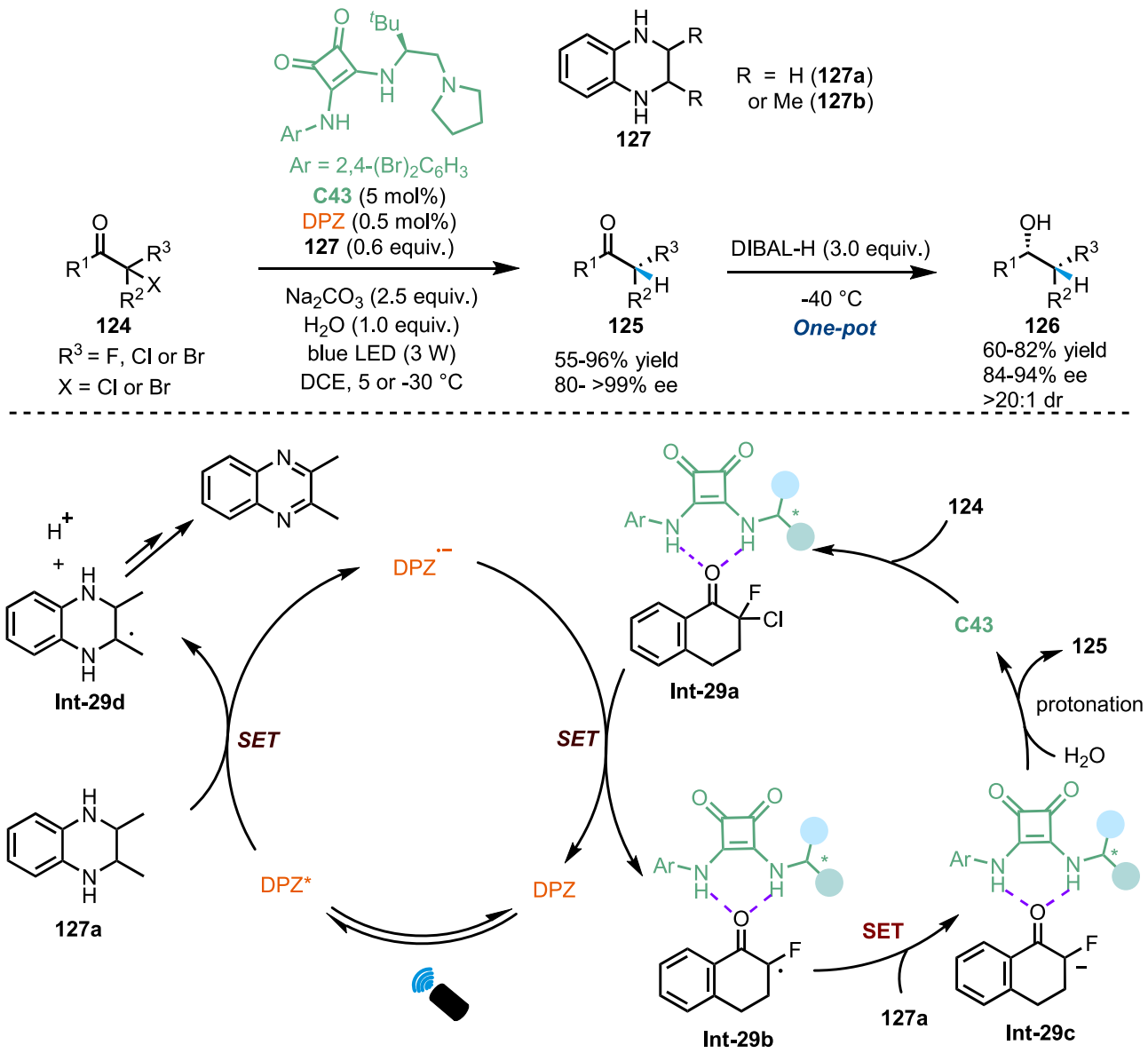
The asymmetric reductive azaarylation continues to pose challenges in organic synthesis. In 2022, Li et al.[104] introduced a photocatalytic strategy that combines the synergistic effects of organophotoredox catalysis and chiral thiourea catalysis. This innovative approach effectively facilitates the reductive azaarylation of α,β-unsaturated carbonyl compounds (**118**) and flavones (**122**) with cyanopyridine derivatives (**120**) (Scheme 30). In the presence of a cinchona alkaloid-derived thiourea (**C38**, or **C39**-**C42**), a diverse range of valuable enantiopure azaarene derivatives (**121**, **123**) were successfully synthesized with high yields and excellent enantioselectivity. Experimental studies and DFT calculations provided insights into the mechanism of these photochemical reactions, suggesting that they proceed through an enantioselective radical coupling between a,β-carbonyl radical and an allyl radical species. These radicals are generated through the photoredox-induced activation of substrates **118** and **120**, respectively. This study demonstrates the potential of chiral



Scheme 30. Photocatalytic enantioselective reductive azaarylation by dual photocatalysis and chiral thiourea catalysis

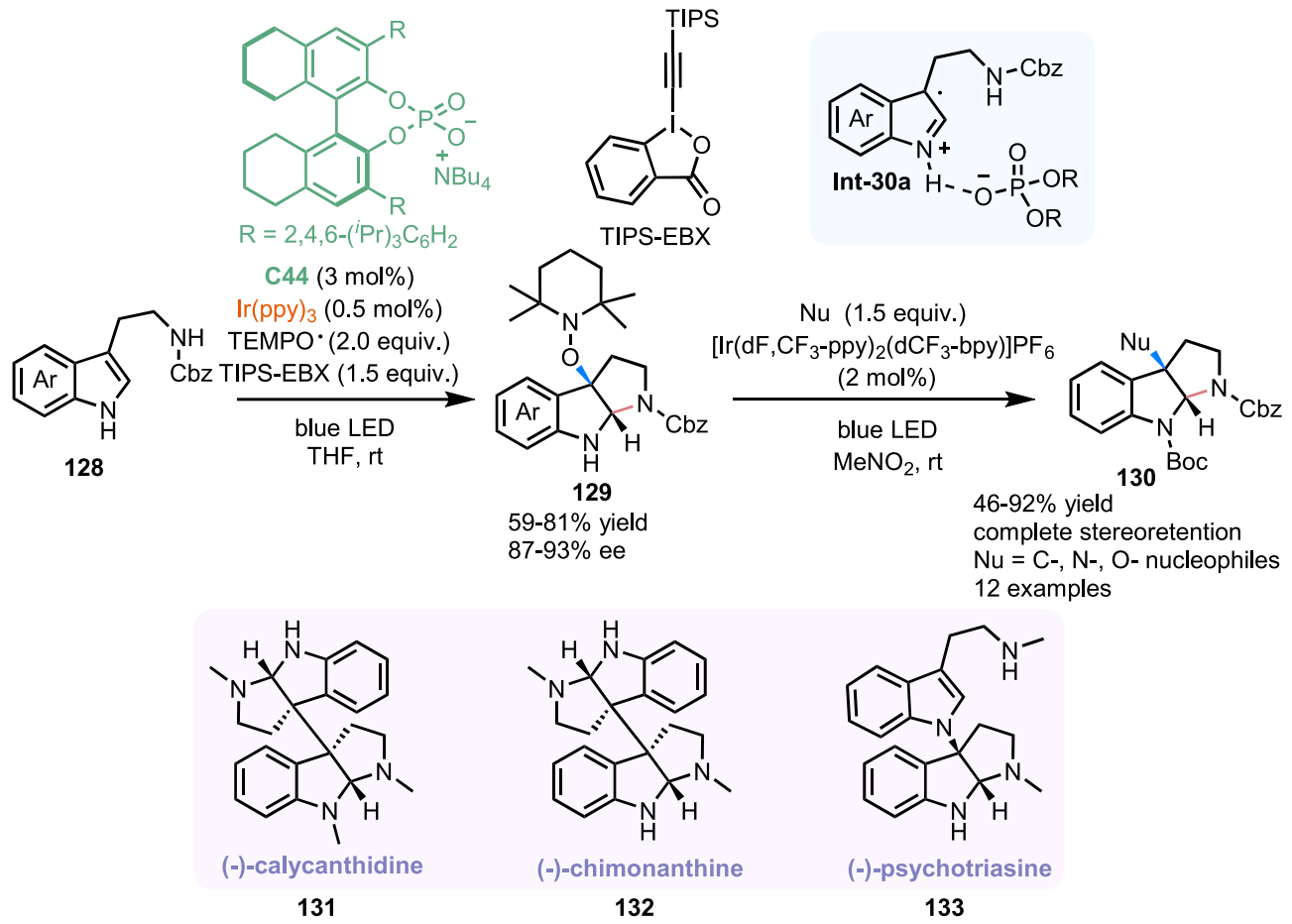
H-bonding catalysts in providing effective enantiocontrol for the highly reactive radical coupling process. The findings not only advance our understanding of reductive azaarylations but also inspire further progress in other important types of radical coupling-based reactions within the field of asymmetric synthesis.

