有机化学 DOI: 10.6023/cjoc202201047 综述与进展
Chinese Journal of Organic Chemistry REVIEW

可见光不对称催化合成手性氮杂芳烃衍生物

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摘要 氮杂芳烃衍生物在众多领域尤其是医药和材料工业中的重要性吸引了化学家对发展其高效合成方法的持续关注. 迄今, 以市售氮杂芳烃或其简单衍生物作为原料, 且利用氮杂芳烃的电子性质引发化学转化的官能团化策略已被认为是一种强有力的工具. 其中, 由于具有条件温和、官能团耐受性良好且反应形式多样等优点, 可见光驱动光催化的方法被广泛探索. 值得注意的是, 许多针对含亚胺氮杂芳烃衍生物合成的反应类型的不对称版本被成功开发, 所获得的对映体纯产物具有令人满意的结果. 依据所构建手性中心相对氮杂芳烃的位置分四个部分总结, 并讨论这一重要领域的发展.

关键词 可见光; 不对称光催化; 自由基加成; 质子化; 氮杂芳烃

Asymmetric Photocatalytic Synthesis of Enantioenriched Azaarene Derivatives

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Abstract The importance of azaarene derivatives in many arenas, especially pharmaceutical and material industry, has attracted increasing attention of chemists to develop highly efficient synthetic methods. To date, functionalization of commercially available azaarenes and their simple derivatives as feedstocks by exploiting the electronic properties of azaarenes to trigger transformations has been appreciated as a powerful tool. Among them, due to the advantages of mild reaction conditions, good functional group tolerance and diverse reaction types, the methods via visible light-driven photocatalysis have been extensively explored. Notably, a number of asymmetric manifolds towards the synthesis of enantioenriched imine-containing azaarene derivatives have been established with satisfactory results. The advances of this important area are summarized and discussed according to the relative positions of the formed stereocenters to azaarenes.

Keywords visible light; asymmetric photocatalysis; radical addition; protonation; azaarene

1 Introduction

Azaarenes, *i.e.*, nitrogen-containing aromatic heterocycles, are structurally diverse, and are prevalent in bioactive natural and non-natural products, agrochemicals, pharmaceuticals, catalysts and ligands in catalysis, and functional materials.[1] It is why chemists are long keen on the development of catalytic methods towards the synthesis of azaarene derivatives with known and new structure features.[2-5] Two fundamental protocols have been employed to explore methodologies, that are construction and functionalization (Scheme 1).[2] Construction refers to building azaarene frameworks from simple substrates (Scheme 1, A). Although starting materials are usually readily accessible, the methods often just lead to one or a handful of specific azaarenes, thus restricting the diversity of aromatic

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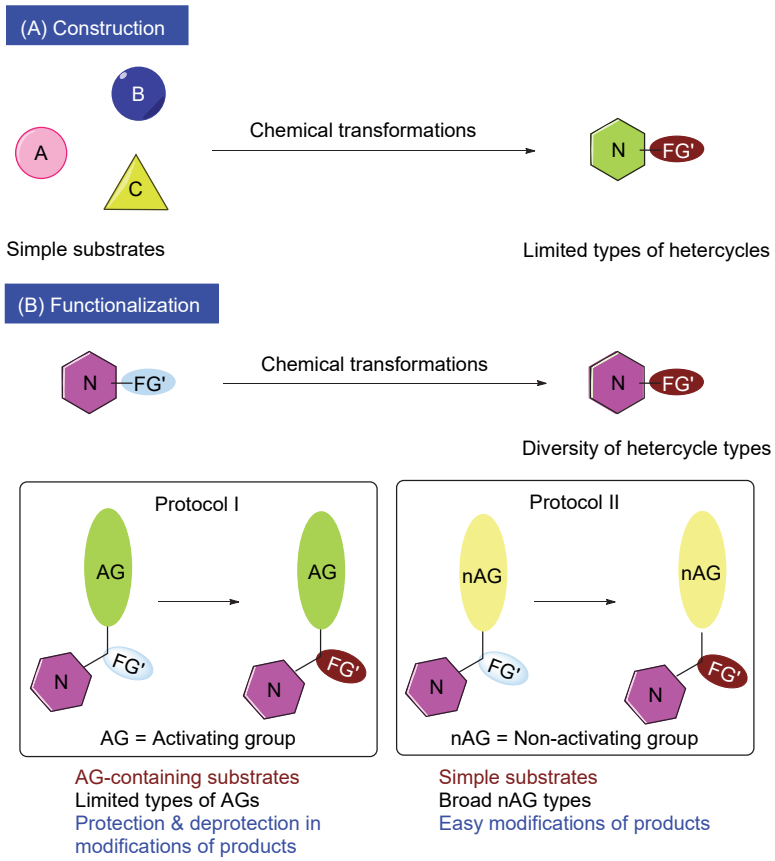
Received January 28, 2022; revised February 21, 2022; published online March 3, 2022
Project supported by the National Natural Science Foundation of China (Nos. 22171072, 21925103) and the China Postdoctoral Science Foundation (No. 2020M680098).
国家自然科学基金(Nos. 22171072, 21925103)和中国博士后科学基金(No. 2020M680098)资助项目.

heterocycles in the products. On the contrary, functionalization with azaarene-based compounds as substrates can effectively avoid such limitations, since various azaarenes have been preassembled onto substrates (Scheme 1, B, including Protocol I and Protocol II). Among them, directly exploiting the electronic properties of azaarenes to trigger transformations has become the research hotspot in the past decade (Protocol II),[3-5] given that no requirement of assembling other activating groups enables simple azaarenes as feedstocks, and leads to late-stage modifications of products more conveniently. Moreover, a variety of functional groups instead of activating groups can effectively increase the varieties of products. These advantages remarkably improve the utility of methods.

Based on either enamine or imine embedded in the structures, azaarenes can be formally classified as two types, which feature opposite electronic properties (Figure 1). With respect to the enamine-containing azaarenes, such as indoles and pyrroles, the π-excessive aromatic systems render them as nucleophiles.[3] The well-known Friedel-Crafts reactions are the representative application of these entities. Since imine (C=N) results in π-deficiency of aromatic systems, such azaarenes (pyridines, quinidines, imidazoles, and benzimidazoles, *etc*.) exhibit electron-withdrawing capability.[4-5] In this context, 2-alkylazaarenes[6] and 2-alkenylazaarenes[7] have been used as nucleophiles and electrophiles, respectively, wherein azaarenes could be identified as the analogues of carbonyls. However, owing to the considerably weaker electron-withdrawing ability of these azaarenes than carbonyls, either strong bases to perform deprotonation or strong nucleophiles are required. In addition to the limited substrates and unsatisfactory functional group tolerance, the methods are difficult to extend to asymmetric synthesis of the more valuable enantioenriched three-dimensional molecules.

The dilemma prompted chemists to explore new platforms to improve the reactivity. As a result, the renaissance of photocatalysis[8] offered precious chance to the attractive Protocol II (Scheme 1, B).[4b-4d,5] In addition to enabling the use of conveniently available substrates as reac-



