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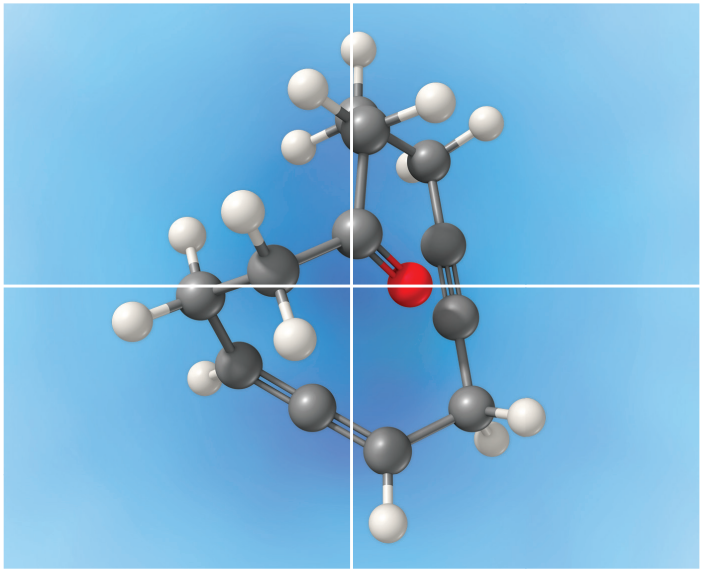

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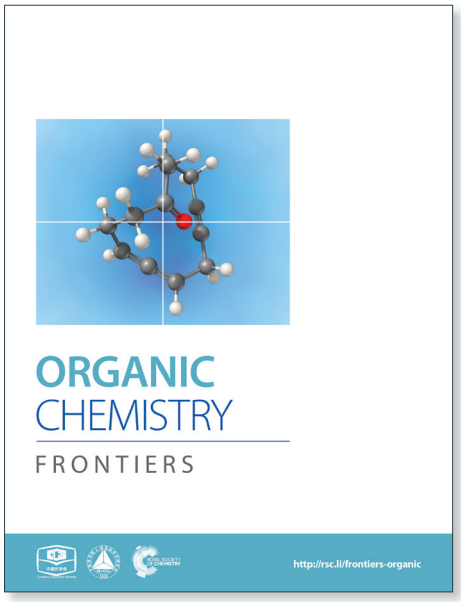

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Catalytically Enantioselective Organic Transformations via Visible Light Photocatalysis

Chengfeng Wang[a] and Zhan Lu*[a]

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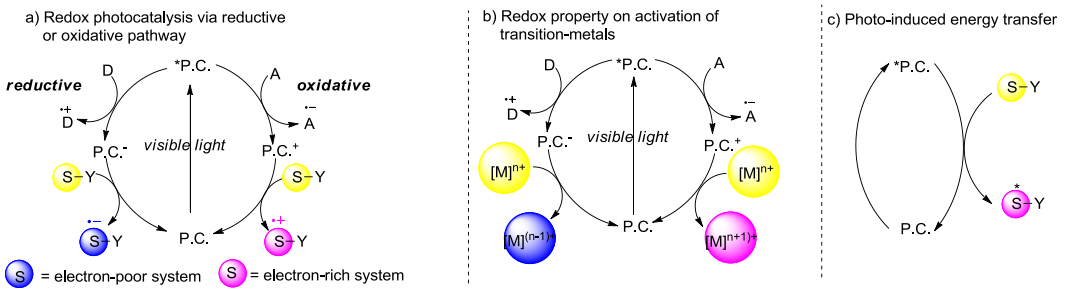
In this minireview, catalytically enantioselecitve transformations via visible light photocatalysis are discussed. High enantioselectivities are achieved in the combination of visible light photocatalysis with chiral organocatalysts. Considering the huge progress made in both asymmetric synthetic chemistry and visible light photocatalysis chemistry, more new chiral catalysts with varieties of transition-metals would be developed and engaged in the field of asymmetric photoreactions.

1.Introduction

Racemic molecules, owned two enantiomers which have the same chemical structure but may differ in biological activities such as pharmacology, toxicology, pharmacokinetics, metabolism etc, are utilized as drugs and used to occupy more than half percent in the sale of drugs.[1] Thalidomide is an example to show this difference of which (*R*)-enantiomer acts as sedative in contrast to deformities caused by (*S*)-enantiomer. Due to unpredictable factors in the presence of the isomer, the enantiopure molecules are quite necessary to be obtained. To date, a huge number of natural or artificial chiral molecules, which have been isolated, synthesized, and identified, do really effect different research area such as chemistry, biology, pharmacology, materials science and so on.[2] Among a variety of different strategies, catalytic asymmetric transformation is one of the most efficient methods.[3]

In the past seven years, there has been a considerable interest in synthetic photochemistry in which visible light can be utilized as the energy source by using transition metal chromophores.[4] In the working model, transition metal complexes or organic molecules (P.C.) as photo-sensitizers absorb visible light to generate photoexcited species which usually have a long life time and remarkable redox property that it may engage in single-electron transfer (SET) process with organic substrates. Because of this unique property, redox transformation of photoexcited species (*P.C.) may conduct reductive quenching or oxidative quenching, respectively. In a reductive quenching cycle, photoexcited species *P.C. could be reduced by the electron donor (**D**) to produce the reductive species $P.C.^{-}$ which has strong reductive potentials and undergo single electron reduction pathway. The electron-poor substrates could trap an electron form $P.C.^{-}$ to generate more active radical anion $\mathbf{S}^{\bullet-}$ which undergo further organic transformations, simultaneously P.C. are regenerated. and the reduced species which subsequently give an electron to and regenerate P.C. back to cycle. Alternatively in an oxidative quenching cycle, single electron oxidation of photoexcited species *P.C. by the electron acceptor (**A**) yields radical anion $\mathbf{A}^{\bullet+}$ and the oxidized species $P.C.^{+}$ which plays a role as an oxidant to capture an electron from the electron-rich substrates and of visible light photocatalyst could also involve with transition-metals in which $P.C.^{+}$ could oxidize $[M]^{n+}$ to a higher valence



Scheme 1 Redox property of visible light photocatalysis.