The prevention of racemization in the enantioselective dehalogenative protonation of ketones poses a significant challenge due to the inherent instability of stereocenters in secondary α-haloketones. Therefore, the development of mild and neutral protonation strategies is essential for facilitating these reaction processes. In 2019, Hou et al.[117] reported an innovative dehalogenation–enantioselective protonation reaction that was facilitated by the synergistic combination of photoredox and chiral squaramide catalysis (Scheme 31). By using a dual organocatalytic system comprising of a L-*tert*-leucine-based squaramide (**C43**) and an organophotoredox catalyst (DPZ), along with a secondary amine (**127**) as the reductant, an extensive array of cyclic and acyclic ketones (**125**) featuring intricate chiral secondary C–F, C–Cl, and C–Br bonds at the α-position were effectively synthesized, showcasing remarkable enantioselectivity of 80% to >99% ee. In regard to the reaction



Scheme 31. Enantioselective dehalogenative protonation via dual photoredox and squaramide catalysis

mechanism, the excited photocatalyst (DPZ*) undergoes single-electron reduction facilitated by the amine additive (**127a**), leading to the generation of a DPZ radical ion ($DPZ^{\bullet-}$). This species then proceeds through a SET process with the chiral squaramide-bonded ketone substrate (**Int-29a**), resulting in the formation of a carbon radical intermediate (**Int-29b**) and simultaneous regeneration of the photocatalyst. The hydrogen bonding interaction between the N–H bonds of the squaramide and the carbonyl moiety of the radical species plays a crucial role in stabilizing the radical intermediate (**Int-29b**) for subsequent transformations. A hydrogen-bonded carbon anion (**Int-29c**) is then formed through a second SET process with the amine (**127a**) acting as the terminal reductant. Following enantioselective protonation, the desired product (**125**) is formed. By using a one-pot reduction using diisobutylaluminium hydride (DIBAL-H), the ketone products were efficiently transformed into halogenated hydrins (**126**) with high enantiomeric excess (ee) values ranging from 84% to

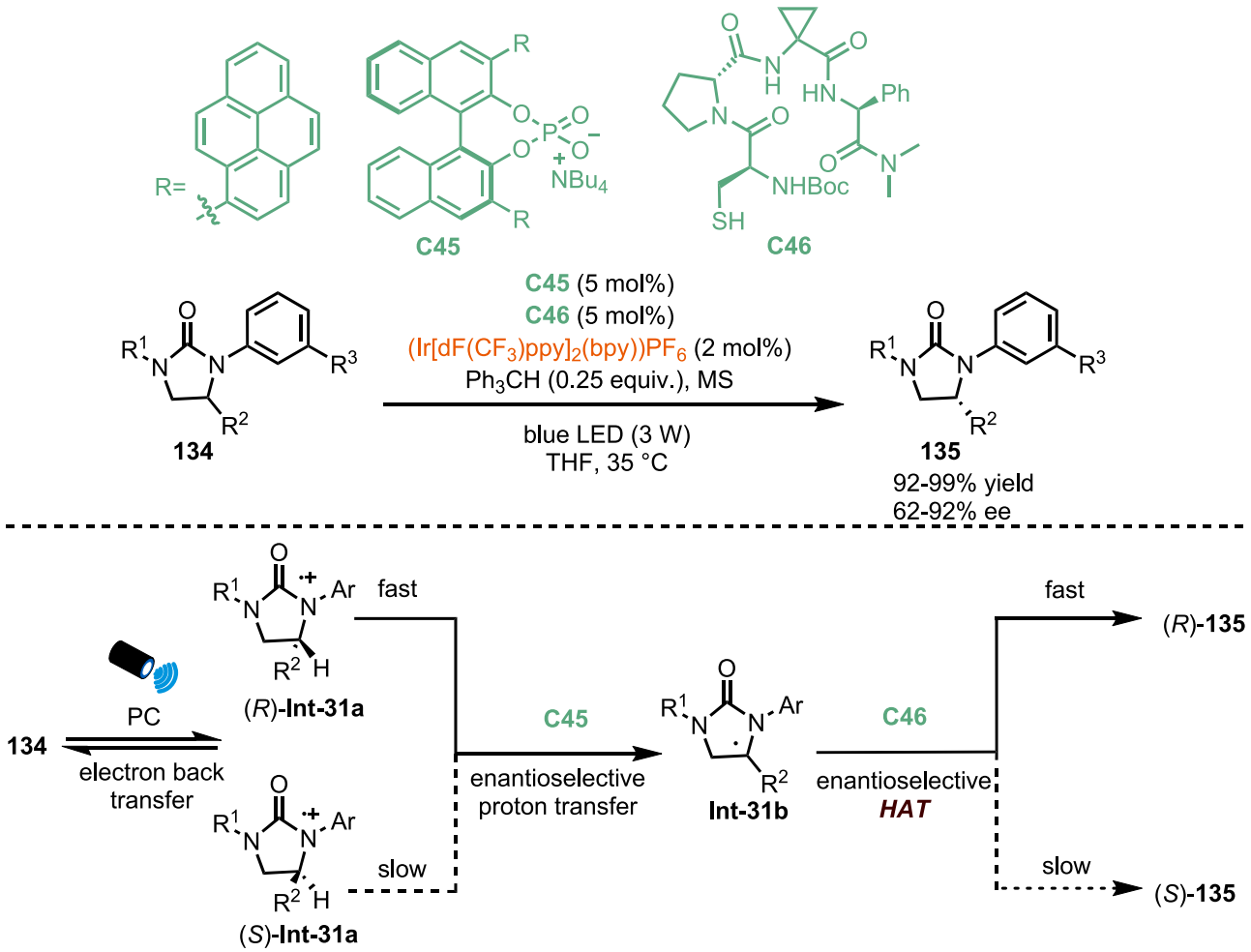


Scheme 32. Photochemical synthesis of enantio-enriched pyrroloindolines via ion-pairing catalysis

94% ee, along with exceptional diastereoselectivity (>20:1 dr) in every instance. Despite the inherent risk for racemization during the reaction process and the presence of competing racemic background reactions, the impressive outcomes highlight the extraordinary feasibility and compatibility of this method.

