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# Iminium and enamine catalysis in enantioselective photochemical reactions

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Although enantioselective catalysis under thermal conditions has been well established over the last few decades, the enantioselective catalysis of photochemical reactions is still a challenging task resulting from the complex enantiotopic face differentiation in the photoexcited state. Recently, remarkable achievements have been reported by a synergistic combination of organocatalysis and photocatalysis, which have led to the expedient construction of a diverse range of enantioenriched molecules which are generally not easily accessible under thermal conditions. In this tutorial review, we summarize and highlight the most significant advances in iminium and enamine catalysis of enantioselective photochemical reactions, with an emphasis on catalytic modes and reaction types.

**Key learning points**
(1) The concept of synergistic combination of iminium and enamine catalysis with photocatalysis.
(2) The photogeneration of *ortho*-quinodimethanes, open-shell free radicals and iminium cations.
(3) The single-electron-transfer (SET) mechanism in enantioselective photochemical reactions.
(4) The direct excitation of iminium ions and enamines in enantioselective photochemical reactions.
(5) The electron donor–acceptor (EDA) complex mechanism in enantioselective photochemical reactions.

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## 1. Introduction

Chiral molecules, which can be found in diverse families of naturally occurring alkaloids and biologically active substances, play an important role in the field of synthetic chemistry, medicinal chemistry, material science, and industrial production. A key feature for the advancement of modern organic chemistry is the development of novel and efficient methods that allow for rapid construction of enantiomerically pure compounds from readily available starting materials.[1] In this regard, enantioselective catalysis, also referred to as asymmetric catalysis,[2] has emerged as a powerful and alluring strategy to advance this goal and it has fascinated chemists for the last decades. A plethora of catalytic transformations based on enantioselective catalysis has been established, and research in this discipline continues to expand vibrantly. Nevertheless, the enantioselective catalysis of photochemical reactions (enantioselective photocatalysis) is still a formidably challenging task resulting from the intrinsic factors of photochemical processes.[3]

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At the dawn of enantioselective photochemistry, circularly polarized light (CPL) was frequently used as the source of chirality.[3] However, the use of CPL was limited to specific starting materials and the relatively low reaction efficiency largely stymied its application as a universal approach in enantioselective photochemistry. Additionally, asymmetric organocatalysis, a relatively large branch of enantioselective catalysis, started to blossom in the beginning of the 21st century, and it has developed into a flourishing research field. A large number of fine and useful enantioenriched chiral compounds with a well defined three-dimensional spatial arrangement have been constructed by means of organocatalytic protocols.[4] The success of asymmetric organocatalysis is attributed to privileged enantiopure structures such as proline, cinchona alkaloids, BINOL (1,1′-bi-2-naphthol), and related compounds. These small molecules could be easily elaborated into different bespoke organocatalysts which have found a myriad of applications in asymmetric organocatalysis. Meanwhile, asymmetric organocatalysis also opens new avenues for chemists to approach the enantioselective catalysis of photochemical reactions. For instance, iminium and enamine catalysis using chiral amines, Brønsted acid catalysis employing chiral phosphoric acids, hydrogen bonding catalysis with chiral ureas and thioureas, N-heterocyclic carbene catalysis using chiral heteroazolium salts as well as phase-transfer catalysis with


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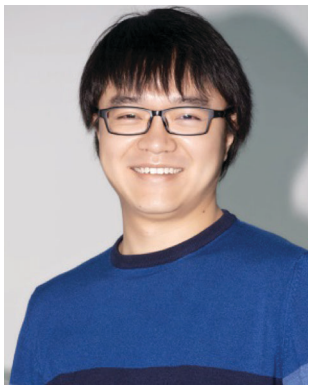
chiral ammonium salts have been successfully introduced into enantioselective photochemical reactions. In this context, iminium and enamine catalysis have recently grown in interest due to their high efficiency to activate aldehydes and ketones with excellent enantioselectivity, thus enabling the synthesis of diversely functionalized chiral carbonyl compounds.

Recently, some reviews have been written by us[5] and other research groups[6,7] in the field of enantioselective catalysis of photochemical reactions. However, to the best of our knowledge, there is still no specific and comprehensive review devoted to iminium and enamine catalysis in enantioselective photochemical reactions. Consequently, we herein provide a tutorial review to give a solid introduction to the field and highlight the recent breakthroughs in this area. Reactions which occur in heterogeneous conditions will be given less attention in this review. Organization of the data follows a subdivision according to catalytic modes (iminium or enamine catalysis) and reaction types. The emission wavelength or wavelength range of the irradiation is given in the schemes. The reaction temperatures are only specified if the reactions were not carried out at room temperature.



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## 2. Iminium catalysis

Iminium catalysis is a frequently used strategy to activate α,β-unsaturated carbonyl compounds.[8] Typically, the condensation of chiral amines with α,β-unsaturated aldehydes or ketones provides a reversible formation of iminium ions. The lowest unoccupied molecular orbitals (LUMO) of these iminium ions are lower in energy, which results in an enhanced electrophilicity and therefore can be more readily intercepted by nucleophiles. Various chiral amines were developed as iminium catalysts over the last decades to induce stereoselective reactions. They exhibit remarkable efficiencies and were largely applied in conventional thermal reactions. Recently, the application of selected chiral amines has also been extended into enantioselective photochemistry. Fig. 1 shows the structures of representative amines such as secondary amines **1–3** and primary amines **4–6** used in iminium catalysis of enantioselective photochemical reactions.

### 2.1 [2+2] Photocycloaddition reaction of iminium salts

One of the first examples involving chiral iminium ions in photochemical reactions was reported by the Mariano group in 2001.[9] As part of their research program on iminium salt photochemistry, they synthesized the alkene-tethered, chiral iminium perchlorate **7** from a $C_2$-symmetric chiral amine and tested its reactivity upon irradiation. The [2+2] photocycloaddition[10] of iminium salt **7** did indeed occur and after hydrolysis ketone **8** was obtained with 82% ee at 40% conversion (Scheme 1). The enantioselectivity was found to decrease at higher conversions. Substituents at positions C2 and C5 of the pyrrolidine were crucial, and the corresponding 2,5-diphenyl iminium ion showed no

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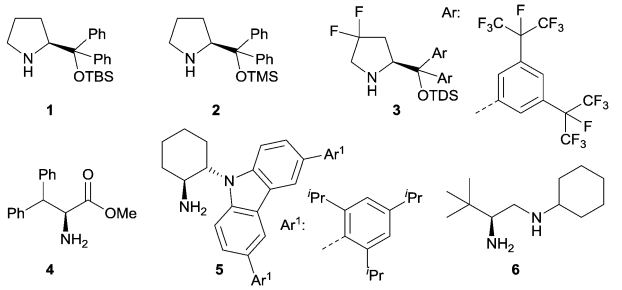
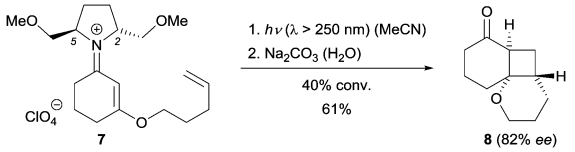
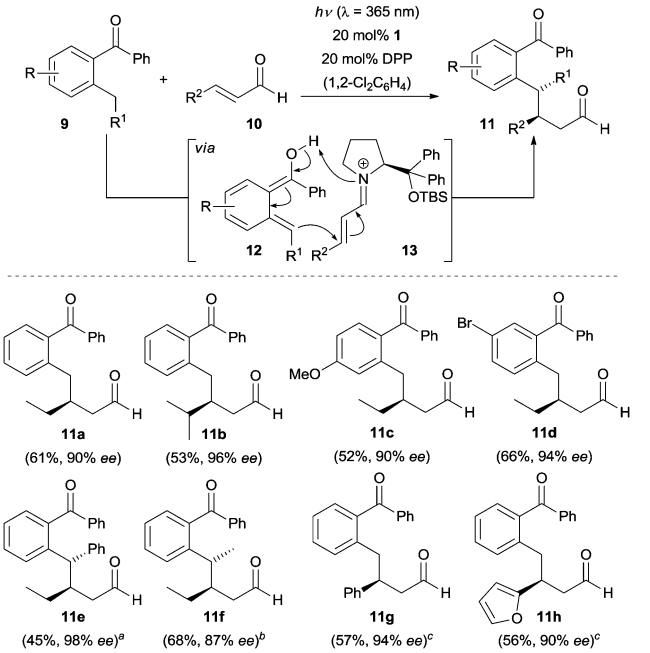



Fig. 1 Structures of representative chiral amines **1–6** for iminium catalysis in enantioselective photochemical reactions. TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, TDS = *tert*-hexyldimethylsilyl.




