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Asymmetric Catalytic Radical Reactions Enabled by Chiral *N,N′*-Dioxide−Metal Complexes

Weidi Cao, Xiaohua Liu,* and Xiaoming Feng*

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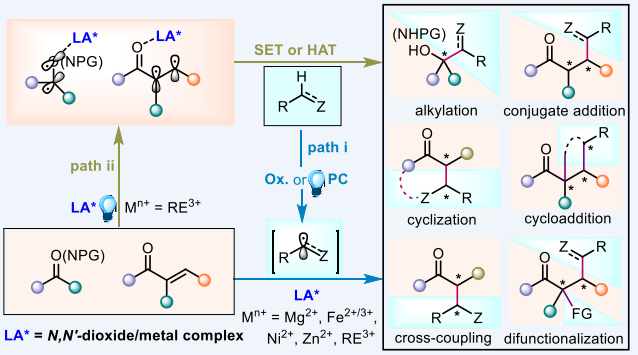
CONSPECTUS: The strategic implementation of asymmetric catalytic radical reactions has evolved into a sophisticated methodology for constructing stereogenic centers, driven by remarkable advancements in radical generation techniques. However, achieving high stereoselectivity remains a formidable challenge due to the inherent high reactivity, transient lifetime of radical species, and presence of competing racemic background pathways. Addressing these limitations necessitates precise catalytic systems capable of orchestrating radical generation and enantioselective transformation in a controlled manner. In this Account, we systematically present our recent progress in enantioselective radical transformations mediated by chiral *N,N′*-dioxide−metal complexes, which have previously been widely used in polar reactions. Our mechanistic investigations categorize these transformations into three distinct paradigms based on radical generation strategies. (1) Oxidant-driven radical generation: Leveraging oxidants—hypervalent iodine reagents, peroxides, or molecular oxygen—we achieved alkyl radical formation. By synergizing these oxidants with redox-active or redox-inert chiral *N,N′*-dioxide-metal catalysts, we accomplished asymmetric difunctionalization of both electron-deficient and electron-rich olefins, alongside enantioselective radical cross-coupling reactions. (2) Merging photocatalytic strategy: Visible light irradiation facilitates the activation of metallic or organic photocatalysts (PCs), generating excited state species for redox or hydrogen atom transfer (HAT) processes. This enables the selective cleavage of inert C(sp^3)−H bonds in hydrocarbons or C(sp^2)−H bonds in aldehydes, producing diverse radical intermediates. Integration with chiral Lewis acid catalysts allows enantioselective radical additions to ketones, imines, and *α,β*-unsaturated carbonyl compounds, establishing C−C bonds under mild conditions without use of preactivated radical generators. Furthermore, energy-transfer photocatalysis combined with chiral Lewis acids promotes cyclization via C═C bond activation. Besides, an electron-shuttle strategy has been developed to balance radical generation from photoactive substrates, enabling asymmetric acylation and alkylation of aldimines. (3) Lewis acid-enabled substrate photoexcitation: We disclosed photocatalyst-free approaches wherein chiral *N,N′*-dioxide−metal complexes modulate substrate photophysics. Chiral Lewis acid coordination with several carbonyls or imines alters their photochemical properties. Interestingly, this activation of some C═X unsaturated compounds under light enhances their reduction potentials for single electron transfer (SET) as a temporary oxidant, enabling direct radical alkylation of ketones/imines. Alternatively, the strategy can stabilize triplet excited states.



Collectively, our studies elucidate mechanistic frameworks for stereocontrol in radical reactions, demonstrating the versatility of chiral Lewis acid catalysts in merging photocatalysis, radical chemistry, and C−H functionalization. The developed methodologies offer practical synthetic routes while addressing fundamental challenges in selectivity and efficiency. We envision that this Account will inspire further exploration of asymmetric radical systems, fostering advancements in catalytic diversity and mechanistic understanding.

KEY REFERENCES

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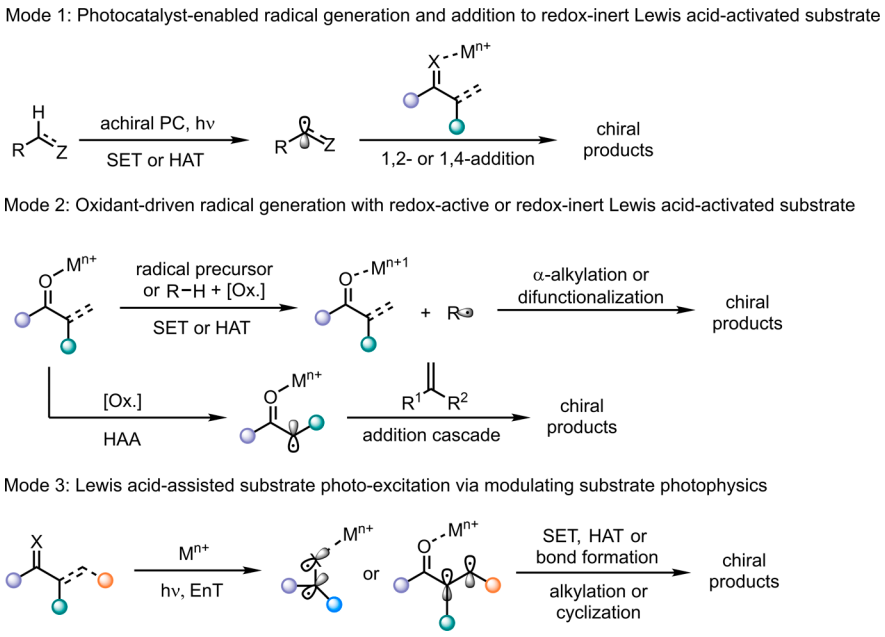

Figure 1. General modes for generation and asymmetric transformations of radical species by *N,N′*-dioxide−metal complexes.

alkanes, which is mediated by synergistic catalysis merging a redox chiral iron complex and an oxidant.

- Yu, H.; Zhan, T. Y.; Zhou, Y. Q.; Chen, L.; Liu, X. H.; Feng, X. M. Visible-Light-Activated Asymmetric Addition of Hydrocarbons to Pyridine-Based Ketones. *ACS Catal.* **2022**, *12*, 5136−5144.[2] *This work introduces the direct photoinduced asymmetric alkylation of ketones with hydrocarbons. An exogenous photocatalyst enables HAT for alkyl radical generation, and chiral Lewis acid assists enantioselective radical addition.*
- Zhong, Z. W.; Wu, H. D.; Chen, X. F.; Luo, Y.; Yang, L. Q.; Feng, X. M.; Liu, X. H. Visible-Light-Promoted Enantioselective Acylation and Alkylation of Aldimines Enabled by 9-Fluorenone Electron-Shuttle Catalysis. *J. Am. Chem. Soc.* **2024**, *146*, 20401−20413.[3] *This work introduces asymmetric acylation and alkylation of imines, wherein 9-fluorenone (FLN) serves as an electron shuttle to leverage radical generation, facilitating enantio-controlled radical addition to chiral Lewis acid-activated imines.*
- Hou, L. Z.; Zhou, Y. Q.; Yu, H.; Zhan, T. Y.; Cao, W. D.; Feng, X. M. Enantioselective Radical Addition to Ketones through Lewis Acid-Enabled Photoredox Catalysis. *J. Am. Chem. Soc.* **2022**, *144*, 22140−22149.[4] *This work introduces a visible light-induced asymmetric alkylation of ketones. It highlights the strategy of photocatalyst-free Lewis acid assisted photoexcitation of ketones, enabling single electron transfer with silanes.*

1. INTRODUCTION

Radical reactions exhibit unique advantages characterized by their low activation energy barriers, high tolerance toward conventional reactive functional groups, and exceptional ability to activate traditionally inert chemical bonds (especially the C−H bond), along with facile realization of polarity inversion (umpolung). Based on these features, catalytic asymmetric radical reactions have opened novel avenues for chiral compound synthesis.[5−18] However, in order to achieve satisfactory reactivity and stereoselectivity, it is critical to leverage radical generation and enantioselective transformation in a controlled manner, overwhelming racemic background reactivity and side reactions, due to the inherent high reactivity and transient lifetime of radical species.

Chiral Lewis acid involving enantioselective radical reactions have been pioneered by Porter, Sibi, and others since 1996,[19,20] and the efficiency and generality of asymmetric catalytic versions have been elevated to a new level based on the harmonious integration of tamed radical reactivity with various chiral catalysts, encompassing both those traditionally employed in classic polar reactions and newly developed ones.[21−26] Previously, our research group developed a type of chiral *N,N′*-dioxide ligands, that in combination with metal salts were recognized as privileged Lewis acid catalysts,[27−33] which have been used in a number of asymmetric catalytic polar reactions of functionalized or weaker C−H-bond-based reactants. Recently, we endeavored to expand the capability of this type of catalyst for transformations involving inert substrates or umpolung reactions, where radical-based routes provide vast potential.

Approaches for radical generation have been widely expanded, including but not limiting to thermal homolysis, redox with or without photochemical initiation, hydrogen atom abstraction (HAA) from C−H bonds by HAT reagents or catalysts, and energy transfer (EnT) to reach singlet or triplet excited states along with redox transformations. The chiral Lewis acids could only participate in a radical transformation step or in the radical generation to the terminal step. For the former situation, synergistic catalysis is important to balance controlled radical generation and enantioselective trapping. We utilized achiral photocatalysts, such as metallic or organic photosensitizers, under visible light irradiation to drive the radical generation, in combination with chiral Lewis acids of *N,N′*-dioxide ligands to guide the radical addition to carbonyls, imines, or *α,β*-unsaturated carbonyls (Figure 1, Mode 1). The latter situation seemed complicated, where the chiral Lewis acid catalysts played multiple roles. The coordination of the substrate to a chiral catalyst delivered changes related to redox ability, photophysics, and photochemistry, which could be utilized for radical initiation, stabilization, and enantioselectivity trapping,

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through the use of exogenous oxidants (Mode 2) or under light irradiation (Mode 3). It should be mentioned that the redox-active ability of some Lewis acid metal ions or Lewis-acid-bound substrates has been disclosed in some cases, which further expands the application of *N,N′*-dioxide−metal complexes.