Ion-pairing catalysis

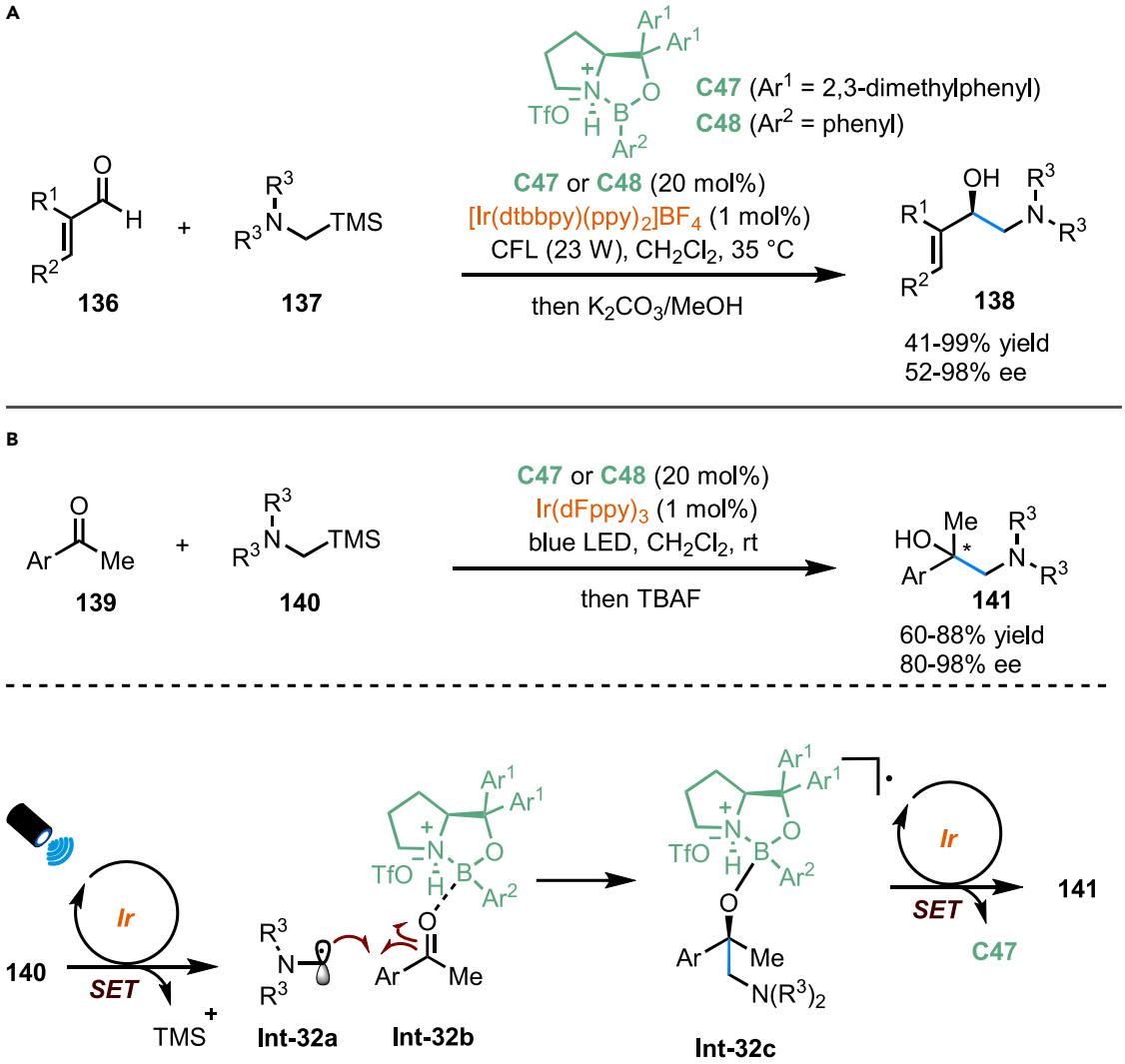
Ion-pairing catalysis has emerged as an increasingly vital design strategy for effectively controlling the enantioselectivities of radical transformations through non-covalent activation modes.[118,119] In 2018, Gentry et al.[120] reported an enantioselective synthesis of pyrroloindolines via the use of chiral phosphate anion-catalyzed sequential reactions involving catalytically generated radical cation intermediates (Scheme 32). In this PCET-involved process, the chiral phosphate catalyst (**C44**) plays bifunctional roles. It not only facilitates the formation of the crucial radical cation intermediate (**Int-30a**) due to its weak basicity but also controls enantioselectivity in the intramolecular radical cyclization step through the association of chiral phosphate anion and radical cation. The alkoxyamine-substituted pyrroloindoline products (**129**) were obtained with yields ranging from 59% to 81% and exhibited high enantioselectivity, with enantiomeric excess values ranging from 87% to 93%. These products displayed reactivity toward a diverse range of nucleophilic coupling partners, including *C*-, *N*-, and *O*-centered nucleophiles. Furthermore, the total synthesis of alkaloid natural products (**131**–**133**) was successfully accomplished starting from the corresponding pyrroloindolines (**129**).



Scheme 33. Light-driven deracemization reaction of cyclic *N*-aryl ureas enabled by a ternary catalytic system

Furthermore, building upon the concept of ion-pairing catalysis combined with photo-triggered PCET processes, Roos et al.[121] successfully developed an enantioselective intramolecular hydroamination of alkenes with sulfonamides, enabling the synthesis of chiral pyrrolidines. Additionally, Morse et al.[122] explored the application of chiral phosphate anions in an asymmetric cation radical Diels-Alder reaction. Their study demonstrated the formation of both intramolecular and intermolecular products with a moderate level of enantioselectivity, achieving ratios of up to 75:25 er.

In 2019, Shin et al.[123] made a significant breakthrough by reporting a visible light-driven deracemization reaction of cyclic *N*-aryl ureas. This achievement was made possible through the synergistic combination of multiple catalysts, including an iridium photocatalyst ($(Ir[dF(CF_3)ppy]_2(bpy))PF_6$), a chiral phosphate base catalyst (**C45**), and a peptide thiol catalyst (**C46**) (Scheme 33). The reaction mechanism entails a series of steps including photoredox-triggered electron transfer, enantioselective proton transfer, and HAT. To be more specific, the photo-induced SET process generates radical cation intermediates, denoted as (*R*)-**Int-31a** and (*S*)-**Int-31a**. Notably, (*R*)-**Int-31a** exhibits a significantly faster rate of proton transfer compared with (*S*)-**Int-31a**, facilitated by the interaction with the chiral phosphate catalyst (**C45**). This eventually leads to the formation of an achiral radical species (**Int-31b**).



