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REVIEW

View Article Online
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Cite this: *Org. Chem. Front.*, 2020, **7**, 1283

Cooperative photoredox and chiral hydrogen-bonding catalysis

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Chiral hydrogen-bonding catalysis is a classic strategy in asymmetric organocatalysis, and it has been extensively used in a variety of fundamental chemical transformations. At the same time, visible light-driven photoredox catalysis is a powerful and sustainable tool commonly used in radical chemistry. The intriguing combination of these two catalysis platforms would open a new avenue for the direct and highly efficient synthesis of enantioenriched compounds. Inspired by the conceptual breakthrough of T. Bach, in recent years, significant progress has been made in cooperative photoredox and chiral hydrogen-bonding catalysis. By developing a variety of important types of reactions, a wide range of valuable chiral compounds have been successfully synthesized. In this review, the advances in this key area are systematically described, and the examples are organized according to the distinct bond-forming patterns in the construction of the stereocentres.

Received 2nd March 2020,
Accepted 12th April 2020

DOI: 10.1039/d0qo00276c

rsc.li/frontiers-organic

Introduction

Due to the remarkable influence of chirality on processes in biology, physics and chemistry, the synthesis of optically pure compounds has always been pursued in many scientific domains, such as pharmaceuticals, functional materials and catalysis. To achieve high atom economy and produce different kinds of chiral molecules, especially those featuring new and complex structures, asymmetric catalysis has been an active field of research in the past few decades. Based on these ongoing efforts, asymmetric organocatalysis, which uses small organic molecules as catalysts, has become an important branch parallel to transition-metal catalysis and enzyme catalysis.[1] Among the defined strategies (*e.g.*, enamine catalysis, iminium catalysis, SOMO catalysis, counterion catalysis, and hydrogen-bonding (H-bonding) catalysis), H-bonding catalysis has been widely used in the synthesis of enantiomerically pure compounds.[2] Chemical transformations could be promoted based on H-bonding interactions between chiral H-bonding catalysts and substrates that possess oxygen- or nitrogen-containing functional groups as H-bonding acceptors and/or protons as H-bond donors, simultaneously providing enantio-

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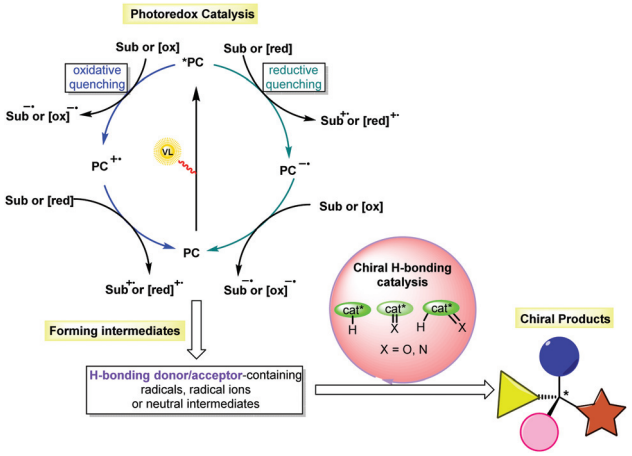
controlling environments for the formation of diverse stereocentres. However, the rather low energy of H-bonding interactions often requires the use of highly reactive substrates, which inarguably leads to limited substrate scopes and amenable reaction types as well as tedious preparations of substrates to achieve sufficient reactivity. Furthermore, the Brønsted acid/base character of the catalyst enabling the generation of the reaction intermediates always results in non-neutral reaction systems, making the construction of labile stereogenic centres quite challenging.[3] Accordingly, designing a highly reactive and mild catalytic system for chiral H-bonding catalysis would overcome this formidable bottleneck and allow new developments in this important catalysis platform.

In addition to reactions of ions, radical-based transformations have been widely used in synthesis, as they enable a wide range of non-traditional bond cleavages and formations under mild reaction conditions, owing to the unique methods used to generate radicals and the high reactivity of these species.[4] In particular, visible light-driven photocatalysis, which allows radical transformations to be performed in a sustainable manner, is a powerful tool in organic synthesis.[5] Among the developed activation modes, photoredox catalysis, in which the catalytic cycle is triggered by an outer-sphere single-electron transfer (SET) between the excited state photosensitizer and the substrate *via* oxidative quenching or reductive quenching (Scheme 1), is one of the most popular due to the rapid development of both photoredox catalysts and cooperative catalytic systems based on other catalytic platforms.[5,6] Notably, this catalysis platform allows the generation of a variety of H-bonding donor/acceptor-containing intermediates, such as radicals, radical ions and neutral intermediates. The use of an extrinsic chiral H-bonding catalyst could recognize these species or their reaction partners bearing H-bonding donors or acceptors through H-bonding interactions. Such a weak interaction should improve the nucleophilicity or electrophilicity of these species and alter their stability, therefore increasing the chemoselectivity of the reaction and the reactivity of the substrate and allowing the chiral catalysts to form the stereocentres with good enantiocontrol. As such, the merger of chiral H-bonding catalysis and photoredox catalysis would be a promising protocol in asymmetric synthesis.[7]



Scheme 1 Cooperative asymmetric and H-bonding catalysis.

In fact, the development of asymmetric photoredox catalysis has attracted the attention of chemists for many years. In 2005, Bach and co-workers made a breakthrough in this field; they reported an enantioselective cyclization using chiral photosensitizer **2** (Scheme 2).[8] Under photoirradiation (λ > 300 nm), the ketone moiety of **2** can be excited to undergo SET with the tertiary amine of substrate **1**. The generated α-amino radical species can then undergo an enantioselective Giese-type addition to the active olefin with the amide moiety of **2** acting as a bifunctional H-bonding catalyst to interact with the amide unit of **1**, thus providing enantiocontrol. Although only a moderate enantiomeric excess was obtained for **3** (70% ee), the realization of enantiocontrol in this highly reactive radical-based transformation, especially when only using weak H-bonding catalysis, demonstrates the viability of asymmetric

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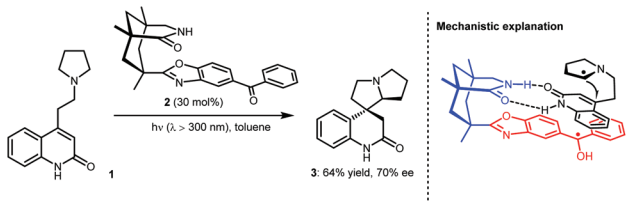


Scheme 2 Chiral photosensitizer-catalysed asymmetric cyclization reaction.

photoredox catalysis. Along with the development of SOMO catalysis, in 2008, MacMillan and co-workers reported a highly enantioselective alkylation of aldehydes by merging photoredox and chiral secondary amine catalysis.[9] Both successes inspired chemists to pursue stereoselective photoredox catalysis by exploiting distinct catalytic asymmetric strategies. Cooperative photoredox and H-bonding catalysis strategies have also been developed; by establishing efficient catalytic systems that can provide robust stereocontrol for highly reactive radical transformations and overcome strong racemic background reactions, a number of valuable but challenging reactions have been achieved with high enantioselectivities.