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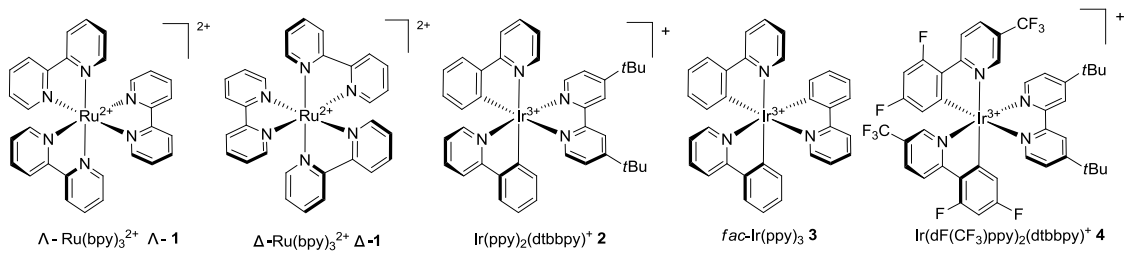

Scheme 2 Several commonly used transition-metal photocatalysts.

state $[M]^{(n+1)+}$ while P.C.$^{-}$ could also reduce $[M]^{n+}$ to a lower valence state $[M]^{(n-1)+}$ instead of working directly with substrates (**Scheme 1b)**. The organic transformations could be also initiated by energy transfer rather than by a single electron-transfer mechanism (**Scheme 1c)**. When the triplet energy of the catalyst is similar with the triplet energy of the substrate, the energy transfer from the photoexcited species *P.C. to the substrate could occur to generate the excited state of the substrate which could undergo further organic transformations. Due to uncontrollable background reactions, although enantioselective photochemical reactions have been studies by Kuhn since 1930s, utilizing a photocatalyst with light to create highly enantioselective chiral molecules is still the Holy grail of photosynthesis. [5] Recently, catalytically asymmetric organic transformations combined with visible light photocatalysis were reported in several cases. There are two reaction models: 1) Radicals or radical ions generated directly by photoreactions under the irradiation of visible light could react with chiral intermediates generated by asymmetric catalysts with other active substrates to create a new chiral center; 2) The chiral catalysts directly combined with substrates to form electron-pair intermediates which could absorb visible light and undergo further transformations. Because of high activation of radical or radical ion, asymmetric visible light photocatalyzed reactions are difficult to control the selectivity. In this minireview, we summarized homogeneous catalytically asymmetric transformation utilized visible light photocatalysis including chiral photocatalysts and racemic photocatalysts with chiral organocatalysts, chiral Brønsted acids or chiral Lewis acids.

2. Chiral-at-Metal visible light photocatalysis

$Ru(bpy)_3^{2+}$ (**1**) complex possesses two enantiomers, a right-handed (**Λ**) helix and a left-handed (**Λ**) helix, which are depended on the chelation of achiral ligands with center metals around the C_3 symmetric axis (**Scheme 2**).[6] Chiral-at-Metal complexes have been used in building chiral environment to induce asymmetric organic reactions. [7] Although visible light transition metal complexes have been widely used in organic transformations, the applications of chiral complexes are quite limited. In the presence of the chiral methol group on the bipyridine ligand, Λ-$Ru(menbpy)_3^{2+}$ (Λ-**9**) could be easily obtained by the column chromatography due to the property of diastereoisomers.[8] Under the irradiation of visible light, the complex Λ-**9** was found to be capable of catalyzing the oxidative dimerization of naphthols **5** to yield 1,1'-bi-2-naphthol (BINOL) **6a** in 16% *ee* or 3-methoxy-2-naphthol **6b** in 4% *ee* (**Scheme 3**). Naphthols **5** are sufficiently electron-rich to be oxidized by the oxidative state Λ-$Ru(menbpy)_3^{3+}$ (Λ-**9**$^{+}$) that could be obtained from the visible-light photoexcited state Λ-**9*** using stoichiometric $Co(acac)_3$ as a terminal oxidant, then deprotonated to yield α-carbonyl radicals intermediate **7**. The intermolecular radical coupling reaction of **7** with naphthols afforded the binaphthol radicals which could undergo aromatization and deprotonation to furnish the binaphthols.

A general feature of photoredox catalysts reflected in this reaction might suggest that photocatalyst typically does promote the generation of reactive radical species, however, rarely serve to affect the step of bond-forming transformation. We proposed that the chiral ion pair complexes **10** and **11** might be formed during the transformation (**Scheme 3**), however, these proposed complexes were not tight enough and easily released to two partners without any further interaction. Ohkubo's effort might enlighten more scientists on the challenge of utilizing visible light to realize catalytically asymmetric photoreactions.

A very recent report presented by Meggers successfully demonstrated that chiral-at-metal visible light photoactivated sensitizers could realize the highly enantioselective α-benzylation of activated ketones (**Scheme 4**). [9] The chiral iridium complexes are demonstrated to absorb the visible light (425 nm) and have excellent redox property. The key intermediate **16** could be formed by the coordination of iridium metal with an oxygen atom on carbonyl group and a nitrogen atom on imidazole group, converting to **18** by deprotonation and asymmetric radical addition of electron withdrawing benyl radical. The reaction afforded the α-benzylated ketones **14** in excellent yields (84-100%) and ee (90-99%). This unique example could be the landmark for designing chiral photosensitizers for catalytically visible-light-induced reactions.

3. Chiral organocatalysts with hydrogen-bonding

3.1 Chiral thiourea

Amines are commonly used as sacrifices to offer an electron to visible light photocatalysts, leading to amino cation radicals. This active amino cation radicals would either deprotonate to generate an α-amino radical as a good radical nucleophile or lose a hydrogen atom to deliver iminium ions which are potentially capable of nucleophilic addition reactions, accelerating the development of diversified α-functionalization reactions of amines as well as asymmetric organic transformations.

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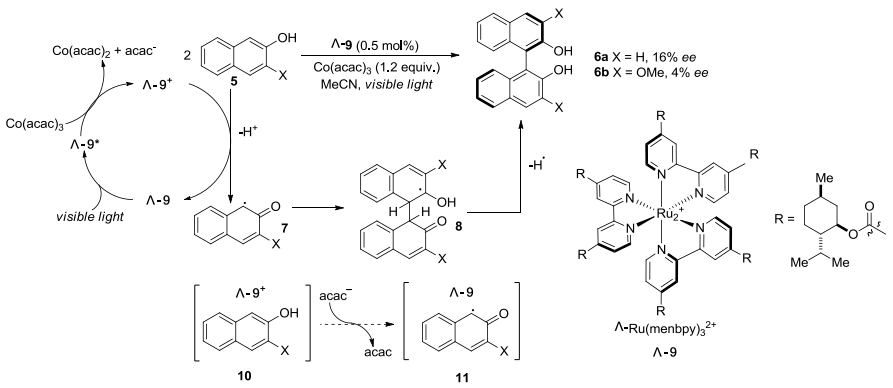
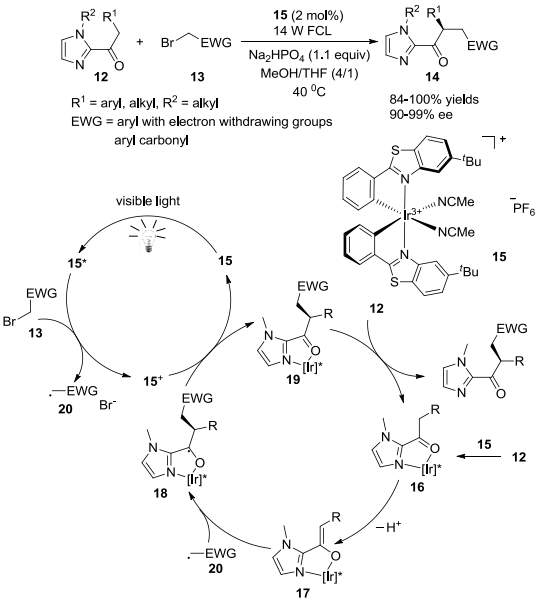
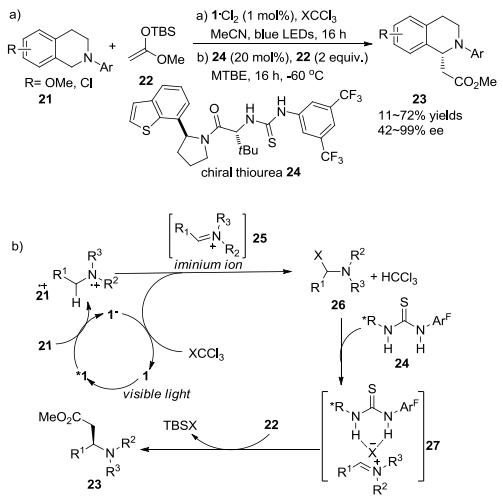


Scheme 3 Visible light promoted asymmetric dimerization of naphthols with catalyst Λ-**9**.