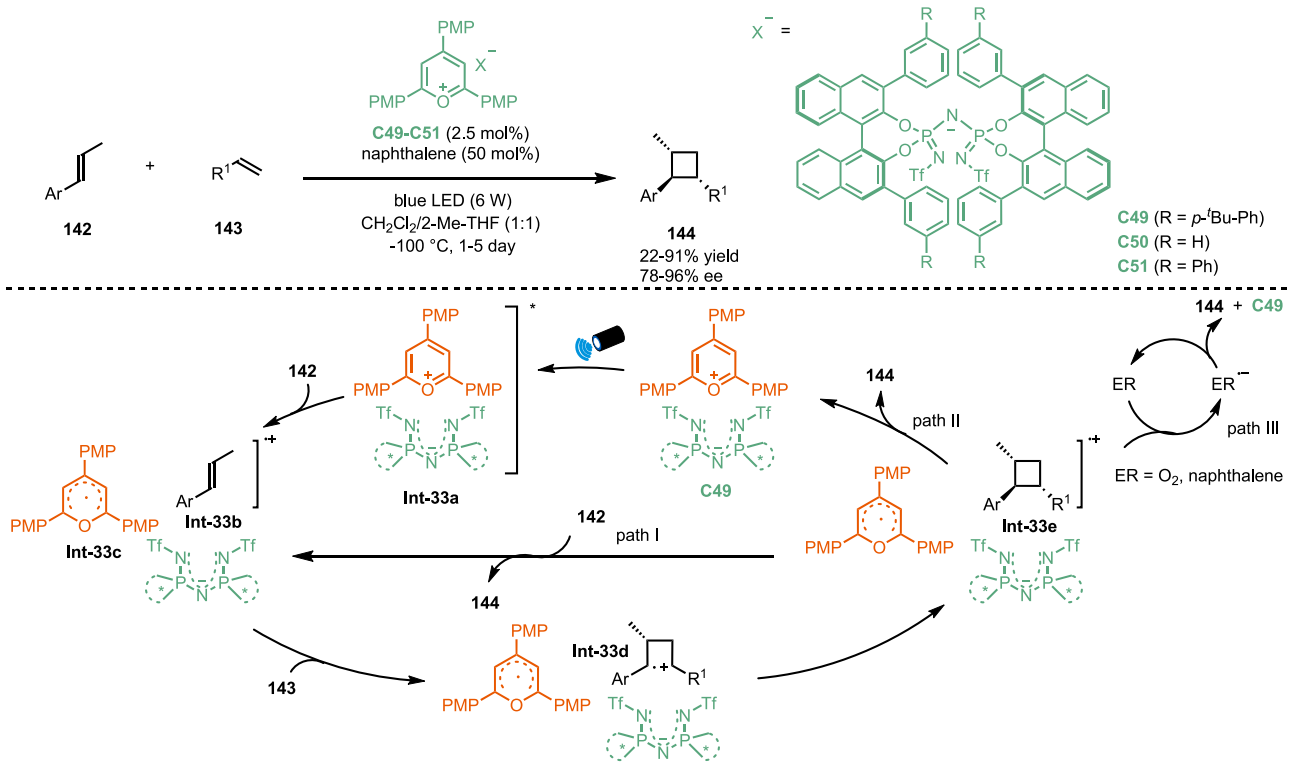
Scheme 34. Photochemical enantioselective 1,2-addition of α-aminoalkyl radicals to α,β-unsaturated aldehydes and methyl aryl ketones

(A) α,β-Unsaturated aldehydes.

(B) Methyl aryl ketones.

Finally, the intermediate **Int-31b** undergoes an enantioselective HAT process governed by the chiral thiol catalyst (**C46**), resulting in the formation of (*R*)-*N*-aryl urea ((*R*)-**135**). This strategic cooperation between two distinct chiral catalysts enables efficient stereocontrol during the deracemization process, effectively mitigating the occurrence of strong racemic background reactions.

Soon after, Ryu and colleagues reported photochemical enantioselective 1,2-addition of α-aminoalkyl radicals to α,β-unsaturated aldehydes (**136**) (Scheme 34A)[124] and to methyl aryl ketones (**139**) (Scheme 34B).[125] Both reactions were successfully accomplished using the identical chiral oxazaborolidinium ion catalysts (**C47** or **C48**) in conjunction with an iridium photocatalyst ($[Ir(dtbbpy)(ppy)_2]BF_4$ or $Ir(dFppy)_3$). Various β-amino alcohol products (**138** or **141**) were obtained with impressive yields and remarkable levels of enantioselectivity (up to 98% ee). In the crucial stereocontrolled step, the chiral oxazaborolidinium ion plays a pivotal role in activating a carbonyl group within the substrate. This activation process generates



Scheme 35. Chiral counteranion-directed photoredox catalysis

a complex intermediate (**Int-32b**) that effectively intercepts the photochemically generated α-aminoalkyl radical (**Int-32a**). As a result, a chiral radical intermediate (**Int-32c**) is formed and subsequently undergoes a final SET process, ultimately leading to the liberation of the desired chiral product (**141**) while simultaneously regenerating the chiral catalyst (**C47**).

These studies exemplify unprecedented instances of visible light-induced, chiral oxazaborolidinium ion-catalyzed enantioselective radical 1,2-addition reactions involving α-aminoalkyl radicals and carbonyl compounds. They not only showcase the power of using visible light as a driving force for these transformations but also highlight the remarkable stereocontrol achieved through the chiral catalyst. Moreover, these findings have paved the way for exciting new prospects in the realm of radical transformations, offering fresh avenues to explore and manipulate stereoselectivity in chemical synthesis.

The incorporation of radical ions and enantiopure counterions in the photoredox reactions represents a potentially effective strategy. In 2023, Das et al.[126] introduced a chiral counteranion-directed photoredox catalysis for enantioselective [2+2]-cross cycloadditions of styrenes (Scheme 35). In the company of an ion-pairing photocatalyst (**C49-C51**), derived from pyrylium tetrafluoroborate and a chiral imidodiphosphoric acid, substances **142** and **143** efficiently yielded enantiopure products **144** under light irradiation. Drawing upon UV-vis and fluorescence spectra, as well as fluorescence quenching experiments, the authors posited plausible mechanisms: the photocatalyst (**C49**) initially transitions to its excited state (**Int-33a**) in the presence of blue light. Subsequently, **Int-33a** captures **142** to form a radical cation (**Int-33b**) and a neutral radical species (**Int-33c**). Following this, **Int-33b** undergoes

a radical addition with **143**, yielding a radical cation (**Int-33e**). Upon SET reduction, a chiral cyclized product (**144**) is produced. Three possible paths exist in the SET reduction process: (1) Substrate **142** serves as an electron donor, providing an electron for the radical cation (**Int-33e**) to generate a radical cation (**Int-33b**) and the product (**144**). (2) Electron transfer from **Int-33c** to the radical cation (**Int-33e**) leads to the generation of the product (**144**) and the regeneration of the photocatalyst (**C49**). (3) The electron relay catalyst, consisting of naphthalene and oxygen, oxidizes the catalyst radical **Int-33c**. The resulting reduction product then reduces the radical cation (**Int-33e**) to afford the product (**144**) and regenerates the electron relay catalyst. Control experiments and EPR experiments verify that all three pathways are feasible and confirm the crucial role of electron relay catalysts. The ion-pairing catalyst derived from chiral imidodiphosphoric acid demonstrates immense potential in asymmetric counteranion-directed photoredox catalysis (ACPC) and offers a novel approach to achieve complex photoredox catalysis processes.