Scheme 1 Fundamental protocols of synthesizing azaarene derivatives

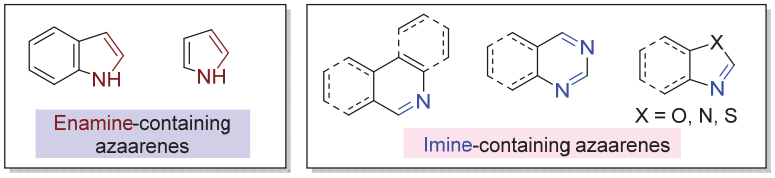


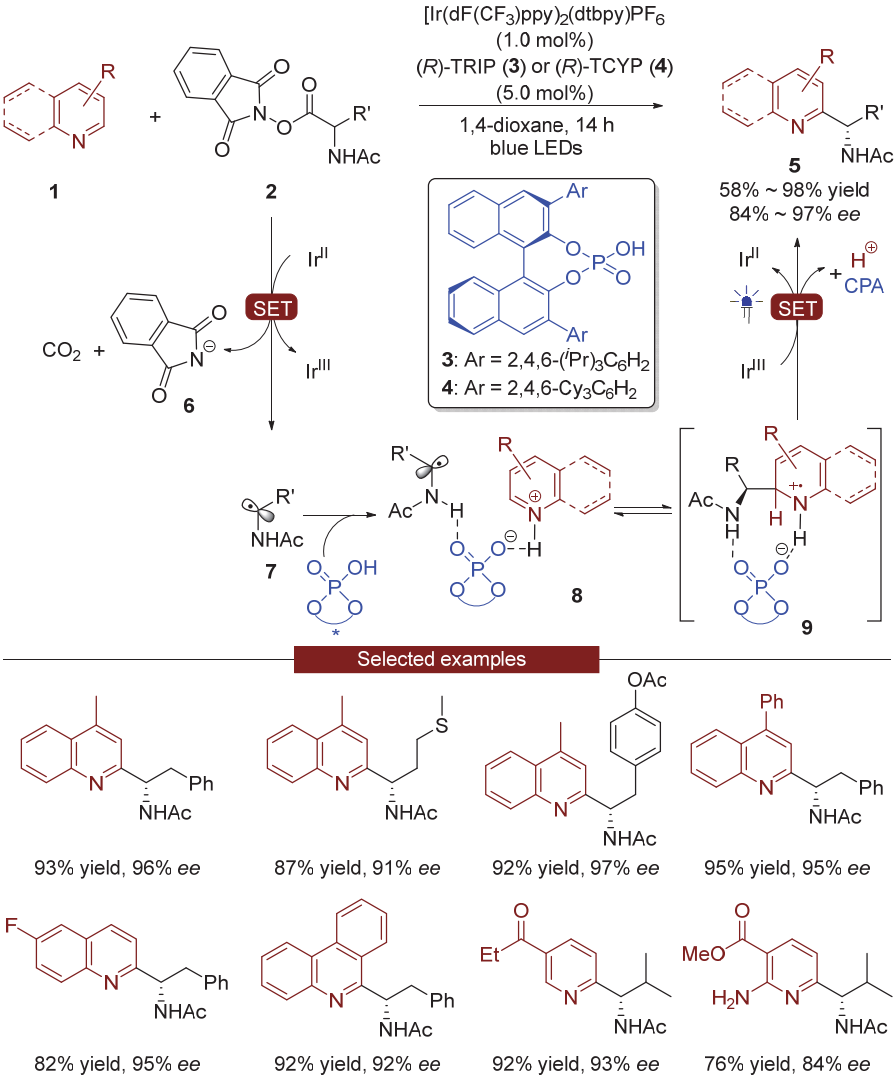
Figure 1 Classification of azaarenes

tion partners, the platforms endow transformations to high reactivity owing to the radical-based processes, which have inspired the establishment of several modular synthetic strategies, including the rational extension of the ionic-type reaction patterns to the radical manifolds and exploiting azaarenes as analogues of imines or single-electron oxidants. Among them, by merging extrinsic asymmetric catalysis,[9] many photocatalytic transformations have been successfully employed to synthesize enantioenriched azaarene variants.

In this review, we will summarize and discuss the advances of this important research area. In order to make readers better understand the status of development, this review is organized into four parts according to the relative positions of the formed stereocenters to azaarenes.

2 Stereocenters *α* to azaarenes

Since Minisci and coworkers[10] demonstrated the high reactivity and specific regioselectivity when under strongly acidic conditions in 1968, C—H functionalization of azaaryl rings via radical addition, named as Minisic reaction, has been long pursued by chemists. It provides a direct synthetic approach from simple and commercially available azaarenes to their derivatives.[5,11] However, the first enantioselective manifold was reported until 2018 by the Phipps group.[12] As shown in Scheme 2, in the presence of 1.0 mol% $[Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ as a photosensitizer and 5.0 mol% (*R*)-BINOL-based chiral phosphoric acid (CPA) **3** or **4** as a Brønsted acid, a variety of azaarenes (**1**), including quinolines, phenanthridines and pyridines react with *α*-amino acid-derived redox-active esters (REAs) **2** with acetyl as the *N*-protecting group smoothly, leading to a series of valuable azaarene-substituted secondary amines in 58% to 98% yields with 84% to 97% *ee*. The photoredox catalytic cycle is similar to that of the previous works, in which *α*-amino radicals **7** generated from single-electron reduction of REAs **2** perform regio-precise addition to 2-position of azaarenes, and the resultant radical interme-



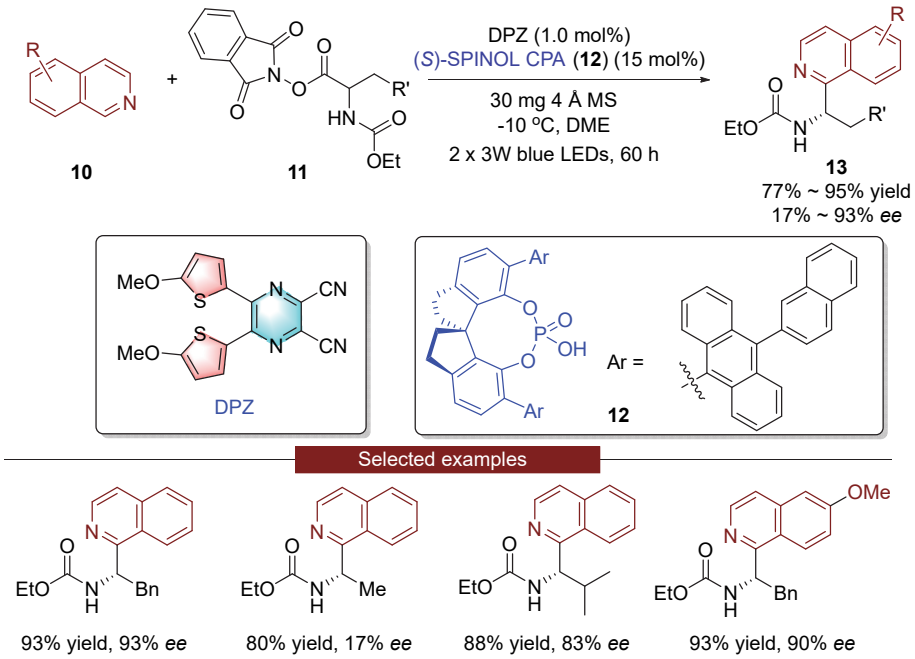
Scheme 2 Enantioselective Minisci-type reaction via cooperative metallophotoredox and chiral Brønsted acid catalysis

diates are oxidized by the excited state Ir^{III} via single-electron transfer (SET). Different with the previous photoredox catalytic Minisci-type reaction, catalytic amount of Brønsted acid is used, representing the first acid-catalytic version. With respect to enantiocontrol, they proposed a ternary transition state **8** wherein CPA acted as a Brønsted acid-base bifunctional catalyst to interact with the basic nitrogen atom of azaarenes and N—H bond of radicals **7** via hydrogen bonds, respectively, thereby leading to intermediates **9** via an enantiocontrolled radical addition process. It was of note that they cooperated with the Goodman group[13] to further investigate the plausible enantioselective mechanism by performing detailed experimental and density function theory (DFT) computational studies. The results supported Curtin-Hammett control in the reaction, with initial radical addition being fast and reversible, and enantioselectivity being obtained in the subsequent slower and irreversible deprotonation. Moreover, by carrying on multivariate linear regression (MLR) analysis to a carefully designed reaction data set, the catalysis platform was successfully extended to asymmetric Minisci-type reactions of pyrimidines with REAs.[14]

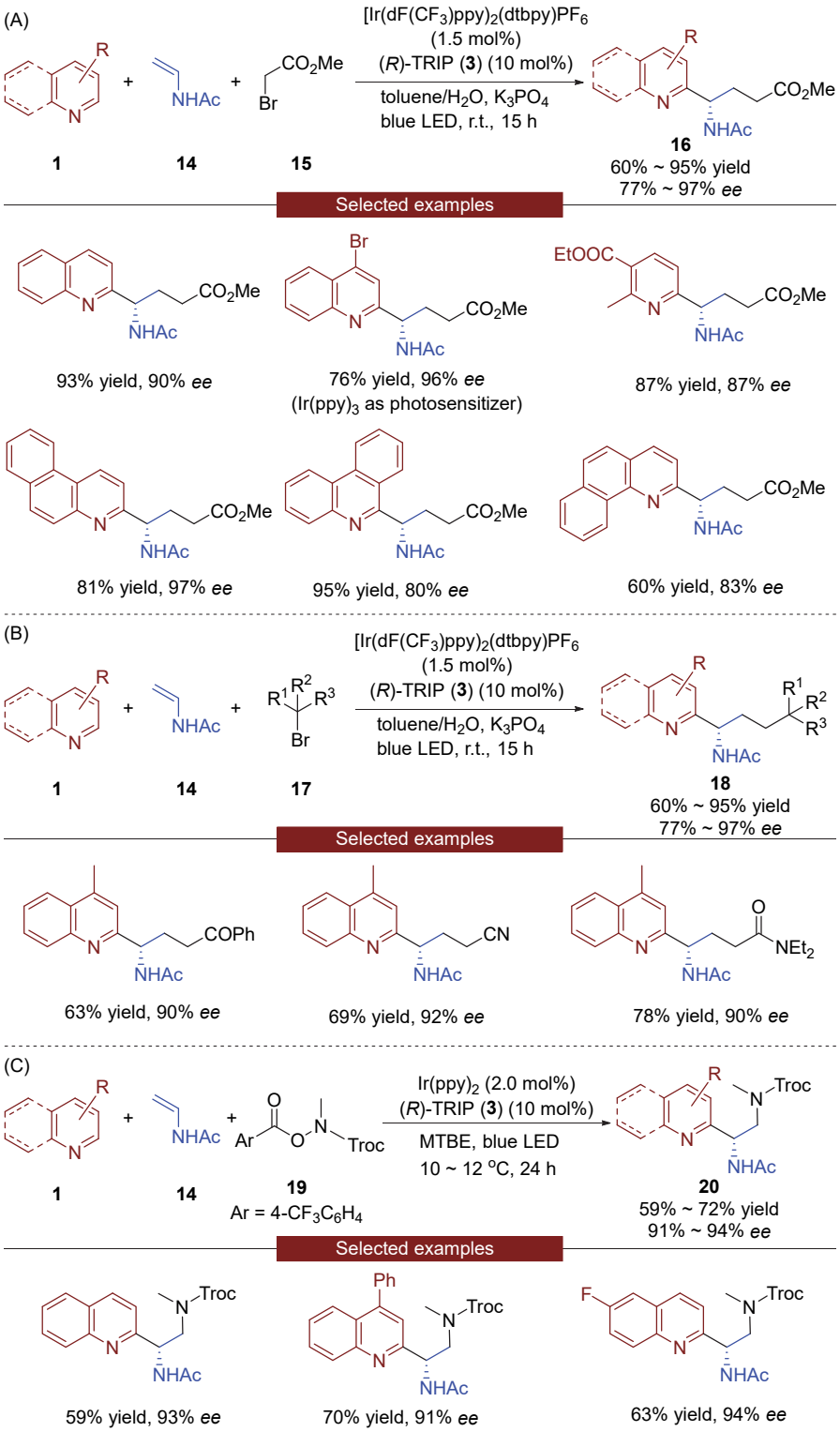
In 2018, Jiang and co-workers[15] also reported enantioselective Minisci-type reaction via cooperative photoredox and chiral Brønsted acid catalysis (Scheme 3). However, the platform was transition-metal free wherein a dicyanopyrazine-derived chromophore (DPZ)[16] developed by them was used as photosensitizer. More interestingly, this dual catalyst system was suitable to isoquinolines **10** which was failed to achieve using Phipps' conditions. The results showed that when using REAs **11** as the partners and SPINOL-derived CPA **12** as the chiral catalyst, a series of isoquinoline-based secondary amines **13** were obtained in 77% to 95% yields with 17% to 93% *ee*. Notably, likely due to the insufficient steric hindrance, REA derived from alanine only afforded product with 17% *ee*. Later, the Fu group[17] developed another transition-metal free platform by using a combination of triphenylphosphine and sodium iodide under irradiation of blue LEDs to asymmetric Minisci-type reactions of pyridines and quinolines **1** with REAs.

