Review

Recent Development of Bis-Cyclometalated Chiral-at-Iridium and Rhodium Complexes for Asymmetric Catalysis

Purusattam Dey,[‡] Pramod Rai,[‡] and Biplab Maji*

Cite This: *ACS Org. Inorg. Au* 2022, 2, 99−125

Read Online

ACCESS | 📊 Metrics & More | 📰 Article Recommendations

ABSTRACT: The field of asymmetric catalysis has been developing to access synthetically efficacious chiral molecules from the last century. Although there are many sustainable ways to produce nonracemic molecules, simplified and unique methodologies are always appreciated. In the recent developments of asymmetric catalysis, chiral-at-metal Lewis acid catalysis has been recognized as an attractive strategy. The catalysts coordinatively activate a substrate while serving the sole source of chirality by virtue of its helical environment. These configurationally stable complexes were utilized in a large number of asymmetric transformations, ranging from asymmetric Lewis acid catalysis to photoredox and electrocatalysis. Here we provide a comprehensive review of the current advancements in asymmetric catalysis utilizing iridium and rhodium-based chiral-at-metal complexes as catalysts. First, the asymmetric transformations via LUMO and HOMO activation assisted by a chiral Lewis acid catalyst are reviewed. In the second part, visible-light-induced asymmetric catalysis is summarized. The asymmetric transformation via the electricity-driven method is discussed in the final section.

KEYWORDS: Chiral-at-metal complexes, Lewis acid catalysis, Asymmetric catalysis, Photoredox catalysis, Electrochemistry, Radicals
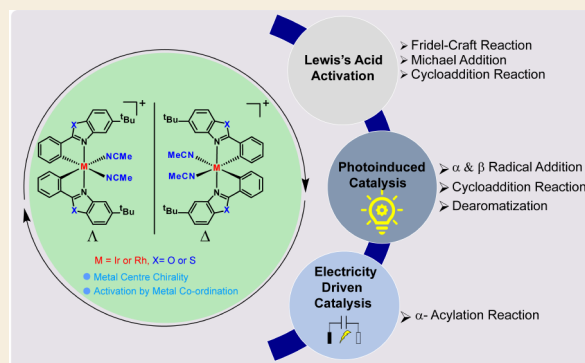
1. INTRODUCTION

The synthesis of a chiral molecule is one of the most challenging yet vital processes in organic synthesis.[1,2] Decades of investigation have shown the transition metal complexes to be one of the most indispensable tools in asymmetric synthesis and catalysis for making nonracemic molecules.[3] Lewis acidity and the availability of interacting orbitals and synergic bonding and back-bonding cooperations are central to their chemistry, where the steric and electronic properties and hence their reactivities are tuned by the presence of organic ligands (Figure 1).[4−7] The reaction happens in the metal center, and the chiral ligands create the asymmetric environment

surrounding the metal ion. Among different possible ways to generate chirality in the metal center, a less studied one involves the chirality in the absence of any chiral ligands, where the metal center itself is chiral. The nonexistence of the dissymmetric ligands around the metal can align the reacting substrate at the metal center to create discriminative faces of the substrates that the reagents can attack. These characteristics finally lead to the enantioenriched products. This type of complex can be called a chiral-at-metal complex, first anticipated and observed by Werner about a century ago.[8] Both tetrahedral and octahedral complexes can become chiral-at-metal depending on their ligand environment.[9,10] In an octahedral topology, nonchiral bidentate and tridentate ligands around the metal center can generate twists in the complex. This forms a propeller type structure that assigns the chirality of the chiral-at-metal complex, Λ for the left- and Δ for the right-handed twist.[11] The advantages of chiral-at-metal to their achiral counterparts include the tremendous scope of achiral
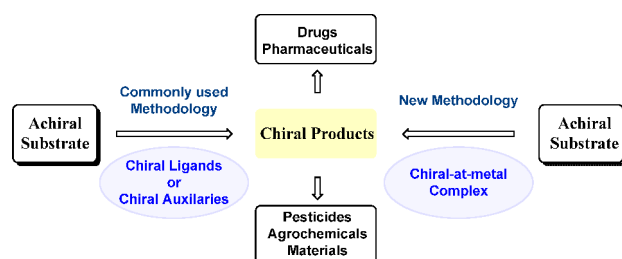

Figure 1. Asymmetric catalysis with well-explored methodology and new methodology.

ligands, enabling the installation of multiple functional groups around the metal center.[12] A plethora of chiral-at-metal complexes can thus be generated. However, several challenges are associated with the synthesis of these complexes: (i) It is troublesome to get high enantiomeric excess (ee) for the complexes. (ii) Often, maintaining their configuration stability is highly difficult. (iii) In addition, there are chances of forming many stereoisomers. For example, an octahedral coordination complex having six individual monodentate ligands can adopt up to 30 individual stereoisomers (15 diastereomers as pairs of enantiomers).[13] It is strenuous to selectively synthesize and isolate a single stereoisomeric complex for catalytic applications. Multidentate ligands can boost selectivity and have recently been applied to isolate configurationally stable single enantiomers of the metal complex.[14] These complexes have recently been involved in a myriad of asymmetric transformations. Some thoughtful reviews focusing on the synthesis and reactivity of chiral-at-metal complexes have been published.[15−20] This Review endeavors to comprehensively summarize the recent applications of bis-cyclometalated chiral-at-iridium and rhodium metal complexes in asymmetric catalysis (Figure 2). It provides historical background,
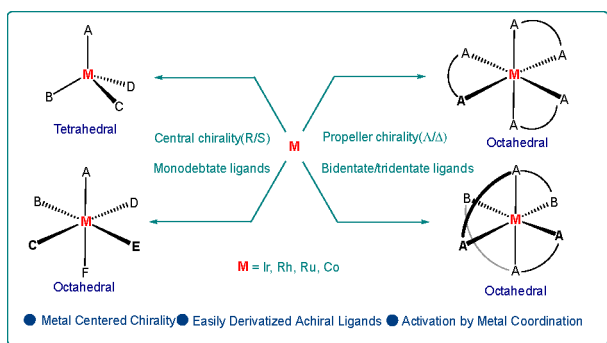
describes different modes of substrate activations under thermal, photochemical, and electrochemical conditions, and discusses current challenges and opportunities that lie ahead.

2. HISTORICAL BACKGROUND

In 1893, Werner proposed his coordination theory, where he revealed octahedral metal complexes with metal center optical activity.[8] Later in 1911, the octahedral chiral-at-metal complexes of cobalt $[Co(en)_2X(NH_3)]^{2+}$ (X = Cl or Br, en = ethylene diamine) and their resolution with the mirror image of Λ and Δ isomers were reported.[9] In the next 100 years, however, the use of these complexes, particularly in asymmetric catalysis, was largely overlooked, and only sporadic accounts appear in the literature (Figure 3).[21] In 1994, the Ohkubo group attempted the enantioselective and photocatalytic oxidation of rac-1,1′-bi-2-naphthols 1, where a chiral-at-ruthenium complex Δ-$[Ru(menbpy)_3]^{2+}$ (menbpy = 4,4′-dimenthoxycarbonyl-2,2′-bipyridine) 3 was used as a photocatalyst and $[Co(acac)_3]$ (acac = pentane-2,4-dione) was used as the terminal oxidant (Scheme 1a).[22] However, the enantioselectivity of the corresponding products was improved only up to 15% ee. In 2001, the Soai group reported highly enantioselective asymmetric autocatalysis induced by chiral-at-cobalt complex 6 (Scheme 1b).[23]

The enantioselective addition of isopropyl zinc with pyrimidine-5-carbaldehyde 4 yielded pyrimidyl alkanol 5 with 94% ee. Although the reported cobalt complexes are not true chiral-at-metal catalysts, it was initial progress from an asymmetric perspective.