In this Account, we present our achievements by dividing these processes into three types from the viewpoint of production of radical species: oxidant-driven radical generation, merging photocatalytic strategy, and Lewis acid-enabled substrate photoexcitation. We highlight the related mechanism of how the radical generation and performance of the catalysts address enantiocontrol.

2. MERGING CHIRAL LEWIS ACIDS WITH EXOGENOUS OXIDANTS

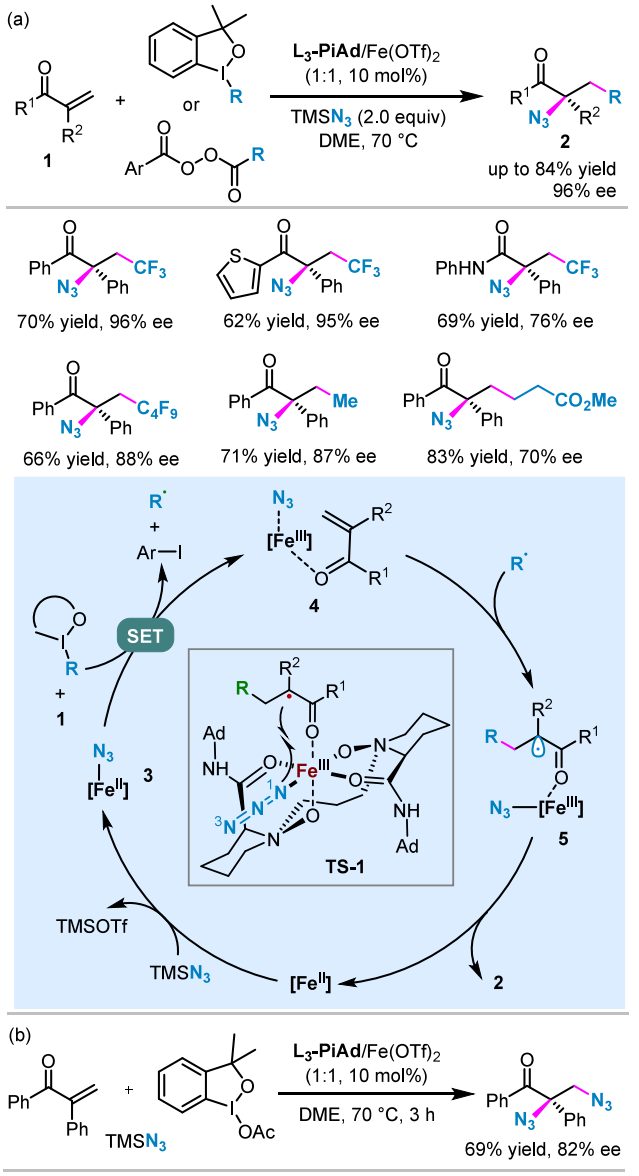
Alkyl radicals are key intermediates in organic synthesis, and their controllable generation and utilization under redox conditions allow novel routes for asymmetric C−C bond construction. The merging of redox-active or redox-inert chiral Lewis acid catalysts with exogenous oxidants could be used for both asymmetric radical additions and radical couplings.

2.1. Asymmetric Carboazidation of α,β-Unsaturated Carbonyl Compounds

Catalytic enantioselective carboazidation of alkenes, which is initiated with a carbon-centered radical addition followed by azido radical transfer, enables direct access to organic azide compounds as versatile building blocks and precursors for the preparation of nitrogen-containing molecules. Given the azido-transfer ability of azide−iron complexes of chiral *N,N′*-dioxide in polar addition,[34,35] we explored the process in radical carboazidation involving open-shell species. Initially, we used preactivated radical precursors, such as Togni's reagent or alkyl peroxides, to generate alkyl radicals. Catalyzed by chiral *N,N′*-dioxide/$Fe(OTf)_2$ complexes, an efficient enantioselective radical carboazidation of *α,β*-unsaturated ketones and amides **1** was realized (Scheme 1a).[36] Suitable carbon partners included both fluoroalkyl and alkyl radicals, accessing a wide array of chiral *α*-azido carbonyl derivatives **2**. Simply changing the oxidant to benziodoxole led to enantioselective diazidation to furnish vicinal diazides (Scheme 1b). Mechanistic study revealed that the oxidation of L−Fe(II)−N_3 species **3** by Togni's reagent generated the chiral Fe(III)−N_3 species **4** and alkyl radical (Scheme 1a). The azido transfer occurred via a five-membered transition state **TS-1** at the internal nitrogen of the Fe−N_3 species **5** through an enantioselective homolytic substitution, which differed from the outer sphere terminal ^{3}N-transfer pathway reported by Bao[37,38] and Liu.[39]

Furthermore, we extended the use of hydrocarbon feedstocks as alkyl radical precursors instead of preactivated ones by integrating the HAA process with chiral iron catalysis.[40,41] The strategy further expands the scope of functionalized chiral azides (Scheme 2). A benzoyl peroxide derivative (BPO-Cl) or *tert*-butyl peroxybenzoate (TBPB) was employed to undergo a SET oxidation of L−Fe(II) to produce the L−Fe(III) species and an aryl carboxyl radical, and the latter species facilitated the cleavage of C(sp^3)−H bond of hydrocarbons to give an alkyl radical. Kinetic isotope effect experiments (KIE, with k_H/k_D = 2.59) and radical trapping experiments indicated that the HAA process was involved in the rate-determining step. The subsequent steps and enantiocontrol followed a similar pathway via radical substitution to afford the products.

Scheme 1. Enantioselective Carboazidation and Diazidation of *α,β*-Unsaturated Carbonyl Compounds



2.2. Asymmetric α-Alkylation of 2-Acylimidazoles with Hydrocarbons

The alkylation of enolates using a nonactivated hydrocarbon feedstock through the cross dehydrogenation coupling (CDC) reaction represents a fundamental process for the construction of C−C bonds. Peroxide-triggered HAA could generate carbon-centered radicals of alkanes, but an efficient chiral redox catalyst is critical to render cross-coupling in an enantioselective manner. Encouraged by facile self-exchange of ferric and ferrous catalysts of *N,N′*-dioxides with distinct and robust coordination geometry, we carried out a direct *α*-alkylation of 2-acylimidazole **7** using hydrocarbon **6** as the alkylation reagent and di-*tert*-butyl peroxide (DTBP) as an oxidant (Scheme 3). In this context, the chiral *N,N′*-dioxide ligands and 2-acylimidazoles **7** were compatible with each, affording the oxidative cross-coupling products **8** with benzylic and allylic hydrocarbons as well as cyclic alkanes in good yields (up to 88% yield) with excellent enantioselectivity (up to 99% ee).[1] Compared with other ligands, such as pybox and salen, the excellent outcome of this

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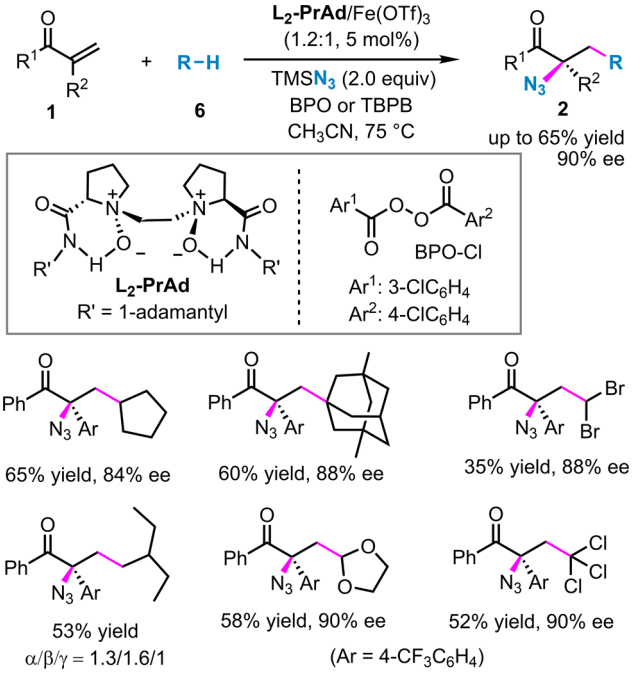
Scheme 2. Enantioselective Carboazidation of α,β-Unsaturated Carbonyl Compounds with Hydrocarbons



tetra-oxygen ligand might stem from a weak-field ligand to form high-spin iron complexes, facilitating the SET process. DFT calculation revealed the influence of *N*-substitution of 2-acylimidazoles on the *Z*/*E*-configuration of enolate intermediate **9**. Spin density analysis indicated that there was a tautomeric equilibrium between Fe(III)-enolate **9** and a Fe(II)-carbon radical species **10** via a ligand-to-metal charge transfer (LMCT) process. Lastly, asymmetric radical cross-coupling yielded chiral alkylation product **8**.