To establish a direct synthetic approach to enantiomerically pure γ-amino acids with azaarenes as γ-substituents, the Studer group[18] developed an enantioselective Minisci-type addition-based three-component cascade reaction strategy by using enamide **14** to first accept the addition of radical species generated from methyl 2-bromoacetate **15** (Scheme 4, A). A series of pyridines and quinolines **1** were compatible to the reaction conditions, resulting in products **16** with satisfactory results. Other analogues of **15** such as α-bromo ketones, α-bromo nitrile, α-bromo amides and so on (**17**) could provide corresponding adducts **18** in 60% to 95% yields with 77% to 97% *ee* (Scheme 4, B). The ability of this cooperative catalysis platform was further disclosed by the transformations of preparing the valuable diamine derivatives (**20**), in which the oxidizing *O*-acyl hydroxylamines **19** were used as the precursors of amine radicals (Scheme 4, C).

In addition to SET, hydrogen atom transfer (HAT) as a fundamental chemical transformation in radical chemistry has also been widely employed in Minisci-type reactions. In 2021, the Phipps group[19] reported the first enantioselective example. As shown in Scheme 5, transformations between azaarenes **1** and linear amides **21** can afford a variety of enantioenriched azaarene-substituted secondary amines **5** with satisfactory results when using CPA **3** or **4**



Scheme 3 Enantioselective Minisci-type reaction via cooperative organophotoredox and chiral Brønsted acid catalysis



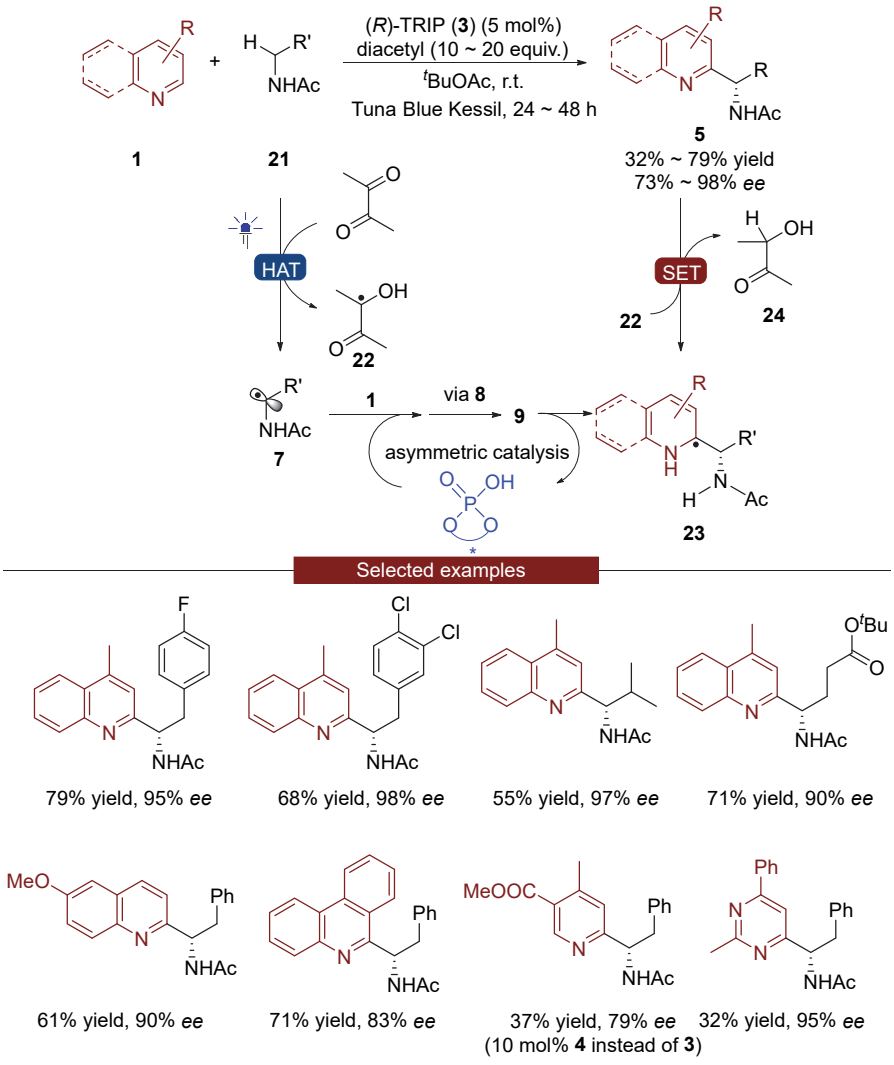
Scheme 4 Three-component asymmetric Minisci-type reactions

as a chiral catalyst and superstoichiometric diacetyl as a combined HAT reagent and oxidant. No extra photocatalyst is required, and the photoexcitable diacetyl is responsible for generating radicals **7** via HAT. Then, CPA perform asymmetric catalysis for radical addition of **7** to azaarenes **1** to produce radical intermediates **23**, wherein stereocenters have been formed. After SET with **23**, radical **22** derived from diacetyl further turns into alcohol **24**. Notably, this method provides products with the same type as their previous works of using REAs as the reaction partners. Given that REAs are synthesized from the corresponding *N*-acetyl amino acids and in low yields in most cases, many amino acids are not commercially available, and several REAs are not so stable upon purification

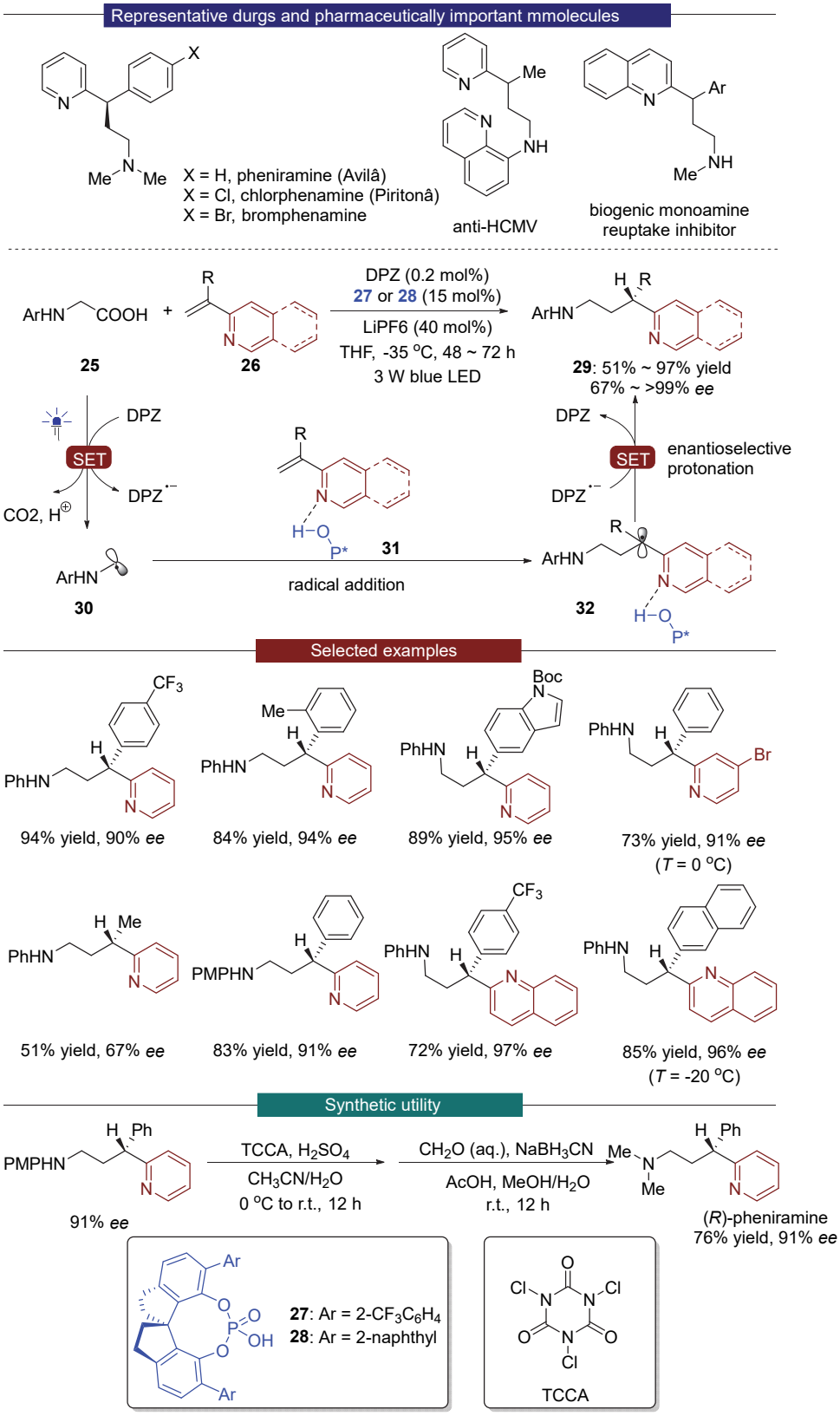
and/or storage, this work represents a more simple and practicable approach to access these important enantiomerically pure azaarene variants.