In this review, we summarize the advances in cooperative photoredox and H-bonding catalysis from the first example by Bach to March 2020. This review is organized into four parts according to the distinct bond-forming patterns in the construction of the stereocentre, namely, radical additions, radical cross couplings, C–C and C–O bond formation *via* ionic-type pathways and C–H bond formation *via* ionic-type pathways.

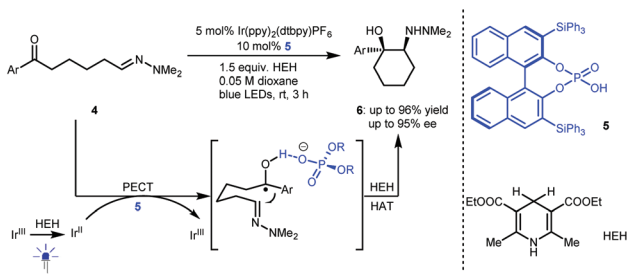
Enantioselective radical addition

Radical addition is a powerful strategy for rapidly constructing chemical bonds.[4] In 2013, Knowles and co-workers reported an intramolecular enantioselective aza-pinacol cyclization of **4** in the presence of a dual catalyst system involving BINOL-derived chiral phosphoric acid (CPA) **5** and $Ir(ppy)_2(dtbpy)PF_6$ as a photosensitizer and using Hantzsch dihydropyridine (HEH) as a stoichiometric reductant (Scheme 3).[10] The CPA was responsible for the reduction of the ketone moiety of **4** *via* a proton-coupled electron transfer (PCET) process.[11] They also verified the strong basicity of the generated ketyl intermediate, which enables CPA to closely interact with the substrate, thus providing perfect enantiocontrol for the subsequent radical addition to an imine. This work represents the first cooperative photoredox and H-bonding catalysis with high enantioselectivity (see **6**). This provided a new starting point for using chiral H-bonding catalysis in radical chemistry.

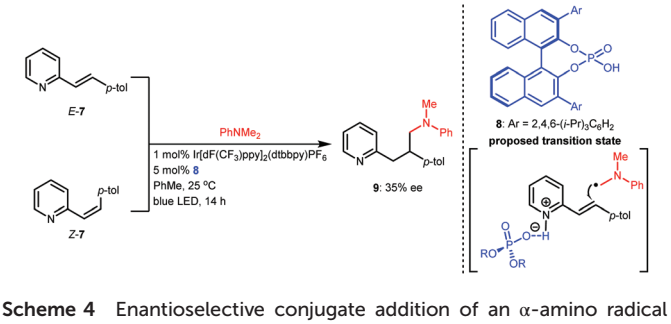
Imine-bearing azaarenes, such as pyridines, quinolines, isoquinolines, and imidazoles, are significant structural motifs that ubiquitous in diverse natural products, pharmaceuticals and materials.[12] Given their electron-deficient properties, in recent years, exploiting these azaarenes as analogues of carbonyls to trigger asymmetric transformations of prochiral azaarene-based substrates has been widely used as a direct approach for accessing chiral azaarene derivatives.[13] The fact that these azaarenes are less able than carbonyls to activate functional groups leads to limited strategies and has inspired chemists to attempt highly reactive radical pathways by using cooperative photoredox and H-bonding catalysis.

Based on the success of racemic phosphoric acid-catalysed conjugate addition of α-amino radicals generated from the single-electron oxidation of *N*,*N*-dimethyl anilines to alkenylpyridines, in 2016, the Melchiorre group attempted the enantioselective variant with alkene **7** as the representative substrate using BINOL-CPA **8** as the chiral catalyst (Scheme 4).[14] Desired product **9** was obtained with 35% ee. Interestingly, both *E*-**7** and the diastereomer *Z*-**7** separately underwent this transformation with the same enantioselectivity, which was likely due to a Curtin–Hammett-type kinetic situation. Although the enantioselectivity was not satisfactory, only 10 mol% of the CPA yielded a product with 35% ee, which strongly supports the feasibility of asymmetric H-bonding catalysis in azaarene-involved radical reactions through the H-bonding interaction of the basic N of azaarenes with the proton of a chiral Brønsted acid.

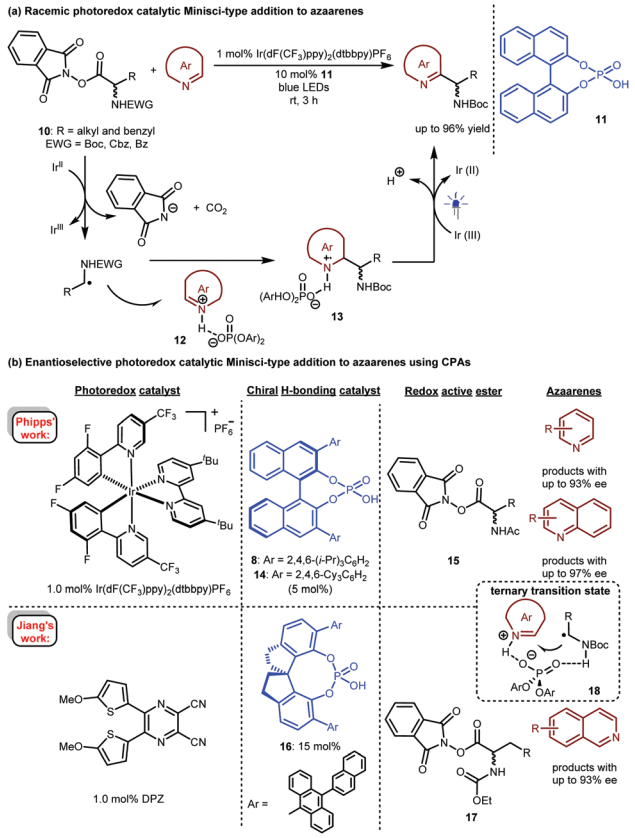
In 2017, Fu and co-workers described a photoredox-catalysed Minisci-type addition of α-amino acid-derived redox active esters (RAEs) **10** to azaarenes (Scheme 5a).[15] In the presence of 1 mol% $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ as a photosensitizer, RAE **10** could be reduced by an Ir(II) species. The obtained α-amino radicals would add to azaarene **12**, which was activated by racemic phosphoric acid **11**, leading to radical intermediate **13**. After single-electron oxidation and deprotonation,



Scheme 3 Enantioselective aza-pinacol cyclization.



Scheme 4 Enantioselective conjugate addition of an α-amino radical to alkenylpyridine.



Scheme 5 Photoredox-catalysed Minisci-type additions to azaarenes.

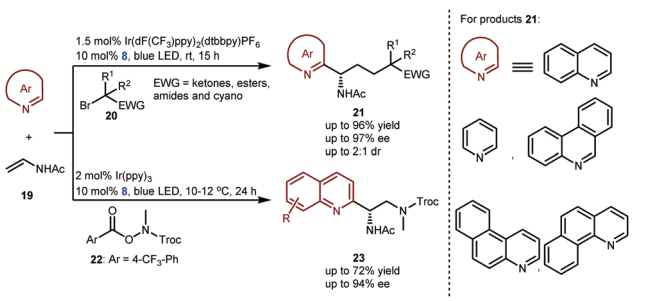
a wide range of valuable azaarene-substituted secondary amines were obtained in up to 96% yield. This work revealed the possibility of realizing stereocontrolled variants.