Scheme 4 Asymmetric α-benzylation of 2-acyl imidazoles.

A report by Jacobsen and Stephenson indicated the feasibility of chiral thiourea as an anion-binding catalyst combined with photoredox catalyst to conduct asymmetric C-H functionalization of *N*-aryltetrahydroisoquinoline.[10] With the employment of **1**•Cl_2 (1 mol%) as a photocatalyst and thiourea **24** (20 mol%) as a organocatalyst under the irradiation of blue LED, *N*-aryltetrahydroisoquinolines **21** could undergo single electron oxidation by photoexcited *$Ru(bpy)_3^{2+}$ (***1**), followed nucleophilic addition of the resulting iminium ion with silyl ketene acetals to give α-alkylated tetrahydroisoquinolines **23** in 11-72% yields and 42-99% *ee* (**Scheme 5a**). Single-electron reduction of $XCCl_3$ by $Ru(bpy)_3^{+}$ (**1**$^-$) followed fragmentation delivered a X anion which could combine with iminium cation to form intermediate **26**, and regenerated the photocatalyst. A variety of chiral thioureas were screened as a chiral anion-binding catalyst[11] and **24** was quite suitable for anion under the catalytic conditions to produce a chiral tight ion pair **27** which was subsequently attacked by silyl ketene acetal to afford α-esterificated tetrahydroisoquinoline derivatives **23** with moderate to excellent enantioselectivities (**Scheme 5b**). During this process, a highly variable enantioselectivity can be observed via the formation of different tight ion pairs among which Cl^- from CCl_4 contributes to more popular interactions of the chloride-bonded thiourea catalyst in the enantioselectivity-determining transition state. Besides, solubility properties of the iminium ion **25** may be enhanced if PF_6^- existed in the reaction, enabling the racemic background12 reaction into a greater extent. For an appreciable application of this enantio-induction, a two-stage protocol was required involving solvent changes from acetonitrile to methyl *tert*-butyl ether and reaction temperature decreases to -60 °C. High enantioselectivity were obtained in this reaction with limited substrates.



Scheme 5 a) Asymmetric α-photoalkylation of *N*-aryl-tetrahydroisoquinioline with chiral thiourea **24**. b) Proposed

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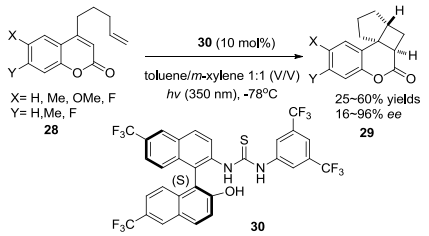
mechanism through hydrogen-halogen bonding.

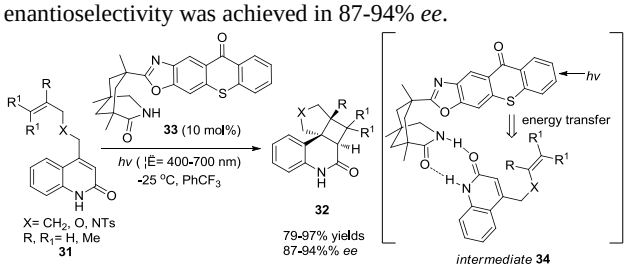
With chiral thiourea organocatalyst under the irradiation of UV, Sibi and Sivaguru have demonstrated an electron or energy free process in enantioselective intramolecular [2+2] photocycloaddition of 4-alkenyl-substituted coumarins (**28**) , which leads to corresponding products **29** in 25~60% yields with 16-96% *ee* in toluene/*m*-xylene(1:1) (**Scheme 6**). [12] The hydrogen-bonds between hydrogen on chiral thiourea **30** and oxygen on the carbonyl moiety of 4-alkenyl-substituted coumarins play a key role to create chirality.



Scheme 6 Enantioselective [2+2] cycloadditions of coumarins with chiral thiourea **30** under UV irridiation.

3.2 Chiral thioaxanthones

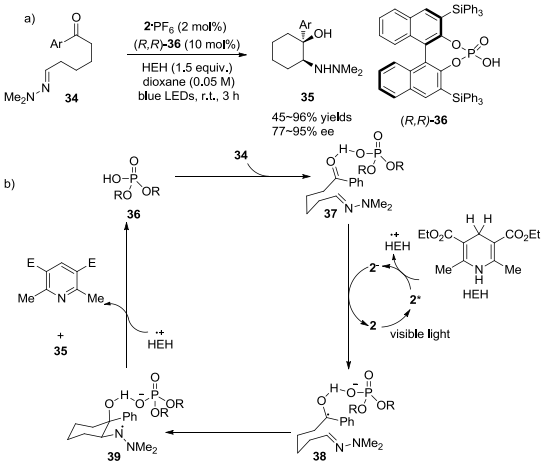
Bach and co-workers reported a catalytic loading of chiral thioaxanthone (10 mol%) as an organocatalyst to conduct asymmetric intramolecular [2+2] cycloadditions of quinolones under visible light irradiation (**Scheme 7**). [13] Chiral thioaxanthone (**33**) could absorb visible light and then transmit to quinolones (**31**) through triplet energy transfer [14] which has not yet been confirmed but apparently revealed in the photostability studies that triplet state of thioaxanthone acts less vigorously towards hydrogen abstraction [15] than the triplet state of xanthone derivatives in photocatalytic cycle. Due to the double hydrogen-bonding effect between chiral thioxanthone and quinolones, high enantioselectivity was achieved in 87-94% *ee*.



Scheme 7 Asymmetric intramolecular [2+2] photocycloaddition reaction with chiral thioaxanthone **33**.