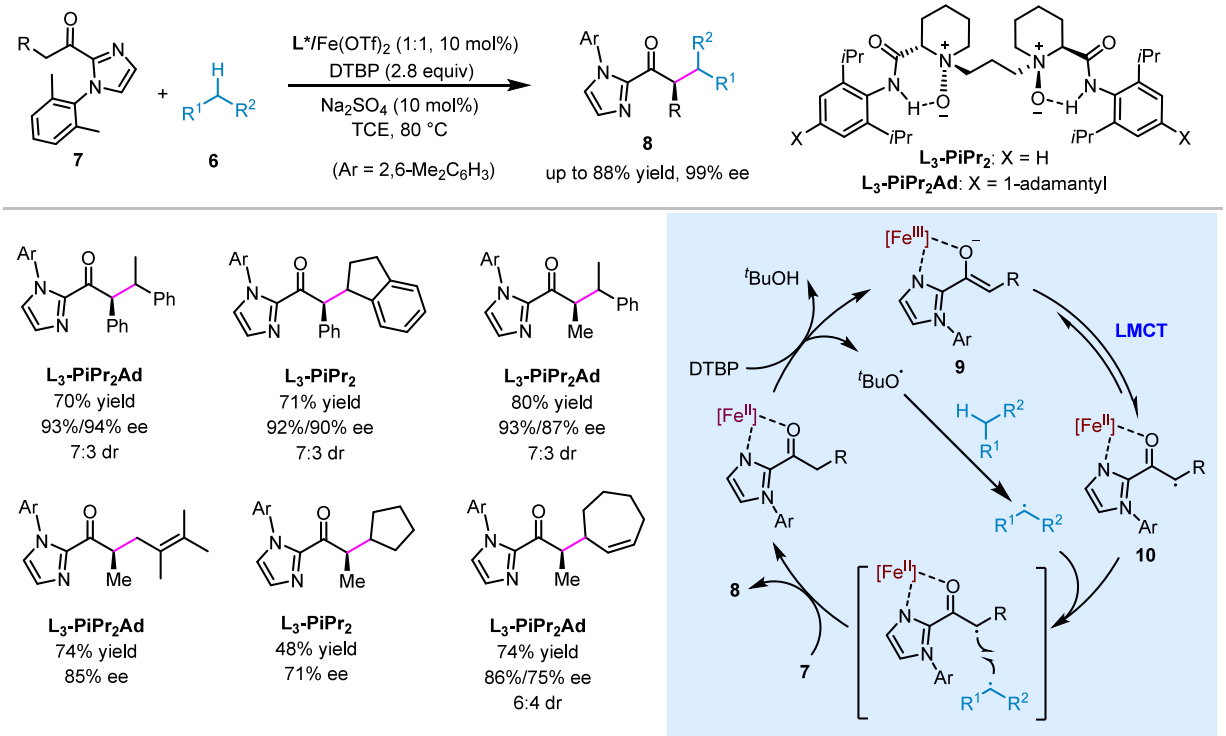
Besides, enantioselective α-alkylation of β-keto amides with glycine derivatives occurred readily with a chiral *N*,*N*′-dioxide-Mg(II) catalyst, peroxybenzoate and a catalytic amount of NaI.[42] Additionally, a chiral *N*,*N*′-dioxide-Ni(II) mediated α-alkylation of β-keto amides with phenyliodonium ylide through a radical-based cross-coupling process driven via a triplet dimethyl malonate carbene intermediate was achieved.[43]

2.3. Enantioselective Radical Addition Cascades of Simple Alkenes

Umpolung via radical species provides an alternative way to construct C−C bonds. 1,3-Dicarbonyls are classic nucleophiles, which can be transformed into electrophilic radicals upon oxidation and then perform addition to electron-rich alkenes. By merging chiral Lewis acid catalysis with a chemical oxidant, we have accomplished the radical addition and polar cyclization of indanonecarboxamides/esters **11** with 1,1-disubstituted ethenes **12** (Scheme 4).[44] Using Ag_2O as the oxidant and chiral *N*,*N*′-dioxide−Ni(II) complex as the catalyst, a series of spirocycles **13** were available in excellent yields and ee values, overwhelming the strong racemic background reaction, probably because the bidentate coordination of the α-radical to the catalyst (**14**) enhances the electrophilicity toward addition to alkene **12** to form chiral radical species **15a**. Further oxidation into carbocation species **15b** could lead to cyclization to yield the spirocycle; otherwise elimination or oxygen-transfer into other unsaturated derivatives **16**−**18** resulted when alkyl-substituted terminal alkenes were involved.

Interestingly, when oxygen was used as the oxidant, an oxidative radical addition/hydroxylation/1,4-aryl migration sequence occurred between indanonecarboxamides **11** with bisaryl substituted ethenes **12** in the presence of a chiral *N*,*N*′-dioxide-Mg(II)/CuI combination system (Scheme 5).[45] This

Scheme 3. Chiral Iron-Catalyzed α-Alkylation of 2-Acylimidazoles with Alkanes



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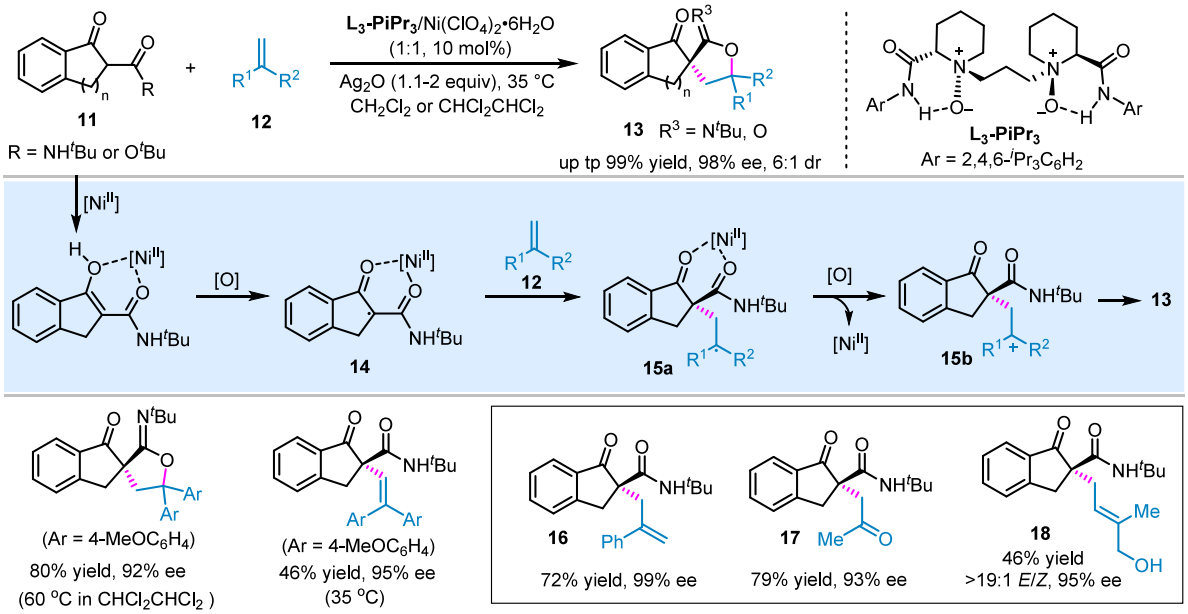
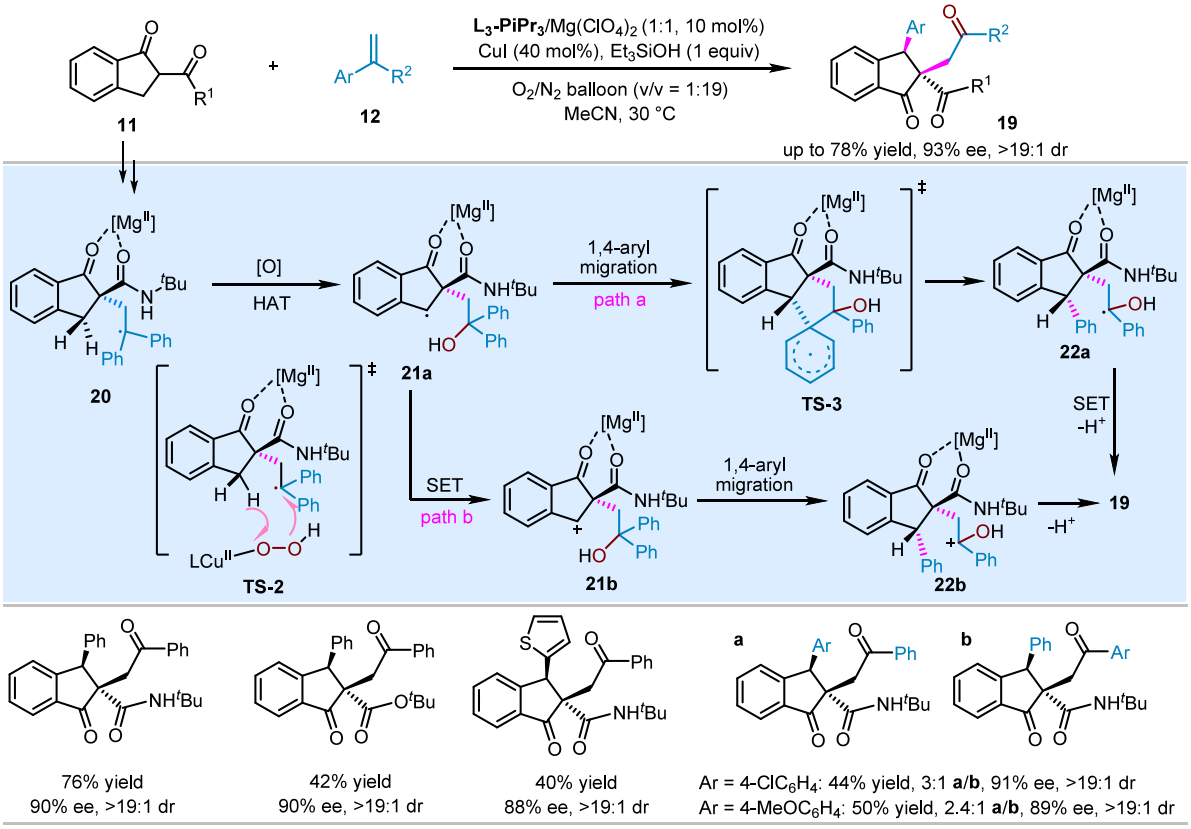
Scheme 4. Chiral Nickel-Catalyzed Enantioselective Radical-Polar Crossover Reaction



Scheme 5. Asymmetric Catalytic Aerobic Oxidative Radical Addition/Hydroxylation/1,4-Aryl Migration of Alkenes



cascade reaction afforded 3-arylated 2-oxo-2-phenylethyl substituted indanone derivatives **19** as the major products in satisfactory yields and stereoselectivities. In this circumstance, the copper-triggered aerobic oxidation of radical **20** occurred to generate diaryl alcohol intermediate **21a**/**21b** *in situ* bearing a distal radical or carbocation. The subsequent 1,4-aryl migration happened in a radical or polar pathway via a five-membered cyclic transition state (**TS-3**), yielding 3-arylated indanone derivative **19**. The chiral magnesium catalyst could relay chiral information in the radical addition and 1,4-aryl migration steps.