Lewis base catalysis

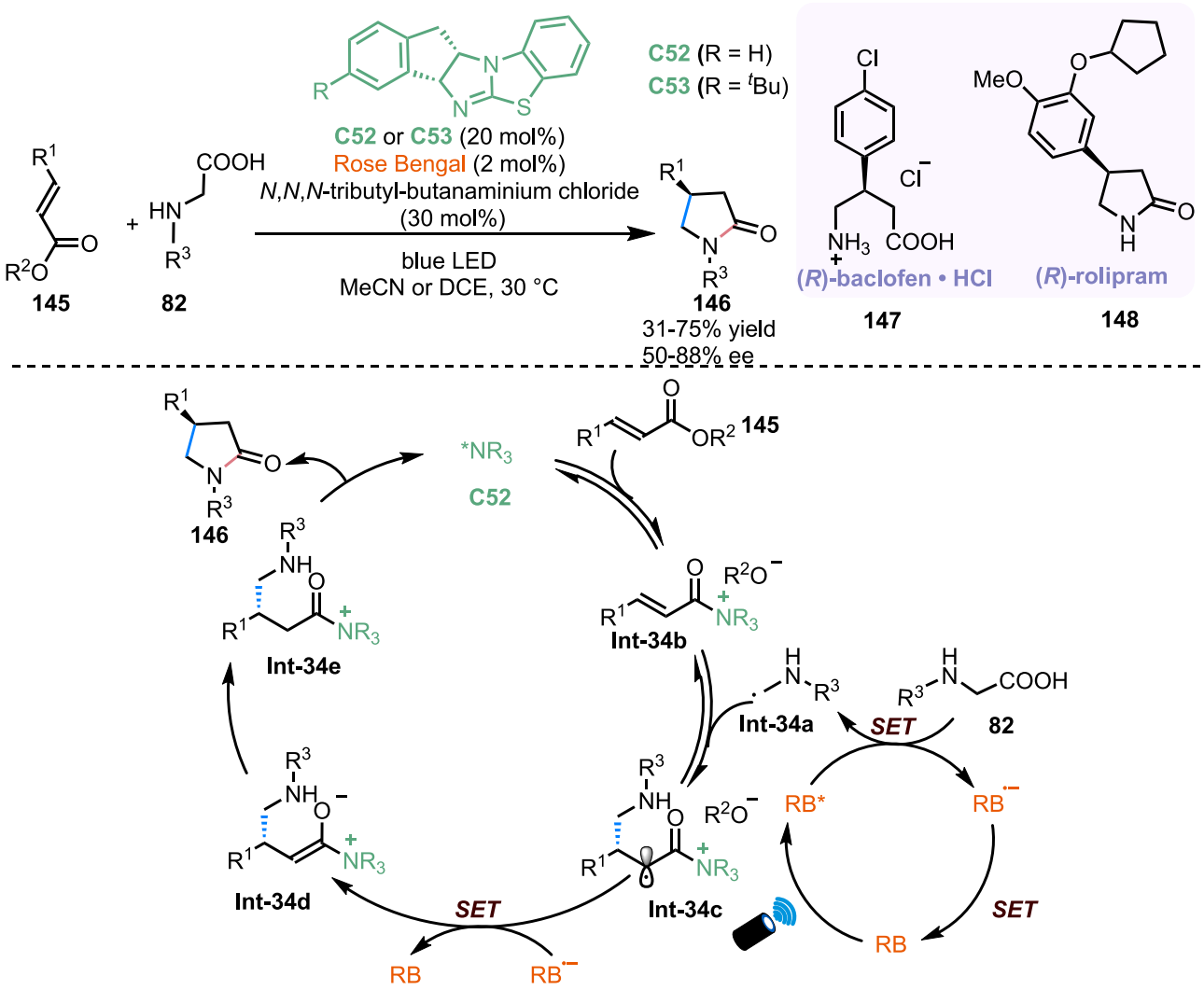
The integration of photoredox catalysis with Lewis acid-based catalytic methods has greatly broadened the range of radicals that can be used in asymmetric radical conjugate addition reactions. Nevertheless, the use of Lewis base catalysis for these transformations remains largely unexplored and limited in scope. In 2022, Hartley et al.[127] developed an enantioselective radical conjugated addition through the implementation of an innovative strategy involving dual photoredox and Lewis base catalysis (Scheme 36). A well-tailored chiral isothiourea (**C52** or **C53**) was discovered as the most effective Lewis base catalyst, in combination with rose bengal (RB) serving as the optimal photocatalyst. This synergistic system demonstrated remarkable reaction efficiency and enantioselectivity in the photochemical transformation of α,β-unsaturated anhydrides and esters (**145**) and *N*-arylglycines (**82**).

In the context of the reaction mechanism, the first step involves the photoredox activation of the *N*-arylglycine (**82**), resulting in the formation of the *N*-α radical intermediate (**Int-34a**). This intermediate subsequently undergoes capture by the chiral isothiourea-substrate adduct (**Int-34b**), leading to the generation of a chiral radical intermediate (**Int-34c**). After undergoing SET reduction, protonation, and intramolecular cyclization, the formation of the enantioenriched pyrrolidinone product (**146**) takes place along with catalyst regeneration. Expanding on this protocol, pharmaceutically significant compounds like baclofen (**147**) and (*R*)-rolipram (**148**) were successfully synthesized.

This study represents a pioneering example of radical chemistry within the realm of enantioselective isothiourea catalysis. Around the same time, del Río-Rodríguez et al.[128] reported an analogous isothiourea-catalyzed asymmetric [3+2] photocycloaddition of mixed α,β-unsaturated anhydrides with *N*-phenylglycines, using both batch and flow conditions.

Thiyl catalysis

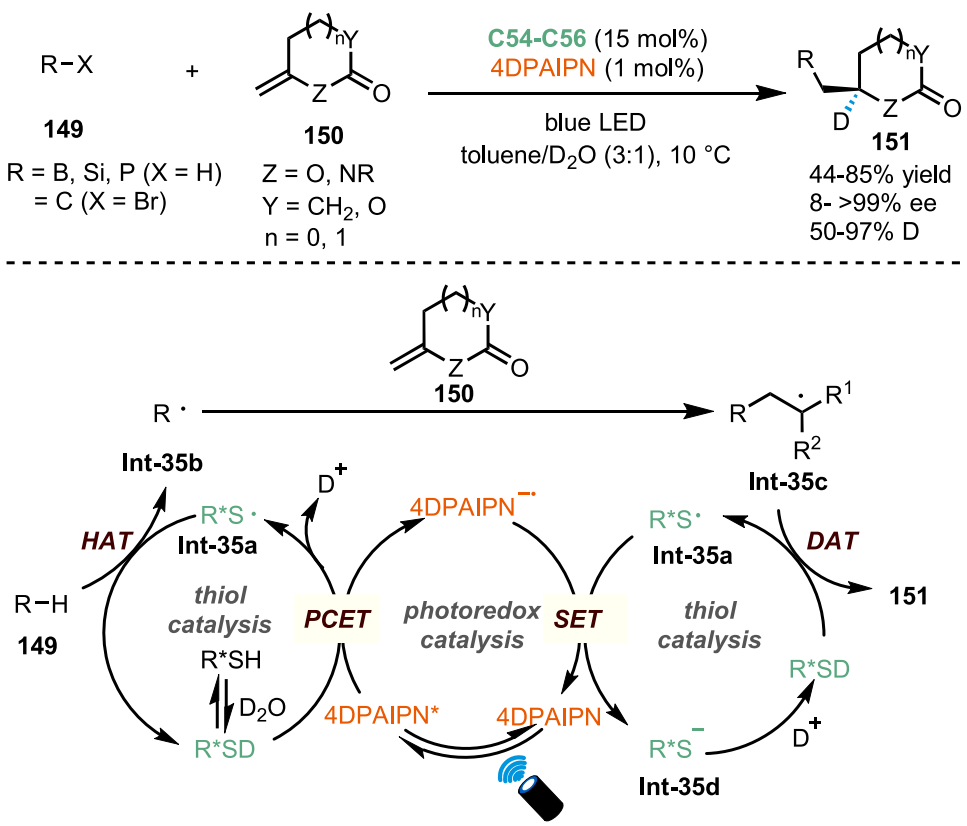
Cysteine-mediated biochemical processes are prevalent in biological systems, where a sulfur-based radical is generated within the active site and plays an active role in chemical reactions. Drawing inspiration from nature, scientists have developed various synthetic transformations using thiyl catalysis, both in racemic and asymmetric manners. In 2022, Shi et al.[129] presented a strategy that incorporates both photocatalysis and thiol catalysis to achieve asymmetric radical deuteration (Scheme 37). This approach used easily accessible peptide- or sugar-derived thiols as chiral catalysts (**C54-C56**), 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile

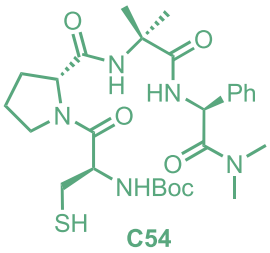


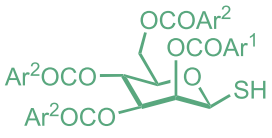
Scheme 36. Isothiourea-catalyzed enantioselective radical conjugate addition for the synthesis of enantioenriched pyrrolidinones

(4DPAIPN) as the organophotocatalyst, and inexpensive deuterium oxide as the source of deuterium atoms. Enantioselective deuteration was successfully achieved through the deuterative boration, silylation, phosphinoylation, and difluoroalkylation of exocyclic olefins (**150**) in non-benzylic positions, furnishing chiral deuterated products (**151**) with impressive enantiomeric excess (up to 99% ee) and significant incorporation of deuterium atoms (up to 97% D-incorporation).