Scheme 1 Diastereoselective intramolecular [2+2] photocycloaddition reaction of iminium salt **7**.




Scheme 2 Enantioselective β-benzylation of enals **10**. [a] d.r. > 95/5. [b] d.r. = 56/44, the ee refers to the major diastereoisomer. [c] Toluene employed as the solvent using **2** as the catalyst.

reactivity which might result from the quenching of the iminium singlet excited state by the phenyl groups *via* single electron transfer (SET). Mechanistically, the reaction takes place at the singlet hypersurface *via* a concerted pathway resulting from the strong $\pi\pi^*$ absorption ($\varepsilon$ = 2–4 × $10^4$ $M^{-1}$ $cm^{-1}$) of the iminium salt at $\lambda \cong 280$ nm. Although the diastereoselectivity is good, the reaction capitalizes on a chiral auxiliary and is not catalytic.

### 2.2 β-Benzylation of enals and enones

The photoexcitation of *ortho*-alkyl substituted benzaldehydes and benzophenones generates *ortho*-quinodimethanes as highly reactive species *via* an intramolecular H-abstraction.[11] The resulting intermediates serve as dienes in Diels–Alder reactions and an enantioselective variant of this reaction was disclosed in 2003.[12] In 2016, Melchiorre and co-workers reported a catalytic enantioselective version of this transformation by using a cinchona alkaloid-derived bifunctional tertiary amine–thiourea catalyst.[13] More recently, Melchiorre, Maseras and co-workers discovered an enantioselective Michael-type addition reaction of photogenerated *ortho*-quinodimethanes to enals in the presence of a chiral secondary amine.[14] Using 20 mol% of diphenylprolinol *tert*-butyldimethylsilylether (**1**) and 20 mol% of diphenylphosphoric acid (DPP), benzophenones **9** reacted with aliphatic enals (*e.g.*, **10a–10f**) smoothly in 1,2-dichlorobenzene upon irradiation at $\lambda$ = 365 nm with a 15 W black light bulb to afford solely the β-benzylated products **11a–11f** in moderate yields with good to excellent enantioselectivity (Scheme 2). By simply switching the catalyst to diphenylprolinol trimethylsilylether (**2**) (*E*)-cinnamaldehyde **10g**, heteroaryl containing enals such as (*E*)-3-(furan-2-yl)acrylaldehyde (**10h**) were coupled with 2-methylbenzophenone in toluene to furnish the desired products with excellent enantioselectivity (94% and 90% ee, respectively).

In this transformation, chiral secondary amine **1** is condensed with enals **10** to iminium salts **13**. Additionally, a light induced enolization of *ortho*-alkyl substituted benzophenones to (*E*)-enol **12** occurs. The latter undergoes nucleophilic addition to the chiral iminium salt **13** to deliver the Michael-type addition products rather than [4+2] cycloadducts. A density functional theory (DFT) computational study was carried out by the authors to shed some light on this unusual reactivity and the results indicated that this transformation proceeds through a water assisted proton shuttle mechanism.

Recently, the Ye group[15] reported an enantioselective β-benzylation reaction of enones **14** *via* a similar strategy. As shown in Scheme 3, 2-cyclohexenone reacts – upon UV irradiation ($\lambda$ = 365 nm) – with a variety of 2-alkyl benzophenones **9** in the presence of 20 mol% of chiral amino acid ester **4** furnishing the β-benzylation products in moderate to good yields with excellent enantioselectivity (*e.g.*, **15a–15d**). Electron donating and electron withdrawing groups on the enolizable aromatic ring of benzophenones did not have a significant effect on the reaction efficiency. The substrate scope included a β-substituted cyclohexenone (product **15e**), an acyclic α,β-unsaturated ketone (product **15f**), and a seven-membered cyclic enone (product **15g**). None of the desired product was observed, when 2-cyclopentenone was used as the substrate. Interestingly, the reaction of 2-cyclopentenone did proceed to give the addition product **15h** in 99% ee when chiral amine **6** was employed as the catalyst.

In biological systems, iminium ions have been found to absorb visible light and induce primary photochemical events. The reactivity of these ions in the excited state[16] is dominated by electron transfer processes and has been extensively studied by the group of Mariano.[17] Very recently, Melchiorre and co-workers

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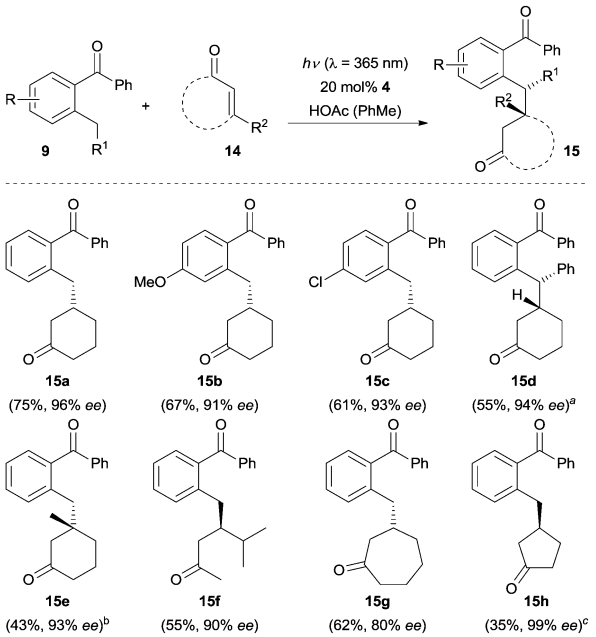


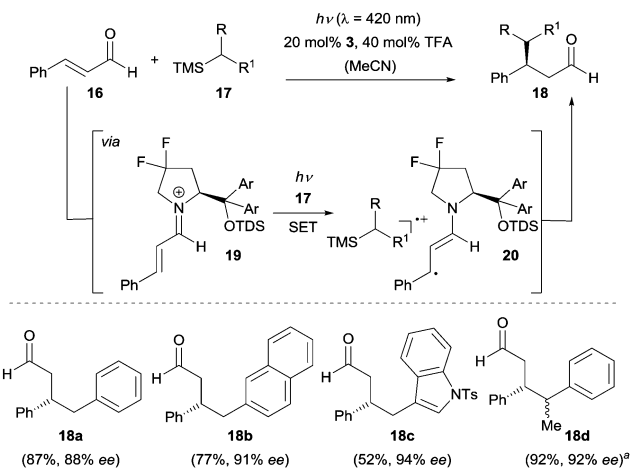

Scheme 3 Enantioselective β-benzylation of enones **14**. [a] d.r. > 95/5. [b] 50 mol% benzoic acid was used instead of acetic acid. [c] **6** was used as the chiral amine catalyst. HOAc = acetic acid.

disclosed the first asymmetric approach based on this reactivity enabling the enantioselective synthesis of β-alkylated aldehydes (Scheme 4).[18] Crucial for the success was (a) the high redox potential of iminium ion **19** in the excited state and (b) the bathochromic shift in absorption which reaches to the visible light region when (*E*)-cinnamaldehyde (**16**) is condensed with chiral secondary amine **3** to iminium ion **19**. Upon irradiation with visible light ($\lambda$ = 420 nm), the iminium ion **19** populates the excited state, which is able to react with trimethylsilane **17** generating β-enaminyl radical **20** and silyl radical cation *via* a SET process. After solvent-assisted desilylation an intermolecular radical–radical coupling occurs and subsequent hydrolysis gives product **18** and amine **3** is regenerated. It is worth mentioning that no photocatalyst was needed in this reaction.