In 2003, the Fontecave group reported the oxidation of sulfide 7 to sulfoxide 8 via chiral-at-ruthenium(II) catalyst 9 (Scheme 1c).[24] However, only 18% ee of the sulfoxide product was achieved. In 2007, the same group demonstrated an octahedral chiral-at-ruthenium complex as a chiral ligand for another ruthenium complex 12 (Scheme 1d).[25] The asymmetric transfer hydrogenation of aryl ketone 10 was performed, and up to 26% ee of the corresponding alcohol product 11 was obtained. A year later, the Gladysz group

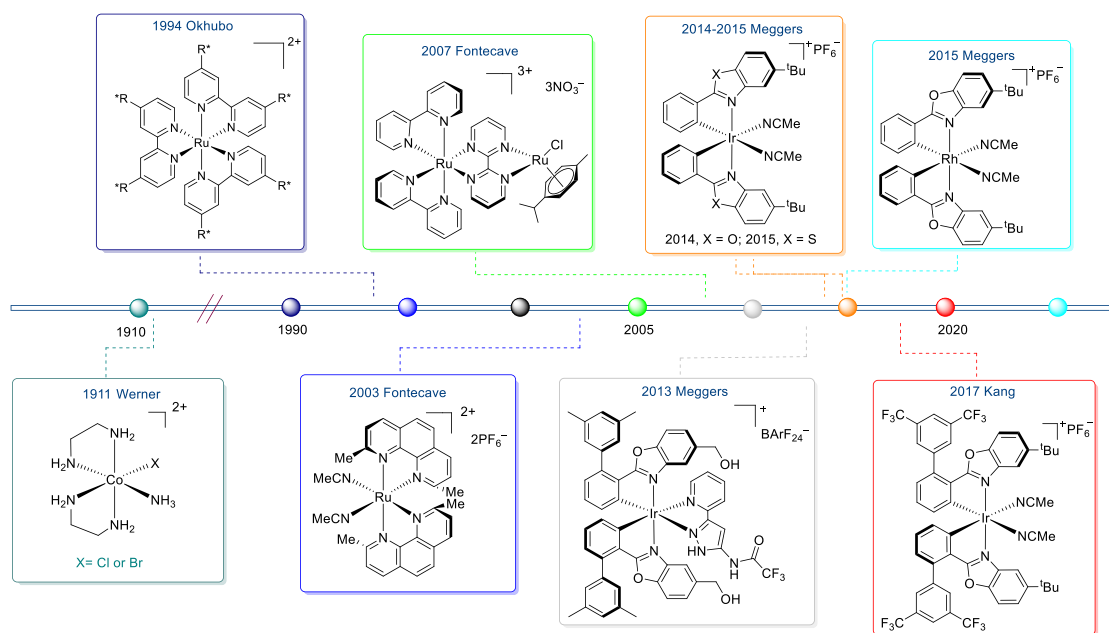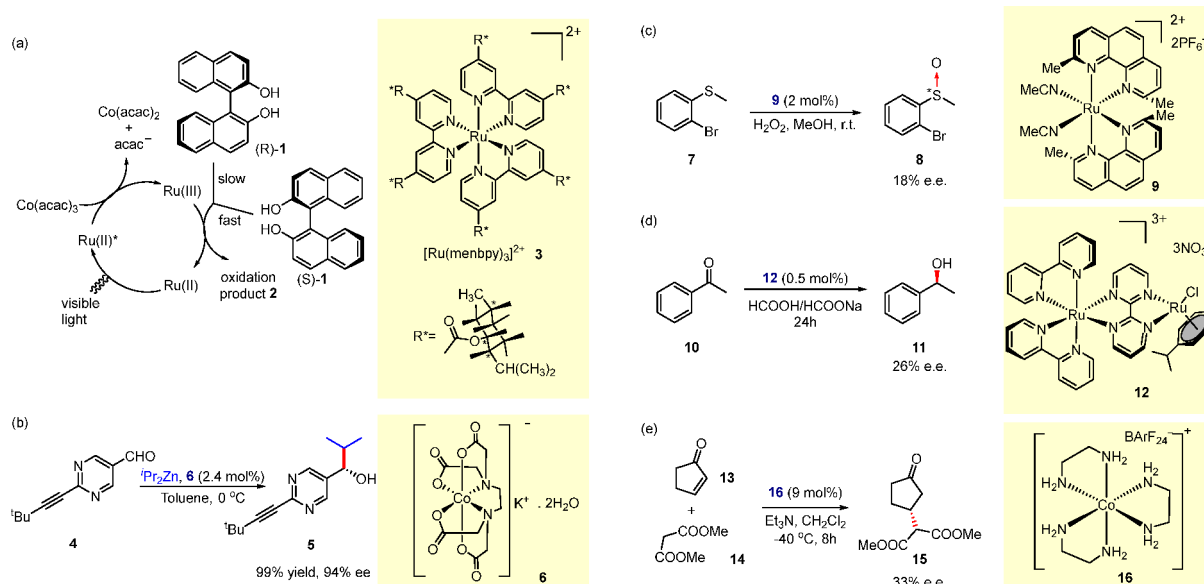**Figure 2.** Tetrahedral and octahedral chiral-at-metal complexes.

Figure 3. Evolution of chiral-at-metal complexes.

**Scheme 1. Early Examples of the Enantioselective Reaction by Chiral-at-Metal Complexes**

reported enantioselective Michael addition of dimethyl malonate **14** to cyclopentenone **13** with simple Werner's complex **16** having BArF$_{24}^-$ (tetrakis[(3,5-trifluoromethyl)-phenyl] borate) as the counteranion, which leads to the corresponding product **15** in 33% ee (Scheme 1e).[26]

Despite the potential of chiral-at-metal complexes in asymmetric synthesis and catalysis, the applications of these catalysts in highly enantioselective transformations remained challenging. In 2013, the Meggers group made an essential contribution in this area in terms of high enantio-induction. The octahedral chiral-at-iridium complexes **21** and **22** having bis-cyclometalated 2-aryl benzoxazoles and amidopyrazole ligands were prepared in high enantiopurity (Scheme 2a).[27] The complex **21** catalyzed the enantioselective transfer hydrogenation of nitroalkene **23**, using Hantzsch ester as the reducing agent (Scheme 2b).[28] The desired nitro alkane products **24** were obtained in excellent yields (89−96%) and outstanding enantioselectivities (93−99% ee). The high enantioselectivity was rationalized by the formation of a highly ordered enantio-determining transition state. It is hypothesized that the amidopyrazole ligand fragment from two-point hydrogen bonding with the nitroalkene substrate not only lowers the lowest unoccupied molecular orbital of the nitroalkene but also creates facial differentiation. Additionally, the hydroxyl group present in the ligand backbone forms a hydrogen bond with the −NH group of the Hantzsch ester that directs a precise hydride transfer. Notably, the catalysis worked with as low as 0.004 mol % loading without affecting the yield and enantioselectivities.