Only one year later, Phipps and co-workers reported an enantioselective version of this important transformation (Scheme 5b).[16] They used a dual catalytic system involving 1.0 mol% of $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ and 5.0 mol% of (*R*)-TRIP (**8**) or (*R*)-TCYP (**14**), realizing the highly enantioselective addition of various RAEs **15** to a variety of pyridines and quinolines. In the same year, Jiang's group[17] achieved the same reaction with their developed highly efficient visible light-absorbing organic photosensitizer, a dicyanopyrazine-derived chromophore (DPZ)[18] and SPINOL-CPA **16** as the catalyst. Unlike Phipps' work, this catalytic system was suitable for isoquinolines; with RAEs **17** as the reaction partners, products were obtainable in up to 93% ee. Both works proposed a H-bonding catalytic mechanism involving a ternary transition state (**18**) in which the CPA acts as a bifunctional catalyst to simultaneously interact with the proton of the radical species and the N of the azaarenes, therefore providing enantiocontrol for the new C–C bond formation. Notably, in 2019, Fu and Shang and co-workers also developed an organocatalytic system[19] based on sodium iodide (20 mol%), triphenylphosphine (20 mol%) and SPINOL-CPA (5.0 mol%), and these reagents furnished azaarene-substituted chiral secondary amines with a similar substrate scope and enantioselectivity to those of Phipps.

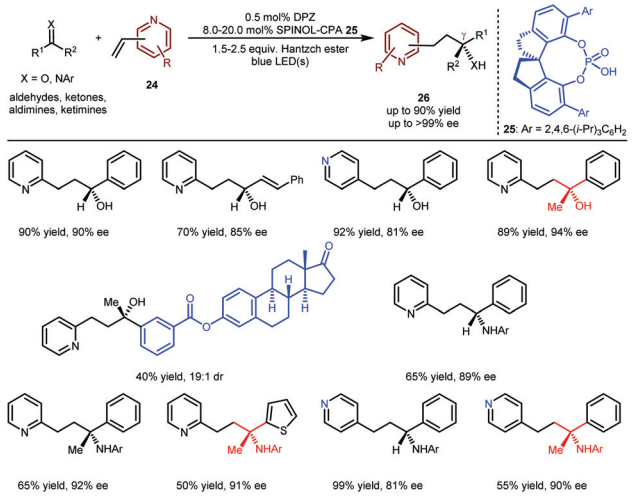
In 2019, the Studer group elegantly extended the enantioselective Minisci-type addition into a more challenging three-component radical cascade reaction (Scheme 6).[20] In the presence of $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ and CPA **8** as a dual catalyst system, the reactions of azaarenes with enamides **19** and α-bromo carbonyl compounds **20** afforded valuable chiral heterocyclic γ-amino acid derivatives **21** in high yields and enantioselectivities. The scope of azaarenes is extremely broad, including quinolines, pyridines, and several quinolines with an additional fused benzene ring. This strategy is also compatible with the sequential addition of amidyl radicals, which are generated from oxidizing substrates **22** to the enamides and then to quinolines, leading to another kind of important chiral azaarene, derivative **23**, with satisfactory results.

The above achievements (Schemes 5 and 6) were focused on building tertiary stereocentres α to azaarenes.[16,17,19,20] As depicted by Melchiorre,[14] the enantioselective formation of chiral centres at the β-position of azaarenes under the catalysis of CPA remains challenging, likely due to the greater distance between the α-amino radical and the nitrogen-coordinated chiral catalyst, which weakens the efficacy of the enantiofacial induction. Nevertheless, the Jiang group still explored the possibility of H-bonding catalysis in constructing even more distant γ-stereocentres through the conjugate addition of prochiral radicals to vinylazaarenes. Given the biological importance of the resulting chiral products, they explored the addition of aldehydes, ketones, aldimines and ketimines to vinylpyridines **24** (Scheme 7) *via* a reductive coupling strategy.[21] As a result,[22] when using DPZ with SPINOL-CPA **25** as cooperative catalysts, desired adducts **26** could be achieved in up to 90% yield with up to >99% ee. Notably, the substrate scope is very broad with respect to the both pro-nucleophiles and the pyridine electrophiles; a series of chiral secondary and tertiary alcohols/amines were embedded at the γ-position of 2-pyridines and 4-pyridines. The high enantioselectivity towards both the complex oestrone-derived ketone and 4-vinylpyridine as substrates further demonstrates the robust abilities of CPAs as bifunctional chiral H-bonding catalysts in asymmetric photoredox-catalysed reactions of prochiral azaarenes.

Very recently, Knowles and co-workers reported an enantioselective intramolecular hydroamination of alkenes with sulfonamides under a dual catalyst system including [$Ir(dF(CF_3)$



Scheme 6 Enantioselective three-component Minisci-type addition to azaarenes.



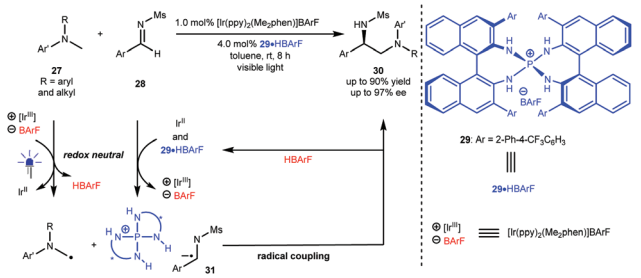
Scheme 7 Catalytic enantioselective addition of prochiral radicals to vinylpyridines.

ppy)$_2$(5,5′-dCF$_3$bpy)]PF$_6$ (2 mol%) and a BINOL-derived phosphate (2.5 mol%).[23] These transformations were proposed to occur *via* *N*-centred radicals generated by PCET activation of sulfonamide N–H bonds. The H-bonding interaction between the neutral sulfonamidyl radical and the CPA generated in the PCET event was hypothesized to be the basis for asymmetric induction in the subsequent C–N bond-forming step, providing enantioenriched pyrrolidine products with up to 96% ee.

Enantioselective radical cross coupling

Radical cross coupling reactions can generally yield new chemical bonds owing to the approximately barrierless docking of the two distinct odd-electron partners.[4] In this context, this strategy can likely provide an efficient and direct synthetic approach to important molecules with high functional group tolerance. However, this synthetic advantage becomes a challenge for enantioselective variants since the high reactive radical content leads to elusive stereocontrol and, at the same time, results in a strong racemic background reaction. Furthermore, the homocoupling of radicals also makes chemoselectivity a significant challenge.[24] As such, it is highly desirable to develop generic and efficient catalysis platforms for diverse enantioselective radical cross coupling reactions in both fundamental research and practical applications.