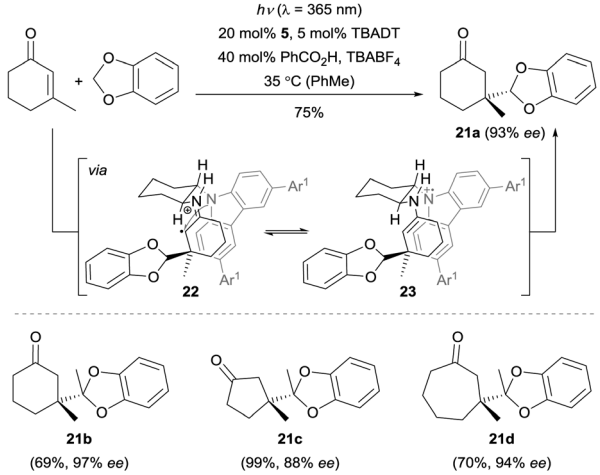
### 2.3 β-Alkylation of enals and enones

The Melchiorre group also achieved the first enantioselective radical conjugate addition (RCA) to β,β-disubstituted cyclic enones by a combination of photoredox catalysis and iminium catalysis (Scheme 5).[19] The key feature for the success of this dual catalysis was the rationally designed organocatalyst **5** bearing a redox-active carbazole moiety (Fig. 1). In this reaction, the primary amine moiety first condenses with the cyclic enone to give the corresponding chiral iminium ion. In parallel, the benzodioxole is – upon irradiation by a single ultraviolet (UV) light-emitting diode (LED) in the presence of tetrabutylammonium decatungstate (TBADT) – converted to the corresponding nucleophilic carbon-centered radical. Subsequently, this radical adds to the chiral iminium ion generating the short-lived and highly reactive α-iminyl radical cation **22**, which is rapidly reduced to enamine **23** by the carbazole moiety of the amine catalyst through an intramolecular SET process. After the enamine–imine tautomerization, regeneration of the photocatalyst TBADT, followed by a hydrolysis step, the terminal products **21** were furnished with good to excellent enantioselectivity with the release of the chiral amine **5**.

This methodology represents a major breakthrough in the field of asymmetric radical chemistry, and it also highlights the application of iminium catalysis in enantioselective photochemical reactions. The carefully designed catalyst not only served as a chiral amine to control the enantioselectivity, but also functioned as an efficient electron-rich center to prevent the radical elimination (β-scission) of radical cation **22** to its iminum ion precursor and to reduce **22** to the key intermediate enamine **23**. This strategy could also be extended to a visible-light-induced enantioselective trapping of α-amino radicals.[20] By using 1 mol% Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (dF(CF$_3$)ppy = 3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) as the photocatalyst and *ent*-**5**




Scheme 4 Enantioselective β-benzylation of enals *via* visible-light excitation of iminium ions catalyzed by chiral secondary amine **3**. [a] d.r. = 55/45, the ee refers to the major diastereoisomer. TFA = trifluoroacetic acid.




Scheme 5 Formation of products **21** by enantioselective trapping of benzodioxole-derived radicals with enones catalyzed by amine **5**. TBABF$_4$ = tetrabutylammonium tetrafluoroborate.

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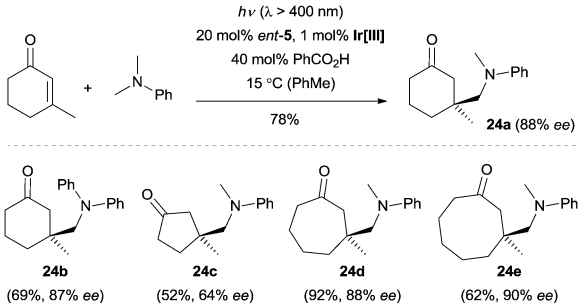



Scheme 6 Enantioselective trapping of α-amino radicals with enones catalyzed by *ent*-**5**. Ir[III] = $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$.

as the organocatalyst, a wide range of cyclic enones could be coupled with various tertiary amines with excellent stereocontrol (Scheme 6). Recently, detailed mechanistic studies regarding this radical conjugated addition reaction were carried out by the same group.[21]

Additionally, an enantioselective photocatalytic Michael addition/oxyamination cascade of enals was discovered by Jang and co-workers.[22] By using chiral secondary amine **2** along with $N719/TiO_2$, a variety of α-oxyaminated β-alkylated aldehydes were produced in moderate to good yields with excellent enantio- and diastereoselectivities.

## 3. Enamine catalysis

In contrast to iminium catalysis, enamine catalysis[23] implies that the carbonyl compound initially reacts with a primary or secondary amine to generate the corresponding enamine *via* dehydration. The highest occupied molecular orbital (HOMO) of the enamine is higher in energy than the HOMO of the carbonyl compound and therefore can more easily interact with the LUMO or SOMO (singly occupied molecular orbital) of an electrophile. Typical reaction pathways for an enamine are therefore reactions with electrophiles or with electrophilic radicals. Additionally, the enamine can be readily oxidized and the resulting radical cation can react with suitable substrates, *e.g.*, olefins.

The benefit of enamine catalysis is the high enantiocontrol which can be achieved by employing chiral amines as catalysts. In this context, a vast majority of amines have been developed and successfully employed in enamine catalysis, rendering enantioenriched functionalized carbonyl compounds under thermal reaction conditions. In recent years, the enamine catalytic mode has also been extended to enantioselective photochemistry, and Fig. 2 depicts the structures of selected chiral amines used in photochemistry, such as chiral secondary amines **25–31** and primary amines **32–37**.

### 3.1 α-Alkylation of aldehydes, ketones and β-ketocarbonyls

In 2008, seminal work was reported by the group of MacMillan in the field of enantioselective α-alkylation of aldehydes by merging photoredox catalysis[24] and organocatalysis. By using 0.5 mol% of $Ru(bpy)_3Cl_2$ (bpy = 2,2′-bipyridine) as the photocatalyst and 20 mol% of chiral imidazolidinone **25a** as the

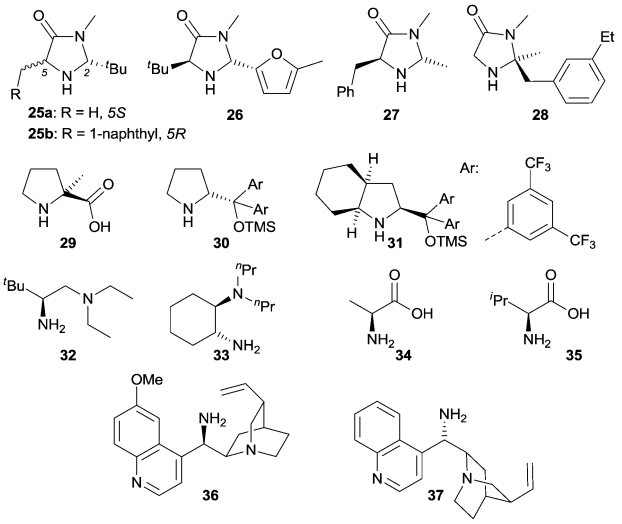
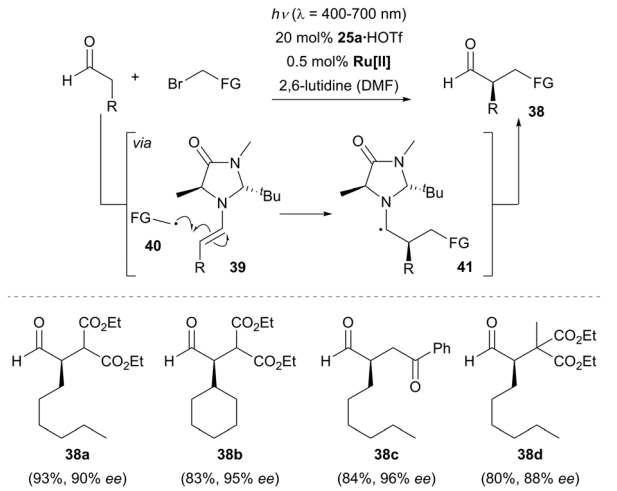



Fig. 2 Structures of representative chiral amines **25–37** for enamine catalysis in enantioselective photochemical reactions.