Later, the same group demonstrated the enantioselective Friedel−Crafts alkylation of indoles using chiral-at-iridium complex **22** having the same amidopyrazole hydrogen bonding site (Scheme 2c).[29] The reaction affords the alkylated carbon quaternary center products **26** with high yields (72−97% yield) and high enantioselectivities (92−98% ee). These two unique examples provide a novel route for designing the chiral-at-metal catalyst and its diverse applications in catalytic asymmetric transformation.

In 2017, the Yoon group developed a highly efficient stereochemically controlled [2 + 2] cycloaddition reaction of
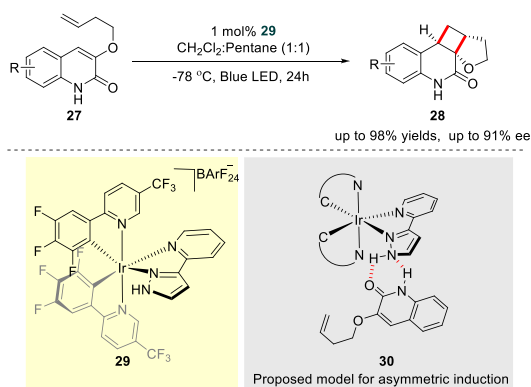
Scheme 2. Initial Reports on Chiral-at-Metal Through Hydrogen Bonding
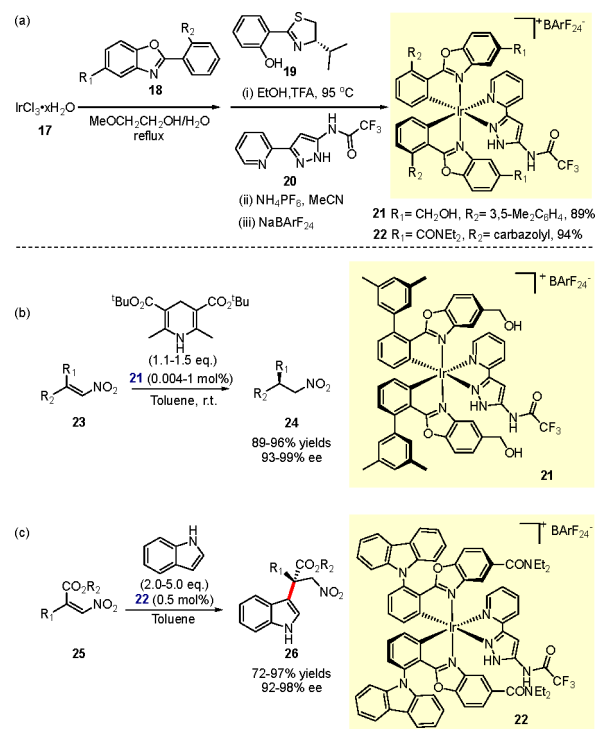
quinolones using a chiral-at-iridium photocatalyst **29** involving a series of hydrogen bonding and π−π interaction (Scheme 3).[30] The quinolone substrates organize themselves with the chiral environment of the Ir(III) photosensitizers, which leads to effective energy transfer and also effective stereoinduction.

However, the developed chiral-at-metal complexes are coordinately saturated. Catalysis via outer-sphere shape recognition is nontrivial and results in poor selectivities, except in a few cases. In this regard, in 2014−2015, the Meggers group synthesized chiral-at-iridium(III) and rhodium(III) complexes with two exchangeable-labile acetonitrile ligands using tailored chiral bidentate auxiliary ligand-mediated

Scheme 3. Enantioselective [2 + 2] Cycloaddition Controlled by a Chiral-at-Metal Catalyst

3.1. LUMO Activation

The two labile acetonitrile ligands of the chiral-at-metal octahedral complex could be displaced by the α,β-unsaturated electrophile, facilitating the LUMO activation for its attachment with the nucleophile. Several reactions belong to this class, showing the importance of this strategy for the vital target.

3.1.1. Friedel−Crafts Alkylation. The Friedel−Crafts reaction is a powerful synthetic tool for constructing carbon−carbon bonds involving an aromatic moiety.[33] The development of efficient Friedel−Crafts alkylations of arenes and heteroarenes using only catalytic amounts of a Lewis acid has gained much attention over the past decade.[34] In this regard, the Meggers group demonstrated the feasibility of utilizing the bis-cyclometalated chiral-at-iridium(III) complex (Λ-IrO) **34** as a Lewis acid catalyst for the Friedel−Crafts alkylation of indoles with α,β-unsaturated 2-acyl imidazole **35** (Scheme 5b).[35] The chiral-at-iridium complex Λ-IrO **34** was prepared

asymmetric synthesis (Scheme 4).[31] Such chiral auxiliaries assist in implementing the absolute metal-centered configuration and are removed afterward in a traceless fashion. Amazingly, the octahedral complexes exhibit high configurational stability even in the presence of labile acetonitrile ligands that can potentially reduce the racemization barrier. It is worth noting that the tailored choice of the chiral auxiliary varies with the metal and the nature of the cyclometalating ligand. The complexes can coordinatively activate a substrate while serving as the sole source of chirality by virtue of their helical environment. These configurationally stable chiral-at-metal complexes were utilized in a large number of asymmetric transformations, ranging from asymmetric Lewis acid catalysis to photoredox and electrocatalysis. In the following sections, we have summarized the progress.
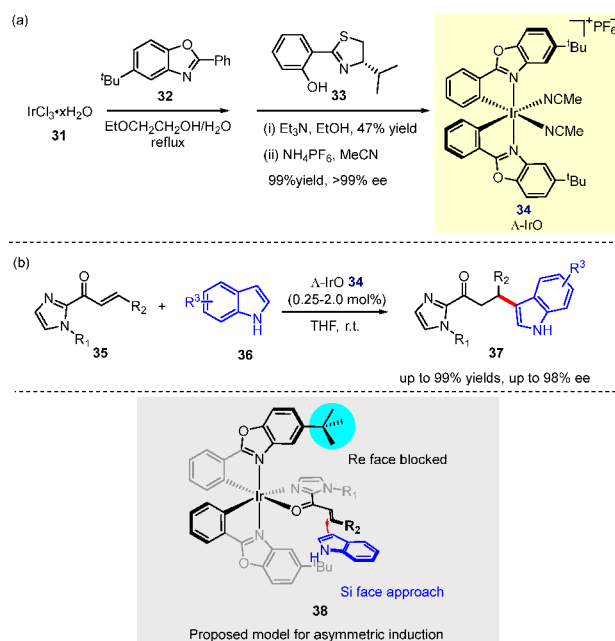
3. CHIRAL LEWIS ACID CATALYSIS