3. MERGING CHIRAL LEWIS ACID WITH AN EXOGENOUS PHOTOCATALYST

The resurgence of photocatalysis has established a convenient platform for asymmetric radical reactions.[46−56] Excited state photocatalysts show particular redox ability to trigger electron-

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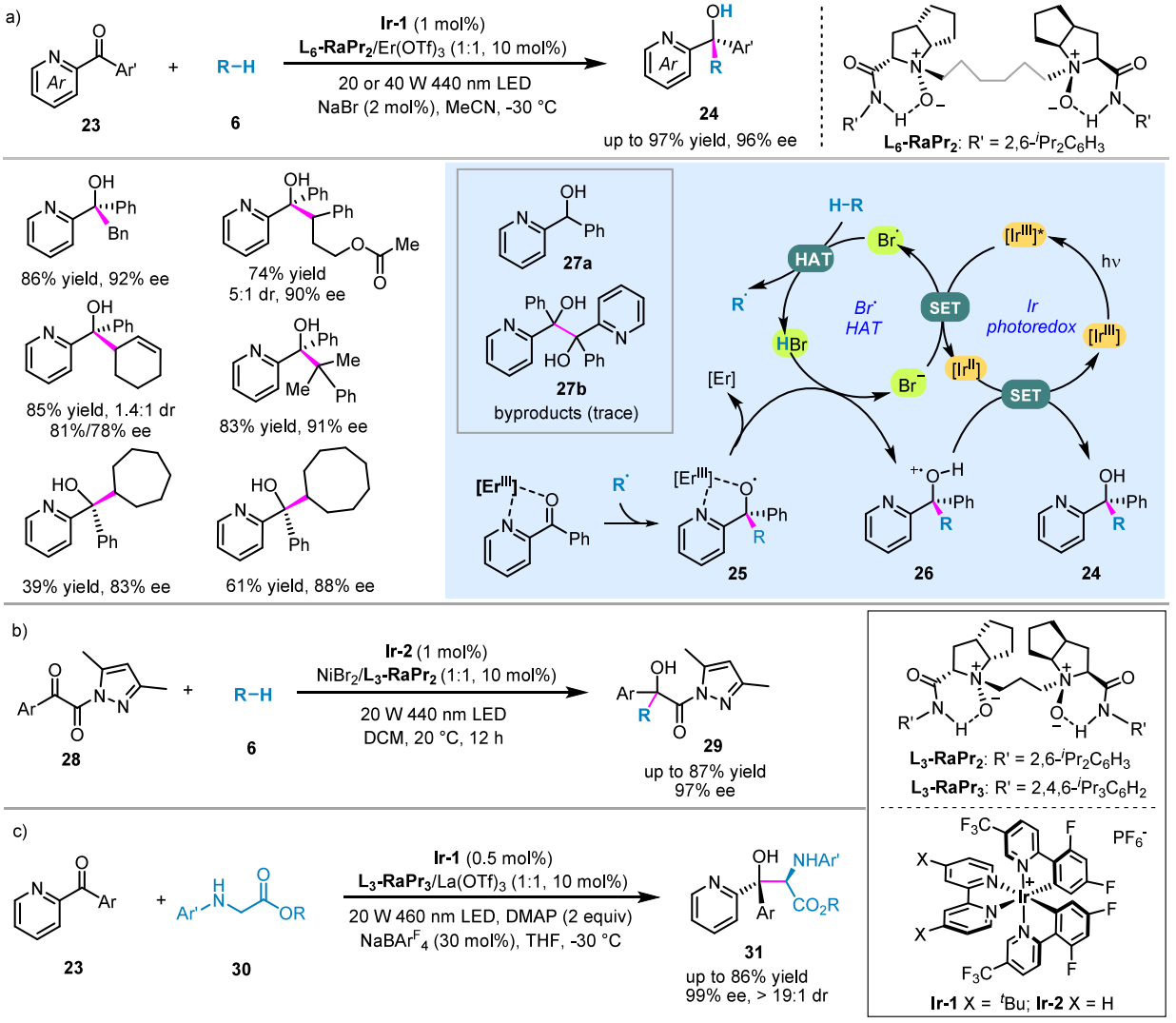
Scheme 6. Asymmetric Radical Addition to Ketones with C(sp^3)−H Donors



or atom-transfer, benefiting the cleavage of inert bonds under mild conditions. Taking account of the soft−hard acid−base principle and chelation ability, ligand exchange between tetradentate *N,N′*-dioxide ligands and bidentate ligands of noble-metal based photocatalysts could be negligible. The redox-inert ability of *N,N′*-dioxide ligands allows the formed chiral Lewis acid catalyst to be promising for radical reactions in combination with either metal or organo-photocatalysts.

3.1. Asymmetric Alkylation of Ketones with Hydrocarbons

Enantioselective 1,2-addition of photogenerated alkyl radicals of hydrocarbons to carbonyls is extremely attractive for chiral alcohol synthesis, but it is challenging due to several competitive side reactions involving ketyl radical upon direct UV-light irradiation. We developed a combined catalytic system including an [Ir^{III}] sensitizer, an Er(III)-based chiral complex, and NaBr for the purpose (Scheme 6a).[2] Under visible light irradiation, the asymmetric alkylation of heteroaryl-based ketones **23** with diverse hydrocarbons (including benzyl, allyl, and cyclic alkanes) proceeded smoothly, delivering a variety of highly congested and enantioenriched tertiary alcohols **24**. The alkyl radical formation from alkanes relied on HAT by a catalytic amount of bromide radical, which was generated from SET oxidation of Br^- by the excited *[Ir^{III}] photocatalyst. KIE experiments determined that C(sp^3)−H cleavage was the rate-determining step from which HBr was generated. Assisted by a bulky Er(OTf)$_3$ complex of a six-carbon-linked *N,N′*-dioxide ligand **L$_6$-RaPr$_2$**, enantioselective radical addition to ketone formed ketyl radical **25**, which could be stabilized by binding to Lewis acid or protonation from HBr.[57] Subsequent SET of radical cation **26** with [Ir^{II}] regenerated [Ir^{III}] and delivered the product **24**. The asymmetric radical addition pathway departed from conventional radical cross-coupling (especially under UV light) minimizing the formation of reduction byproduct **27a** and self-coupling byproduct **27b**, and this process was proposed to benefit from the choice of bulky and non-redox chiral Lewis acid.

The simplified [Ir^{III}]/NiBr$_2$/*N,N′*-dioxide combined system could be applied to alkylation of *α*-keto pyrazole amides **28** (Scheme 6b), giving access to chiral tertiary alcohols **29** (up to 87% yield and 97% ee) as well vicinal diols and *α*-hydroxyl ester derivatives.[58] For the direct addition of glycinates **30** to ketones **23**, merging chiral lanthanide catalyst with [Ir^{III}] photoredox catalyst in the presence of 4-dimethylaminopyridine (DMAP) without a bromide source enabled the transformation efficiently (Scheme 6c). A wide range of *β*-diaryl-*β*-hydroxy-*α*-amino acetate derivatives **31** containing adjacent stereocenters were obtained via an *α*-amino radical addition and a reductive quenching pathway.[57]

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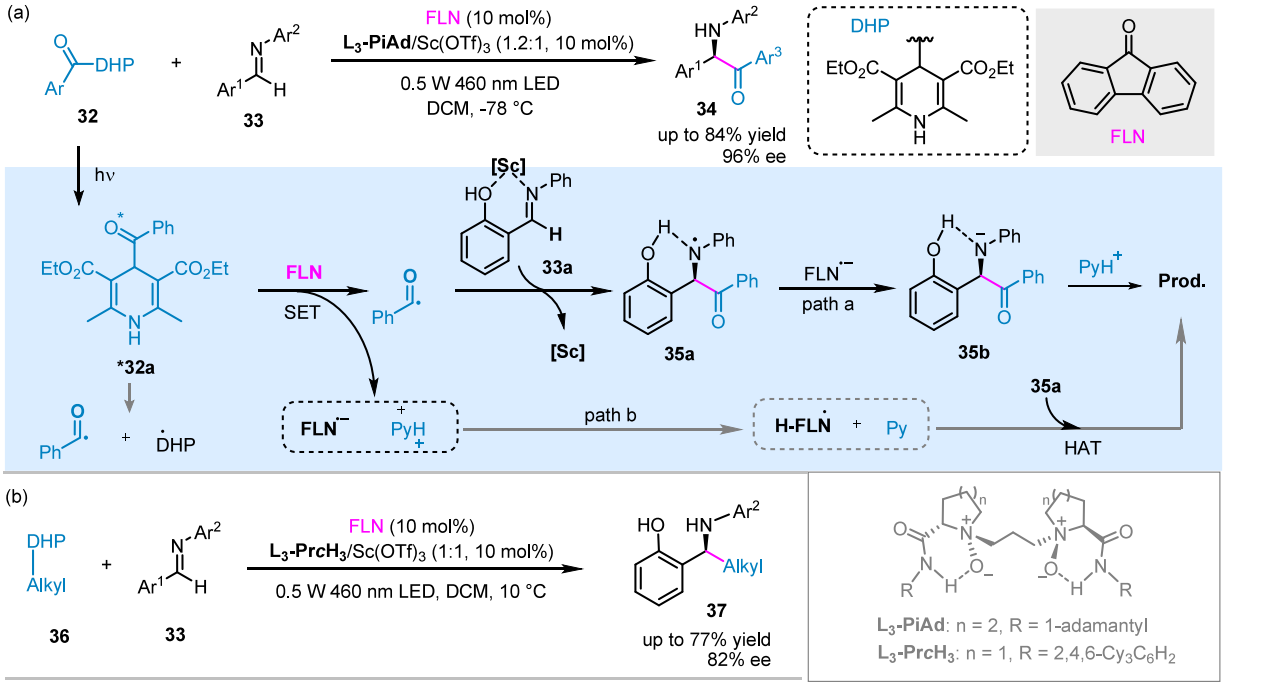
Scheme 7. Visible Light Photoinduced Asymmetric Acylation and Alkylation of Imines