organocatalyst, a number of aldehydes reacted effectively with various electron-deficient α-bromo carbonyls and produced the α-alkylated aldehydes in good yields with excellent enantioselectivity (Scheme 7).[25] Mechanistically, the reactant aldehyde was suggested to be transiently converted to the more nucleophilic chiral enamine intermediate **39** in the organocatalytic cycle. Meanwhile, in the photoredox catalytic cycle, the photocatalyst is initially populated into its excited state *Ru[II] upon irradiation by visible light. The photoexcited metal complex accepts a single electron from a sacrificial quantity of enamine **39** and generates the strong reductant Ru[I] in the first catalytic cycle. Subsequently, the Ru[I] species reduces the α-bromo carbonyl compound to an electrophilic free radical **40**, while regenerating the photocatalyst Ru[II]. An intermolecular radical–radical coupling was proposed to rationalize the formation of the electron-rich α-amino radical **41**, which acts as a reductive




Scheme 7 Enantioselective α-alkylation of aldehydes catalyzed by chiral imidazolidinone **25a**. Ru[II] = $Ru(bpy)_3Cl_2$, FG = functional group, HOTf = trifluoromethanesulfonic acid, DMF = *N*,*N*-dimethylformamide.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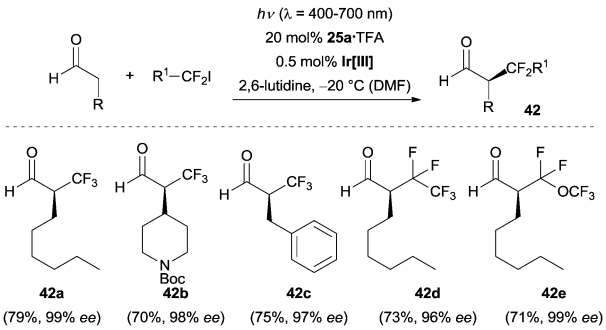
quencher to reduce the excited *Ru[II] to Ru[I] in the following catalytic cycle with release of the iminium ion. Rapid hydrolysis of the iminium ion gives the optically enriched α-alkylated aldehyde **38** and the chiral organocatalyst **25a** is regenerated.

Recent work from the Yoon group shed some doubt on the proposed action of two synergistic catalytic cycles.[26] It was found that the quantum yield for the formation of product **38a** was $\Phi = 18$, which indicates that the enantioselective α-alkylation reaction likely proceeds through a radical chain propagation mechanism. Chain propagation can occur if α-amino radical **41** is oxidized by the α-bromo carbonyl substrate but not by the excited photocatalyst. Ceroni, Cozzi and co-workers postulated a similar chain process when using $Fe(bpy)_3Br_2$ as the photocatalyst.[27]

Organic dyes, a class of environmentally friendly, cheap, readily available and easy to handle photocatalysts, have been successfully applied in photocatalysis.[28] In 2011, Zeitler and co-workers realized an enantioselective α-alkylation reaction of aldehydes by using eosin Y as the photocatalyst.[29] As exemplarily shown in Scheme 8, the reaction of octanal and diethyl 2-bromomalonate in the presence of 20 mol% of imidazolidinone **25a** and 0.5 mol% of eosin Y gave the desired product in 85% yield with 88% ee. From a mechanistic point of view, the authors proposed that the photocatalyst eosin Y initially undergoes a rapid intersystem crossing (ISC) upon irradiation. Subsequently, the excited triplet state of eosin Y follows the same pathway as the excited state *Ru[II] to mediate the following steps. The Ferroud group found Rose Bengal was also suitable for this transformation.[30] Both metal free methods gave comparable results to the ruthenium catalyzed process.

Heterogeneous catalysts are often highly efficient and recyclable, and therefore would provide an alternative to the use of noble metal photocatalysts and organic dyes in photochemistry. In this regard, several heterogeneous photocatalysts such as $PbBiO_2Br$, $Bi_2O_3$ as well as $NbSe_2$ nanosheet supported $PbBiO_2Br$ have been used in the visible light-driven asymmetric α-alkylation of aldehydes by the König group,[31] the Pericàs and Palomares groups,[32] and the Fan group,[33] respectively. Duan and co-workers demonstrated that chiral metal–organic frameworks (MOFs) of Zn-PYI1 and Zn-PYI1 also showed remarkable catalytic activity in the same transformation.[34]

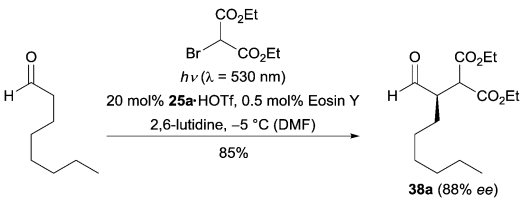
The MacMillan group successfully expanded their dual catalysis platform to target enantioenriched α-trifluoromethylated and α-perfluoromethylated aldehydes.[35] Using a combination of $Ir(ppy)_2(dtbbpy)PF_6$ and chiral secondary amine **25a**, a wide range of aldehydes could be coupled with trifluoromethyl iodide furnishing the α-trifluoromethylation products in moderate to good yields with excellent enantioselectivity (Scheme 9). Functional groups such as ethers, esters, amines, carbamates (*e.g.*, **42b**) and aromatic rings (*e.g.*, **42c**) were tolerant under the optimized reaction conditions. Perfluoroalkyl iodides were also suitable in this enantioselective alkylation reaction, and various chiral α-perfluoromethylated aldehydes were synthesized under the same reaction conditions (*e.g.*, **42d** and **42e**). To demonstrate the potential synthetic applications of this methodology, α-trifluoromethyl 3-phenylpropanal (**42c**) was readily converted to the corresponding α-trifluoromethyl-substituted acid, the respective β-trifluoromethyl-substituted amine, as well as to the β-trifluoromethyl-substituted alcohol without significant loss of enantiopurity. Notably, high enantioselectivities could only be achieved at −20 °C but not at ambient temperature.




Scheme 9 Enantioselective α-trifluoromethylation and α-perfluoromethylation of aldehydes catalyzed by chiral imidazolidinone **25a**. Ir[III] = $Ir(ppy)_2(dtbbpy)PF_6$, Boc = *tert*-butyloxycarbonyl.

Nitrile group containing compounds are a class of versatile building blocks in organic synthesis, which can be readily transformed into carbonyl, amine, imidate motifs, *etc.* Similarly, β-cyanoaldehydes can be readily converted into their corresponding lactone, pyrrolidine, lactam and cyanoalcohol derivatives. In light of the synthetic potential of nitrile compounds, the enantioselective synthesis of β-cyanoaldehydes is highly desirable. In 2015, MacMillan and co-workers reported the first example of enantioselective α-cyanoalkylation of aldehydes by means of their synergistic combination of photoredox catalysis and organocatalysis, providing rapid access to chiral β-cyanoaldehydes **43**.[36] As depicted in Scheme 10, under the optimal conditions, a large array of α-bromoacetonitriles reacted with aldehydes to give the desired products (*e.g.*, **43a–43d**) with excellent enantioselectivity. Interestingly, the product derived from 3-phenylpropanal could be smoothly converted to the corresponding alcohol, ether, lactone, aldehyde, ketone, amide, amine and lactam without erosion of stereochemical integrity. A four-step synthesis of the natural product (−)-bursehernin was also carried out using the aforementioned strategy.

Since all of the above-mentioned dual catalysis examples require the use of photocatalyst, the Melchiorre group developed a conceptually new approach for the enantioselective α-alkylation of aldehydes *via* an electron donor–acceptor (EDA) complex[37] mechanism. As illustrated in Scheme 11, an enamine intermediate was first generated by condensing butyraldehyde (**44**) with the chiral secondary amine **31**.[38] Upon association of




Scheme 8 Enantioselective α-alkylation of aldehydes catalyzed by chiral imidazolidinone **25a** using eosin Y as the photocatalyst.