Lewis acid catalysis plays an essential role in organic synthesis.[32] A Lewis acid functions as an electron pair acceptor to enhance a substrate's reactivity either by lowering the lowest unoccupied molecular orbital (LUMO lowering catalysis) or by raising the highest occupied molecular orbital (HOMO raising catalysis). In the past few years, chiral-at-metal complexes have been successfully used in asymmetric Lewis acid catalysis. The following sections summarize the progress into two parts, depending upon the reacting substrates.
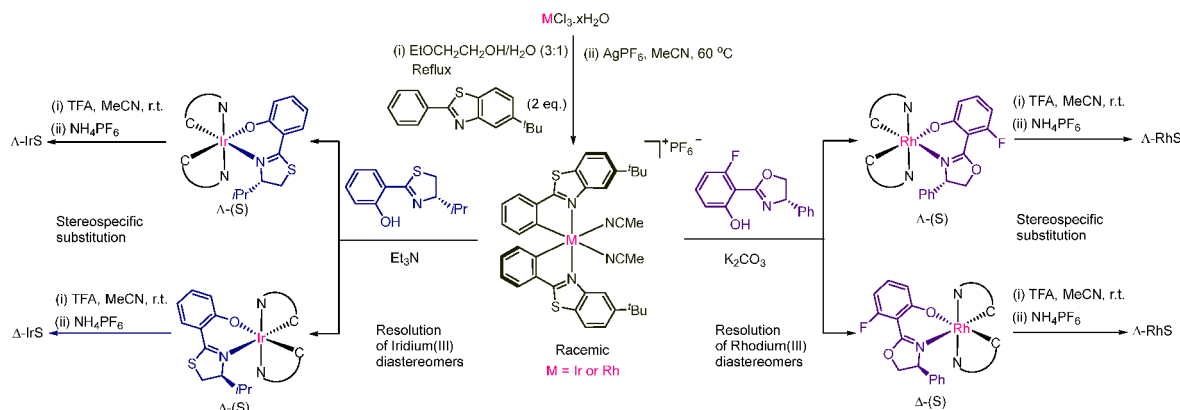
Scheme 5. Friedel−Crafts Addition of Indole to α,β-Unsaturated 2-Acyl Imidazole

Scheme 4. Auxiliary Mediated Synthesis of Λ- and Δ-IrS, and Λ- and Δ-RhS Complexes

via subsequent reaction of iridium trichloride hydrate with 2-phenyl benzoxazole and the chiral auxiliary ligand (*S*)-4-isopropyl-2-(2′-hydroxyphenyl)-2-thiazoline followed by the substitution of the chiral auxiliary ligand by two acetonitrile groups in the presence of NH_4PF_6 (Scheme 5a). By displacing the labile acetonitrile ligands, the *α,β*-unsaturated electrophile coordinates with the octahedral complex, facilitating the LUMO activation for its attachment with the nucleophile. With the employment of 0.25−2 mol % Λ-IrO **34** in THF at room temperature, *α,β*-unsaturated electrophile **36** undergoes the Friedel−Crafts alkylation reaction with indole derivatives **36** to form 3-alkylated products **37** in 75−99% yields and up to 98% ee.

The proposed model for the asymmetric induction is shown in Scheme 5b, where the bulky *tert*-butyl group effectively blocks one of the faces of the alkene and the alkylation takes place from the opposite face. Notably, in this enantioselective Friedel−Crafts alkylation method, the chiral Lewis acid catalyst plays a dual role by activating the substrates as well as creating the chiral environment in the reaction medium.

Similarly, the chiral-at-iridium catalysts **34** were employed for the Friedel−Crafts alkylation reactions with other aromatic compounds (Scheme 6).[36] It was conceptualized that the

Scheme 6. Octahedral Chiral-at-Iridium Complex Catalyzed Friedel−Crafts Alkylation and Michael Addition Reaction
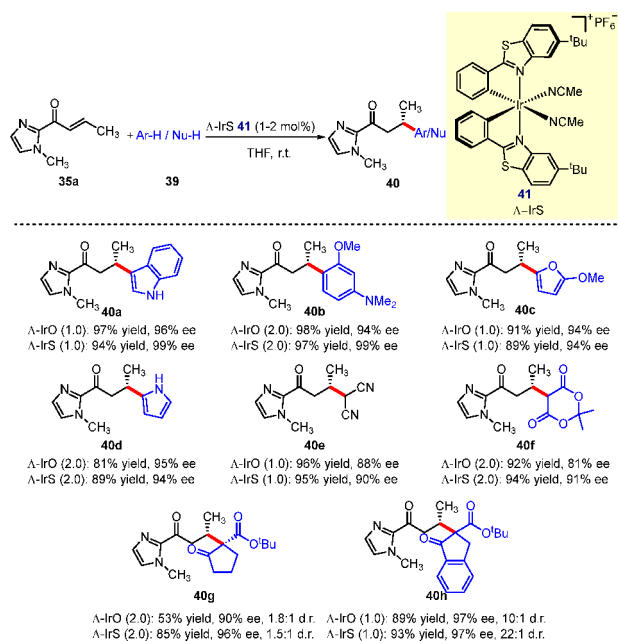
cyclometalated 2-phenyl benzothiazole ligand (Λ-IrS complex, **41**) might create a higher asymmetric induction because of a longer C−S bond when compared with the 2-phenyl benzoxazole ligand (Λ-IrO complex, **34**). The Λ-IrS complex **41** catalyzed Friedel−Crafts alkylation of indole delivered the product **40a** in 99% ee, compared to 96% ee for Λ-IrO. A similar trend was also observed for 3-methoxy-*N,N*-dimethylaniline substrate. However, the Friedel-Craft alkylations of 2-methoxyfuran **40c** and pyrrole **40d** proceeded in similar enantiomeric excess in both cases. A similar observation was made for the addition of C−H acidic malononitrile and 1,3-dicarbonyls to the *α,β*-unsaturated 2-acyl imidazole as a Michael acceptor (Scheme 6). This procedure is equally

capable of constructing molecules with all-carbon quaternary stereocenters **40g**, **40h**. In general, the Λ-IrS complex **41** gave better enantioselectivity (ee) than the Λ-IrO complex **34**. In fact, the benzothiazole complex's superiority over the benzoxazole complex was also demonstrated for the chiral-at-rhodium catalyst.[37]

3.1.2. Cycloaddition Reactions. Cycloaddition reaction is a versatile and straightforward reaction where two or more bonds are formed in a single operation accessing carbocyclic or heterocyclic organic compounds.[38,39] Commonly, olefins serve as one reaction partner in a cycloaddition reaction and bond formation occurs at both carbon atoms of the multiple bonds. For the most valuable processes in chemical synthesis, it is highly challenging to develop new efficient chiral catalysts for enantioselective cycloaddition reactions. Various highly enantioselective metal catalysts have been developed for versatile cycloaddition reactions in the past few years. In this regard, chiral-at-iridium(III) complexes **34** and **41** were found to be capable of catalyzing various cycloaddition reactions (Scheme 7).[40] Using 2.0 mol % Λ-IrS, the reaction of nitrone