During the same period, another modular strategy via enantioselective protonation[20] has also been developed to assemble the valuable azaarene derivatives featuring α-tertiary stereocenters. The first example was reported by Jiang and co-workers[21] in 2018, which was stemmed from the exploration of the first catalytic method to access the pharmaceutically important 3-azaarene-3-substituted amines in an enantioselective manner (Scheme 6). As a result, by using a dual catalytic system involving a CPA (**27** or **28**) and a DPZ photosensitizer that is driven by visible light, transformations of *N*-aryl glycines **25** with a variety of α-branched 2-vinylazaarenes **26** could experience a radical addition-enantioselective protonation process, resulting in a large array of desired products **29** in 51% to 97% yields with 67% to >99% *ee*. The viable substrate scope is broad, and only α-alkyl 2-vinylazaarenes afforded moderate yields and *ee*s. Mechanistically, the photoredox catalytic cycle is triggered from reduction of photoactived DPZ (*DPZ). α-Amino radicals **30** are generated through single-electron oxidation of *N*-aryl glycines. After addition of **30** to CPA-activated **26** (*i.e.*, **31**), radical intermediates **32** are produced, which can experience single-electron reduction by $DPZ^{\bullet-}$ and enantioselective protonation to present enantioenriched **29**. Low reaction temperature was demonstrated to be beneficial to high enantioselectivity, given that the transformation without CPA catalyst rendered racemic product in a considerable yield at 25 ℃, indicating the existence of strong background racemic reaction. From the obtained product, the enantiomerically pure antihistamine drug pheniramine (Avil®) could be readily synthesized through convenient two-step reactions.

Although the above-mentioned work demonstrates the viability of enantioselective protonation to construct the attractive azaarene derivatives featuring α-stereocenters, the requirement of preassembling *N*-aryl glycines and two-step synthesis of pheniramine inarguably damages practicability. Meanwhile, the partners of olefins are limi-

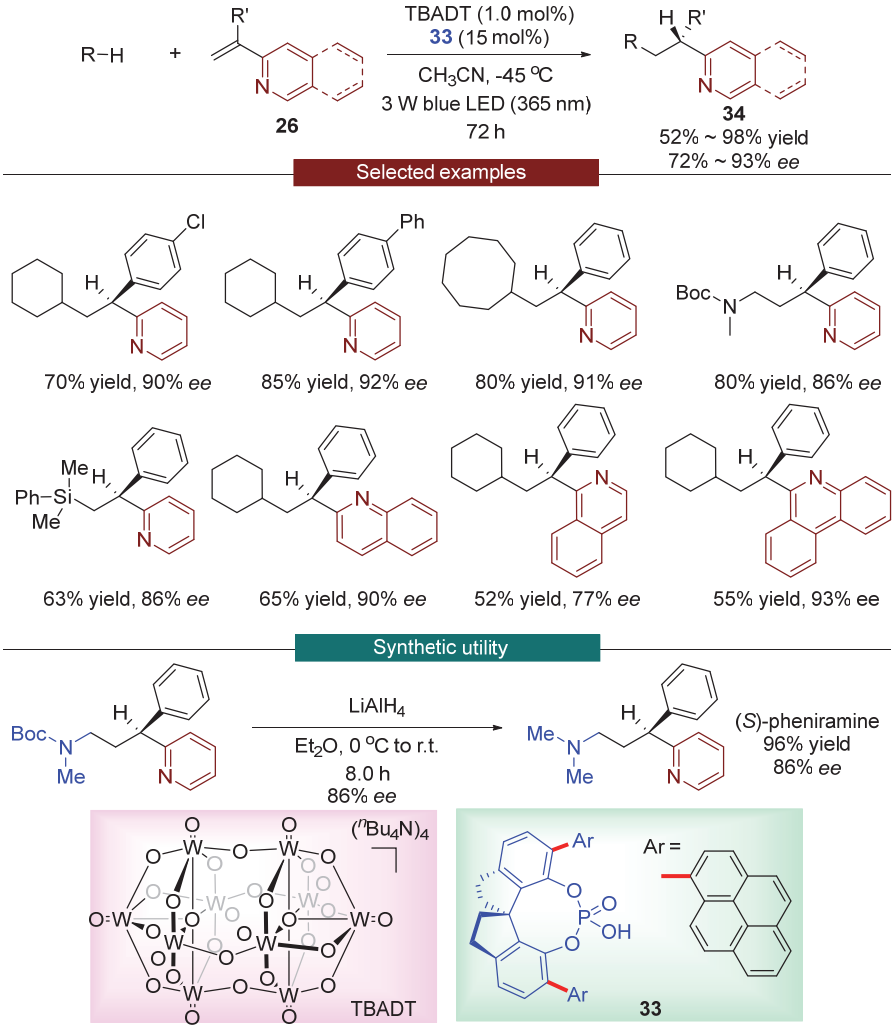


Scheme 5 Hydrogen atom transfer-enabled enantioselective Minisci-type reactions of amides



Scheme 6 Radical addition-enantioselective protonation via cooperative photoredox and chiral Brønsted acid catalysis

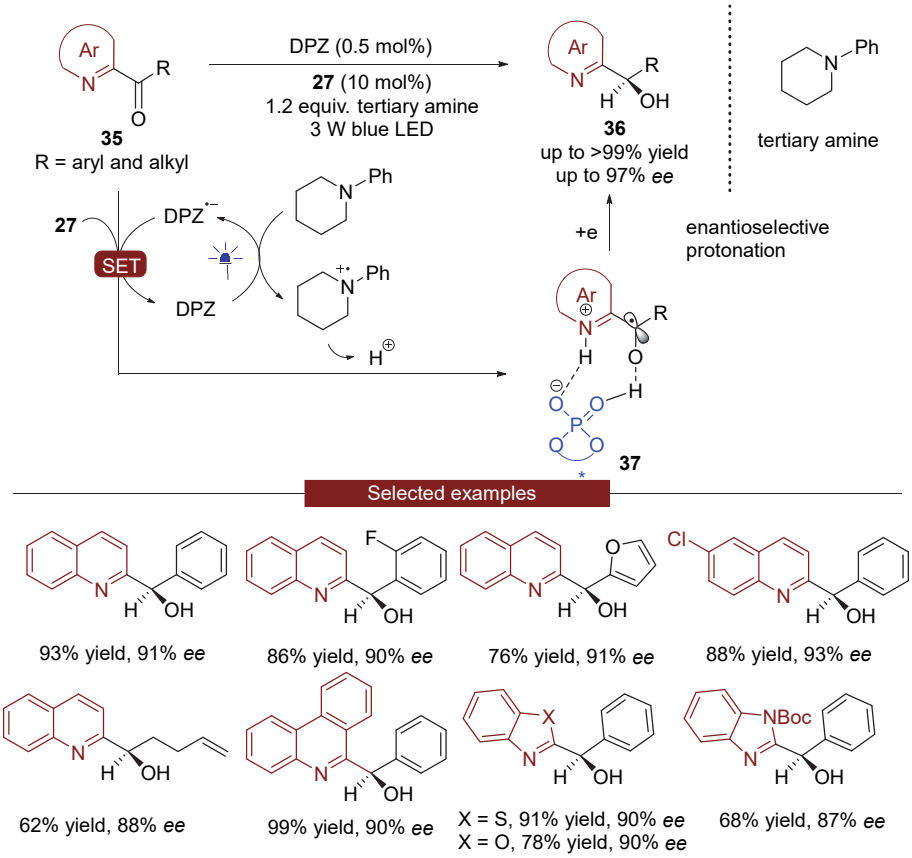
ted to α-amino radicals. To overcome these challenges, very recently, the Jiang group[22] developed a new cooperative catalysis platform based on HAT to produce radical intermediates for this kind of reaction (Scheme 7). By using a tetrabutylammonium decatungstate (TBADT) as the photocatalyst and a CPA (**33**) as the hydrogen-bonding



Scheme 7 Radical addition-enantioselective protonation via cooperative HAT and chiral Brønsted acid catalysis

(H-bonding) catalyst, transformations to diverse *α*-branched 2-vinylazaarenes are suitable to a variety of commercially available hydrocarbons and silanes, leading to a range of valuable enantioenriched *α*-tertiary azaarenes **34** in high yields (up to 98%) and with good to excellent enantioselectivities (up to 93% *ee*). Furthermore, the capability of using *tert*-butyl methylcarbamate as the feedstock enables a highly practical and concise synthesis (only one reduction step from the corresponding adduct by using inexpensive $LiAlH_4$) of (*S*)-pheniramine with satisfactory results. This work demonstrates the feasibility of cooperative HAT and chiral H-bonding catalysis for the synthesis of enantioenriched azaarene variants.