3.2. Asymmetric Acylation and Alkylation of Imines

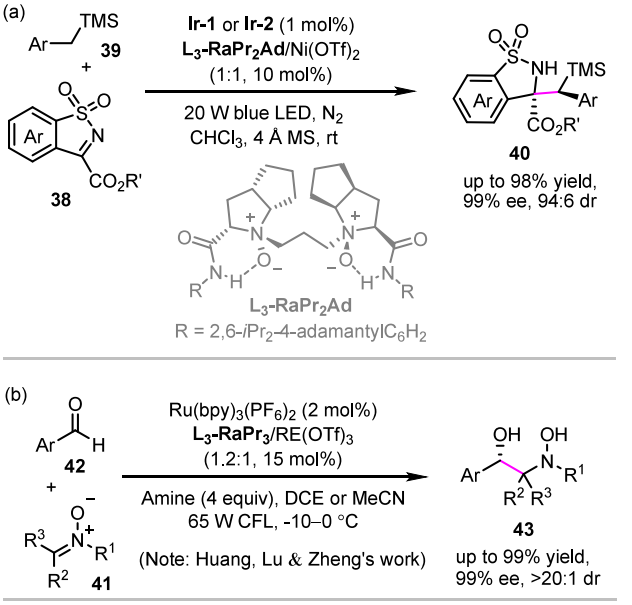
Due to the weak absorption in the visible light region and lower reduction potential of several imines, the transformation of imine via α-amino radical coupling is usually difficult. Alternatively, the enantioselective radical addition strategy could also be used for the acylation and alkylation of imines. Acyl radicals are regarded as exceptionally nucleophilic radicals and are feasibly available from 4-acyl dihydropyridine (DHP) **32**, providing a notable umpolung strategy for α-amino ketone synthesis (Scheme 7a).[3] To compete with the uncontrollable spontaneous pathway via homolysis of excited 4-acyl DHP, we introduced an electron shuttle, 9-fluorenone (FLN), which regulated the concentration of acyl radical via a SET process from visible light excited 4-acyl DHP at a lower temperature as the rate-determining step. With the assistance of chiral *N*,*N*′-dioxide−Sc(OTf)$_3$ complex catalyst, acyl radical addition to aldimine, as the enantioselectivity-determining step, occurred efficiently via intermediate **35a** to afford chiral β-amino carbonyl compound **34**, after another SET/protonation sequence with the radical anion of FLN (path a) or a HAT step with the ketyl radical of FLN (path b). This protocol was further extended to asymmetric alkylation using 4-alkyl DHP **36** as the alkyl radical precursor, enabling the production of chiral secondary amine **37**.

In addition, asymmetric radical alkylation of benzosultams **38** with alkyl silanes **39** was also realized (Scheme 8a), a series of chiral organosilanes **40** containing two adjacent tri- and tetra-substituted stereocenters were obtained under chiral Ni(II)/Ir(III) synergistic catalysis.[59] Huang and co-workers developed achiral Ru(II) with chiral rare earth (RE) complex synergistic catalysis for the reductive cross-coupling reaction of nitrones **41** with aromatic aldehydes **42** (Scheme 8b), producing vicinal amino alcohols **43** with high yields and stereoselectivities.[60]

3.3. Asymmetric Acylation and Alkylation of Electron-Deficient Alkenes

Asymmetric Giese radical addition, trapping carbon-centered radicals with electron-deficient alkenes, represents a kind of

Scheme 8. Visible Light Photoinduced Asymmetric Alkylation of Imines



classic and efficient radical type transformation to construct a C−C bond. It is important to choose a photocatalyst to initiate the carbon radical generation from C−H based materials via the HAT process. Similar to other asymmetric radical addition reactions, a chiral Lewis acid catalyst could promote asymmetric 1,4-addition of electron-deficient alkenes with nucleophilic radicals. Hydroacylation of alkenes with aldehydes represents a high-atom-economy approach to introduce carbonyl motifs into organic molecules. We merged a quinone photocatalyst (AQ) and chiral rare earth metal complexes under light irradiation for direct hydroacylation of α-substituted terminal enones with aldehydes (Scheme 9).[61] This synergistic catalysis exhibited a

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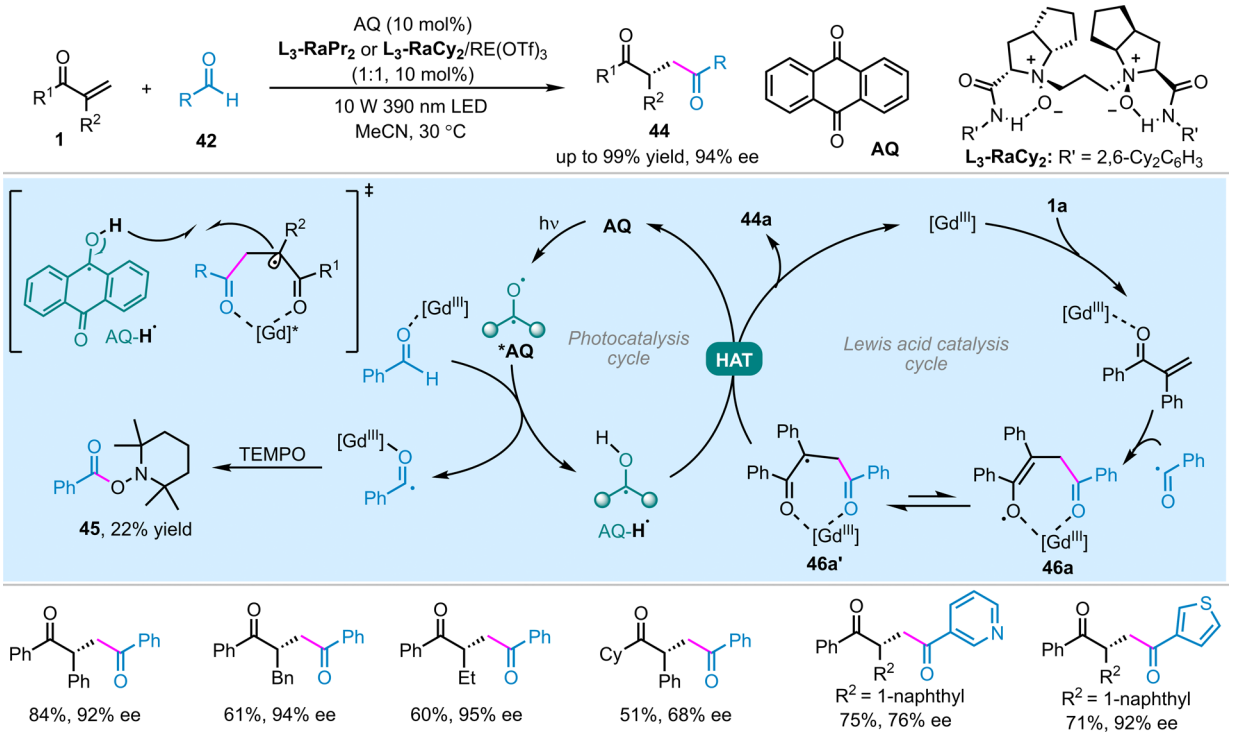
Scheme 9. Enantioselective Radical Hydroacylation of α,β-Unsaturated Carbonyl Compounds



broad substrate scope involving both aromatic and aliphatic aldehydes with good functional group tolerance, providing a straightforward route to chiral 1,4-diketone derivatives **44**. The isolation of the TEMPO-adduct **45** and radical clock experiments established the generation of the acyl radical via direct HAT between the excited photocatalyst *AQ and the aldehyde. Stern–Volmer fluorescence quenching studies revealed that the HAT process was accelerated in the presence of the Lewis acid catalyst (K_{SV} = 265.3 vs 80 M^{-1}). Following nucleophilic acyl radical addition to the chiral Ga(III)-activated enone, an O-radical **46a** or the α-radical intermediate **46a′** was generated. For the enantiocontrol step, the relatively low deuterated ratios observed with the addition of excess D_2O, as well as the minimal dependence of deuterated ratios on the electronic effects of the α-aryl groups, suggested that a direct HAT process from the AQ–$H^{\bullet}$ radical was more likely involved rather than a SET/PT (proton transfer) sequence, which was further supported by DFT calculations. During these processes, the AQ photocatalyst worked as a hydrogen-atom shuttle.

In addition, quinone photocatalyst synergistic catalysis has proven effective for the direct asymmetric hydroalkylation of α-substituted acrylamides **47**.[62] A wide range of abundant feedstock C(sp^3)–H donors, including alkanes, alkyl ethers, thioethers, selenides, and amines could undergo radical addition to produce the corresponding chiral α-aryl amide derivatives **48**, and a similar HAT/radical addition/back HAT sequence was suggested (Scheme 10a). For the asymmetric hydroalkylation of α-substituted vinylphosphine oxides **49** (Scheme 10b), the use of the tetracen-5(12*H*)-one (NQ) photocatalyst and a chiral magnesium complex worked well, but the final step varied via a photoredox SET/PT process of α-radical **51a** into anion **51b** as the major process based on deuterium labeling experiments and Hammett analysis, producing α-chiral alkyl phosphines **50** with up to 85% yield and 95% ee.[63] This stepwise SET/PT pathway was also applicable to enantioselective hydrosilylation/hydrogermylation of α,β-unsaturated amides with silanes or germanes.[64]

3.4. Asymmetric Photocycloaddition and Photocyclization

Lewis acid activation of carbonyl compounds could alter their photophysical and photochemical properties,[65] such as bathochromic shift in the UV–vis absorption spectrum, decrease of the energy of the triplet state, acceleration of the intersystem crossing (ISC) process, increase of reduction potential, and so on. These changes result in initiating the reaction under milder conditions and visible light illumination in connection with an appropriate photocatalyst.

On the basis of this concept, we accomplished an asymmetric intermolecular [2 + 2]-photocycloaddition reaction[66] of bidentate 2′-hydroxychalcones **52** with 2,3-dimethylbuta-1,3-diene by employing **L_3-PiEt$_2$Me**/Sc(OTf)$_3$ complex catalyst and [Ru(bpy)$_3$]Cl$_2$ as the sensitizer under visible light illumination (Scheme 11).[67] No reaction occurred in the absence of either the photocatalyst or the chiral Lewis acid catalyst, demonstrating the integral parts of the two catalyst components. The UV–vis study of 2′-hydroxychalcone **52a** showed that the addition of the chiral Sc(III) complex led to a clear bathochromic shift, enabling the excitation of **52a** in the visible light region through energy transfer with [Ru(bpy)$_3$]Cl$_2$. The diradical species **54a** performed an enantioselective radical addition to alkene 2,3-dimethylbuta-1,3-diene to generate radical species **55a**, and the following radical coupling afforded the chiral cyclobutene product **53**.