In 2015, Ooi *et al.*[25] reported a redox neutral, highly enantioselective coupling between *N*-arylaminomethanes **27** and *N*-sulfonyl aldimines **28** by harnessing the dual catalysis of *P*-spiro chiral arylaminophosphonium barfate (**29**·HBArF) and [Ir(ppy)$_2$(Me$_2$phen)]BArF as the photosensitizer under visible light irradiation (Scheme 8). The reaction was triggered by the reductive quenching of the photoactivated Ir(III) complex with **27**, resulting in an Ir(II) intermediate and α-amino radicals. Aldimines **28** were then reduced by Ir(II) to generate radical anions, which can be captured by a chiral

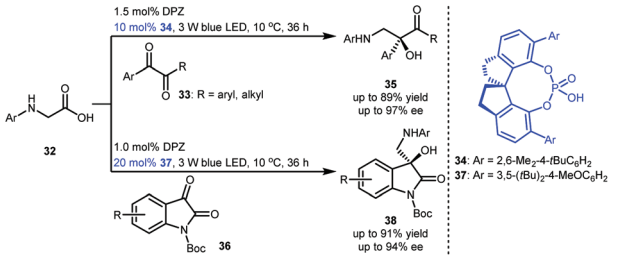


Scheme 8 Redox neutral α-coupling of *N*-arylaminomethanes with aldimines.

catalyst *via* counterion and H-bonding interactions (see **31**). The coupling of α-amino radicals with **31** afforded valuable chiral diamine products **30** containing a tertiary stereocentre in up to 90% yield with up to 97% ee. This work represents the first enantioselective radical coupling reaction by asymmetric photoredox catalysis. Subsequently, they established a catalytic cycle initiated by the oxidative quenching of the excited photosensitizer (Ir*(ppy)$_3$) for the same transformations.[26]

To develop a strategy for synthesizing important chiral tertiary alcohols containing a primary amine at the β-position, Jiang and co-workers developed an enantioselective radical coupling of *N*-aryl glycines **32** with acyclic activated ketones (*i.e.*, 1,2-diketones **33**) and cyclic activated ketones (*i.e.*, *N*-Boc isatins **36**) (Scheme 9).[27] By exploiting a cooperative photoredox and chiral H-bonding catalytic system involving DPZ and SPINOL-CPAs **34** and **37**, corresponding products **35** and **38** were synthesized in high yields and enantioselectivities. In this work, more challenging heteroquaternary stereocentres were also successfully constructed.

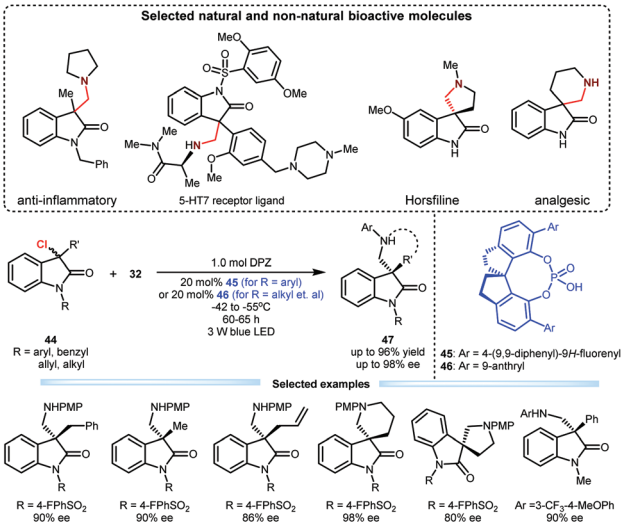
Alkyl halides are diverse, abundant and readily accessible feedstocks in organic synthesis. The nucleophilic substitution of alkyl halides is a fundamental chemical transformation for accurately delivering molecular fragments to sp^3-hybridized carbon atoms utilizing the halide as the directing group.[28] Although many methods, especially classic S$_N$1 and S$_N$2 reactions, have been established and extensively used in the synthesis of complex molecules, enantioconvergent substitutions that form a carbon stereocentre in simple alkyl halides remains challenging, thus attracting the attention of chemists.[29] Given the oxidative ability of alkyl halides and a wide



Scheme 9 Redox neutral, enantioselective radical coupling of *N*-aryl glycines with activated ketones.

array of readily available and bench-stable reducible organic molecules, Jiang and co-workers developed an asymmetric photoredox catalytic strategy that offers a new and direct synthetic approach with high functional group tolerance. They explored the viability of transformations of *N*-aryl amino acids and α-halo carbonyl compounds by using cooperative photoredox and chiral bifunctional H-bonding catalysis (Scheme 10a).[30] Two distinct radical species could be generated through this redox neutral pathway, and the H-bonding interactions of the chiral catalyst with both the α-amino radicals and the α-radicals of the carbonyl compounds would improve their nucleophilicity and electrophilicity, respectively, thus providing a stereocontrolling environment for C–C bond formation *via* radical coupling. As a result, by using DPZ and SPINOL-CPA (**25**, **37**, **41** or **42**), a variety of α-bromo ketones could smoothly react with diverse *N*-aryl amino acids (**32** and **40**), affording a wide range of valuable enantiomerically pure β^2- and $\beta^{2,2}$-amino ketones **43** in satisfactory yields with good to excellent enantioselectivities (Scheme 10b). Fluoro-heteroquaternary and full-carbon quaternary stereogenic centres that are otherwise difficult to prepare were successfully constructed. Notably, after the single-electron reductive debromination of **39**, the generated radicals more easily undergo single-electron reduction-protonation in the absence of CPA, indicating that H-bonding catalysis is crucial for the chemoselectivity.

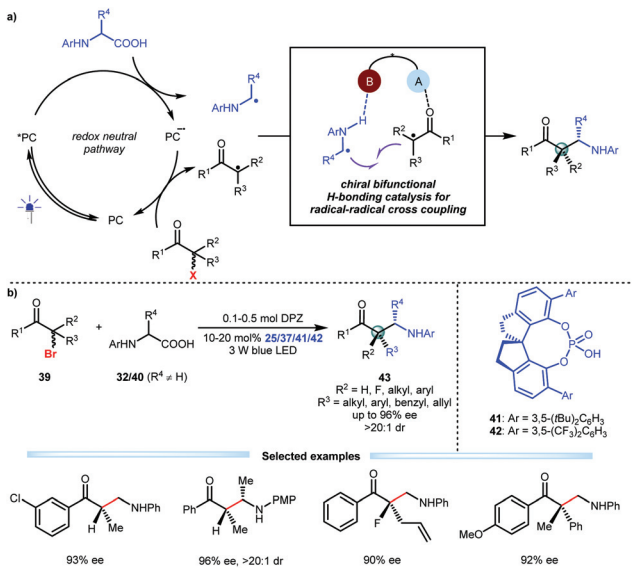
Upon the above success, they subsequently tested this cooperative catalysis platform in the reaction of 3-chlorooxindoles **44** with *N*-aryl glycines **32** given the biological importance of the resulting adducts (Scheme 11).[31] In the presence of DPZ and SPINOL-CPA (**45** or **46**), the transformations could efficiently furnish products **47** in up to 96% yield with up to 98% ee. The substrate scope is satisfactory since 3-aryl, 3-alkyl and