Mechanistically, the electron-withdrawing ability of imine-containing azaarenes allows them as the analogues of carbonyls to facilitate single-electron reduction of *α*-radicals, thus forming the key prochiral *α*-anions to experience the subsequent enantioselective protonation. Accordingly, as the extension of their works in the construction of labile tertiary stereocenters *α* to aromatic ketones through single-electron reduction and enantioselective protonation of 1,2-diketones,[23] Jiang and co-workers[24] further addressed the challenging reduction of azaarene-substituted ketones **35** by utilizing the transition-metal free dual catalyst system involving DPZ and CPA **27** and *N*-phenyl piperidine as the sacrificial reductant (Scheme 8). The generation of radical intermediates **37** was disclosed to undergo single-electron reduction of **35** by $DPZ^{\bullet-}$ via reductive quenching of *DPZ by *N*-phenyl piperidine. Through the subsequent single-electron reduction and enantioselective protonation, diverse azaarene-substituted secondary alcohols **37** were achieved in up to >99% yield with up to 97% *ee*. Inspired by the success of this work and photoredox dehalogenative enantioselective protonation of *α*,*α*-dihaloketones to forge labile chiral secondary C—F, C—Cl and C—Br bonds at the *α*-position of ketones,[25] the same group[26] subsequently developed photoredox-catalyzed enantioselective *α*-deuteration of azaarenes with prochiral azaarene-substituted ketones and racemic *α*-chloro-azaarenes as the substrates utilizing the inexpensive D_2O as the deuterium source. Although excess D_2O was used, good to excellent enantioselectivities were obtained, suggesting the efficacy of the catalytic system.

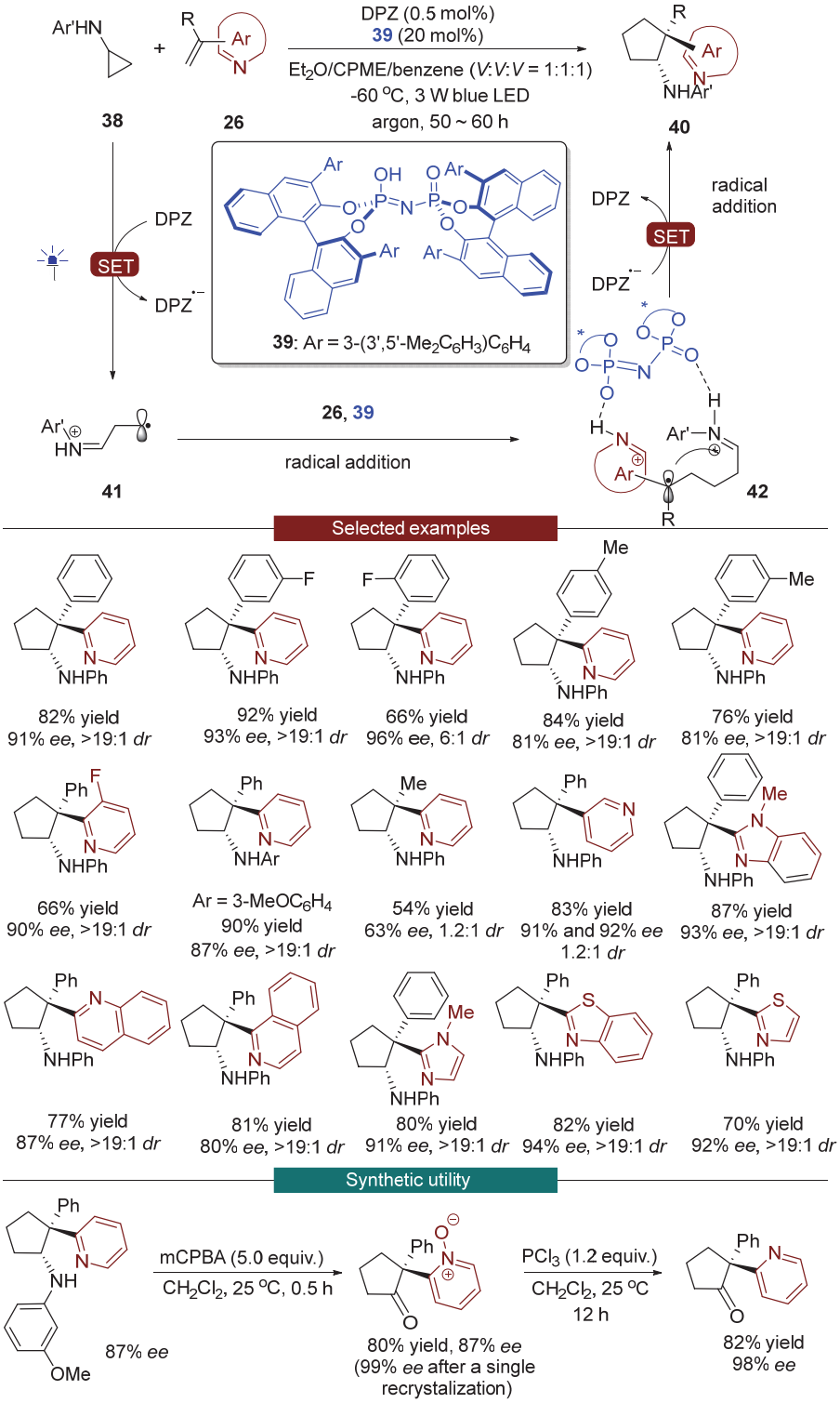


Scheme 8 Single-electron reduction-enantioselective protonation

Compared to tertiary carbon stereocenters, construction of all-carbon quaternary stereocenters represents a more attractive task in asymmetric synthesis, given their prevalence in natural products and pharmaceuticals, and the higher challenge in stereocontrol.[6c] In 2020, Jiang and co-workers[27] reported an asymmetric olefin difunctionalization strategy to address the elusive issue of building all-carbon quaternary stereocenters *α* to azaarenes by using simple azaarene substrates wherein no extra activating groups were required (Scheme 9). Under visible light-driven cooperative C_2-symmetric imidodiphosphoric acid **39** and DPZ catalysis, cyclopropylamines **38** and *α*-branched 2-vinylazaarenes **26** can efficiently undergo an asymmetric, redox-neutral [3+2] cycloaddition, leading to a variety of valuable chiral azaarene-substituted cyclopentane variants **40** in high yields (up to >99%) with good to excellent enantio- and diastereoselectivities (up to 96% *ee* and >19∶1 *dr*). Diverse azaarene-substituted all-carbon quaternary stereocentres have been constructed, underscoring the generality of the method. The reaction pathways involve single-electron oxidation of **38** by *DPZ to generate distonic ions **41**, radical addition of **41** to olefins **26** under activation by chiral Brønsted acid **39**, and intramolecular addition of the resultant radical intermediates **42** to the highly reactive iminiums.[28] The [3+2] cycloaddition adducts are biologically important, and meanwhile, are useful synthetic intermediates. As an example, they could be used to readily synthesize *α*,*α*-diaryl-substituted ketones. In addition to representing the first construction of chiral azaarene-substituted cyclopentane variants, notably, this work demonstrates the viability of confined C_2-symmetric imidodiphosphoric acids in asymmetric photoredox catalysis, which enriches the catalyst systems and makes cooperative photoredox and chiral Brønsted acid becoming a more powerful tool in the synthesis of chiral azaarenes.