Smith and Paton exploited the dual catalyst system of chiral Sc(III)/Ir(III) to realize the enantioselective intramolecular 6π photocyclization of acrylanilides **56** (Scheme 12a).[68] Jiang's group disclosed a chiral scandium catalyst with a dicyanopyrazine-derived chromophore (DPZ) as photosensitizer for intramolecular [2 + 2] cycloaddition of pyridine-based alkenes **58** (Scheme 12b).[69] The chiral *N*,*N*′-dioxide-Sc(OTf)$_3$ complexes play significant roles in not only lowering the triplet

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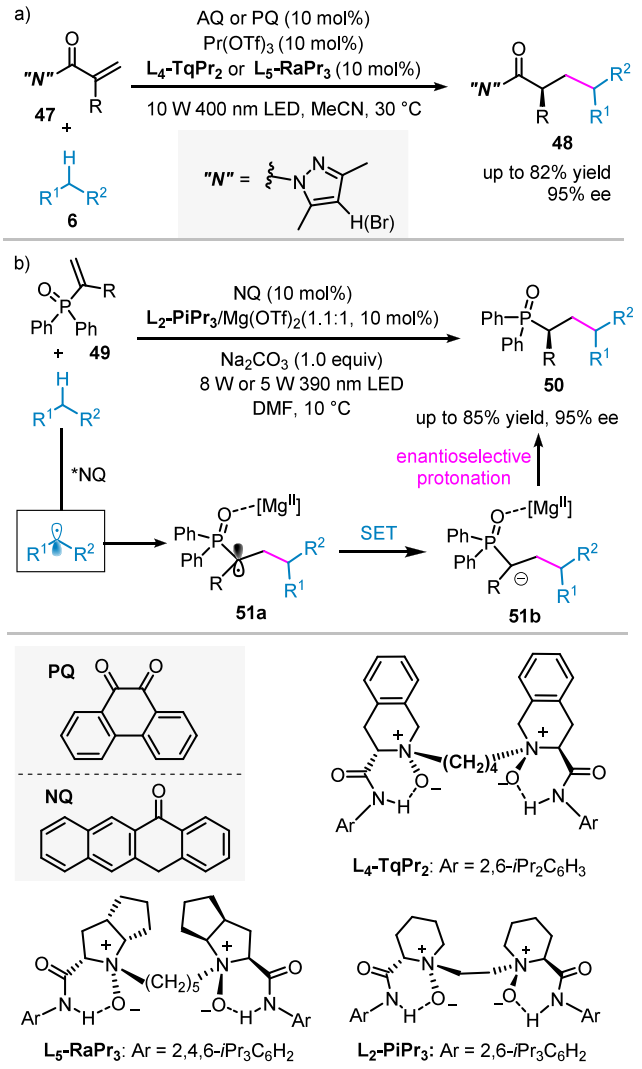
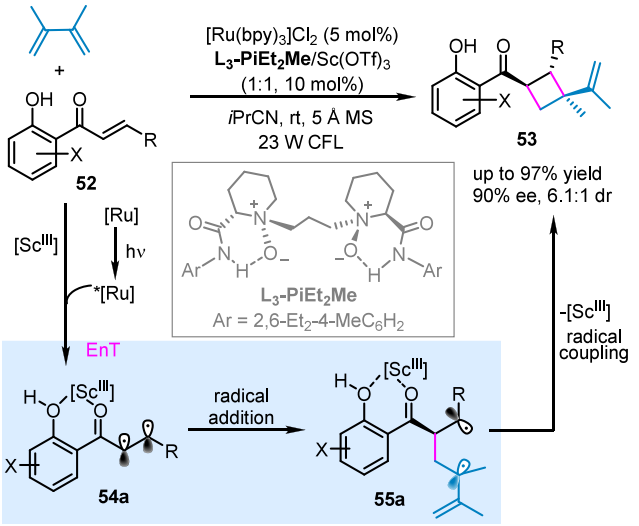
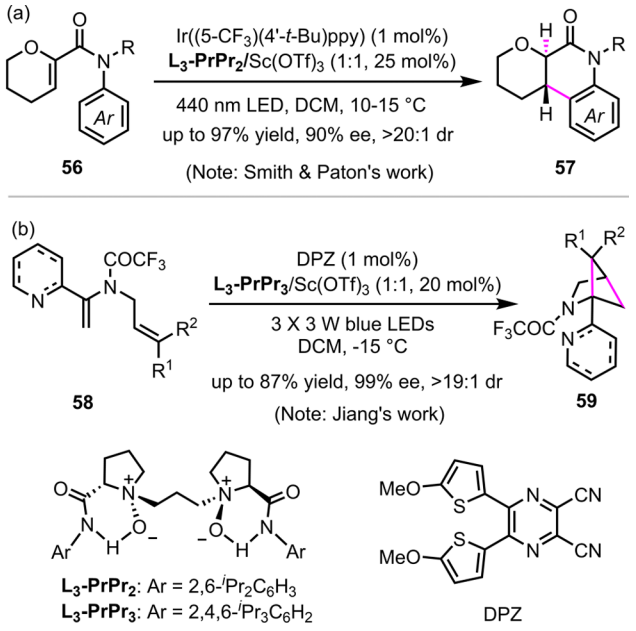
Scheme 10. Enantioselective Radical Hydroalkylation of α,β-Unsaturated Carbonyls



Scheme 11. Intermolecular Enantioselective [2 + 2]-Photocycloaddition Reaction



Scheme 12. Intramolecular Asymmetric Photocycloaddition and Photocyclization

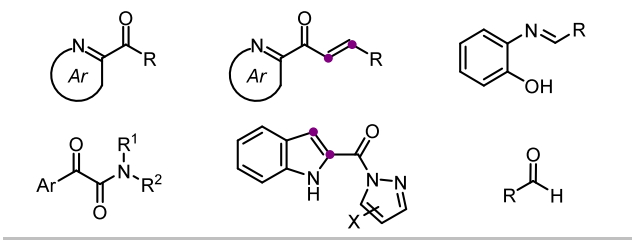


energy of electron-deficient alkenes but also controlling stereoselectivity.

4. SINGLE CHIRAL LEWIS ACID-ASSISTED PHOTOCATALYSIS

In comparison to synergistic catalysis, asymmetric photochemical transformations using a single catalyst to streamline the radical reactions is undoubtedly a useful and simple alternative.[70,71] In our established works, we found that several special substrates could be directly excited upon binding to chiral *N,N′*-dioxide−metal complexes (Scheme 13), such as

Scheme 13. Representative Substrates for Direct Photoexcitation Assisted by Chiral Lewis Acid



aza-heterocycle-based (*α,β*-unsaturated) ketones, *ortho*-hydroxylaniline-derived imines, *α*-ketoamides, and pyrazoleamide-based indoles under visible light, as well as simple aldehydes under near-ultraviolet light. Their photochemical transformations could occur via diradical species or the SET process to form new radical species with proper partners.

4.1. Asymmetric Alkylation of Ketones with Silanes or Sulfides

In the case of photoinduced asymmetric alkylation of *aza*-heterocycle-based ketones with silanes (Scheme 14),[4] the coordination with a chiral Sc(III) complex both facilitated an obvious red shift of quinolin-2-ylethanone **60a** from ultraviolet

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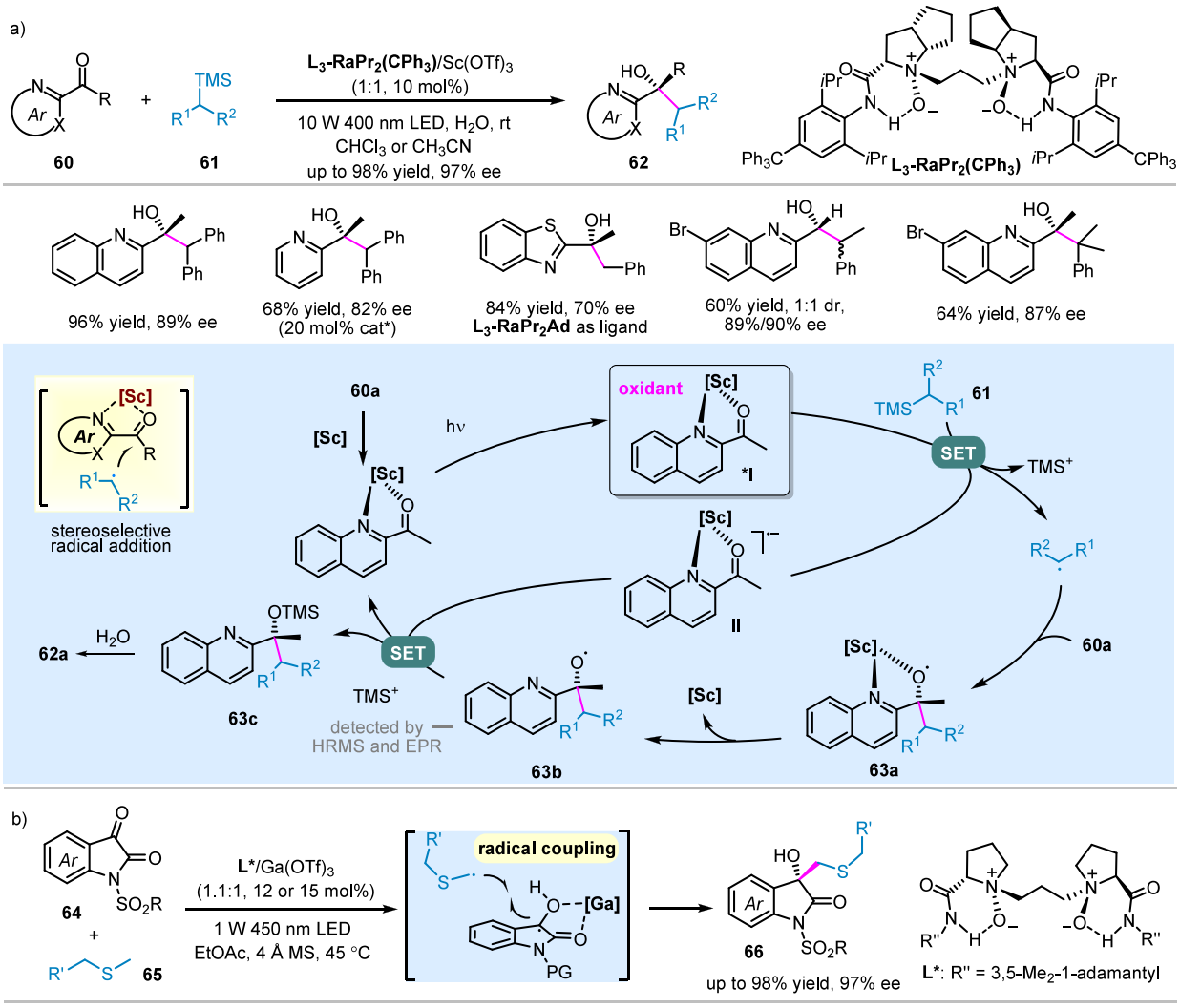
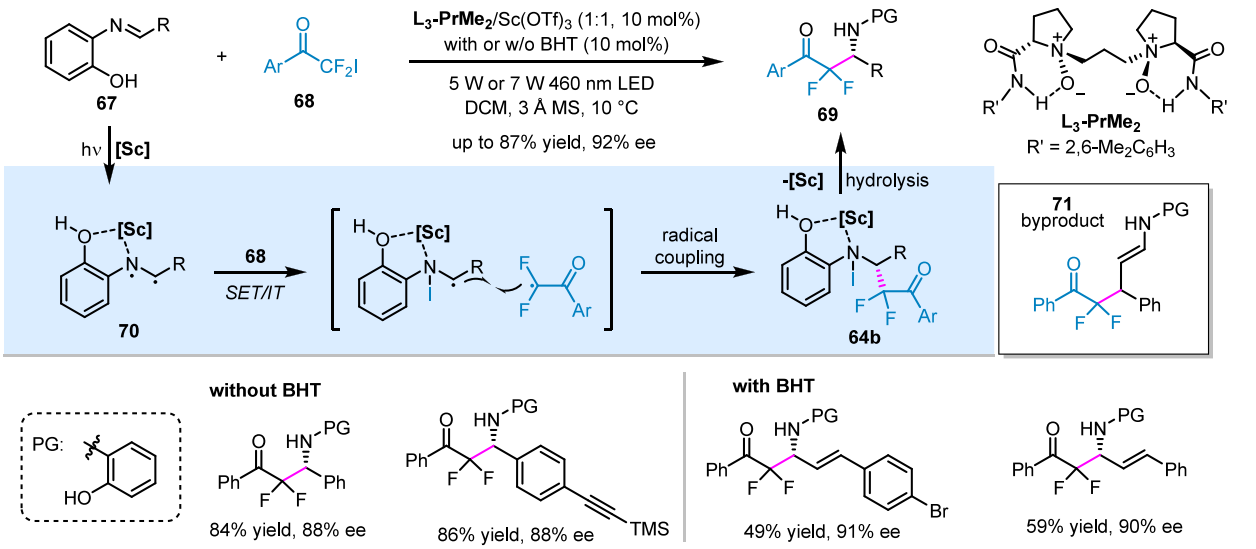
Scheme 14. Visible Light-Photoinduced Asymmetric Alkylation of Ketones with Silanes or Sulfides