### Scheme 7. Octahedral Chiral-at-Iridium Complex Catalyzed Cycloaddition Reaction
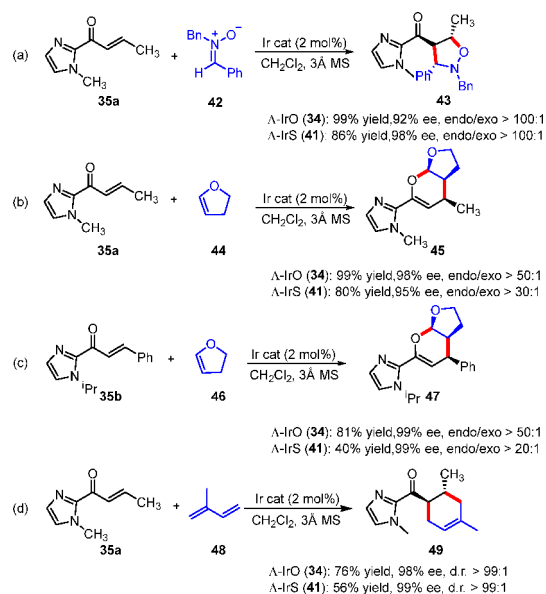
42 with *α,β*-unsaturated 2-acyl imidazole **35a** delivered the 1,3-dipolar cycloaddition product **43** with 86% yield and excellent 98% ee, with only one diastereoisomer (Scheme 7a). Lower enantioselectivity was observed with **34** (92% ee) as a catalyst. However, for the inverse electron demand Diels−Alder reaction of **35a,b** with dihydrofuran **46**, **34** shows superior performance (Scheme 7b,c). On the other hand, both **34** and **41** performed equally in catalyzing the Diels−Alder reaction of **35a** with isoprene **48** (Scheme 7d).

The Kang group realized that the chiral-at-rhodium complex **52** (Δ-RhO) acts as an excellent Lewis acid catalyst for the enantioselective cyclopropanation reaction (Scheme 8).[41] Multisubstituted cyclopropanes **51** were obtained from *α,β*-unsaturated 2-acyl imidazole **35** and *α*-bromomalonate **50** in high yields and enantioselectivities. It was proposed that, at first, the acyl imidazole substrate **35** was activated by the Lewis acid catalyst **52**. The *Re*-face is blocked by the *tert*-butyl group present in the achiral ligand enabling the nucleophilic attack by

Scheme 8. Enantioselective Cyclopropanation Reaction by a Chiral-at-Rhodium Catalyst

Scheme 9. Relay Gold(I)-Chiral-at-Rhodium Catalyzed Asymmetric Synthesis of Spiroketals and Spiroaminals
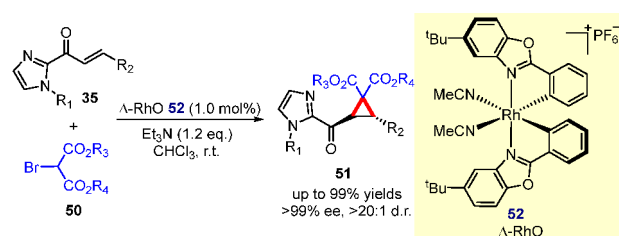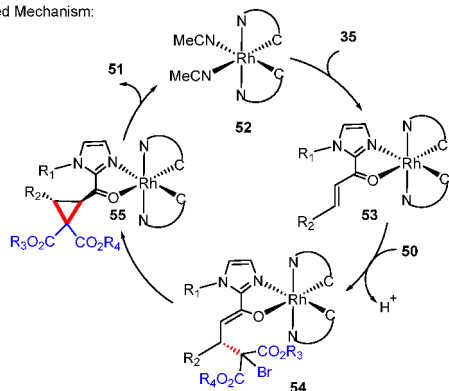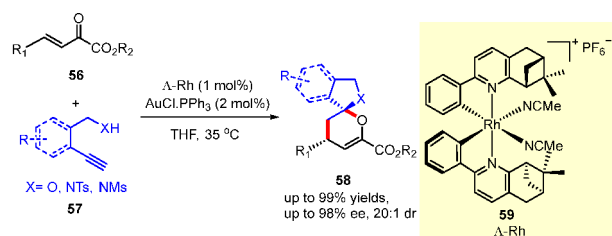

the α-bromomalonate anion from the *Si*-face to afford the rhodium enolate complex **54**. The intramolecular cyclization from **54** yields the intermediate **55**, releasing the product and regenerating the catalyst. The practical utility of this methodology was also demonstrated by the gram scale reaction with low catalyst loading (0.1 mol %), obtaining the desired product with 99% yield, 95% enantioselectivity, and >20:1 diastereoselectivity.
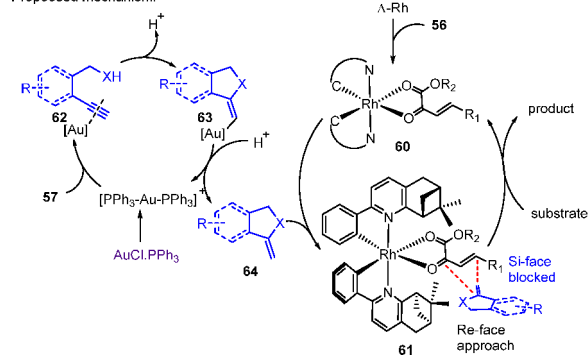
In the past decade, the merger of a gold catalyst with Lewis acid catalysts has made remarkable progress for the enantioselective transformations.[42,43] In this regard, with a combination of achiral gold(I) catalysts, the chiral-at-rhodium-(III) Lewis acid catalyst **59** was found to be highly active for the asymmetric relay catalysis of β,γ-unsaturated keto ester **56** with alkynyl alcohols and amides **57** (Scheme 9).[44] The spiroketal and spiroaminal products **58** were isolated in excellent yields (up to 99% yields) and excellent selectivities (up to 98% ee, and 20:1 dr). The pinene-modified pyridine ligand-based catalyst **59** gave superior yields and selectivities among different chiral-at-metal complexes. It is attributed to the higher steric bulk around the rhodium center. Mechanistically, the gold catalyzed 5-exo-dig intramolecular cyclization of **62** yields an electron-rich exocyclic enol ether intermediate **64**. In parallel, **56** coordinates with the chiral Lewis acid to yield the intermediate **61**. The inverse-electron-demand hetero-Diels–Alder reaction took place from the *Re*-face of the chiral Rh(III) complex **61** to deliver the desired product **58** after ligand exchange with the substrate.

1,3-Dipolar cycloaddition between a 1,3-dipole and a dipolarophile is an enticing strategy for forming a five-membered architecture. Several 1,3-dipoles, such as azomethine ylides,[45,46] nitrones,[47,48] nitrile imines,[49] and nitrile oxides,[50] have been employed for the cycloaddition reactions. In this context, recently, chiral-at-rhodium(III) complex **67** was implemented for the asymmetric [3 + 2] cycloaddition reaction of *N,N'*-cyclic azomethine imines **65** with α,β-unsaturated 2-acyl imidazoles **35c** (Scheme 10).[51] The Lewis
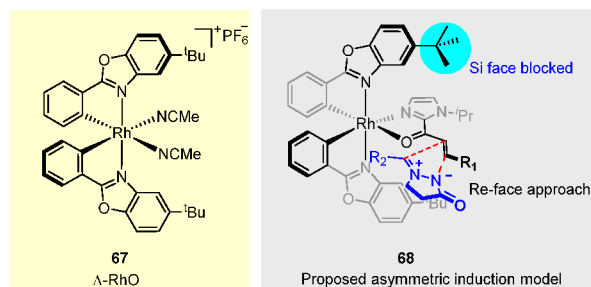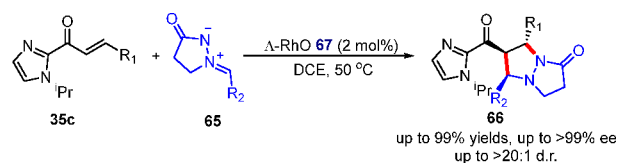
## Scheme 10. Asymmetric [3 + 2] Cycloaddition by a Chiral-at-Rhodium Complex

acid catalyst **67** in 2 mol % loading catalyzed the reaction affording the *N,N'*-bicyclic pyrazolidine derivatives **66**, having three contiguous stereocenters in high yields (up to 99%) and excellent stereoselectivities (>99% ee, >20:1 dr). In the proposed stereochemical model **68**, the 1,3-dipole approaches the Lewis acid activated electrophile from the *Re*-face, avoiding the steric crowding in the *Si*-face.