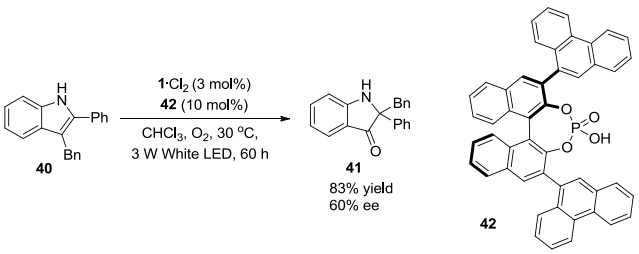
3.3 Chiral phosphoric acids

In a conceptually distinct contribution, Brønsted acids can also be utilized together with visible light photocatalyst to promote asymmetric Aza-Pinacol photoreactions between ketone and hydrazone efficiently via a proton-coupled electron transfer (PCET) event by Knowles.[16] With chiral phosphoric acid (*R*,*R*)-**36** (10 mol%) and **2**•PF_6 (2 mol%), **34** could undergo radical cyclization to convert to cyclic amino alcohol derivatives **35** in 45-96% yields with highest *ee* ups to 95% (**Scheme 7a**). Hantzsch ester has been employed not only as a single-electron reductant but also as a hydrogen source. Ketones, which is a good hydrogen-bond acceptor activated by (*R*,*R*)-**36**, could trap an electron from photoreduced species $\mathbf{2}^{-}$ to afford the radical intermediate **38**. Intramolecular radical cyclization of **38** could afford amino-radical intermediate **39** which then receive a hydrogen atom from the oxidized HEH to furnish the final product and regenerate the phosphoric acid (**Scheme 7b**). Chirality of this reaction is introduced through activation of the aryl carbonyl group by hydrogen-bonding effect with chiral phosphoric acid. This work demonstrates the concerted PCET activation as a potentially approach to further development of asymmetric radical chemistry.



Scheme 8 a) Chiral phosphoric acid catalyzed intramolecular cyclizations via visible light photocatalysis. b) Proposed mechanism.

A photo-induced aerobic oxidation/semipinacol rearrangement reaction of indoles was presented recently by Lu and Xiao (**Scheme 9**).[17] The asymmetric reaction could be achieved by using chiral phosphoric acid **42** as a Brønsted acid, giving the 2,2-disubstituted indolin-3-one in 83% yield and 60% ee.



Scheme 9 asymmetric aerobic oxidation/semipinacol rearrangement reaction of indoles.

4. Chiral *N*-heterocyclic carbenes

In 2012, Rovis introduced *N*-heterocyclic carbenes (NHCs) as the organocatalysts into photocatalytic reactions and successfully operated the asymmetric α-acylation of *N*-phenyltetrahydroisoquinoline.[18] A catalyst system containing 5 mol% of chiral NHC **45**, 1 mol% of **1**•Cl_2 and 1.2 equiv. of *m*-dinitrobenzene (*m*-DNB) was capable of effecting reactions between *N*-phenyltetrahydroisoquinoline **21** and aldehydes **43** upon irradiation of a 15 W blue LED to afford α-acylated *N*-phenyltetrahydroisoquinoline products **44** in 51-94% yields and 59-92% *ee* (**Scheme 10a**). The reaction could tolerate alkenes,

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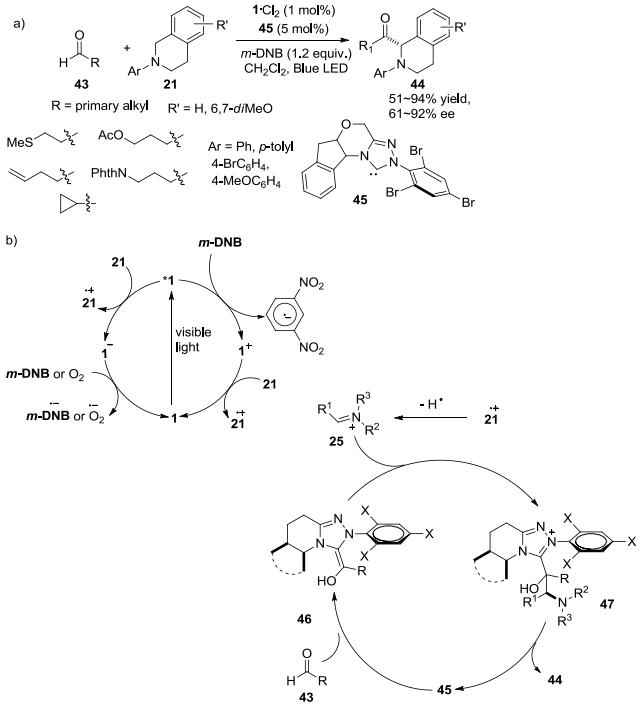
cyclopropanes and a variety of functionalized groups with protecting groups, such as thiols, alcohols and amines. Stochiometric *m*-DNB serves as an oxidative quencher of photoexcited ***1** to result $Ru(bpy)_3^{3+}$ ($\mathbf{1}^{+}$) during which trace oxygen might act as a terminal oxidant. *N*-Phenyltetrahydroisoquinoline **21** could be oxidized both photoexcited ***1** and oxidized species $\mathbf{1}^{+}$ followed by hydrogen atom abstraction to convert to electrophilic iminium ion **25**. Condensation of chiral NHC with aldehydes would form the highly nucleophilic Breslow intermediates **46** which could undergo nucleophilic addition of iminium ion **25** to give the intermediated adduct **47**. Releasement of the NHC from **47** could afford α-acylated *N*-phenyltetrahydroisoquinolines and recycle the NHC (**Scheme 10b**). In this manner, activated sp^3 C-H bond can be converted to C-C bond with no pre-activated substrates, providing new access to enantioselective α-acylated *N*-aryl-tetrahydroisoquiniolines.

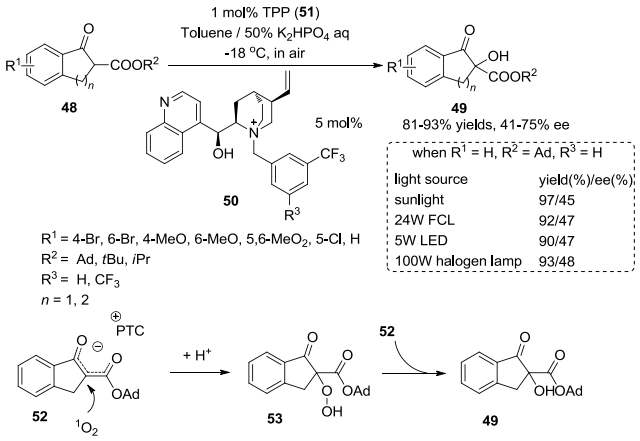


Scheme 10 a) Asymmetric α-acylation of *N*-aryl-tetrahydroisoquinioline merged with chiral NHC and visible light photocatalyst. b) Proposed mechanism.

5. Chiral amines

5.1 Chiral quaternary ammonium salts

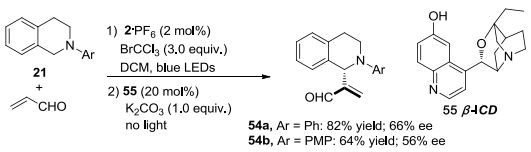
Chiral phase-transfer catalysts have been received much attention in asymmetric organic transformations. Under the irradiation of sunlight, the combination of chiral phase-transfer catalyst with photosensitizer TPP could promote the oxidation reaction of the 1,3-dicarbonyl compound to afford the hydroxylation product in 97% yield and 45% ee (**Scheme 11**).[19] The chiral counter ion pair **52** formed in the reaction could be oxidized by singlet oxygen and then be protonated to afford a relatively stable hydroperoxide **53**. The mechanism study showed that the hydroperoxide might react with ion pair **52** and be utilized as an oxidant to form the final product **49**.



Scheme 11 Enantioselective α-photooxygenation of β–keto esters.