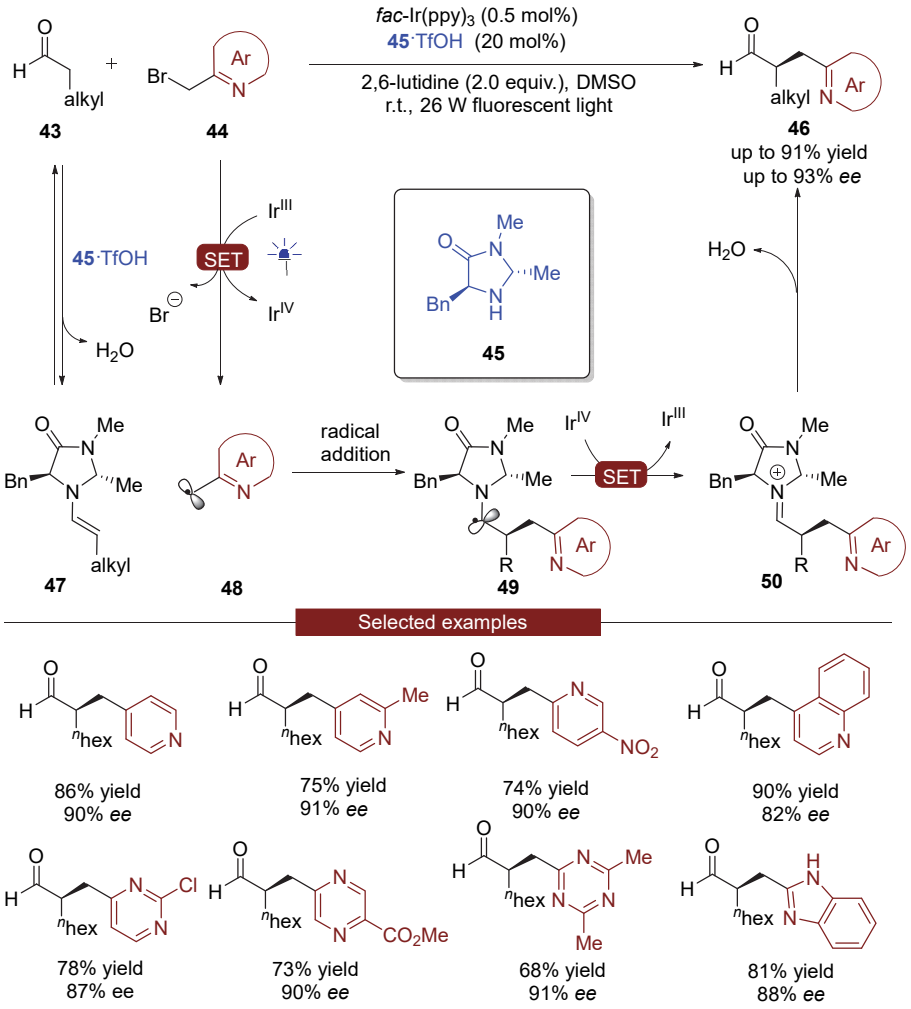
3 Stereocenters *β* to azaarenes

The first successful example of cooperative photoredox and asymmetric catalysis is worth mentioning here. In 2008, the MacMillan group[29] reported a highly enantioselective *α*-alkylation of aldehydes with carbonyl-substituted bromomethanes driven by visible light using a chiral imidazolidinone as an enamine-based catalyst and $Ru(bpy)_3Cl_2$ as a photosensitizer. Subsequently, they exploited the similar electronic properties of imine-containing azaarenes to carbonyls to extend this platform to the enantioselective *α*-alkylation of aldehydes **43** with azaarene-substituted bromomethanes **44** (Scheme 10).[30] The dual catalyst system was tuned as *fac*-$Ir(ppy)_3$ owing to the higher reduction potentials of its excited state with chiral imidazolidinone-based complex **45**, of which the benzylic moiety was used to protect the π-nucleophilic *Re*-face of *E*-enamine intermediates **47** generated from aldehydes **43** and



Scheme 9 Asymmetric olefin difunctionalization to assemble all-carbon quaternary stereocenters *α* to azaarenes

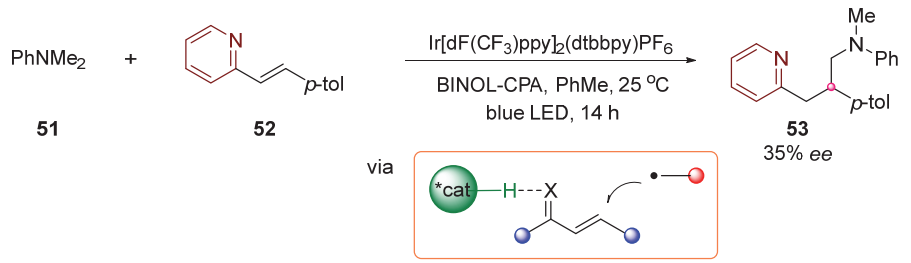
catalyst **45**. The photoredox catalysis begun with single-electron reduction of bromides **44**, delivering *α*-azaaryl radicals **48**. After addition of **48** to **47**, the resultant radicals **49** could be oxidized by Ir^{IV} to render iminium intermediate **50**. A series of enantioenriched azaarene-bearing aldehydes **46** in which various tertiary stereocenters were forged at the *β*-position of diverse azaarenes were obtained. Subsequently to 2018, this cooperative catalysis platform was used by them once more to enantioselective *α*-benzylation of aldehydes with azaarene-substituted methanols. The formation of benzylic radicals is through a "spin-center shift" (SCS) strategy.[31]



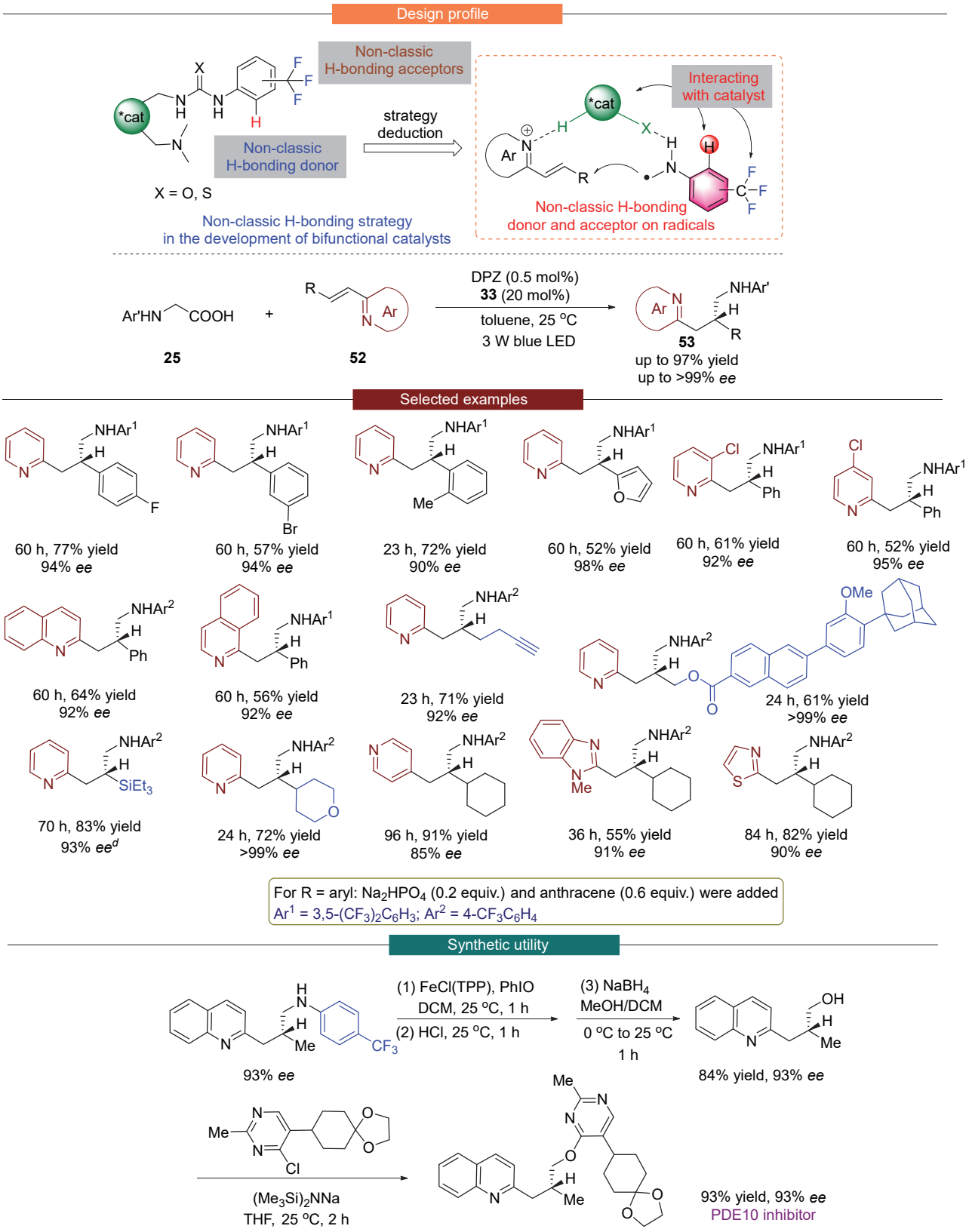
Scheme 10 Enantioselective *α*-alkylation of aldehydes with heteroaryl methylene bromides

Inarguably, asymmetric conjugate addition of radicals to alkenylazaarenes, *i.e.*, *β*-substituted vinylazaarenes, should be a direct approach to assemble stereocenters at the *β*-position of azaarenes. However, it seems a formidable challenge to the transformations via radical-based process. The first example was reported by the Melchiorre group[32] in 2016. After accomplishing a series of high-yielding racemic radical addition of *α*-amino radicals to alkenylazaarenes, they attempted the enantioselective manifolds accordingly (Scheme 11). Although considerable efforts to improve enantioselectivity were carried out, transformation of *N*,*N*-dimethyl aniline (**51**) with olefin **52** provided the corresponding product **53** with only 35% *ee*. The incompact catalytic pattern that is via H-bonding interaction between pyridyl of **52** and CPA might be a critical factor to result in the poor enantioselectivity, since the high reactivity of radical species would readily experience a noncatalytic racemic background reaction.