Spirocyclic oxindoles moieties represent core structural elements in many natural products, alkaloids, and biologically active compounds.[52,53] The importance of these building blocks prompted synthetic chemists to explore novel methods for producing particularly enantiopure spirocyclic oxindoles. One such approach includes a [3 + 2]-annulation reaction of an activated olefin with a 2-oxindole derived spirovinylcylopropane (SVCP) where a Pd(0)-catalyst assists in creating a three-carbon dipole by releasing the strain energy of the cyclopropane ring from the vinyl cyclopropane (VCPs) moieties.[54] Recently, Du and co-workers reported the synthesis of multisubstituted spirocyclopentane oxindoles **70** empow-

ered by Pd/chiral-at-rhodium(III) cooperative catalysis (Scheme 11).[55] The reaction proceeds with extreme synergism

Scheme 11. Synthesis of Multisubstituted Spirocyclopentane Oxindoles Enabled by a Pd/Rh(III) Complex
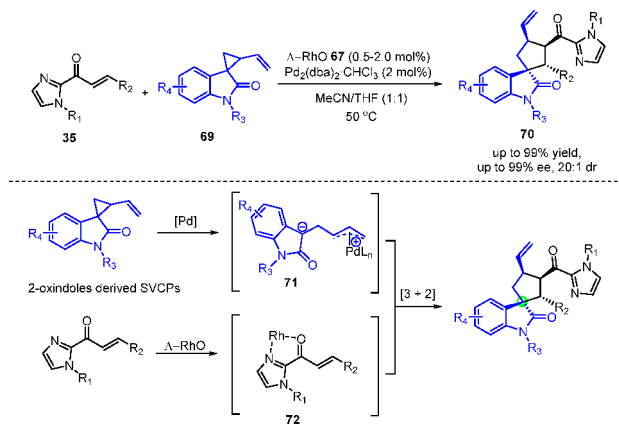
where the Pd(0) catalyst enables the generation of a three-carbon dipole and the chiral Lewis acid lowers the LUMO of the olefin partner. The desired product was obtained with up to 99% yield and outstanding selectivities, 99% ee, and 20:1 dr.

Very recently, Du and Su collaboratively reported the asymmetric decarboxylative cycloaddition of racemic vinyl ethylene carbonates (VECs) and α,β-unsaturated 2-acyl imidazoles for the catalytic synthesis of multisubstituted chiral tetrahydrofuran derivative via Pd(0)/chiral-at-rhodium(III) synergistic catalysis (Scheme 12).[56] It is noted that the

Scheme 12. Asymmetric Synthesis of Multisubstituted Tetrahydrofuran via Pd/Rh Catalysis
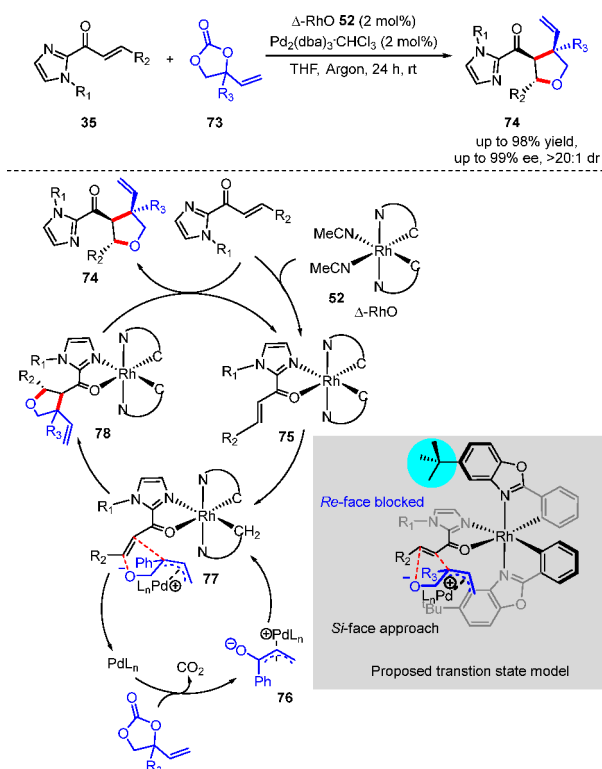

nucleophilic 1,3-dipolar π-allylpalladium intermediate **76** formed after the decarboxylation from the VEC **73** can undergo [3 + 2] cycloaddition with α,β-unsaturated 2-acyl imidazole **35** to provide the desired product **74** with up to 98% yield, 99% ee, and >20:1 dr. The mechanism of the reaction is described in Scheme 12. The α,β-unsaturated 2-acyl imidazole substrate was activated by the chiral-at-rhodium(III) complex via bidentate N,O-coordination. Simultaneously, VEC forms zwitterionic 1,3-dipolar π-allylpalladium intermediate **76** via the Pd(0)-mediated decarboxylation process. Then, the intermediate **76** attacks the intermediate **75** from the *Si*-face and the intermediate **78** is formed after coordination dissociation and electron neutralization. Finally, the ligand exchange delivers the target molecule and closes the cycle.

3.1.3. Enantioselective Michael Addition to α,β-Unsaturated Carbonyls. The Michael addition reaction is one of the powerful and valuable tools for forming C–X (X = C, O, N, S) bonds in organic synthesis.[57−60] Recently, the Meggers and the Kang groups independently demonstrated synergistic dual catalysis by a chiral-at-metal Lewis acid and organocatalyst for the Michael addition of α,α-disubstituted aldehydes to α,β-unsaturated 2-acyl imidazoles (Scheme 13).[61,62] The chiral-at-rhodium complex Δ_{Rh}-S_C-Rh1 (**81**) was prepared as a single stereoisomer via the reaction of rhodium trichloride hydrate with 2-phenyl benzoxazole and subsequently with L-β-phenylalanine (Scheme 13a).[61] It was