5.2 Chiral tertiary amines

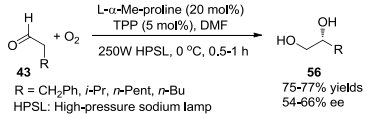
Xiao and co-workers reported an alternative dual catalysis system in direct sp^3 C-H acroleination of *N*-aryl-tetrahydroisoquinioline reactions using $\mathbf{2}\bullet PF_6$ (2 mol%) as a photocatalyst, $BrCCl_3$ (3.0 equiv) as the oxidant under the irradiation of blue light in cascade with addition of β-isocupreidine **55** (**β-*ICD***, 20 mol%) as a chiral nucleophilic organoamine catalyst.[20] *N*-aryl-tetrahydroisoquinioline **21** could react with acrolein to afford **54a** in 82% yield with 66% *ee* and **54b** in 64% yield with 56% *ee*, respectively (**Scheme 12**).



Scheme 12 Asymmetric α–alkylation of *N*-aryl-tetrahydroisoquinioline.

5.3 Chiral secondary amines

Córdova reported the direct amino acid-catalyzed asymmetric α-photooxygenation of aldehydes in 2004.[21] While the TPP used as a photosensitizer under the irradiation of a 250-W high-pressure sodium lamp, the aldehydes could be oxidized by molecular dioxygen and then be reduced by $NaBH_4$ to give 1,2-dihydroxylation products in moderate yields and ee.



Scheme 13 Enantioselective α-photooxygenation of aldehydes

Direct asymmetric alkylation of aldehydes with alkyl bromide bearing electron-withdrawing functional groups was carried out in MacMillan's laboratory with combination of $\mathbf{1}\bullet Cl_2$ (0.5 mol%) and chiral imidazolidinone **59** (20 mol%).[22] The reaction could offer various α-alkylaldehydes derivatives **58** in 70-93% yields and 88-99% *ee* without any strong oxidant under visible-light irradiation from a 15 W CFL (CFL = compact fluorescent light)

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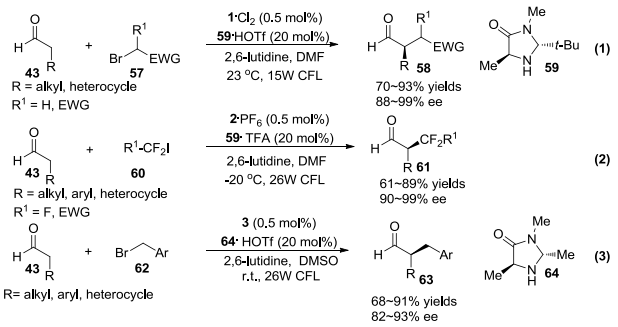
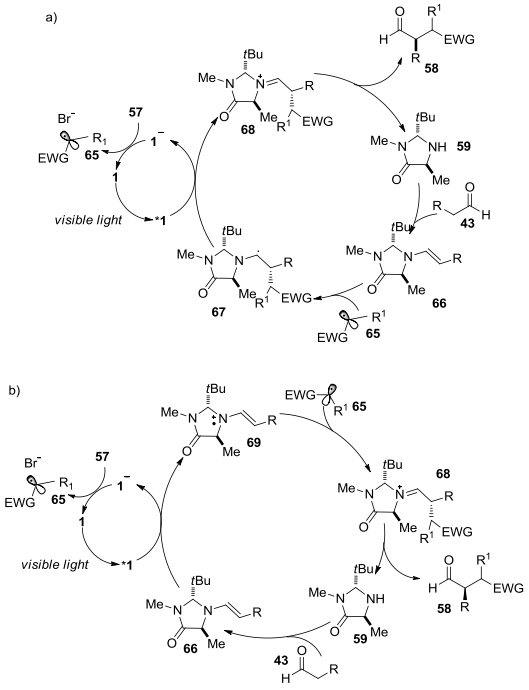
at room temperature **(eq 1**). Electrophilic alkyl radical is formed through single-electron oxidation of the electron-deficient alkyl bromide by **1**$^-$ and fragmentation. Simultaneously, enamine intermediate **66** generated from interaction of chiral imidazolidinone with aldehyde reacts with alkyl radical **65** to form α-radical amine intermediates **67**, which subjects to oxidization by photo-induced complex ***1** to yield the iminium ion which could then be hydrolyzed to yield products **58** (**Scheme 14a**). However, there is a puzzle in the above catalytic cycle that which intermediates come into being first: electron-withdrawing alkyl radicals or **1**$^-$. In fact, the reduction potential of ***1** ($E_{1/2}^{*II/I}$ = +0.77 V vs SCE) indicates its ability to oxidize enamine intermediates **66**.[23] There is another possible catalytic cycle (**Scheme 14b**). Both organocatalysis and visible light photocatalysis cycles could be initiated by the direct oxidation of enamine **66** by ***1**.

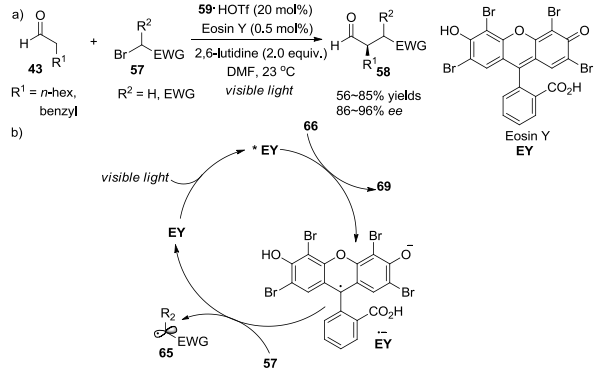
α-Perfluoromethylation and α-benzylation of aldehydes can also be realized in a conceptually similar manner.[24] Under visible-light irradiation, 0.5 mol% of **2**•PF_6 with 20 mol% of **59**·TFA or 0.5 mol% of [*fac*-Ir(ppy)$_3$] **3** with 20 mol% of **64**·HOTf were employed to catalyze the corresponding reactions, affording α-trifluoromethyl aldehydes **61** in 61-89% yields with 90-99% *ee* or α-benzylation of aldehydes **63** in 72-94% yields with 82-93% *ee*, respectively (**eq. 2 and 3**).





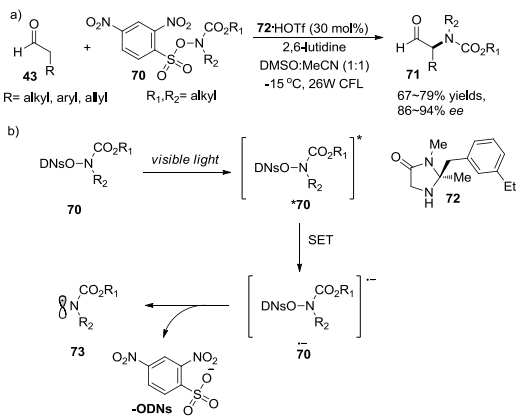
Scheme 14 a) Proposed mechanism. b) Alternatively proposed mechanism.