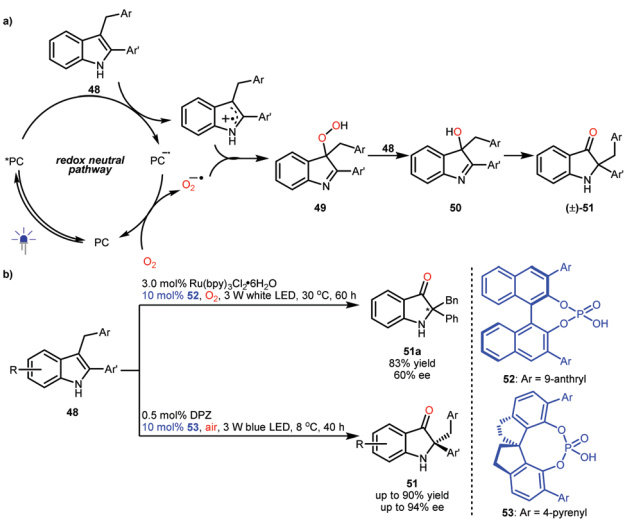
Scheme 11 Enantioconvergent substitution of 3-chlorooxindoles.

3-allyl 3-chlorooxindoles were all compatible. This method enables the direct synthesis of important spiro-five- and -six-membered ring-based products, which include horsfiline and analgesic therapeutic derivatives.

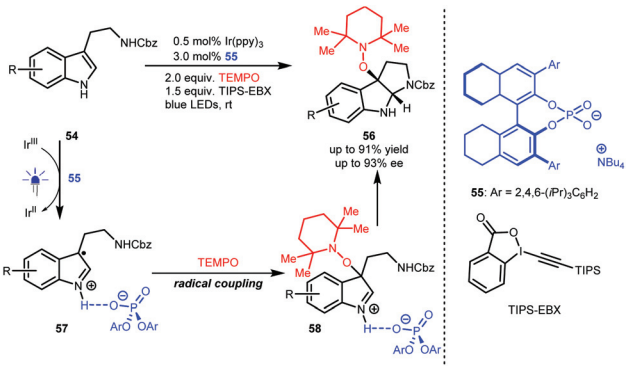
2,2-Disubstituted indolin-3-ones are privileged molecular architectures found in a number of pseudoindoxyl alkaloids. In 2014, the groups of Brasholz[32a] and Xiao[32b] independently reported an efficient synthetic method for accessing these valuable entities *via* a visible light-driven photoredox-catalysed aerobic oxidation and semipinacol rearrangement of 2-aryl-3-alkyl-substituted indoles (**48**) (Scheme 12a). Mechanistically, the two radical species obtained from **48** *via* single-electron oxidation and from oxygen gas *via* single-electron reduction (superoxide anion radical) will couple to produce intermediates **49**. Then, intermediates **50** were produced from the reac-



Scheme 10 Enantioconvergent substitution of alkyl halides *via* catalytic asymmetric photoredox radical coupling.



Scheme 12 Photoredox-catalysed aerobic cascade oxidation and semipinacol rearrangement.



Scheme 13 Enantioselective synthesis of pyrroloindolines.

tion between **48** and **49**, and **50** could subsequently undergo a semipinacol transformation to furnish 2,2-disubstituted indolin-3-ones ((±)-**51**). Notably, if the radical coupling could be achieved with enantiocontrol, enantioenriched **51** would be obtained. The viability of this hypothesis was revealed by the Xiao group, although only one example (**51a**) with moderate enantioselectivity was achieved by using a dual catalysis system of a Ru-based photosensitizer and BINOL-CPA (**52**) and under a pure oxygen atmosphere (Scheme 12b).[32b] In 2018, the Jiang group realized the first highly enantioselective example and they used a more convenient ambient atmosphere.[33] This organocatalytic system includes DPZ and SPINOL-CPA **53**. Their investigation also revealed that the formed chiral 3-hydroxy intermediates **50** could affect the enantioselectivity of the radical coupling, making enantiocontrol more difficult.

In 2018, Knowles and co-workers used TEMPO as the radical source and TIPS-EBX as the sacrificial oxidant and proton acceptor and developed an enantioselective synthesis of pyrroloindolines from *N*′-Cbz-protected tryptamines (**54**) *via* a sequential single-electron oxidation, radical coupling and addition processes.[34] As depicted in Scheme 13, H8-TRIP BINOL phosphate **55** acts as a Brønsted base and interacts with the radical cations generated from **54** to form radical species **57**, which is crucial to constructing stereocentres *via* C–O bond formation (**58**). Obtained products **56** are valuable since they were shown to react with diverse nucleophiles, affording important derivatives, most notably in the synthesis of (−)-calycanthidine.

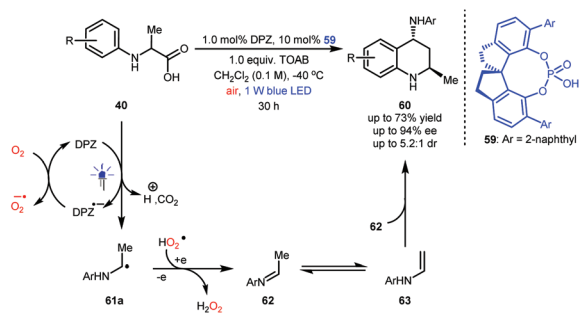
C–C and C–O bond formation *via* ionic-type pathways

In addition to offering highly reactive radical intermediates, photoredox catalysis can provide key electron-neutral or ionic intermediates that are difficult to prepare or are unstable. In conjunction with extrinsic asymmetric catalysis, this strategy has been widely applied in the synthesis of optically pure compounds.[35] There are also several elegant examples involving the exploitation of cooperative photoredox and H-bonding catalysis.

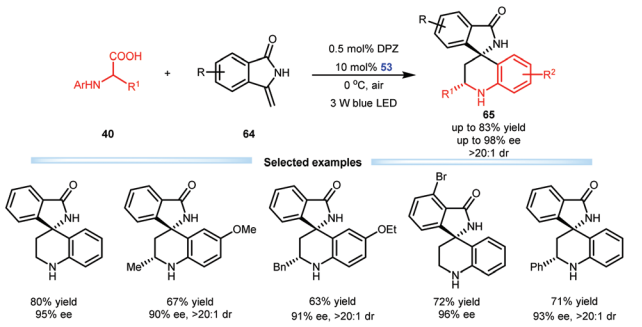
N-Aryl α-amino acids **40** can generate α-amino radicals **61a** after a single-electron oxidation (Scheme 14).[26–28] In fact, these species can be further oxidized, leading to imines (*e.g.*, **62**) that are not easily purified due to their lability in acidic silica gel.[36] Notably, alkyl-substituted imines are prone to tautomerization, resulting in enamines (*e.g.*, **63**). Jiang and co-workers hypothesized that *N*-aryl α-amino acids might undergo aerobic decarboxylative [4 + 2] cycloaddition (Povarov reaction) under photoredox catalysis, which would efficiently provide important 4-amino tetrahydroquinolines (THQs).[37] After careful investigations, this synthesis was realized, and a series of 4-amino THQs and even the corresponding quinolines were obtained in satisfactory yields. Given that there were no examples of the synthesis of chiral 4-amino-2-methyl-substituted THQs, likely due to the inconvenient manipulation of acetaldehyde and the instability of acetaldehyde-derived imines, they also engaged in developing a dual catalysis enantioselective manifold for the aerobic decarboxylative Povarov reaction of *N*-aryl alanines **40**. Finally, desired products **60** were obtained in up to 73% yield and with up to 94% ee and 5.2 : 1 dr by using 1.0 mol% DPZ, 10 mol% SPINOL-CPA **59** and 1.0 equiv. of *tetra-n*-octylammonium bromide (TOAB) as an additive and under ambient atmosphere.