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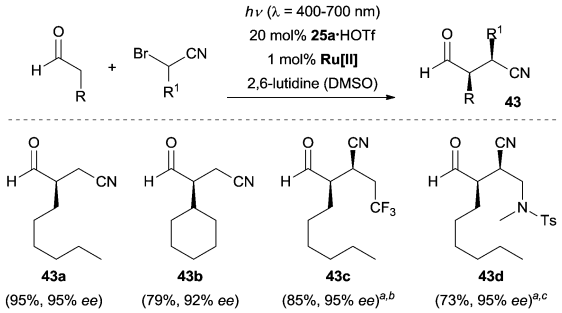
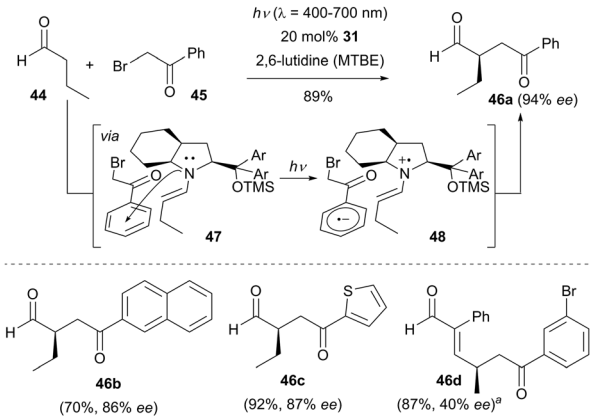



Scheme 10 Enantioselective synthesis of β-cyanoaldehydes **43** by photoredox organocatalysis. Ru[II] = $Ru(bpy)_3Cl_2$. [a] Chiral secondary amine 26 was used as the organocatalyst. [b] d.r. = 53/47. [c] d.r. = 55/45. The ee refers to major diastereoisomer. DMSO = dimethyl sulfoxide, Ts = *para*-toluenesulfonyl.

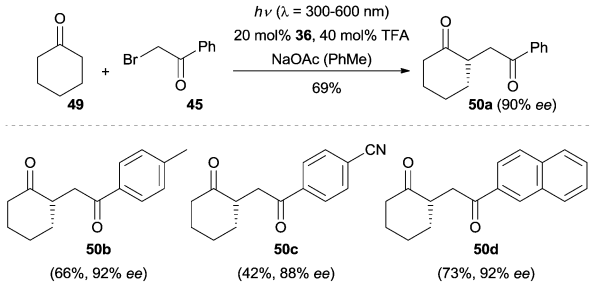



Scheme 11 Enantioselective α-alkylation of aldehydes catalyzed by **31** *via* an electron donor–acceptor (EDA) complex mechanism. [a] Chiral amine **2** was used as the organocatalyst. MTBE = methyl *tert*-butyl ether.

enamine with the electron-deficient 2-bromo-1-phenylethan-1-one (**45**), a transient photo-absorbing chiral EDA complex **47** was formed *via* an n → π* interaction in the ground state. Visible light irradiation of the colored EDA complex **47** initiated a SET process to give the contact radical ion pair **48**, which is stabilized by coulombic attractive forces to preserve the original orientation. Subsequently, a positively charged intermediate pair was generated with the release of the bromide anion. Following radical–radical coupling and hydrolysis, the enantio-enriched α-alkylated aldehyde was produced in the absence of any external photocatalyst.

It should be noted that a radical-chain propagation pathway cannot entirely ruled out at this stage. The success of this reaction is attributed to the formation of the colored EDA complex **47** which absorbs the visible light. This methodology tolerates a wide range of aldehydes and phenacyl bromides, even a thiophene containing bromide reacted with butanal to give the product **46c** in 92% isolated yield with 87% ee. γ-Site selective alkylation of enals was also achieved by using chiral amine **2** as the organocatalyst (*e.g.*, **46d**).

The EDA complex strategy could also be applied to the enantioselective α-alkylation of cyclohexanone (**49**).[39] Switching

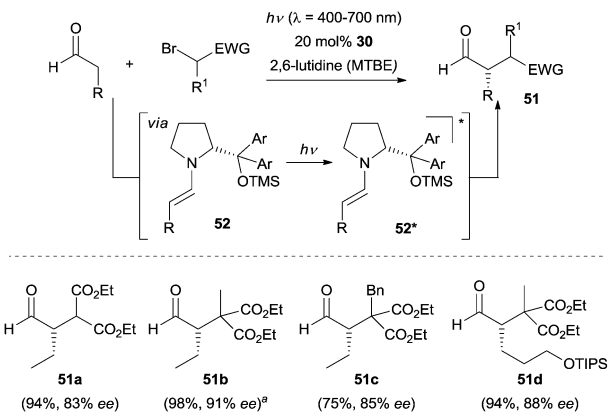



Scheme 12 Enantioselective α-alkylation of cyclohexanone (**49**) *via* an electron donor–acceptor (EDA) complex mechanism.

the light source to a 300 W xenon lamp (λ = 300–600 nm), cyclohexanone (**49**) was coupled with a broad array of phenacyl bromides in the presence of quinidine-derived chiral primary amine **36**, which led to the α-alkylated cyclohexanones **50** with excellent enantioselectivity (Scheme 12). The work described here expanded the substrate scope of enantioselective amine-catalyzed α-alkylation reactions to cyclic ketones.

At a later stage, Melchiorre and co-workers disclosed a direct photoexcitation strategy to achieve the enantioselective α-alkylation of aldehydes.[40] By using bromomalonates as the reaction partners, no color change was observed when exposed to the enamine intermediate **52**. This observation led the authors to propose a unique direct excitation pathway, where upon irradiation the enamine **52** populates its excited state **52*** (Scheme 13). Then **52*** acts as a photosensitizer to reduce the bromomalonate to the open-shell radical species, which in turn couples with the ground state enamine **52** followed by an oxidation *via* another bromomalonate and following hydrolysis the final products are generated. In the entire catalytic cycle, the excited **52*** was sacrificed and a chain propagation mechanism was involved. To gain more insight into the mechanism of this transformation, detailed photophysical studies, nuclear magnetic resonance (NMR) spectroscopy as well as kinetic studies were recently conducted by the same group.[41]

Furthermore, the above direct excitation protocol could be extended to the enantioselective α-(phenylsulfonyl)methylation




Scheme 13 Enantioselective α-alkylation of aldehydes *via* the direct excitation of enamines **52**. [a] Reaction performed upon sunlight irradiation. TIPS = triisopropylsilyl.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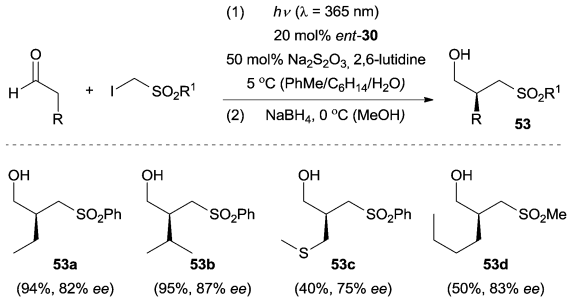
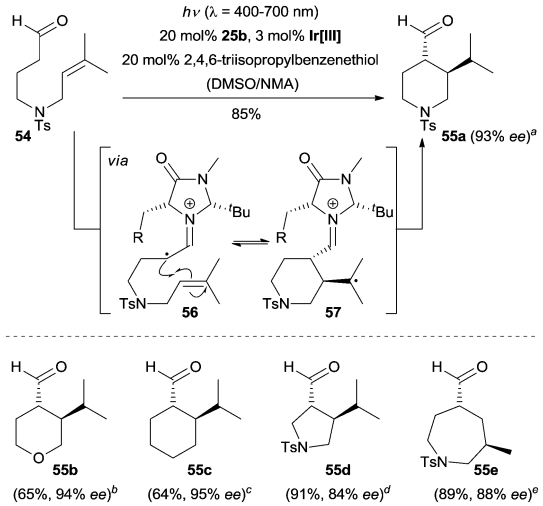



Scheme 14 Enantioselective α-(phenylsulfonyl)- and α-(methylsulfonyl)-methylation of aldehydes catalyzed by *ent*-**30**.

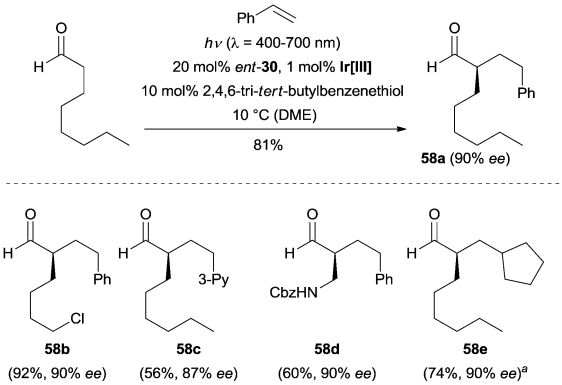
of aldehydes by using *ent*-**30** as the organocatalyst.[42] $Na_2S_2O_3$ was added to remove possible trace amounts of iodine in the reaction mixture and therefore improved the reaction efficiency. A (phenylsulfonyl)methyl or (methylsulfonyl)methyl group could readily be incorporated into various aldehyde components, and the chiral α-alkylated products were isolated as the corresponding alcohols after *in situ* reduction with $NaBH_4$ in moderate to good yields with good enantioselectivity (Scheme 14). The reaction proceeds *via* an atom-transfer radical addition (ATRA) mechanism and the phenylsulfonyl moiety from the iodide substrates acted as a redox auxiliary group to facilitate the formation of the radical key intermediate.