Scheme 13. Example of Dual Catalysis of Chiral Lewis Acid Catalysis and Amine Catalysis
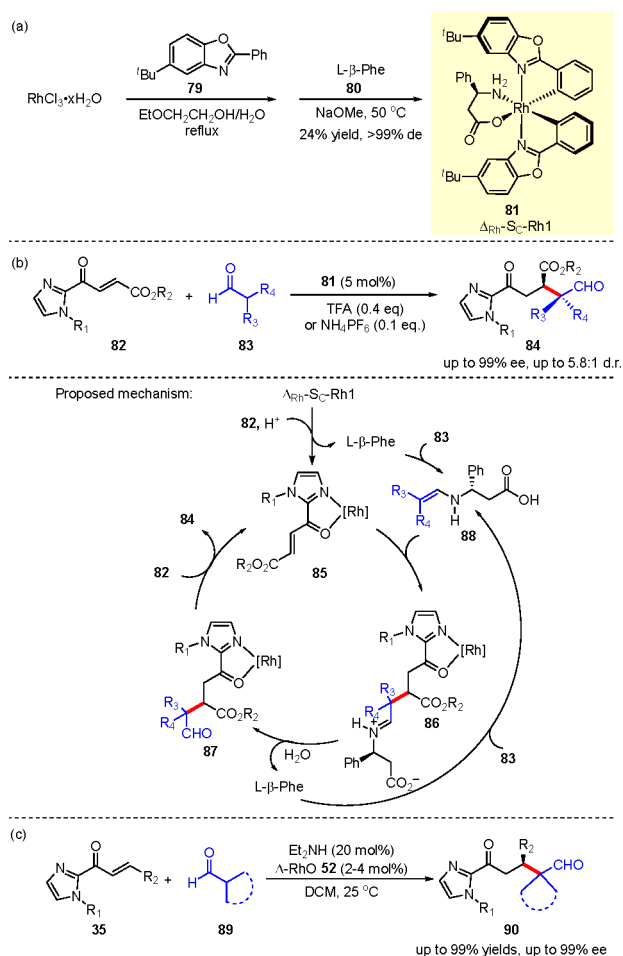
found that Δ_{Rh}-S_C-Rh1 (**81**) acts as an excellent precatalyst for the Michael addition of **83** with **82**, and the products **84** were isolated in high yields and up to 99% ee and 5.8:1 dr (Scheme 13b). It was shown that the protonation of the precatalyst released the amine L-β-Phe and formed the rhodium complex **85** after coordination with **82** in a bidentate fashion. The amine condenses with the aldehyde **83** to form the enamine intermediate **88**, which was intercepted by **85**. The hydrolysis of the resultant intermediate **86** yields the intermediate **87** that upon substrate exchange delivers the product **84** and closes the cycle. Kang utilized the combination of Δ-RhO (**52**) and diethylamine as a catalyst for the same reaction and observed a similar level of isolated yields and enantioselectivities (Scheme 13c).

Additionally, to increase the Lewis acidity of the chiral-at-metal catalysts, the Kang group incorporated a strongly electron-withdrawing 3,5-ditrifluoromethyl phenyl group in the ligand backbone of the chiral-at-rhodium complex Λ-RhO(Ar') **93** (Scheme 14).[63] The newly designed complex **93**

Scheme 14. Chiral-at-Rhodium Complex Catalyzed Asymmetric Conjugate Addition of *p*-Vinyl Anilines to α,β-Unsaturated 2-Acyl Imidazoles
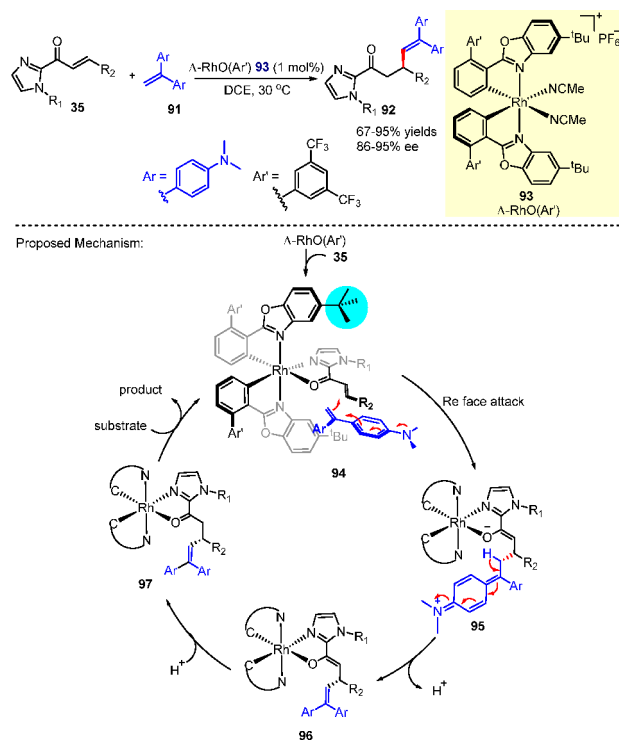

was found to be efficient for the asymmetric conjugate addition of *p*-vinylanilines **91** to **35**, affording the products **92** with good yields (67–95% yield) and excellent enantioselectivities (86–95% ee). Mechanistically, substrate **35** is activated by the Rh(III)-complex **93** through bidentate N,O-coordination to form intermediate **94**. The bulky *tert*-butyl group blocked the *Si*-face. The nucleophile **91** attacked the *Re*-face of **94** to form iminium cation **95**. Rearomatization and protonation of the rhodium enolate **95** yielded the product-bound intermediate **96**. Product **92** is released after the ligand exchange with the substrate. The aliphatic groups at the β-position of α,β-unsaturated 2-acyl imidazoles (Me, Et, ^{i}Pr, CO$_2$Et) were also equally compatible under the reaction conditions, affording the

corresponding vinylated adducts **92** in 67–84% yields with 93–95% ee.

The asymmetric decarboxylative addition reaction is a valuable method for constructing C-X (X = C, O, N, S) bonds.[64] In the past decade, much progress has been made to develop catalytic asymmetric decarboxylative reactions with various organocatalysts[65] and the transition metal catalyst.[66] Recently, the enantioselective decarboxylative Michael addition of β-keto acids **99** to α,β-unsaturated 2-acyl imidazole **35d** and α,β-unsaturated 2-acylpyridines **98** was explored using a chiral-at-rhodium(III) Lewis acid catalyst (Scheme 15).[67] The

Scheme 15. Chiral-at-Rhodium Complex Catalyzed Decarboxylative Michael Addition of β-Keto Acids
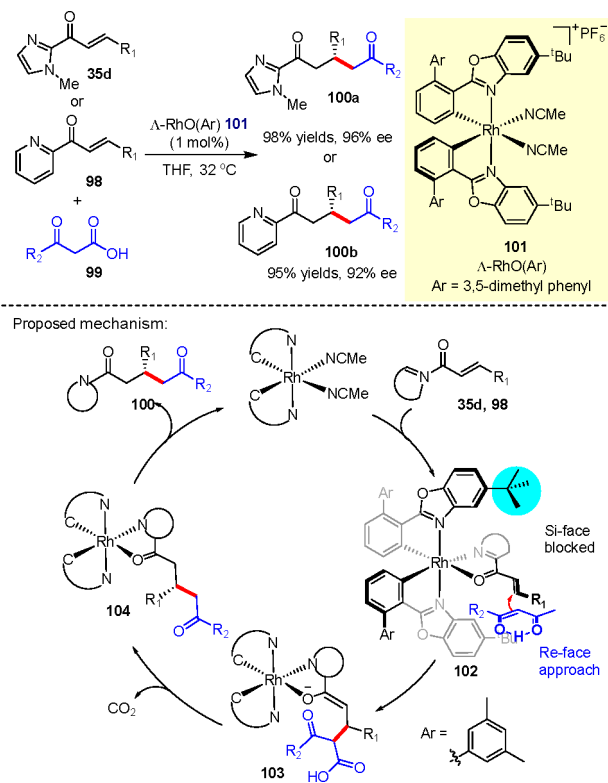
complex Λ-RhO(Ar) **101** having a 3,5-dimethyl phenyl group in the ligand backbone was found to be most effective for this transformation, delivering the products **100** in 94–98% yields with 88–96% ee. The α,β-unsaturated substrate has similarly been activated through bidentate N,O-coordination to form the intermediate **102**. The nucleophilic attack then takes place from the *Re*-face to yield the rhodium enolate **103**. Subsequent protonation, decarboxylation, and ligand exchange delivers the product **100** and closes the cycle. The practical utility of this protocol is demonstrated by a gram-scale reaction of α,β-unsaturated 2-acyl imidazoles with β-keto acid, affording the desired product in 98% yield with 96% ee. It was observed that when lowering the catalyst loading to 0.05 mol % the reactivity and selectivity remained unchanged.