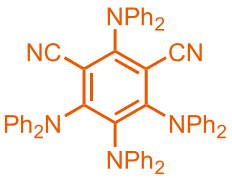
During the reaction process, 4DPAIPN absorbs photons and undergoes a transformation into its excited state (4DPAIPN*) upon exposure to light. Following this, an electrophilic thiyl radical (**Int-35a**) is formed from the thiol catalyst via a PCET process. This radical then engages in a polarity-matched HAT with the R–H substrate (where R = B, Si, or P) (**149**). The resulting radical species (**Int-35b**) undergoes a radical addition process with the olefin (**150**), resulting in the formation of an achiral radical (**Int-35c**). Subsequently, a polarity-matched and enantioselective deuterium atom transfer (DAT) reaction with the *in situ* generated deuterated chiral thiol (R*SD) gives rise to the final product (**151**) and the thiyl radical (**Int-35a**). Finally, **Int-35a** can be converted back into the deuterated chiral thiol through SET reduction with $4DPAIPN^{\bullet-}$ and subsequent







C55 (Ar^1= 4-^{t}BuC$_6$H$_4$)
C56 (Ar^2= 4-FC$_6$H$_4$)



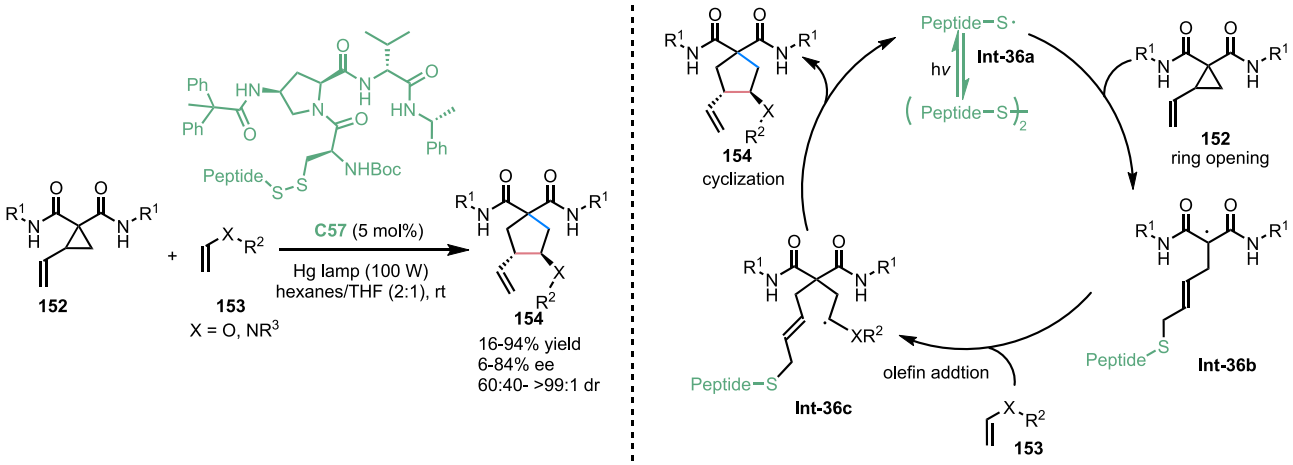
Scheme 37. Enantioselective radical deuteration via dual photoredox and thiyl catalysis

protonation, thus completing both the thiol catalytic and photocatalytic cycles. Chiral deuterated drugs have extensive applications in the pharmaceutical industry, yet reports on catalytic asymmetric deuteration are scarce. This study offers a convenient and effective approach to achieve these transformations.

Furthermore, Ryss et al.[130] reported an enantioselective cycloaddition of vinylcyclopropanes with electron-rich olefins using thiyl radical catalysis under UV light (Scheme 38). By using a peptide-based disulfide (**C57**) as the pre-catalyst, vinylcyclopropanes (**152**) and alkenes (**153**) were irradiated with a 100 W Hg lamp in a 2:1 mixed solvent of hexanes and THF, resulting in the formation of cyclopentane derivatives with moderate to good stereoselectivity (6%–84% ee and 60:40 to >99:1 dr). In terms of mechanism, upon UV light irradiation, the peptide-based disulfide (**C57**) undergoes homolytic cleavage, yielding a chiral thiyl radical (**Int-36a**). **Int-36a** then adds to the vinylcyclopropane (**152**), yielding an α-carbonyl radical intermediate (**Int-36b**) through a radical-mediated ring-opening process. Subsequently, **Int-36b** reacts with the electron-rich alkene (**153**), generating a chiral radical (**Int-36c**), which goes through intramolecular asymmetric cyclization to produce the desired product (**154**). The stereo-determining step relies on crucial hydrogen bonding interactions between the peptide moiety of the catalyst and the substrate backbone for asymmetric induction.

ELECTROCHEMICAL APPROACHES FOR RADICAL-MEDIATED ORGANOCATALYTIC ASYMMETRIC TRANSFORMATIONS

Organic electrochemical synthesis has attracted significant attention due to its ability to harness inexpensive, safe, environmentally friendly electrons as traceless redox