As shown above, the alkylation reagents used in the enantioselective synthesis of α-alkylated carbonyl compounds are always pre-activated halides, which do not meet the atom economy ideals of modern organic synthesis. Consequently, the direct enantioselective α-alkylation of carbonyl compounds from simple and abundant synthetic building blocks is highly desirable. Recently, MacMillan and co-workers reported an elegant enantioselective α-alkylation of aldehydes with simple olefins by synergistically merging photoredox, enamine and hydrogen-atom transfer (HAT) catalysis.[43] As described in Scheme 15, the *N*-tethered aldehydic olefin **54** is initially converted to the chiral enamine by condensation with organocatalyst **25b**, which in turn is oxidized to the enaminyl radical **56** by the excited photocatalyst *Ir[III]. The enaminyl radical **56** rapidly adds to the olefin moiety to generate a nucleophilic radical **57** through an intramolecular radical–radical coupling. Subsequently, radical **57** participates in a HAT catalytic cycle mediated by 2,4,6-triisopropylbenzenethiol affording the key iminium ion following a hydrolysis to the desired product **55a**. Concurrently, the thiyl radical arising from the HAT catalytic cycle reacts with the reduced photocatalyst Ir[II] to regenerate the ground state photocatalyst Ir[III] and the HAT thiol catalyst. *N*-Tethered, *O*-tethered and even alkyl tethered aldehydic olefins were all compatible with the optimised conditions, giving rise to chiral hetero- or carbocyclic ring systems (*e.g.*, **55a–55e**) in moderate to good yields with high enantiocontrol.

The authors found this tricatalytic strategy was also suitable for an intermolecular variant. Using 20 mol% of chiral amine *ent*-**30** as the organocatalyst, 1 mol% of $Ir(dmppy)_2(dtbbpy)PF_6$ [dmppy = 2-(4-methylphenyl)-4-(methylpyridine)] as the photocatalyst and 10 mol% of 2,4,6-tri-*tert*-butyl benzenethiol as the




Scheme 15 Enantioselective α-alkylation of aldehydes catalyzed by **25b**. Ir[III] = $Ir(Fmppy)_2(dtbbpy)PF_6$ [Fmppy = 2-(4-fluorophenyl)-4-(methylpyridine)]. [a] d.r. = 91/9. [b] d.r. = 91/9. [c] d.r. > 95/5. [d] d.r. > 95/5. [e] d.r. = 87.5/12.5. The ee refers to the major diastereoisomer. NMA = *N*-methyl acetamide.




Scheme 16 Intermolecular enantioselective α-alkylation of aldehydes catalyzed by *ent*-**30**. Ir[III] = $Ir(dmppy)_2(dtbbpy)PF_6$. [a] Reaction was performed at −65 °C. DME = dimethoxyethane, 3-Py = 3-pyridine, Cbz = carboxybenzyl.

HAT catalyst, a large number of aldehydes reacted with different styrenes, providing the α-alkylated aldehydes with excellent enantioselectivity (*e.g.*, **58a–58d**). Additionally, methylenecyclopentane was also subjected to these conditions outlined in Scheme 16, and product **58e** was obtained in 90% ee.

The Luo group recognized that the chiral primary amine **32** was a robust catalyst for the enantioselective α-alkylation of β-ketocarbonyl compounds by merging photoredox catalysis and enamine catalysis.[44] Under their optimized reaction conditions, a large array of acyclic ketoesters, cyclic ketoesters, and aliphatic 1,3-diketones were coupled to various phenylacyl bromides, and the enantioenriched compounds **59a–59d** bearing an all-carbon quaternary stereogenic center were constructed in a highly concise fashion (Scheme 17). Surprisingly, when *N*-aryl substituted β-ketoamides were employed as the reactants, spiro-γ-lactams (*e.g.*, **59e–59g**) with two nonadjacent quaternary stereogenic centers were isolated as products of

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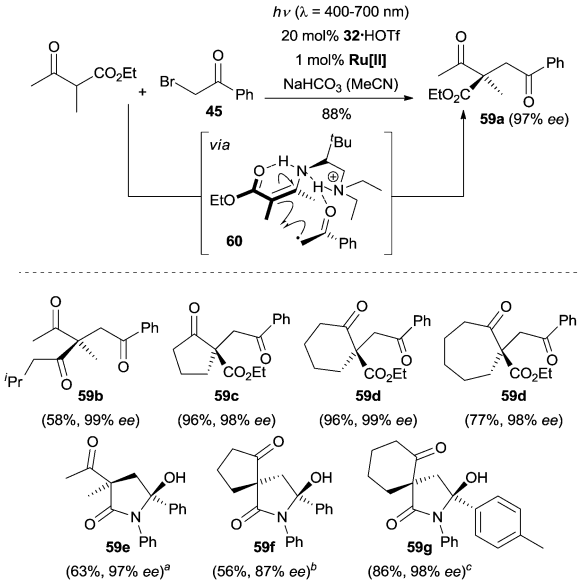
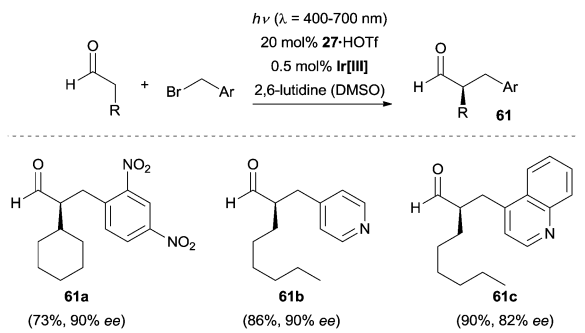



Scheme 17 Enantioselective α-alkylation of β-ketocarbonyl compounds catalyzed by **32**. Ru[II] = $Ru(bpy)_3Cl_2{\cdot}6H_2O$. [a] d.r. = 96/4. [b] d.r. = 94/6. [c] d.r. > 99/1.

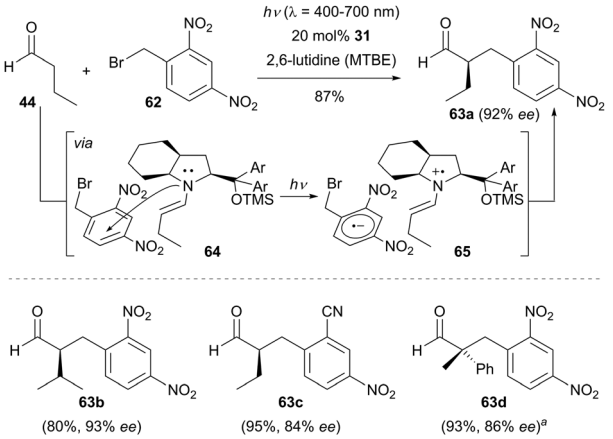
an α-alkylation/intramolecular ketalization cascade with excellent enantioselectivity and diastereoselectivity. The hydrogen bonding between the protonated chiral tertiary amine moiety and the keto moiety of β-ketocarbonyl compounds was crucial for the stereocontrol, which guided the well-defined orientation of the chiral complex **60** formed from enamine intermediate and the open-shell radical species.

### 3.2 α-Benzylation of aldehydes and ketones

Although α-benzylation represents a subdivision of α-alkylation of carbonyl compounds, a subchapter is included to highlight the recent advances in the enantioselective photocatalytic α-benzylation of carbonyl compounds *via* enamine catalysis. The synergistic strategy combining photoredox catalysis and organocatalysis pioneered by the MacMillan group also proved to be effective for the enantioselective α-benzylation of aldehydes.[45] Scheme 18 shows that various electron-deficient aryl and heteroaryl methylene bromides can serve as viable benzylation reagents. The redox conditions were compatible with a wide




Scheme 18 Enantioselective α-benzylation of aldehydes catalyzed by **27**. Ir[III] = *fac*-$Ir(ppy)_3$.