Subsequently, Jiang *et al.* developed an enantioselective aerobic decarboxylative Povarov reaction of *N*-aryl α-amino acids **40** with methylenephthalimidines **64** in the presence of a dual catalysis system involving DPZ and SPINOL-CPA **53** (Scheme 15).[38] A range of important optically pure isoindolin-1-ones **65** that feature a 3,3-spiro-tetrahydroquinoline-based stereocentre were prepared in high yields, ees and drs. This work represents the first construction of the 3,3-spiro-six-membered ring of an isoindolin-1-ones through asymmetric catalysis. Notably, the unsatisfactory results of the SPINOL-CPA **53**-catalysed three-component Povarov reaction of **64** with aniline and distinct forms of formaldehyde underscore the synthetic importance of this protocol.

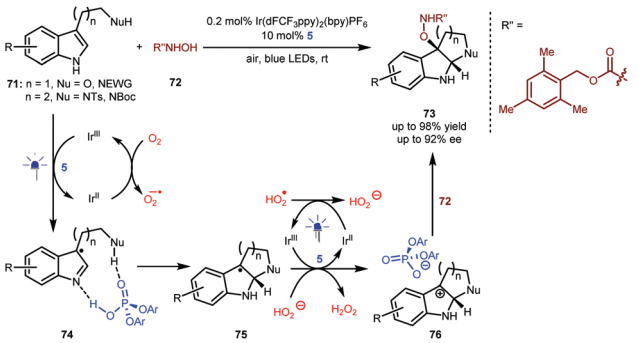
Wang and co-workers also developed oxygen-free conditions by using oxidizing α-amino acid-derived RAEs **15** as precursors



Scheme 14 Enantioselective synthesis of chiral 4-amino-2-methyl THQs.



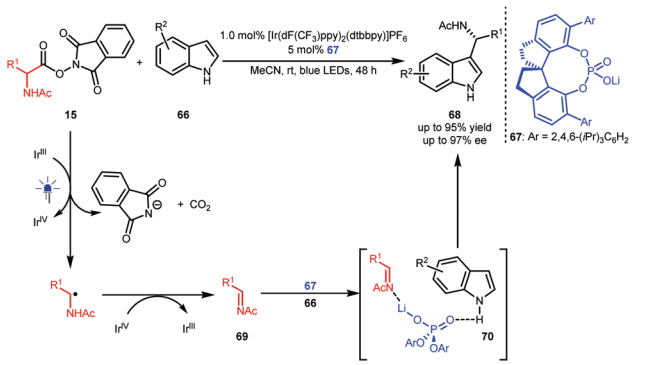
Scheme 15 Asymmetric aerobic decarboxylative Povarov reactions of *N*-aryl α-amino acids with methylenephthalimidines.



Scheme 17 Asymmetric dearomatization of indole derivatives.

of imines **69** (Scheme 16).[39] With indoles **66** as the reaction partners, an asymmetric Friedel–Crafts reaction occurred in the presence of BINOL-CPA-derived phosphate **67** as the catalyst, leading to enantioenriched 1-indolyl-1-alkylamine derivatives **68** in up to 95% yield with up to 97% ee. Ternary transition state **70** was proposed, wherein **67** acts as a Lewis acid-Brønsted base bifunctional catalyst to interact with both the N atom of the imine and the H atom of the indole.

As shown above (Scheme 13), Knowles reported an enantioselective synthesis of pyrroloindolines through a sequential process including a single-electron oxidation, a radical coupling and an addition.[34] The formation of the stereocentre at the 3-position of the indole ring *via* a radical coupling occurs prior to the formation of the stereocentre at the 2-position *via* the aza-Mannich reaction. Very recently, You and Zhang and co-workers reported an elegant alternative method that enables the use of hydroxycarbamate **72** as the nucleophile (Scheme 17).[40] In the presence of 0.2 mol% $Ir(dFCF_3ppy)_2(bpy)PF_6$ as a photosensitizer and under the irradiation of blue LEDs, a variety of tryptophols and tryptamines (**71**) with diverse protecting groups as well as indoles containing an amide side chain first underwent a single-electron oxidation to generate a radical species, which subsequently interacts with BINOL-CPA **5** (see **74**). Since the oxygen atmosphere allows the regeneration of the Ir(III) catalyst and the H-bonding interactions lower the activation energy, the enantioselective Mannich-type addition becomes the more favourable step, thus forming radical species **75** possessing a stereocentre at the 2-position of the indole ring. After the second single-electron oxidation, the generated cations would interact with the phosphate anion of **5** to offer complexes **76**, which then were attacked by nucleophilic **72**. As such, the formation of this C–O bond occurs *via* an ionic-type pathway. This umpolung method provides a general and efficient synthetic approach for accessing diverse valuable chiral pyrroloindolines and indolo[2,3-*b*] quinolines **73** bearing a fully substituted quaternary centre.



Scheme 16 Enantioselective Friedel–Crafts reaction.

C–H bond formation *via* ionic-type pathways

The construction of stereocentres *via* an ionic-type C–H bond formation process, namely, enantioselective protonation, has been widely used in the asymmetric synthesis of valuable enantioenriched compounds containing diverse tertiary carbon stereogenic centres.[3] The development of novel strategies to expand the utility of this classic transformation is always attractive. In this context, the merger of radical-based photoredox catalysis and enantioselective catalytic protonation would be a significant and promising research area, as it could offer a new pathway for accessing important chiral compounds and might unlock readily accessible but poorly reactive feedstocks for direct use as substrates. However, since protons are very small and thus feature high mobility, achieving excellent enantioselectivity in enantioselective protonations is always a formidable challenge. More importantly, the rapid radical process to form the prochiral tertiary carbon anion intermediate would lead to a racemic background reaction, further increasing the difficulty of achieving high enantioselectivity. Even when using stoichiometric chiral Brønsted acid in the asymmetric visible-light-induced radical reactions of 3-alkylidene indolin-2-ones, the enantioselectivity in the generation of the corresponding stereocentres *via* protonation was poor.[41] Nevertheless, the Jiang group focused on the development of photoredox-catalysed enantioselective protonation due to its significant advantage, that is, the ability to generate anion