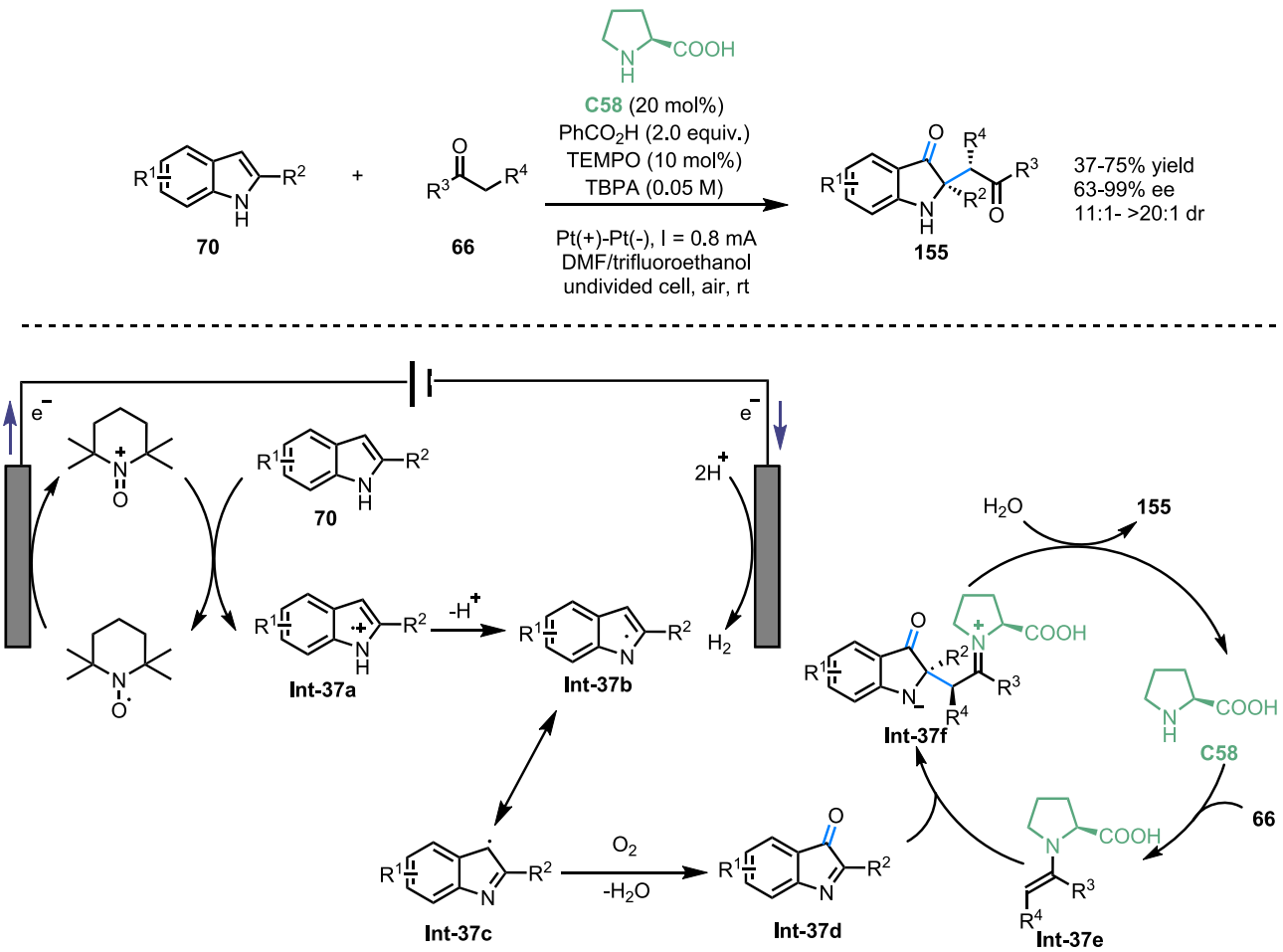


Scheme 38. UV light-promoted enantioselective cycloaddition of vinylcyclopropanes with electron-rich olefins by thiyl radical catalysis

agents. This approach offers a distinct advantage by eliminating the need for hazardous chemical oxidants or reductants that are typically used in traditional redox transformations. By integrating the principles of asymmetric synthesis with electrochemistry, a new frontier known as asymmetric electrochemical synthesis has emerged. This exciting and rapidly growing field aims to combine the advantages of both asymmetric synthesis and electrochemistry to enable the selective construction of complex molecular architectures.[131–136]

In 2020, Lu et al.[137] used prolines as asymmetric organocatalysts, successfully facilitating the enantioselective electrosynthesis of C2-quaternary indolin-3-ones (Scheme 39). A wide range of indole derivatives (**70**) and ketones (**66**) proved to be compatible with this reaction, affording the desired products (**155**) with exceptional diastereoselectivity (most >20:1 dr) and impressive enantioselectivity (up to 99% ee). Regarding the reaction mechanism, TEMPO is first oxidized to its corresponding cation ($TEMPO^+$) on a Pt anode. Next, a SET process between the 2-arylindole (**70**) and $TEMPO^+$ generates an *N*-centered radical cation (**Int-37a**). Upon deprotonation, a radical intermediate **Int-37b** is formed, with resonance to **Int-37c**. This is followed by air oxidation, which leads to a key indolinone intermediate (**Int-37d**). Conversely, the condensation of L-proline catalyst (**C58**) with ketone substrate (**66**) produces a chiral enamine intermediate (**Int-37e**). On the other hand, the condensation of L-proline catalyst (**C58**) with ketone substrate (**66**) gives rise to a chiral enamine intermediate (**Int-37e**). Ultimately, the nucleophilic addition of **Int-37e** to the electrophilic **Int-37d** leads to the formation of the chiral indolin-3-one product (**155**), accompanied by the regeneration of **C58** after hydrolysis. This protocol eliminates the need for oxidizing agents and metals, and boasts mild reaction conditions, a broad substrate scope, and excellent functional group tolerance.

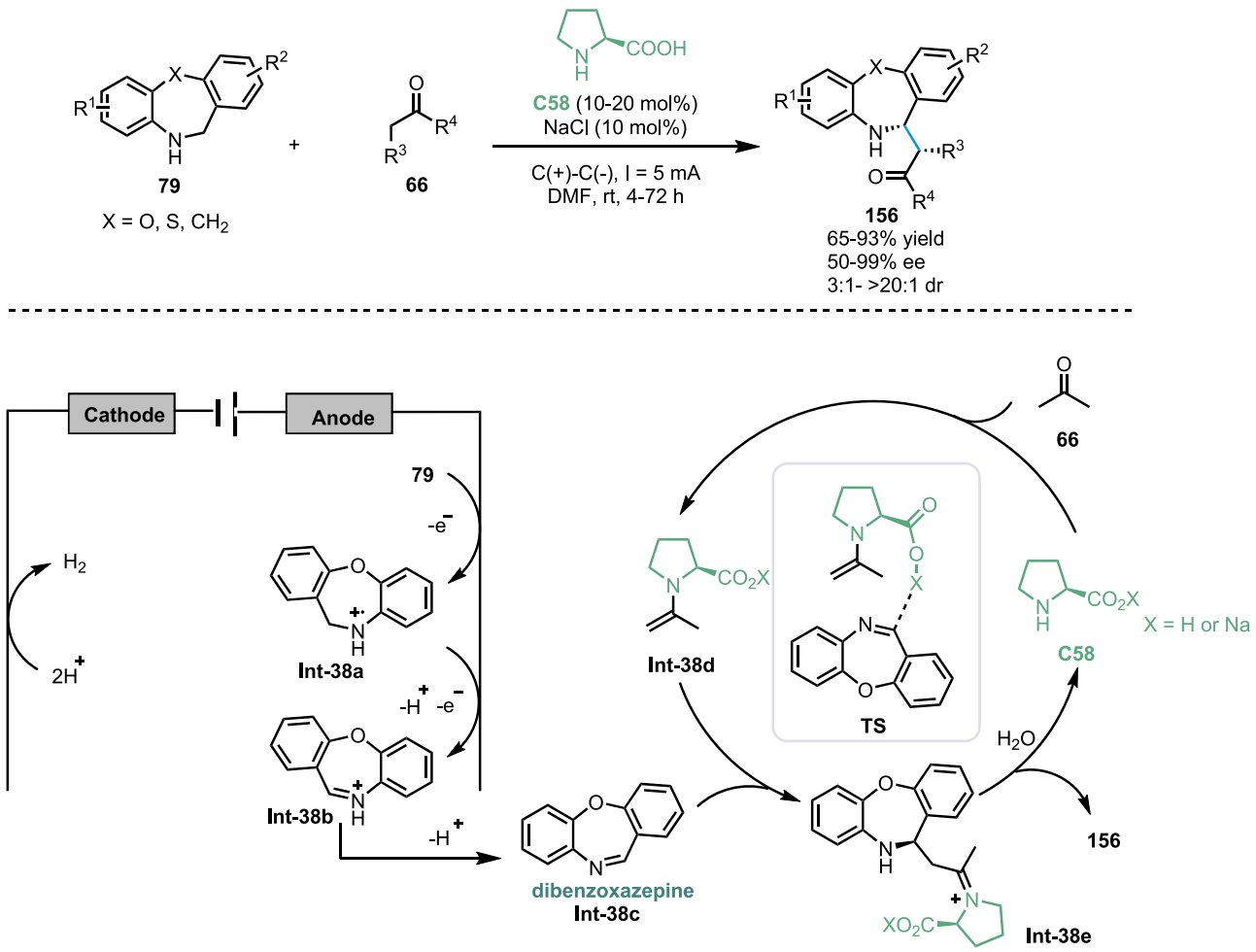
In 2022, Hussain et al.[138] described an enantioselective oxidative Mannich reaction involving ketones and dihydrodibenzo-oxazepines. This reaction was achieved through the synergistic combination of electrocatalysis and organocatalysis (Scheme 40). By using dihydrodibenzo-oxazepines (**79**) and acyclic/cyclic ketones (**66**) as reactants, commercially available **C58** as an organocatalyst, and NaCl as an additive, the corresponding products (**156**) were generated in high yield (up to 93% yield) and excellent enantioselectivity (up to 99% ee). In the proposed mechanism, **79** undergoes sequential single-electron oxidation on a C anode to generate



Scheme 39. Enantioselective electrosynthesis of C2-quaternary indolin-3-ones

the intermediate dibenzoxazepine (**Int-38c**). The iminium (**Int-38e**) can be afforded by the nucleophilic addition of the chiral enamine intermediate (**Int-38d**) to the electrophilic **Int-38c**. Following hydrolysis, the corresponding product (**156**) is formed, and **C58** is liberated. This reaction represents a safe and efficient approach to synthesize a variety of enantiopure dihydrodibenzo-oxazepines. Moreover, this enantioselective sp^3-sp^3 coupling reaction has also been successfully achieved through a photochemical pathway.