Scheme 15. Asymmetric *aza*-Reformatsky Reaction



to the visible light region and enhanced its reduction potential. These changes of photophysical properties enabled the direct excitation of chiral Sc(III)-bound ketone species under visible light illumination into the species ***I**, which served as an oxidant to trigger SET with silane **61**[72] to form the radical anion species **II** and alkyl radical upon release of a TMS cation. The

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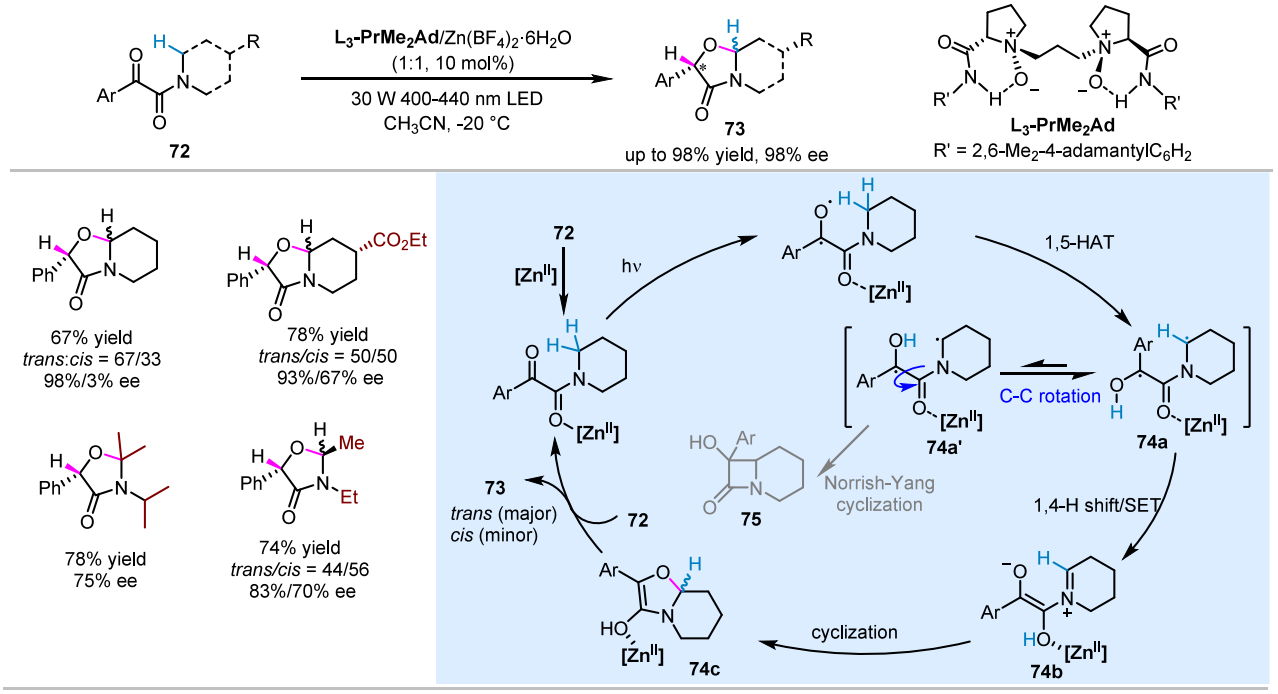
Scheme 16. Asymmetric Norrish Type II Cyclization



observation of an O-radical intermediate by high-resolution mass spectrometry (HRMS) and electron paramagnetic resonance (EPR) experiments suggested an enantio-controlled alkyl radical addition to the chiral Sc(III)-bound ketone. The following SET reduction with radical anion species **II** and protonation yielded the chiral tertiary alcohol **62** (Scheme 14a). A range of *aza*-heterocycle-based ketones were coupled with primary, secondary, and tertiary alkyl radical precursors to produce the desired products.

This chiral Lewis acid-assisted photocatalysis was also able to mediate the enantioselective alkylation of isatins **64** with sulfides **65** (Scheme 14b).[73] In this case, an enantioselective radical cross-coupling process was suggested based on control experiments, wherein catalyzed by a chiral *N,N′*-dioxide-Ga(III) complex, blue light irradiation resulted in excited triplet isatin as a photoredox reagent to perform the SET/PT sequence with sulfide, generating α-thiomethyl radical and ketyl radical coupling partners *in situ*. This transformation had excellent functional group tolerance and was highly selective for the direct late-stage functionalization of methionine-related peptides.

4.2. Photoinduced Asymmetric *aza*-Reformatsky Reaction with Difluoroiodoarylethanone

aza-Reformatsky reaction, traditionally relying on metal enolate addition, is a classic method for constructing β-amino carbonyl compounds. Difluoro-Reformatsky reagent is uniquely suited for highly functionalized difluoroalkylated amines. We recently disclosed a new route for this purpose, avoiding the use of metal reductants for nucleophile preparation.[74] This reaction was carried out using *N*-phenol protected aldimines **67** with 2,2-difluoro-2-iodo-1-arylethanones **68** as the reactants. Under visible light irradiation, the chiral Sc(III)−imine complex could be excited into diradical species **70**, which promoted an electron transfer/iodine transfer (IT) sequence with difluoroalkyl iodide. The resulting radical species coupled in an enantioselective way to produce the chiral β-amino α,α-difluoro ketones **69** with up to 87% yield with 92% ee (Scheme 15). Imines derived from both benzaldehydes and cinnamaldehydes were compatible, but for the latter, the addition of a catalytic amount of 2,6-dibutyl-4-methylphenol (BHT) effectively suppressed the competitive formation of the 1,4-coupling product **71**.

4.3. Asymmetric Norrish Type II Cyclization and Cycloaddition/Rearrangement

The Norrish type reactions are quintessential photochemical transformations, involving either cleavage or cyclization processes due to the stability and lifetime of the radical intermediates. In consideration of potential influence of chiral Lewis acid catalysts on the photophysical and photochemical properties of the carbonyls, we initiated a Norrish type II cyclization of aryl α-oxoamides **72**.[75] A range of aryl α-oxoamides were smoothly converted into the optically active α-oxazolidinones **73** in the presence of a chiral *N,N′*-dioxide−$Zn(OTf)_2$ complex under visible light irradiation (Scheme 16). This reaction involved three hydrogen transfer steps, interspersed with a cyclization process. Upon coordination with the chiral Lewis acid, the phosphorescence intensity and lifetime of the substrate were significantly enhanced. This not only facilitated the intramolecular 1,5-HAT to generate a 1,4-biradical intermediate **74a** but also promoted the rotation for the 1,4-hydrogen transfer/ion-type cyclization sequence to form α-oxazolidinone **74c**, rather than the Norrish−Yang cyclization product **75**. Noteworthily, a compact hydrogen network accounted for the diastereoselective protonation, effectively overwhelming the background reaction.