Until this year, a highly enantioselective example was described by Jiang and co-workers (Scheme 12).[33] In addition to employing the robust bifunctional H-bonding catalysis to improve enantioselectivity to a good level, the well-established strategy of forming non-classic H-bonding interaction cites on the structure of chiral bifunctional



Scheme 11 Asymmetric radical addition of *α*-amino radicals to alkenylazaarenes: the pioneering result



Scheme 12 Capitalizing on non-classic H-bonding strategy to supplement chiral bifunctional H-bonding catalysis

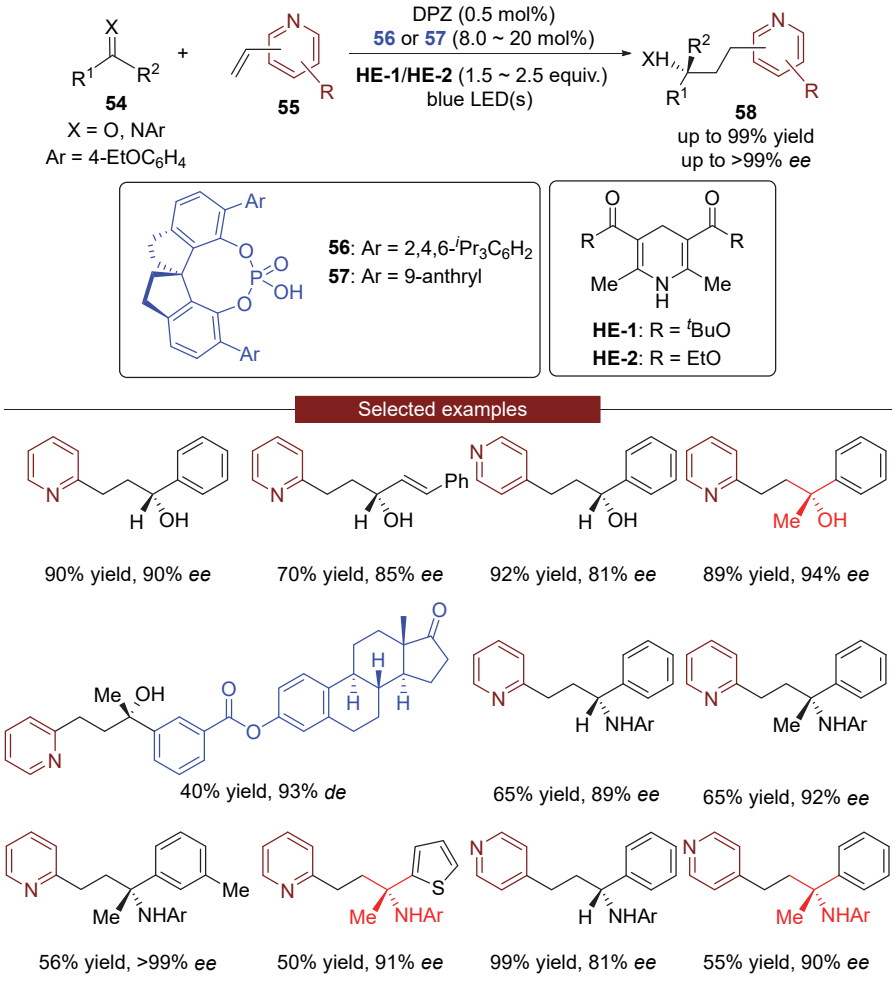
organocatalysts[34] was used to devise the precursors of *α*-amino radical species, that is introducing the strong electron-withdrawing CF_3 groups on the N-aromatic rings of glycines to assemble H-bonding donors and acceptors. As a result, in the presence of 0.5 mol% DPZ and 20 mol% CPA **33** under irradiation of 3 W blue LED, transfor-

mations between glycines **25** containing 3,5-ditrifluoromethylphenyl (for 2-aryl-substituted vinylazaarenes) or 4-trifluoromethylphenyl (for 2-alkyl and 2-silyl-substituted vinylazaarenes) as the *N*-protecting groups and a variety of alkenylazaarenes **52** led to adducts **53** in up to 97% yield with up to >99% *ee*. In addition to the diversity of azaarenes, the method is capable of building aryl-, alkyl- and silyl-substituted stereocenters. Notably, in most cases, *ee* values of products are above 90%. These results underscore the generality of this catalytic system. In addition, the synthetic utility of the method was demonstrated by the first asymmetric synthesis of PED10 inhibitor from the corresponding adduct via several facile chemical transformations.

4 Stereocenters *γ* to azaarenes

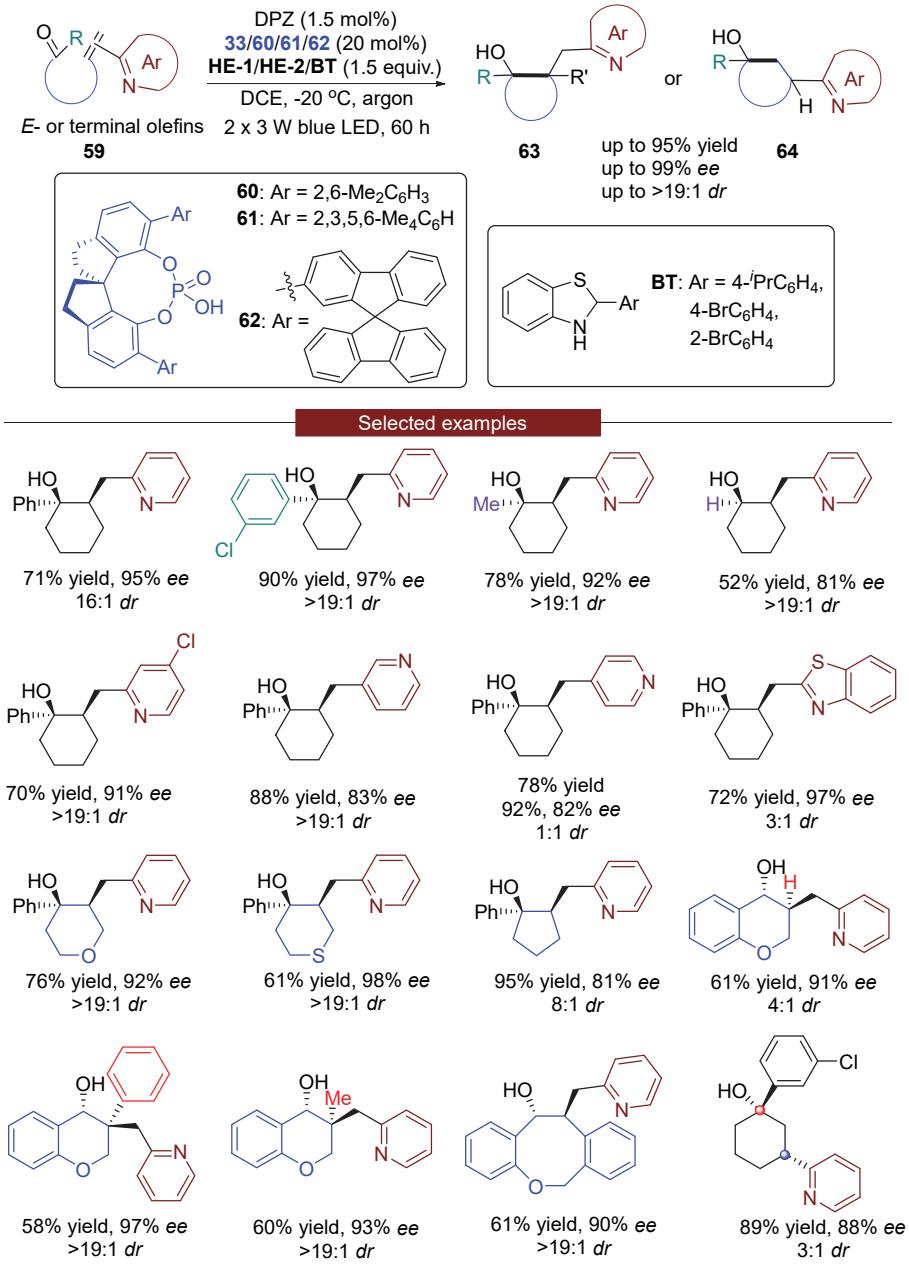
Precisely constructing remote stereocenters of functional groups is of particular importance in asymmetric synthesis, given the capability of providing a straightforward approach to construct enantioenriched complex molecules. In 2015, Wang and co-workers[35] presented a chiral secondary amine-catalyzed asymmetric conjugate addition of aldehydes to 4-vinylpyridines, representing the first example of assembling tertiary carbon stereocenters *γ* to pyridines. Using 0.5 equiv. of trifluoromethanesulfonic acid (TFA) is crucial to transformation occurring, demonstrating the weak electron-withdrawing ability of pyridines, and the exploration of new platforms with high reactivity is thereby highly desirable.

Indeed, a number of photocatalytic addition reactions of prochiral radicals to terminal olefins have been presented since 2013.[36] Nevertheless, the first enantioselective example was reported until 2019 by the Jiang group,[37] likely due to the formidable challenge in stereocontrol originating from the long distance between the interacting position of substrates with chiral catalysts and the site of forming stereocenters (Scheme 13). The developed reaction is an enantioselective reductive coupling of diverse aldehydes, ketones and imines with vinylpyridines **55**. When the catalyst combination of DPZ with (*S*)-SPINOL-derived CPA **56** or **57** was used and Hantzsch ester (HE) **HE-1** or **HE-2** was used as the terminal reductant, the transformations worked smoothly, affording a large variety of the valuable pyridine derivatives that contain the appealing secondary/tertiary alcohols and amines at the *γ*-position of pyridines in up to 99% yield with up to >99% *ee*. 4-Vinylpyridines were also tolerated well, although the H-bonding interaction position was tremendously far away from the formed stereocenters.