Scheme 19 Enantioselective α-benzylation of aldehydes catalyzed by **31** *via* an electron donor–acceptor (EDA) complex mechanism. [a] Chiral amine **2** was used as the organocatalyst.

range of aldehydes bearing different functional groups, all coupling reactions worked efficiently and enabled the facile access to α-benzylated aldehydes (*e.g.*, **61a–61c**) with excellent enantioselectivity.

In contrast to MacMillan's dual catalysis, the EDA complex mechanism can operate without the need of any external photocatalyst and this reaction has found wide applications in the enantioselective α-benzylation of aldehydes.[38] The coloured EDA complex **64** was observed by Melchiorre and co-workers when treating electron-deficient benzyl bromides such as 1-(bromomethyl)-2,4-dinitrobenzene (**62**) with the chiral enamine intermediate derived from the corresponding aldehydes and the secondary amine **31**. The EDA complex **64** undergoes an intermolecular SET process to generate a chiral radical ion pair **65** which in turn triggers the following radical–radical coupling step. As shown in Scheme 19, several electron-deficient benzyl bromides reacted with a range of aldehydes to achieve the α-benzylation of aldehydes with good enantiocontrol. Interestingly, 2-phenylpropanal could also be employed in the reaction when using chiral amine **2** as the organocatalyst and the transformation forged an all-carbon quaternary stereogenic centre product **63d** in 86% ee.

The majority of α-alkylations and α-benzylations of carbonyl compounds are largely based on aldehyde precursors, and the α-alkylation or benzylation of ketones is still largely unexplored. In 2014, Melchiorre and co-workers realized the direct enantioselective α-alkylation of cyclohexanone *via* an EDA complex mechanism.[39] They demonstrated that this protocol was also suitable for the α-benzylation of cyclic ketones by simply switching the light source to a 23 W compact fluorescent light (CFL) bulb (Scheme 20). Various cyclic ketones such as cyclopentanone, cyclohexanone, cycloheptanone as well as *N*-Boc-piperidin-4-one could be benzylated with 1-(bromomethyl)-2,4-dinitrobenzene (**62**) as the reaction partner, generating the desired products (*e.g.* **66a–66d**) with moderate to good enantioselectivity.

More recently, Wu, Luo and co-workers reported a unique tricatalytic system involving enamine catalysis, photocatalysis and transition metal catalysis to realize the enantioselective

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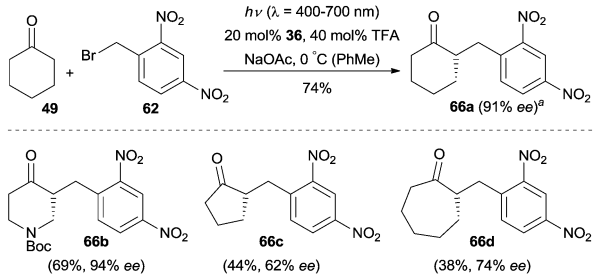
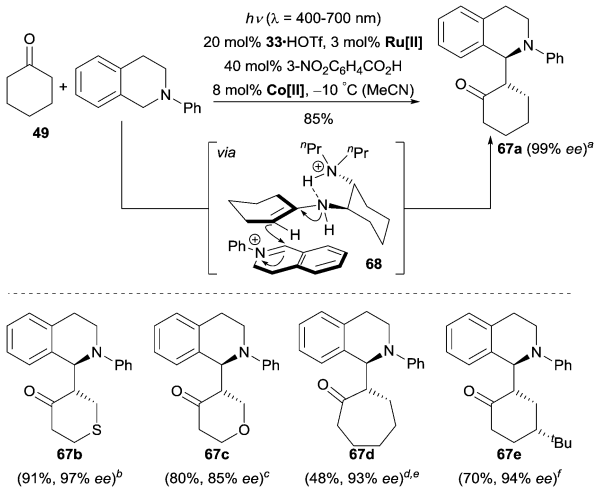



Scheme 20 Enantioselective α-benzylation of cyclic ketones catalyzed by **36** *via* an electron donor–acceptor (EDA) complex mechanism. [a] Reaction performed on a 1 mmol scale.




Scheme 21 Enantioselective α-benzylation of cyclic ketones catalyzed by **33**. Ru[II] = $Ru(bpy)_3Cl_2{\cdot}6H_2O$, Co[II] = $Co(dmgH)_2Cl_2$. [a] d.r. = 90/10. [b] d.r. = 89/11. [c] d.r. = 67/33. [d] d.r. = 92/8. [e] Reaction performed at −5 °C. [f] d.r. = 89/11. The ee refers to the major diastereoisomer.

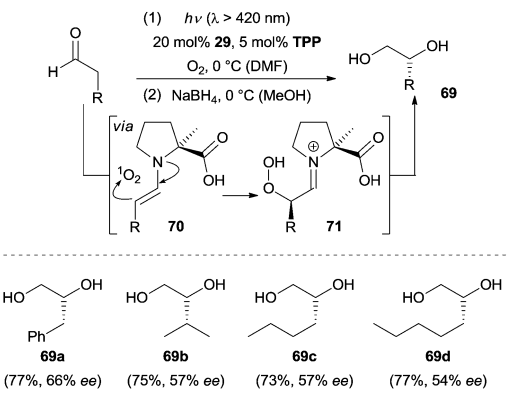
cross-dehydrogenative coupling (CDC) reaction between tetrahydroisoquinolines and ketones.[46] By using 3 mol% of $Ru(bpy)_3Cl_2{\cdot}6H_2O$ and 8 mol% of $Co(dmgH)_2Cl_2$ (dmgH = dimethylglyoximate), numerous cyclic and acyclic ketones were coupled with *N*-aryl tetrahydroisoquinolines and an enantioselective α-benzylation of ketones could be achieved by irradiation with visible light in the presence of 20 mol% of chiral amine **33** and 40 mol% of 3-nitrobenzoic acid (Scheme 21). The authors proposed an oxidative quenching mechanism in the photocatalytic cycle, where the excited photocatalyst Ru[II]* is first oxidized to Ru[III] by Co[III]. Subsequently, Ru[III] is suggested to oxidize the *N*-aryl tetrahydroisoquinoline to the iminium cation by SET and the release of an additional electron and a proton. By the aid of 3-nitrobenzoic acid, the reduced Co[II] captures the electron and the proton to regenerate Co[III]. In the enamine catalytic cycle, the ketone condenses with amine **33** to form a chiral enamine, which then intercepts the iminium cation *via* the transition state **68** to give the corresponding products. It is worth mentioning that 3-nitrobenzoic acid not only acts as an acid additive to promote the formation of the chiral enamine intermediate, but also plays an important role as a hydrogen acceptor undergoing an *in situ* hydrogenation step to 3-aminobenzoic acid.

### 3.3 α-Hydroxylation of aldehydes and ketones

Molecular oxygen is regarded as a green oxidant and has been widely used in organic synthesis. The direct incorporation of molecular oxygen into organic molecules is a straightforward and effective method for the oxidation of a desired target molecule. Given the fact that excited singlet oxygen ($^1O_2$) is more reactive than the ground state triplet oxygen ($^3O_2$), Córdova and co-workers reported the first example of an amine-catalyzed enantioselective α-hydroxylation of aldehydes under photochemical conditions.[47] Optimization of the reaction conditions revealed L-α-Me proline (**29**) as the most effective organocatalyst. As depicted in Scheme 22, the 1,2-diols were isolated with moderate enantioselectivity after *in situ* reduction by $NaBH_4$. The authors postulated a possible mechanism which was related to the enamine catalysis under thermal reactions. The chiral amino acid converts the aldehyde to the more electron-rich enamine **70**, which exhibits increased nucleophilicity. Simultaneously, the photosensitizer tetraphenylporphyrin (TPP) sensitizes $^3O_2$ to $^1O_2$ upon irradiation with visible light. An ene-type reaction was suggested to operate linking $^1O_2$ and enamines **70** and leading to the formation of α-hydroperoxides **71** followed by a reduction to afford diols **69**. Later work from the same group showed that chiral amine **2** proved to be a more effective catalyst and the ee could be improved to 98% in some cases.[48] Mechanistic studies of this transformation were carried out by the group of Gryko.[49] They proposed the formation of a zwitterionic enamine peroxide intermediate and elucidated the enantioface preference for the individual amine catalysts in this reaction.