In addition, photoenolization of 2-methylbenzaldehydes or 2-alkylbenzophenones could form photoenol intermediates *in situ* as electron-rich dienes, participating in Diels−Alder reaction with chromones,[76] or Mannich reaction with *N*-sulfonyl cyclic ketimines.[77]

Although the excited carbonyls or α,β-unsaturated carbonyls could directly undergo cyclization via triplet diradical species, the asymmetric catalytic versions meet the challenge of high triplet state energy and short lifetime. In [4 + 2]-photo-

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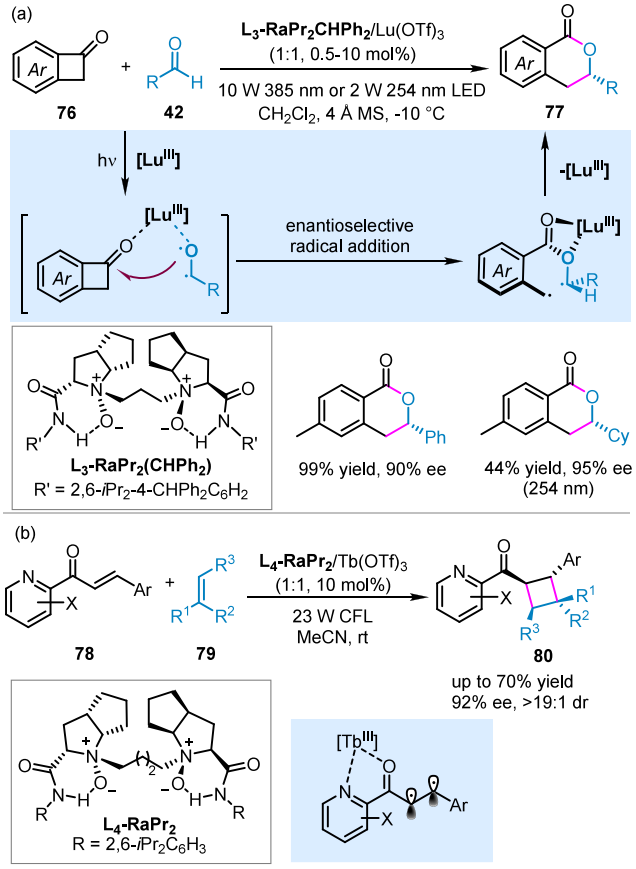
cycloaddition between aldehydes and benzocyclobutenones **76** (Scheme 17a),[78] near-ultraviolet light or UV light were used to excite aromatic aldehydes and aliphatic aldehydes, respectively. The *N*,*N*′-dioxide−Lu(III) complex catalyst played a pivotal role in enhancing the phosphorescence emission intensity and extending the triplet lifetime of aldehydes. DFT calculation revealed that the cyclization followed a stepwise mechanism, and the second C−C bond formation was performed in a highly stereospecific manner. Even at low catalyst loadings (as low as 0.5 mol %), aldehydes were smoothly transformed into chiral 3,4-dihydroisocoumarins **77**. Intriguingly, *aza*-[4 + 2]-photocycloaddition of benzosulfonimides **38** with benzocyclobutenones **76** catalyzed by the chiral *N*,*N*′-dioxide−Ni(II) complex gave rise to isoquinolinone derivatives.[79] Benzocyclobutenones **76** were excited to mediate Norrish type I cleavage, forming the *ortho*-quinoid ketene methide intermediates as the diene components, undergoing enantioselective *aza*-[4 + 2]-cyclization with imines.

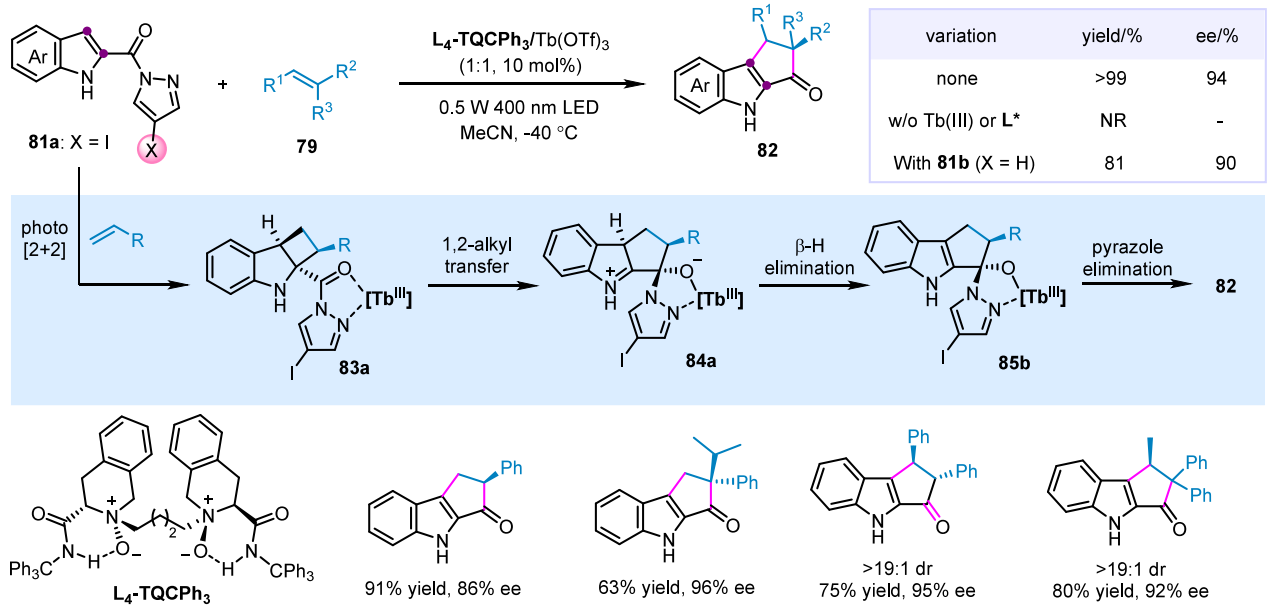
With regard to *α*,*β*-unsaturated carbonyl compounds, the *π*−*π** transition of the activated C═C double bond is generally more favorable than the n−*π** transition of the C═O double bond under light illumination, leading to the formation of highly reactive diradical species. For instance, 2-alkenoylpyridines **78** could serve as an antenna in the complex upon coordination with the chiral *N*,*N*′-dioxide−Tb(III) catalyst, featuring a lower excitation energy and facile intersystem crossing. Thus, [2 + 2]-photocycloaddition with alkenes performed well in the absence of an extra photosensitizer to yield the acyl substituted cyclobutanes **80** (Scheme 17b). The activation pattern herein differed from that of 2′-hydroxychalcones (Scheme 11).[67]

Similarly, indole derivatives **81** could be excited under visible light irradiation with the assistance of the chiral *N*,*N*′-dioxide−Tb(III) complex.[80,81] An interesting [2 + 2]-photocycloaddition/rearrangement cascade of indole derivatives **81** with simple alkenes **79** was established to produce cyclopenta[*b*]indoles **82** with good to high yields and enantioselectivities (Scheme 18). No reaction occurred in the absence of either metal salt or ligand because chiral Lewis acid coordination with pyrazolamide induced a pronounced bathochromic shift and accelerated the intersystem crossing process. We also confirmed that the heavy atom effect of the iodine atom on **81a** had an obvious influence on both reactivity and stereoselectivity. DFT calculations

Scheme 17. Asymmetric [4 + 2]- and [2 + 2]-Photocycloadditions



Scheme 18. Asymmetric [2 + 2]-Photocycloaddition/Ring-Expansion Sequence of Indoles with Alkenes



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supported that the reaction proceeded via a [2 + 2]-photocycloaddition, followed by 1,2-alkyl migration, β-hydrogen elimination, and pyrazole elimination. The $\pi-\pi$ interaction between the substrate and chiral ligand was essential for stereocontrol.

5. CONCLUSION AND OUTLOOK

Achieving simultaneous control over radical generation and stereoselective transformation is essential for asymmetric radical reactions but remains highly challenging. In this Account, we introduce a unique class of tetradentate chiral *N*,*N*′-dioxide ligands. These ligands, upon coordination with redox or non-redox metals, form privileged chiral Lewis acid catalysts that enable a broad range of radical-based asymmetric transformations involving inert substrates under thermal catalysis or photocatalysis, including alkylation and acylation of ketones or imines, oxidative cross-coupling reactions, difunctionalization of alkenes, radical conjugate additions, cyclization, cycloaddition, and rearrangement, delivering various enantioenriched compounds with a high level of efficiency. Notably, in some cases of chiral *N*,*N*′-dioxide−metal complex assisted radical generation via SET, HAT, or EnT in the ground state or excited state, this kind of catalyst exhibits catalytic performance beyond Lewis acids, unlocking new capabilities for organic synthesis.

We hope that this Account, presented from a unique perspective, will not only inspire the design of novel substrates and catalyst systems but also drive the development of more challenging asymmetric radical reactions. Additionally, we aim to encourage in-depth mechanistic studies using diverse approaches, thereby further advancing the fields of radical chemistry, asymmetric catalysis, photocatalysis, and C−H functionalization.

AUTHOR INFORMATION

Corresponding Authors

Xiaohua Liu − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China;* orcid.org/0000-0001-9555-0555; Email: liuxh@scu.edu.cn

Xiaoming Feng − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China;* orcid.org/0000-0003-4507-0478; Email: xmfeng@scu.edu.cn

Author

Weidi Cao − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China;* orcid.org/0000-0003-1440-4682

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.accounts.5c00370

Author Contributions

Weidi Cao, Xiaohua Liu, and Xiaoming Feng: conceptualization; writing - review and editing.

Notes

The authors declare no competing financial interest.

Biographies

Weidi Cao received his B.S. (2010) and Ph.D. degrees (2015 with Prof. Xiaoming Feng) from Sichuan University. Then he joined Nanyang Technological University as a research fellow with Prof. Choon-Hong Tan. After his postdoctoral studies (2015−2018), he got back to Sichuan University and joined the faculty of Prof. Feng's group as an associate professor. In 2021, he was promoted to professor. His research interests focus on asymmetric photocatalysis and organosilicon chemistry.

Xiaohua Liu received her B.S. degree from Hubei Normal University in 2000 and M.S. degree and Ph.D. from Sichuan University in 2003 and 2006 sequentially. She joined the faculty of Prof. Feng's group at Sichuan University, where she was promoted to professor in 2010. Her current research interests include chiral catalyst design and novel asymmetric catalysis, bioactive molecule synthesis, and reaction mechanisms.

Xiaoming Feng received his B.S. (1985) and M.S. degrees (1988) from Lanzhou University. In 1996, he received his Ph.D. degree from the Institute of Chemistry, CAS. He worked at the Chengdu Institute of Organic Chemistry, CAS (1996−2000), and was appointed as a professor in 1997. He did postdoctoral research at Colorado State University (1998−1999). In 2000, he joined Sichuan University as a professor. In 2013, he was selected as an academician of CAS. His research interests include the design of chiral catalysts, development of new synthetic methods, and synthesis of bioactive compounds.

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