Alternatively, the photoredox organocatalysis strategy was demonstrated by Zeitler to access the similar products.[25] Readily accessible xanthenes dye eosin Y (EY) (0.5 mol%) serves as organic photo-sensitizer in concert with imidazolidinone **59** (20 mol%) to manipulate α-alkylation of aldehydes **43** with electrophilic alkyl bromides **57**, giving the adducts **58** in 56-85% yields with 86-96% *ee* (**Scheme 15a**). In the photoredox cycle, as an analogue of the transition-metal photocatalyst **1**, the redox property of EY (*EY ($E_{1/2}$(*EY/EY$^{\cdot-}$) = +0.83 V vs SCE) or EY$^{\cdot-}$ ($E_{1/2}$(EY/EY$^{\cdot-}$) = -1.06 V vs SCE)) is sufficiently capable of conducting SET processes (**Scheme 15b**). Ferroud *et al.* also achieved enantioselective α-alkylated aldehydes using Rose Bengal (RB) as a photosensitizer.[26]



Scheme 15 a) Asymmetric α-alkylation of aldehyde with Eosin Y. b) Proposed mechanism.

Later on, MacMillan and co-workers developed a new methodology for the asymmetric α-amination of aldehydes.[27] Sulfonyl-protected hydroxyamides **70** are not only amido radical sources but also good photosensitizers which would absorb visible light to be photoexcited state species ***70**. Photoexcited species ***70** would capture an electron, then eliminate the 2,4-dinitrophenylsulfate ion to give amido radicals **73**. The reaction could proceed with chiral secondary amine **72**·HOTf (30 mol%) as an organocatalyst, affording α-amino aldehydes **71** in 67-79% yields with 86-94% *ee* (**Scheme 16a**). The mechanism is similar with previous reported cycle (**Scheme 14**) in the difference of generation of amido radicals (**Scheme 16b**).



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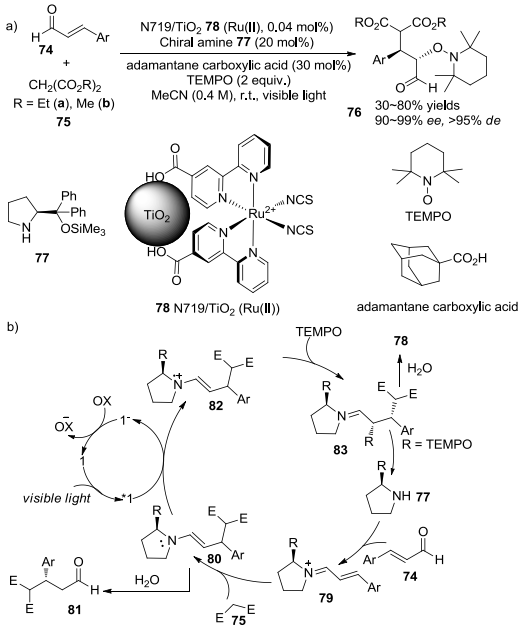
Scheme 16 a) Asymmetric α-amination of aldehydes via iminium ion. b) Proposed mechanism.

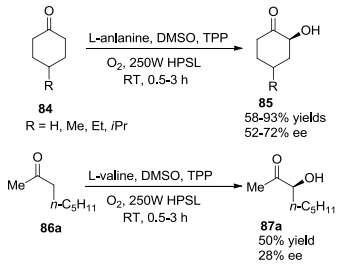
Enantioselective tandem Michael addition/oxyamination reaction of α,β-unsaturated aldhydes with diethyl malonate and TEMPO was demonstrated by Jang using (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine **77** (20 mol%) as an organocatalyst combined with N719/TiO_2 Ru(II) **78** (0.04 nol%) as photosensitizer to achieve α,β-substituted aldehydes **74** in 53-80% yields with 96-99% *ee* and >95% *de* (Scheme **17a**).[28] Using dimethyl malonate instead of diethyl malonate, the addition gave a decreased yield and selectivity (30% yield and 90% ee). Side-products **81** can also obtained through hydrolysis of enamine intermediate **80**. Enantioselectivity of this reaction is controlled by chiral pyrrolidine[29] while diastereoselectivity is controlled by N719/TiO_2 Ru(II), respectively.



Scheme 17 a) Enantioselective tandem Michael addition/oxidation of aldehydes. b) Proposed mechanism.

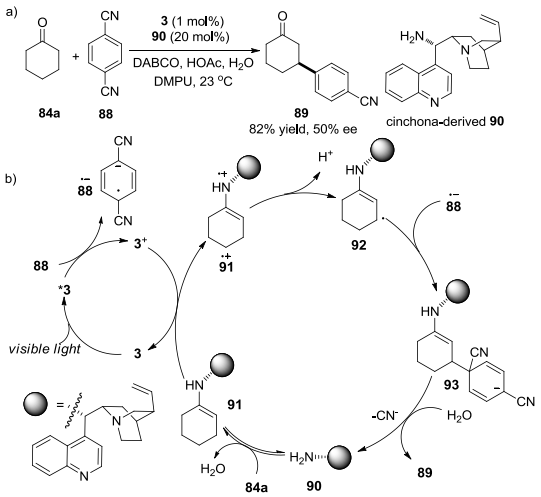
5.4 Chiral primary amines

In 2004, Córdova demonstrated a similar protocol to achieve asymmetric α-photooxygenation of cyclic ketones in combination of photosensitizer TPP and natural amino acids, yielding α-hydroxylated ketones with moderate ee (**Scheme 18**).[30] The acyclic ketone showed a slightly low reactivity, even though the enantioselectivity was compromised.



Scheme 18 Enantioselective α-photooxygenation of ketones.

MacMillan and co-workers developed a fancy dual catalytic model to promote β-arylation of aldehydes or cyclic ketones with cyanoarenes.[31] In the photosensitizer $Ir(ppy)_3$ (**3**)-catalyzed reaction, *iso*propyl benzylamine or azepene were utilized as the organocatalysts for aldehydes or cyclic ketones, respectively. Using cinchona-derived organocatalyst **90** (20 mol%) in conjunction with **3** (1 mol%), the asymmetric reaction of cyclohexanone with 1,4-dicyanobenzene gave the chiral product **89** in 82% yield and 50% *ee* (**Scheme 19a**). 1,4-Dicyanobenzene **88** would function as an oxidant of photo-induced excited complex ***3** to yield $\mathbf{3}^+$ which could oxidize electron-rich enamine **91** to the enamine radical cation $\mathbf{91}^{\bullet+}$. Due to the weak allylic C-H bond, deprotonation of radical cation $\mathbf{91}^{\bullet+}$ at β-position of the carbonyl group could occur to form cyclohexenyl radical **92**. Radical coupling of **92** with radical anion $\mathbf{88}^{\bullet-}$ would give rise to anion **93** which would undergo elimination of cyano anion in the presence of water to deliver the desired product **89** and regenerate amine catalyst **90** (**Scheme 19b**).



Scheme 19 a) Direct asymmetric β-arylation of cyclohexane. b) Proposed mechanism.