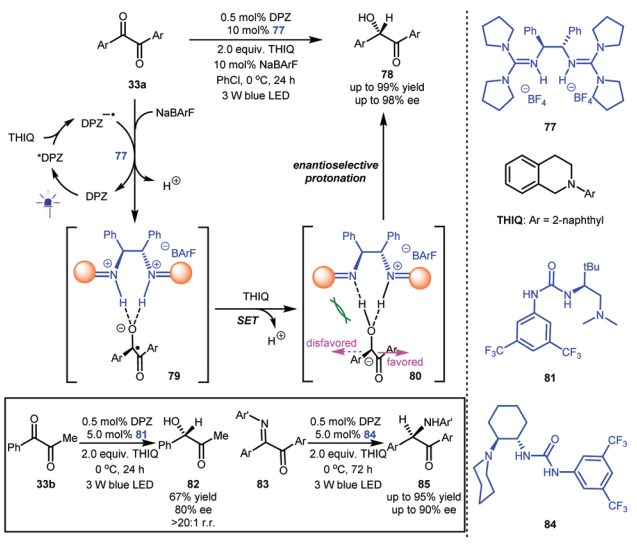
intermediates under controllable and near-neutral conditions *via* a radical process, and this would facilitate the construction of acid/base-labile tertiary stereocentres.

Optically enriched α-hydroxy ketones (*e.g.*, **78** and **82**, Scheme 18) are biologically and synthetically important molecular skeletons, and the asymmetric reduction of readily available 1,2-diketones (*e.g.*, **33a** and **33b**) could provide a direct approach to these valuable entities.[42] However, in addition to two reductions leading to poor chemoselectivity,[42b] in the reaction process, the strong electron-withdrawing ability of the ketone and the high electronegativity of the oxygen make the tertiary stereocentre lead to facile racemization of α-hydroxy ketones under the non-neutral reaction conditions.[42c] Therefore, the catalytic asymmetric transformation of 1,2-diketones into chiral α-hydroxy ketones has always been a challenging task.

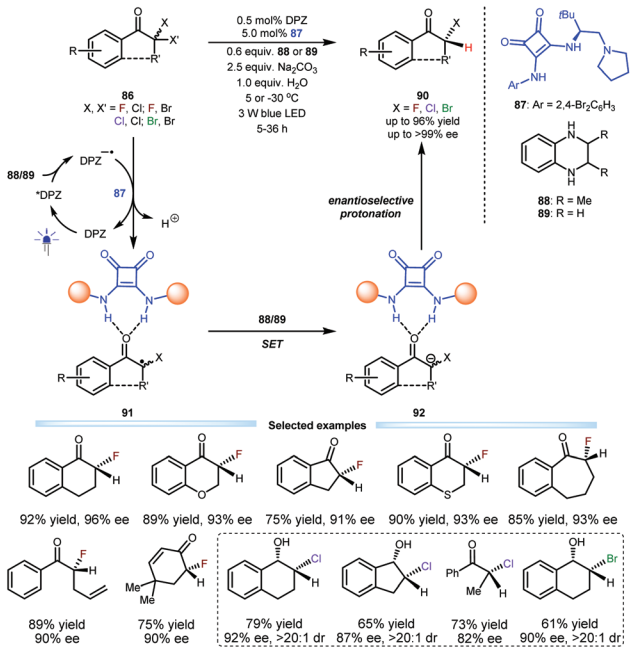
In 1990, Willner *et al.* described the reduction of benzil to benzoin with $[Ru(bpy)_3]Cl_2$ as a photoredox catalyst and Et_3N as a sacrificial reductant, and protonation was suggested as the final step in the formation of the secondary alcohol.[43] Inspired by this preliminary work as well as Knowles' report[10] on ketyl intermediates featuring a strong basicity, Jiang and co-workers reported the highly enantioselective reduction of 1,2-diketones (**33a** and **33b**, Scheme 18) by establishing a dual catalytic system including DPZ and chiral guanidinium salt **77** as a Brønsted acid.[44] With symmetric 1,2-diketones **33a** as an example, the obtained $DPZ^{-\bullet}$ from the reductive quenching of photoactivated DPZ by *N*-2-naphthyl tetrahydroisoquinoline (THIQ) could reduce **33a** to generate the corresponding ketyl intermediates, which were then captured by **77** to form neutral radical species **79**. The second single-electron reduction by THIQ afforded anion **80**. In the stereocontrol environment provided by **78**, enantioselective protonation was accomplished with good to excellent enantioselectivity (up to 98% ee). This investigation showed that the transformation occurred even without DPZ because it proceeds through an 'electron donor-acceptor' (EDA) mechanism, but the enantioselectivities of most of the products were lower than those obtained *via* the photoredox catalytic system. They next evaluated 1-phenyl-1,2-propanedione **33b** as a representative unsymmetrical diketone, and *tert*-L-leucine-derived urea-tertiary amine[45] **81** was determined to be the most suitable chiral catalyst; chiral alcohol **82** was obtained in 67% yield with 80% ee and excellent regioselectivity and chemoselectivity. By using Takemoto's 1,2-cyclohexanediamine-based urea-tertiary amine **84** and DPZ as the catalytic system, α-keto ketimines **83** could be efficiently reduced to α-amino ketones **85** in up to 95% yield with up to 90% ee. The fact that using three different kinds of H-bonding catalysts achieved excellent enantioselectivities suggests that similar dual catalyst systems could provide good results by carefully selecting the catalysts. Certainly, it also demonstrates chiral H-bonding catalysis in highly reactive radical-based transformations.

Their success in that reaction inspired them to exploit this dual catalysis platform for the construction of secondary α-carbon-halogen (*i.e.*, F, Cl and Br) bonds of ketones, which are important in the pharmaceutical and synthetic fields, but there are few efficient strategies that can provide high enantioselectivity due to the lability of stereocentres. To this end, a series of α,α-dihaloketones **86** were selected as the starting substrates; in the presence of 0.5 mol% DPZ and 5.0 mol% L-*tert*-leucine-derived squaramide-tertiary amine **87** and using secondary amine **88** or **89** as the terminal reductant, desired products **90** containing secondary C–F, C–Cl and C–Br bonds were obtained in up to 96% yield and up to >99% ee with a broad substrate scope. Notably, the control experiment disclosed a strong competitive racemic background reaction in the reaction system (Scheme 19).[46] The photoredox catalytic cycle was triggered by the single-electron transfer between photoactivated DPZ and the secondary amine (**88** or **89**). Subsequently, a C–Cl or C–Br bond of **86** would be reduced by $DPZ^{-\bullet}$ due to their matched redox potentials. Because of the weaker basicity of carbonyl relative to ketyl, the two H-bonding interactions between the two N–H units of squaramide and oxygen of the carbonyl (see **91**) are crucial, as they can stabilize the radical intermediates. After a secondary single-electron reduction to generate anions **92**, enantioselective protonation to access products **90** was achieved with satisfactory results. Notably, their investigation revealed the considerable lability of C–Cl/Br bond-based stereocentres, since the ee value of the products deteriorated during flash column chromatography. Accordingly, a sequential strategy involving a subsequent one-pot reduction of ketones by diisobutylaluminium hydride (DIBAL-H) was established. Therefore, a series of valuable chloro/bromo-hydrins were prepared.