Scheme 13 Enantioselective intermolecular reductive coupling of carbonyls and imines with vinylpyridines

For more than fifty years, Beckwith-Enholm cyclization, that is, the radical-mediated reductive cyclization of enals and enones, has been widely used to synthesize various valuable carbocyclic and heterocyclic alcohols.[38] The pursuit of new reaction systems by harnessing this classic and powerful tool, especially for attaining the modular and even divergent synthesis of novel cyclic alcohols, always represents an attractive task. In addition, although chiral three-dimensional molecules are of synthetic importance in the pharmaceutical industry, no examples of catalytic asymmetric Beckwith-Enholm cyclizations have been reported, likely due to the challenging stereocontrol for the highly reactive radical conjugate addition process. Accordingly, based on the success of intermolecular enantioselective reductive coupling reactions between carbonyls and vinylazaarenes, Jiang and co-workers[39] explored the viability of the intramolecular manifolds, representing an unprecedented reaction system of Beckwith-Enholm cyclization. In 2021, they reported the corresponding results (Scheme 14). A transition-metal-free dual catalyst system involving DPZ and an (*S*)-SPINOL CPA (**30**/**60**/**61**/**62**) is effective for the cyclization of various carbonyls with diverse imine-containing azaarene-derived terminal or non-terminal olefins by using **59** as the substrates. A variety of biologically important enantioenriched azaarene-functionalized cyclic alcohols (**63** and **64**), which contain adjacent

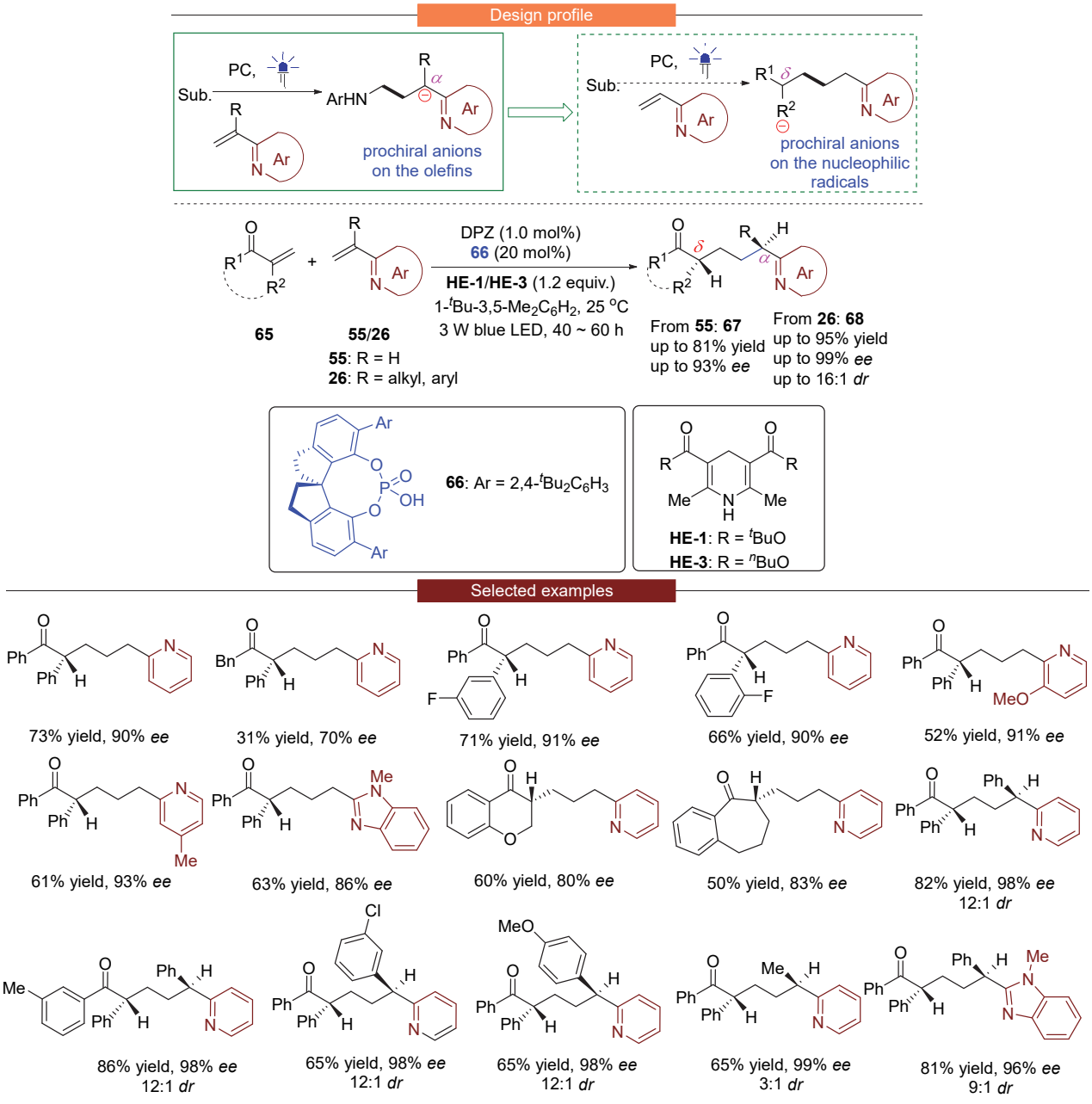


Scheme 14 Enantioselective Beckwith-Enholm cyclizations to divergent asymmetric synthesis of azaarene-functionalized cyclic alcohols

1,2- or nonadjacent 1,3-stereocentres on diverse cyclic frameworks, were obtained in high yields (up to 95%) with satisfactory stereoselective results (up to 99% *ee* and> 19∶1 *dr*). The substrate scope is extremely broad considering the diversity of azaarenes and cyclic structures, the compatibility of aldehydes and aliphatic ketones and the formation of all-carbon quaternary stereocentres. In addition, the reaction system using terminal olefins has been demonstrated as a viable method to introduce pharmaceutically important deuterium into valuable azaarene- based cyclic alcohols. Notably, to attain satisfactory enantioselectivities, different CPAs (*e.g.*, **33**, **60**, **61** and **62**) and terminal reductants [*e.g*, **HE-1**, **HE-2** and 2,3-dihydro-2-substituted-benzothiazole (**BT**)] were used, suggesting the formidable challenge in stereocontrol. As a distinguished contribution, this work has discovered a promising lead compound of an antioxidant stress drug.

5 Stereocenters δ to azaarenes

Although molecules that contain stereocenters at the *δ*-position of azaarenes feature multitudinous and important bioactivities, the direct synthesis of these entities, especially in an enantioselective manner, is still underdeveloped.[6e] In 2021, the Jiang group[40] described the first relevant example of asymmetric photocatalysis. The design scenario with respect to the reaction strategy arises from their previous works on radical addition-enantioselective protonation, in which the prochiral stereocenters via radical addition locate on the olefins (Scheme 15).[21-22] They



Scheme 15 Reductive cross coupling and enantioselective protonation of olefins to construct stereocenters *δ* to azaarenes

considered that the formation of these anions on the radical species but not olefins would be a viable approach to construct the remote *δ*-stereocenters. In this context, an asymmetric reductive cross coupling of acyclic and cyclic *α*-branched vinylketones **65** with diverse vinylazaarenes **55** was developed. By using 1.0 mol% DPZ, 20 mol% (*S*)-SPINOL-based CPA **66** and HE (**HE-1**/**HE-3**) as the terminal reductant, a variety of enantioenriched azaarene derivatives **67** bearing ketone-substituted *δ*-tertiary stereogenic centres were obtained in high yields (up to 81%) and enantioselectivities (up to 93% *ee*). The current method is also effective for *α*-branched vinylazaarenes **26**, assembling elusive nonadjacent 1,4-stereocentres with satisfactory results (products **68**, up to 95% yield, up to 99% *ee* and up to 15∶1 *dr*), in which the mechanistic study demonstrated that the formation of new C—H bonds of *α*-azaarenes should undergo an attractive enantioselective hydrogen atom transfer process.

6 Conclusions

Exploiting the electronic properties of azaarenes to directly trigger transformations of azaarene-based feedstocks has been one of the most important synthetic approach to access azaarene derivatives. Such an expedient functionalization protocol has inspired the development of many viable methodologies. Among them, visible light-driven photocatalysis offers a robust and sustainable tool to allow transformations with high reactivity, thus accomplishing synthesis under mild reaction conditions. More importantly, the ability to engage in non-traditional bond cleavages and formations renders several unique strategies. As a result, a large variety of general and efficient photocatalytic methods have been devised, and some of them have been successfully extended to the realm of asymmetric synthesis by using extrinsic chiral catalysts. To date, chiral enamine catalysis and especially chiral H-bonding catalysis have been revealed as the powerful tools to offer sufficient enantiocontrol. A number of important enantioenriched azaarenes featuring diverse stereocenters at the different positions of azaarenes have been synthesized with satisfactory results. However, compared to the well-established racemic versions, the enantioselective manifolds are still limited. For example, the transformations via enantioselective radical couplings and energy transfer-based catalysis are still undeveloped. It is also highly desired to realize the enantioselective fashion towards the newly developed functionalization-oriented construction, a useful strategy to assemble more than two azaarene motifs into the molecular architectures.[41] In addition, to provide more kinds of valuable enantiomerically pure azaarene variants to serve on the advance of pharmaceutical and material industry, new methods and other viable asymmetric catalysis platforms require to explore. Notably, the exploitation of the unmet enamine-containing azaarene-triggering reactions, wherein the aromaticity of azaarenes is maintained, still remains an attractive task.

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