Compared with chemical redox or photoredox methods, electroredox techniques have seen far less development in NHC-catalyzed asymmetric synthesis. In 2022, Zhou et al.[139] introduced an innovative iodide-promoted system incorporating with electroredox NHC organocatalysis (Scheme 41). This method can be adapted to various activation modes, such as α-, β-, γ-, δ- or carbonyl carbon functionalization, and distinct reaction types like cyclization, benzannulation, dynamic kinetic resolution, etc. Mechanistically, a Breslow intermediate (**Int-39a**) is initially formed from the carbene precursor (**C6**) and the carbonyl substrate in the presence of a base. In electrochemical conditions, the intermediate **Int-39a** and an iodine ion undergo anodic oxidation, leading to a radical cation intermediate (**Int-39b**) and an iodine radical. Upon radical combination, an iodide intermediate (**Int-39c**) is generated, which undergoes elimination to furnish an acyl azolium intermediate (**Int-39d**) and an iodide ion. Eventually, the chiral product

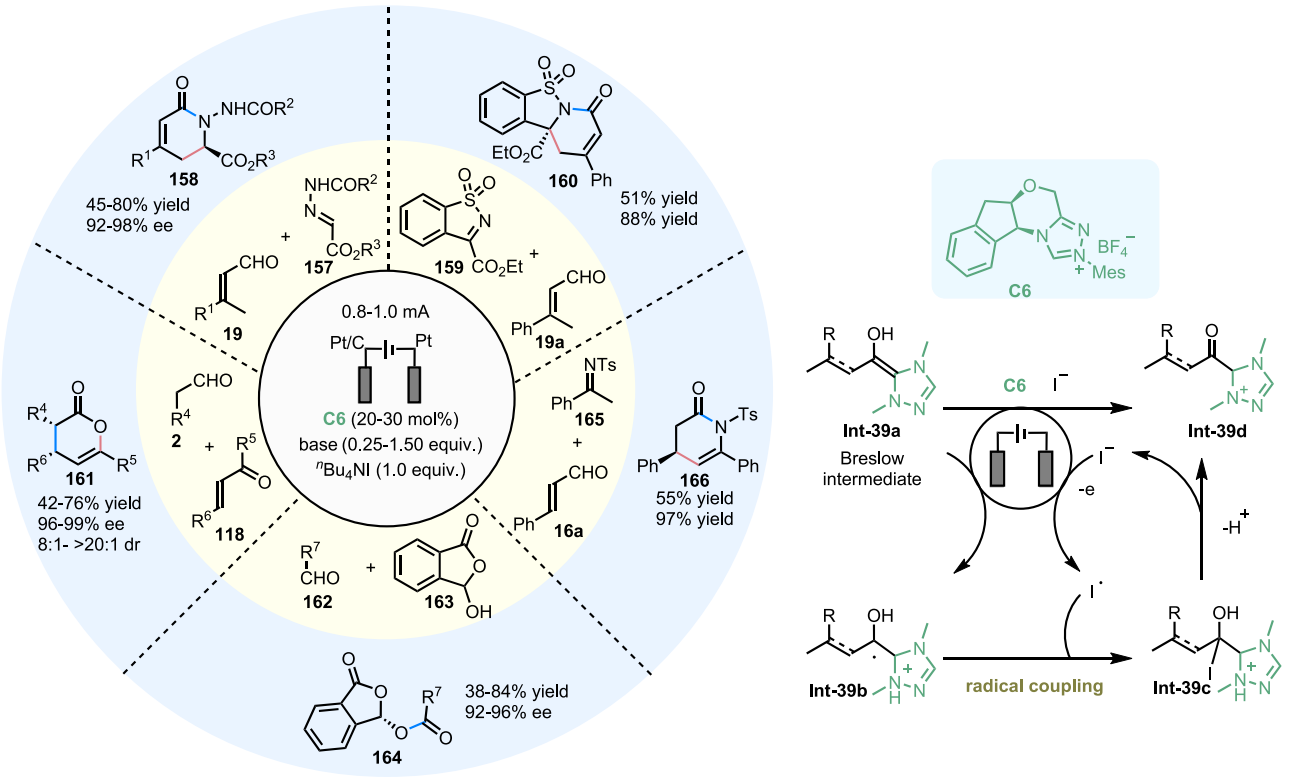


Scheme 40. Enantioselective synthesis of dihydrodibenzo-oxazepines via synergistic combination of electrocatalysis with asymmetric aminocatalysis

is formed through hydrolysis, concurrent with the regeneration of the NHC catalyst. This study not only enhances the feasibility for large-scale applications but also paves the way for new opportunities in NHC-catalyzed radical reactions.

SUMMARY AND OUTLOOK

Asymmetric radical transformations have arisen as powerful techniques for generating chiral structures with diverse structural features and revealing innovative reaction mechanisms. Over the past 5 years, remarkable advances have been made in the realm of organocatalytic radical reactions. Although achieving high levels of stereoselectivity in processes involving radical intermediates is still a formidable challenge, a dozen organocatalysts, such as chiral amines, NHCs, CPAs, ion-pairing catalysts, chiral Lewis bases, and chiral thiols, have demonstrated notable potential in facilitating these reactions and managing their stereochemistry. Organocatalytic strategies that involve distinct substrate activation modes, such as SOMO activation, hydrogen bonding, and ion-pairing interactions, are incorporated with the formation of radicals through thermal, photochemical, and electrochemical pathways. These approaches have resulted in the development of numerous efficient techniques for stereoselective C-C and C–X bond formation, which are relevant to the synthesis of pharmaceutically important molecules.



Scheme 41. Iodide-promoted electroredox NHC organocatalysis

Despite these advances, several challenges and unexplored aspects persist. For instance, in the domain of established photochemical methods, the majority of organocatalytic strategies focus on aminocatalysis, CPA catalysis, and ion-pairing catalysis, with fewer new organocatalytic approaches being developed. Additionally, only a limited number of electrochemical strategies have been reported, potentially due to the difficulties in identifying effective systems that are compatible with organocatalysis and capable of providing useful reactivity and selectivity. We envision that as novel catalysts and state-of-the-art synthetic techniques continue to evolve at a rapid pace, organocatalytic radical transformations will undergo substantial breakthroughs and progress. The extended applications of these groundbreaking methods might potentially encompass various aspects, such as the generation of axial, planar, and helical chirality, which are crucial for the development of chiral molecules with unique properties. The synthesis of heteroatom-stereogenic compounds will become increasingly more accessible, thereby amplifying the scope of organocatalysis.

Furthermore, the integration of multi-component and cascade reactions will facilitate the creation of even more intricate chiral molecules, thereby broadening the horizons of organocatalytic research. This advancement will not only enhance our comprehension of organocatalysis but also clear the path for novel applications across diverse disciplines, such as pharmaceuticals, materials science, and green chemistry.

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AUTHOR CONTRIBUTIONS

Conceptualization, L.G.; investigation, F.Y.; writing – original draft, F.Y.; writing – review & editing, L.G., Y.-M.L., F.Y., and T.H; supervision, L.G.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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