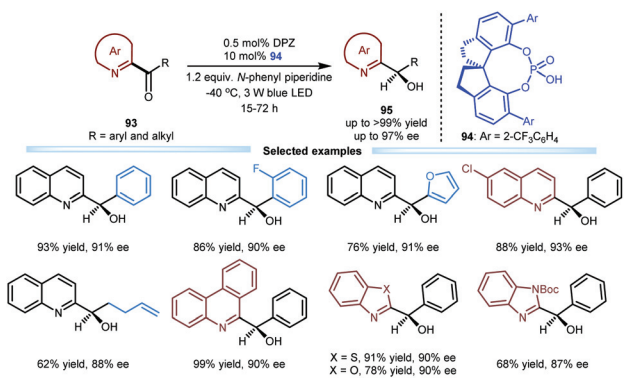
Due to the biological importance of imine-bearing azaarene-substituted secondary alcohols and the lack of general and expedient catalytic methods for accessing these compounds, Jiang and co-workers also investigated the enantioselective reduction of azaarene-based ketones **93** *via* visible light-driven photoredox asymmetric catalysis (Scheme 20). This work can



Scheme 18 Enantioselective photoredox-catalysed reductive protonation.

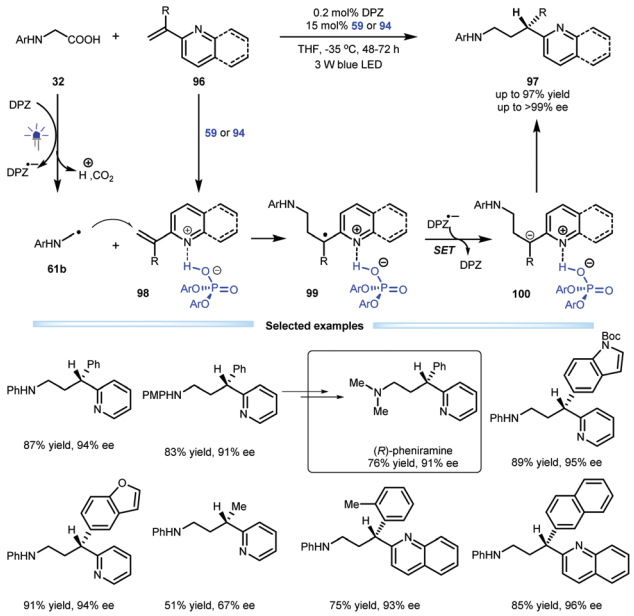


Scheme 19 Enantioselective photoredox dehalogenative protonation.



Scheme 20 Enantioselective reduction of azaarene-based ketones.

be considered a logical and highly useful extension of the photoreduction of 1,2-diketones by using these azaarenes as analogues of carbonyls.[47] As a result, under the established dual catalytic system involving SPINOL-CPA **94** and DPZ and using *N*-phenyl piperidine as the terminal reductant, various ketones **93** could efficiently undergo this tandem process involving two single-electron-transfer reductions and an enantioselective protonation. A wide range of chiral azaarene-based secondary alcohols **95** with diverse aryl and alkyl substituents and different azaarene moieties could be prepared in high yields (up to >99%) with moderate to excellent enantioselectivities (up to 97% ee). On the basis of these achievements in enantioselective reductive protonation[44,47] and enantioselective reductive dehalogenative protonation,[46] they subsequently developed an enantioselective reductive deuteration of azaarene-substituted ketones and an enantioselective reductive dehalogenative deuteration of racemic α-chloro-azaarenes



Scheme 21 Radical conjugate addition-enantioselective protonation.

with inexpensive D_2O as the deuterium source.[48] Under cooperative photoredox and H-bonding catalysis (*i.e.*, DPZ with SPINOL-CPA), a variety of chiral α-deuterated azaarenes were obtained in satisfactory yields with good to excellent enantioselectivities (up to 99% ee) and substantial deuterium incorporation.

Indeed, the first example of the construction of chiral azaarene-based derivatives *via* enantioselective protonation was reported by the Jiang group in 2018, and they used a radical conjugate addition-enantioselective protonation of *N*-aryl glycine **32** to afford α-branched 2-vinylazaarenes **96** (Scheme 21).[49] By using a dual catalytic system involving DPZ and SPINOL-CPA **59** or **94** mediated by visible light, the transformations afforded a variety of valuable chiral 3-(2-pyridine/quinoline)-3-substituted amines **97** in up to 97% yield with up to >99% ee. The mechanism studies revealed that α-amino radicals **61b**, which are derived from **32** after a sequential process involving single-electron oxidation, deprotonation, proton transfer and decarboxylation, can smoothly attack Brønsted acid-activated olefins (**98**), leading to radical species **99**. After the second single-electron reduction, resulting anions **100** can then undergo enantioselective protonation to generate products **97**. The low reaction temperature was crucial to achieving excellent enantioselectivity since it could completely supress the racemic background reaction. Notably, the enantiomerically pure therapeutic compound pheniramine (Avil) was conveniently synthesized from the obtained product.

Conclusions

Based on the continuous contributions of chemists in recent years, cooperative photoredox and H-bonding catalysis has

become a powerful tool in asymmetric synthesis. Although radical-based transformations are highly reactive and the energy of H-bonding interactions is rather low, a number of amazing and useful asymmetric chemical transformations have been successfully developed, even though racemic background reactions are apparent in most cases. In particular, several highly challenging reactions that have been long-standing challenges in the field have been successfully conquered, such as asymmetric Minisci-type reactions, enantioconvergent substitutions of alkyl halides, and enantioselective protonations to construct labile tertiary carbon stereocentres. A large array of important enantioenriched compounds have been achieved through various bond-forming patterns, including radical addition, radical coupling and different ionic-type pathways. Among them, the successful enantioselective construction of all-carbon quaternary stereocentres *via* highly reactive radical couplings robustly demonstrates the powerful stereocontrol possible with chiral H-bonding catalysis. Moreover, the capacity of H-bonding catalysis to improve the poor chemoselectivity seen in photoredox catalysis, which has represented a major challenge in the past, has been disclosed. It is foreseeable that there is ample scope for the greater use of this robust catalysis platform following the development of photoredox catalysts, chiral H-bonding catalysts and new methodologies. In addition to the new reaction types and allowing the use of more kinds of readily accessible substrates, especially abundant industrial feedstocks, cooperative photoredox and H-bonding catalysis will be applied to the more challenging multicomponent reactions and the synthesis of complex chiral molecules in the future. Such discoveries should find broad application in the total synthesis of bioactive natural and non-natural products, drugs and functional materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Grants from the National Science Foundation of China (21672052 and 21925103), the PhD Research Foundation of Henan University of Technology (2019BS003) and Young Elite Scientists Sponsorship Program by CAST (2017QNRC001) are gratefully acknowledged.

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