Melchiorre group demonstrated a chiral ion pair driven asymmetric α-alkylation of cyclic ketones. Easily obtained quinidine-derived primary amine **95** (20 mol%) is involved in both activation of carbonyl compound **13** and the enantioselectivity-defining event to achieve enantioselective α-alkylcycloketones **94** in 38-94% yields with 74-95% *ee* (**Scheme 20a**).[32] Initially, the electron donor-acceptor (EDA) complex **97** is formed via aggregation of aryl bromides with electron-rich enamine. Single electron transfer inside this EDA complex **97** from nitrogen to alky bromide could afford a chiral radical ion pair **98** which combined of aryl radical anion with amino radical cation. Then facile fragmentation of Br^- on $\mathbf{13}^{\bullet-}$ followed by coupling with amino radical cation **99** could afford an imine cation **101** which is known to easily release α-alkylcycloketone **94** (**Scheme 20b**).

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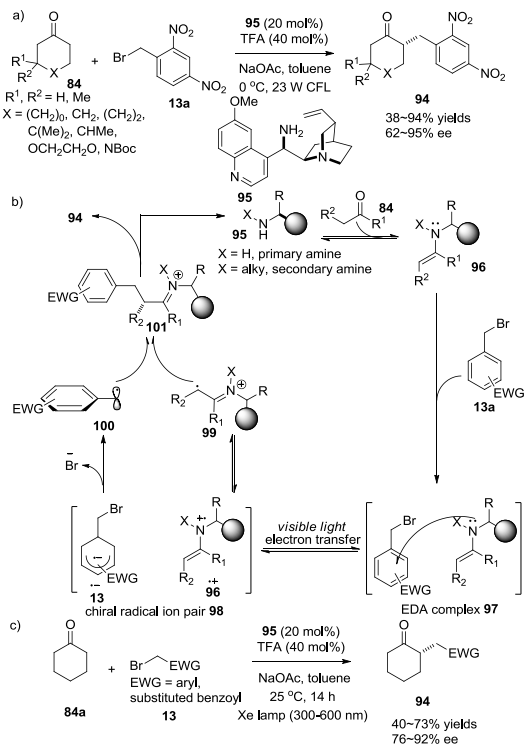
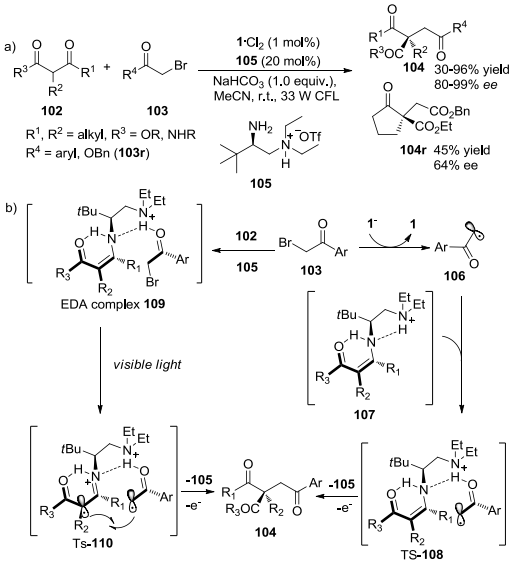


Scheme 20 a) and c) Asymmetric catalytic α-alkylation of cycloketones with alkyl halides. b) Proposed mechanism.

Subsequent to Melchiorre' report, Luo and his co-workers have revealed that chiral primary amine do really help to construct chiral quarenary carbon centers in asymmetric enamine-based transformation of β-ketocarbonyls. [33] The reaction of β-ketocarbonyls and α-bromocarbonyls employing **1**•Cl_2 (1 mol%) and chiral diamine salt **105** (20 mol%) as co-catalyst could offer α-alkylated β-ketonyls in 30-96% yields with 64-99% *ee* (**Scheme 21a**). There are two possible transition intermediates: the proposed major intermediate TS-**108** could be formed in the photoredox pathway and the proposed minor intermediate TS-**110** could be generated in the electron donor-acceptor (EDA) pathway. In the photoredox pathway, the acetophenone radicals formed by photoreduction of 2-bromoacetophenones could be banded with the enamine intermediates **107**, generated from condensation of the chiral primary amine catalyst with β-ketocarbonyls **102**, via hydrogen-bonding between hydrogen of enamines and keto moiety of acetophenone radicals, forming the transition state TS-**108**. Intramolecular radical addition of TS-**108** followed by releasing an electron and **105** afforded products **104**. While in the EDA pathway, 2-bromoacetophenones could interact directly with β-ketocarbonyls catalyzed by chiral amine to afford the EDA complexes **109** which could undergo intramolecular electron transfer from enamines to 2-bromoacetophenones under the irradiation of a 33 W CFL to give the transition state TS-**110** (**Scheme 21b**). Intramolecular radical-radical coupling followed by hydrolysis of this transition state would achieve final product **104**. Benzyl bromoacetate which has lower electron-withdrawing property of ester moiety compared with keto moiety on 2-bromoacetophenones was also suitable for this transformation to give the desired product, however, in decreased yield and enantioselectivity. The result dedicated that the weaker hydrogen-bonding between carbonyl and protonated tertiary amine, the poorer reactivity and enantioselectivity.



Scheme 21 a) Enantioselective α-photoalkylation of β-ketocarbonyls with combination of chiral primary amine with photocatalyst. b) Proposed mechanism.

6. Chiral Lewis acids

Yoon group has developed a new strategy to construct chiral cyclobutanes via highly enantioselective [2+2] photocycloadditions of α,β-unsaturated ketones involving the visible light photocatalyst and stereo-controlling chiral Lewis acids. [34] Employing 5 mol% of **1** • Cl_2 as a visible light photocatalyst, 10 mol% of $Eu(OTf)_3$ as a Lewis acid, 30 mol% of peptide ligand **93** as the chiral ligand in conjuction with 2 equiv. of *i*-Pr_2NEt, the reaction of aryl enones **111** with alkyl vinyl ketones **112** gave *trans*-cyclobutanes **113A** in 34-72% yields and 86-93% *ee* (**Scheme 22a**). Additionally, when ligand **115** is used instead of **114**, *cis*-cyclobutanes **113B** are obtained in 49-80% yield with 84-97% *ee*. Radical **117** derived from single-electron reduction of activated aryl enone by the excited state complex ***1** adds to enone **112** to form a chiral Lewis acid mediated radical **118** which subsequently undergos intermolecular cyclization before elimination of cyclobutane **113** (**Scheme 22b**). Their research suggests that enantioselectivity can be controlled by a chiral Lewis acid mediated substrate complex.