A further application of the oxygenation methodology was achieved with ketones as the substrates and chiral amine **34** as the catalyst (Scheme 23).[50] Cyclohexanone and $C_4$-substituted cyclohexanones were readily oxidized, allowing for the synthesis of chiral α-hydroxylated cyclic ketones (*e.g.*, **72a–72c**). Furthermore, acyclic ketones such as octan-2-one could also be favourably employed for the enantioselective α-hydroxylation, albeit with lower ee (**72d**, 28% ee) by using **35** as the organocatalyst.

Jang and co-workers developed an enantioselective photocatalytic α-oxyamination of aldehydes under heterogeneous conditions.[51] In this case, commercially available $TiO_2$ was




Scheme 22 Enantioselective α-hydroxylation of aldehydes catalyzed by **29**.

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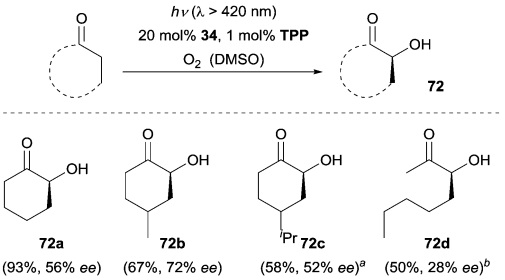


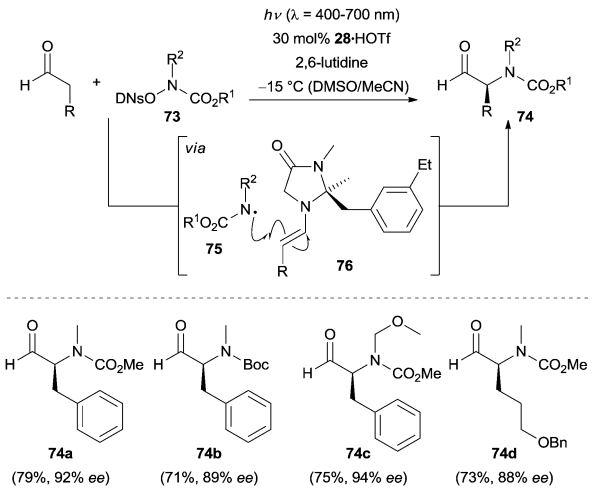

Scheme 23 Enantioselective α-hydroxylation of ketones catalyzed by **34**. [a] Reaction was performed in *N*-methylpyrrolidinone (NMP). [b] **35** was used as the catalyst.

introduced as the photocatalyst, and chiral amines **2** or *ent*-**30** were employed as the chiral amine catalysts. Remarkably, a wide range of aldehydes were coupled with (2,2,6,6-tetramethylpiperidine-1-yl)oxyl (TEMPO) to deliver the desired α-oxyaminated aldehydes with moderate to good enantioselectivity (up to 78% ee).

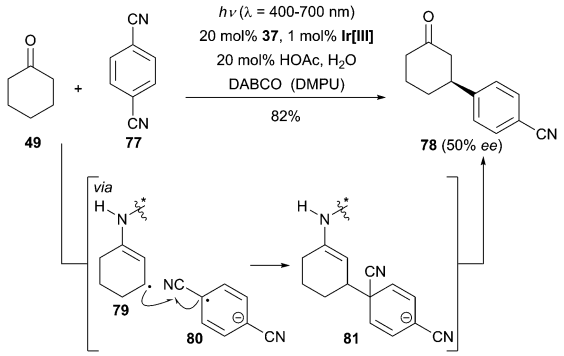
### 3.4 α-Amination of aldehydes

The photocatalytic generation of *N*-centered radicals has recently attracted increasing attention, resulting in new methods for the synthesis of nitrogen-containing compounds.[52] In 2013, a breakthrough in this field was achieved by the group of MacMillan. They accomplished the direct enantioselective α-amination of aldehydes *via* a combination of photoredox catalysis and enamine catalysis.[53] High enantioselectivities were observed when using chiral secondary amine **28** as the catalyst. Some representative products **74a–74d** are shown in Scheme 24. Under optimal conditions the corresponding α-aminated aldehydes were produced in good yields with high enantioselectivity.

An external photocatalyst was not employed in this amination reaction. The success of the transformation strongly depends on the leaving group 2,4-dinitrophenylsulfonyl (DNs) in the amination reagent **73**. Mechanistically, the open-shell *N*-centered radical **75** is initially generated upon irradiation with visible light, which then rapidly adds to the electron-rich enamine **76** generated from the condensation of aldehyde and




Scheme 24 Enantioselective α-amination of aldehydes catalyzed by **28**.




Scheme 25 Enantioselective β-arylation of cyclohexanone (**49**) catalyzed by **37**. Ir[III] = $Ir(ppy)_3$, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMPU = 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one.

chiral amine **28**. Oxidation of the resulting α-amino radical intermediate by the photoexcited amination reagent **73** forms the second equivalent of *N*-centered radical **75** accompanying the formation of the iminium ion. Hydrolysis of the iminium ion furnishes the final product and releases the chiral amine **28** to re-enter the catalytic cycle.

### 3.5 β-Arylation of ketones

Owing to the low reactivity of the β-methylene position of saturated aldehydes and ketones, the direct β-functionalization of this class of substrates is a challenging task. Previous methods used for β-carbonyl activation were exclusively based on the addition of soft nucleophiles to pre-oxidized α,β-unsaturated aldehydes and ketones. By means of their synergistic photoredox and organocatalysis, MacMillan and his group illustrated that a variety of saturated aldehydes and ketones react efficiently with a large array of cyanobenzenes and cyanoheteroarenes to deliver the β-arylated carbonyl compounds without the formation of any α-arylated products (Scheme 25).[54] As an asymmetric variant of this reaction, a promising level of enantioselectivity was reported in the reaction of cyclohexanone (**49**) and 1,4-dicyanobenzene (**77**) using the cinchona-derived catalyst **37** (50% ee).

The authors postulated a possible mechanism to explain the formation of the β-arylated products. The initial step entailed an oxidative quenching of the photoexcited catalyst Ir[III] by 1,4-dicyanobenzene (**77**) giving rise to the arene radical anion **80**. The authors hypothesized that the resulting Ir[IV] would oxidize the enamine intermediate following deprotonation to yield the β-enamine radical **79**. Subsequently, intermolecular radical–radical coupling occurs allowing the formation of intermediate **81**, which then undergoes rapid elimination of cyanide and hydrolysis to the desired products. Later, the above-mentioned strategy was also expanded to the β-alkylation of aldehydes.[55]

## 4. Conclusions and outlook

The continuously growing interest in enantioselective catalysis has resulted in new developments in the field of enantioselective photocatalysis especially using visible light. This research area

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promises use of light as an abundant and sustainable source of energy. The development of enantioselective organocatalysis has inspired chemists to develop novel concepts in the pursuit of enantioselective photochemistry, and numerous elegant transformations have been designed and implemented by synergistic enantioselective organocatalysis and photocatalysis. In this tutorial review, we have described the recent achievements in iminium and enamine catalysis in enantioselective photochemical reactions. Two different chiral active species, iminium ions or enamines derived from the condensation of carbonyl groups and chiral amines are generated in the organocatalytic cycle, which are intercepted by the photogenerated reactive species to furnish enantioenriched useful molecules.

Despite the advances in the field, several challenges and research topics remain: (1) the enantioselective photochemical reactions illustrated above are mainly based on the α-functionalization of aldehydes and ketones and the β-functionalization of enals and enones. It would be desirable to extend these protocols to other reactions types. (2) The chiral amine toolbox is not yet as versatile as the toolbox for thermal iminium and enamine catalysis and the development of novel and robust chiral amines is highly required. (3) Although some experimental data have been obtained, further theoretical and spectroscopic studies are required, which will help to understand the detailed mechanisms and guide the design of novel methods. (4) Applying the concepts described in this review to the total synthesis of some biologically important natural products and pharmaceuticals would be attractive and further work is expected along these lines.

## Conflicts of interest

There are no conflicts to declare.

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