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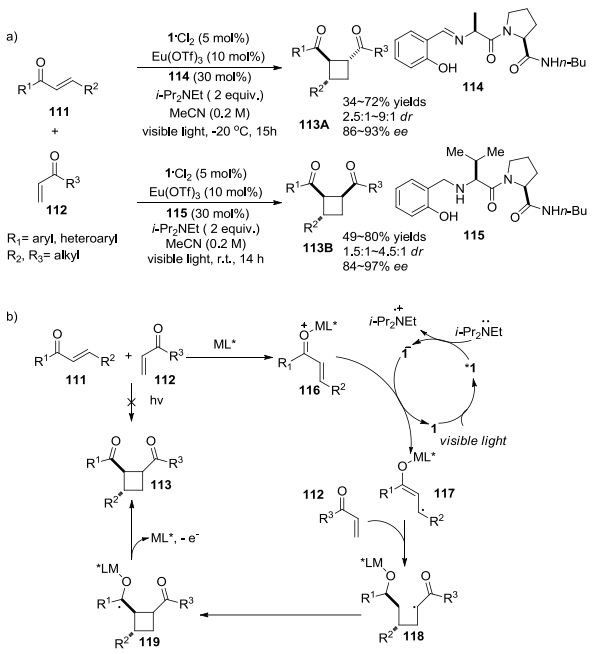
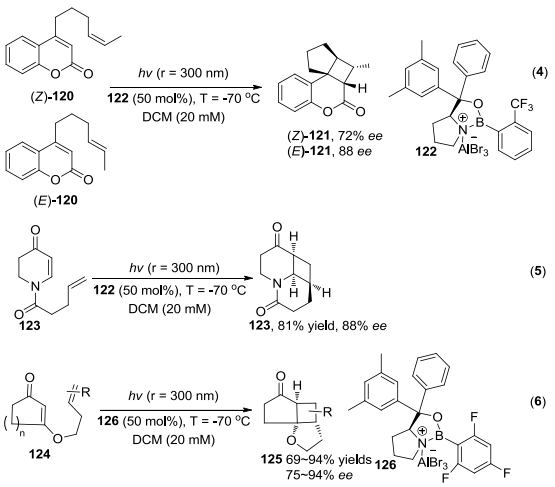


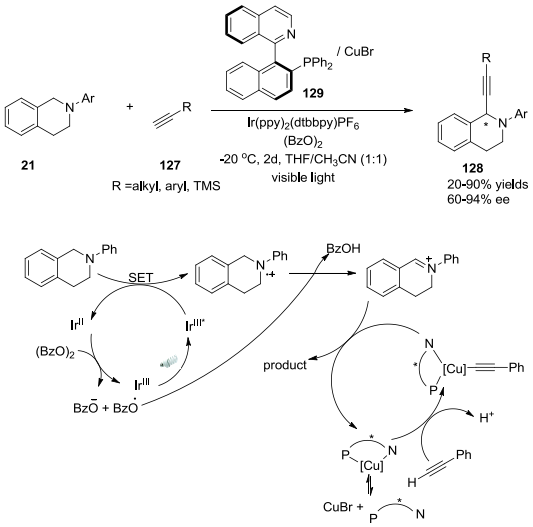
Scheme 22 a) Europium and ruthenium co-catalyzed asymmetric [2+2] photocycloaddition. b) Proposed mechanism.

While under the irradiation of ultraviolet light, a series of interesting results using chiral Lewis acids were reported by Bach and his co-workers to successfully construct high enantioseletive cyclobutanes through asymmetric intramolecular [2+2] photocycloadditions (**Scheme 23**).[35]



Scheme 23 Enantioselective Lewis acid catalyzed intramolecular [2+2] photocycloaddition under the irradiation of UV.

Very recently, visible-light-induced asymmetrically cross-dehydrogenative coupling (CDC) reactioin of *N*-aryl-tetrahydroisoquinolines with alkynes is demonstrated by Li and his co-workers (**Scheme 24**).[36] In the reactions, *N*-aryl-tetrahydroisoquinolines could be oxidized by the photoexcited sensitizer using benzoyl peroxide as the terminal oxidant, undergoing deprotonation to yield the imine intermediate. A chiral Cu-QUINAP-acetylide species formed copper-mediated deprotonation of alkynes nucleophilically added to the imine intermediate, resulting in the formation of chiral α-alkynylation *N*-aryl-tetrahydroisoquinolines in 20-90% yields and 60-94% ee.



Scheme 24 Asymmetrically cross-dehydrogenative coupling (CDC) reactioin of *N*-aryl-tetrahydroisoquinolines with alkynes.

7. Asymmetric cross-coupling reactions

A very recent report from Molander group revealed that asymmetric Suzuki cross-coupling of potassium methyl benzyltrifluoroborate with methyl 3-bromobenzoate could be facilitated by a combination of **4**•PF_6 (2 mol%), $Ni(COD)_2$ (3 mol%) and chiral ligand **133** (3 mol%) to yield methyl 3-(1-phenylethyl)benzoate **132** in 52% yield with 50% *ee* (**Scheme 25a**).[37] Under the irradiation of visible light, photoexcited ***4** accepted an electron from **130** to become more reductive species **4**$^-$. Classic oxidative addition of $Ni(COD)_2$ with aryl halide would deliver a Ni(II) species **136** that can intercept benzyl radical to afford high valent Ni(III) species **137**. Subsequent reductive elimination of high valent Ni(III) species **137** would furnish the cross-coupling product, meanwhile give Ni(I) species **138** which could undergo single-electron reduction by **4**$^-$ to regenerate Ni(0) catalyst (**Scheme 25b**). Compared to traditional cross-coupling, this photoredox cross-coupling could dramatically promote single-electron transmetallation instead of two-electron transmetallation. Although there is only one example with moderate yield and enantioselectivity, their findings would significantly provide a new access to the catalytic asymmetric cross-coupling reactions using Sp3-carbon as the partner.

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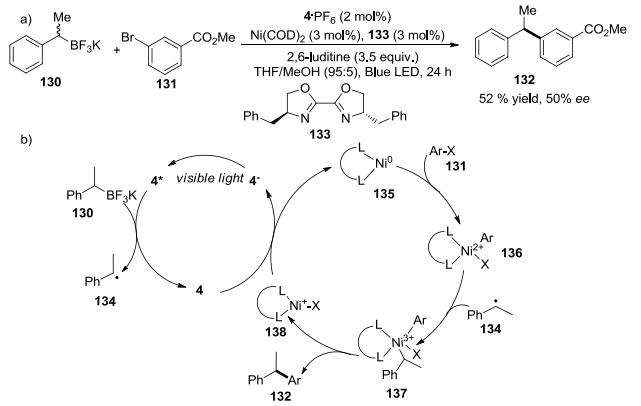

Scheme 25 a) Nickel and iridium co-catalyzed asymmetric Suzuki cross-coupling reaction. b) Proposed mechanism.

8.Conclusions

Under the irritation of visible light, the highly enantioselective transformations could be successfully achieved by combination of visible light photocatalysts and other chiral catalysts, such as thioureas, amines, carbenes, Lewis acids, phosphoric acids. Mild conditions, such as room temperature, no strong base or acid, low energy light source, are utilized in most of reactions which could tolerate variously functionalized groups, decrease environment pollution, save energy and realize sustainable chemistry. Meggers's landmark work on designing visible-light-induced chiral photocatalyst might make a huge improvement in asymmetric phototransformations. The another interesting initial result for asymmetric cross-coupling reaction for C_{Sp3}- C_{Sp2} bond formation would explore a new strategy to regenerate transition-metal catalysts by photoredox single-electron transmetallation. Although the type of reactions is so far limited, considering the huge progress made in asymmetric catalysis chemistry, more new organocatalysts and varieties of transition-metals with novel chiral ligands will be developed and engaged in the field of asymmetric photoreactions.

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Notes and references

[a] *Department of chemistry, Zhejiang University, 148 Tianmushan Road, Hangzhou, China. Fax: +86-571-88273389; Tel: +86-571-88273389; E-mail: luzhan@zju.edu.cn*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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