Similarly, it was found that the chiral-at-rhodium Lewis acid **101** is highly efficient in catalyzing the enantioselective Michael addition of pyrazolones **105** to α,β-unsaturated 2-acyl imidazoles **35e** (Scheme 16).[68] The products **106** were isolated in good yields (85–96% yield) and excellent enantioselectivities (up to >99% ee).

Scheme 16. Asymmetric Michael Addition of Pyrazolones by a Chiral-at-Rhodium Complex

85–96% yields, up to >99% ee
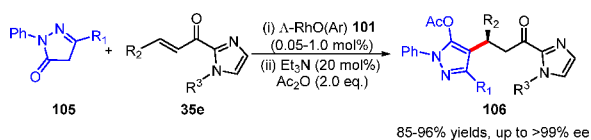
The collaborative work of the Du and Kang groups revealed an asymmetric reduction–Michael addition cascade for the coupling of α,β-unsaturated 2-acyl imidazoles **35** with malononitrile **107** catalyzed by chiral-at-metal rhodium catalyst **93** in the presence of a Hantzsch ester as the hydride source (Scheme 17).[69] The chiral-at-rhodium complex **93**, having a

Scheme 17. Chiral-at-Rhodium Complex Catalyzed Cascade Reduction–Michael Addition Reaction

up to 99% yields, up to 97% ee

Proposed mechanism and chiral induction model
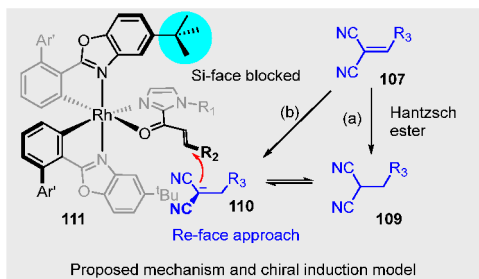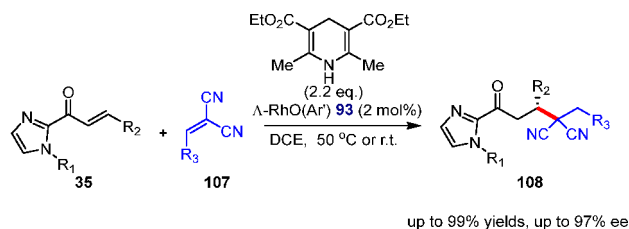
3,5-ditrifluoromethyl phenyl group in the ligand backbone, was found to be superior in reactivity and selectivity. The desired product **108** was obtained in up to 82% yield and up to 96% ee in CCl$_4$ solvent. The substrate **35** was similarly activated through the bidentate coordination with the chiral Rh(III) complex. On the other hand, the hydride transfer to **107** from the Hantzsch ester generated nucleophilic anionic intermediate **110**, which attacked the *Re*-face of **111**.

Recently, our group proposed a new approach for the enantioselective C(sp^3)–H bond functionalizations of 2-alkyl azaarenes via cooperative dual Lewis acid catalysis (Scheme 18).[70] The strategy utilizes the activation of unactivated azaarene partners **112** by an achiral Lewis acid catalyst. Cooperatively, a chiral-at-iridium Lewis acid catalyst enables LUMO lowering of α,β-unsaturated 2-acyl imidazoles **35** to induce chirality. The complex Λ-IrO(Ph) having a phenyl group in the ligand backbone was found to be the most effective chiral-at-metal Lewis acid catalyst, while among the achiral Lewis acid catalysts scandium triflate shows the best efficiency for this transformation, delivering products **113** in excellent yields (up to 99%) and good enantiomeric ratios (up to 1.9:98.1 er), tolerating a wide range of functionalities in both the coupling partner. It was proposed that a stronger scandium Lewis acid preferentially activates the more basic quinoline moiety **112**, enabling the generation of nucleophilic metal enamine species **115**. It was supported by speedy

Scheme 18. Enantioselective C(sp^3)–H Bond Functionalization of 2-Alkyl Azaarenes Enabled by Cooperative Lewis Acid Catalysis

up to 99 % yields, up to 96% ee
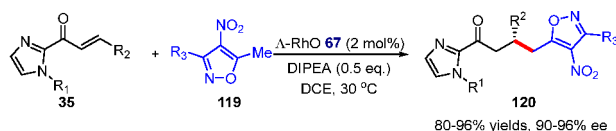up to 92:8 d.r.

Proposed mechanism
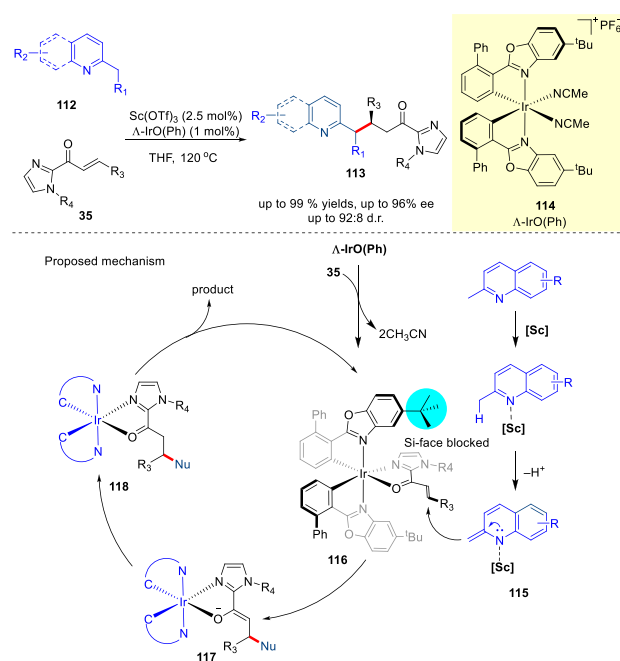
deuterium incorporation in the presence of scandium triflate. On the other hand, a chiral-at-iridium complex undergoes bidentate N,O-coordination with α,β-unsaturated acyl imidazole substrate **116**, facilitating the LUMO activation. The nucleophilic attack could then take place from the *Re*-face to yield the iridium enolate **117**. Subsequent protonation and ligand exchange could deliver product **113** and effectively close the catalytic cycle. The practical utility of this methodology was also demonstrated by the gram scale reaction obtaining the desired product in a high yield of 71% and a good enantiomeric ratio of 3.9:96.1 er.
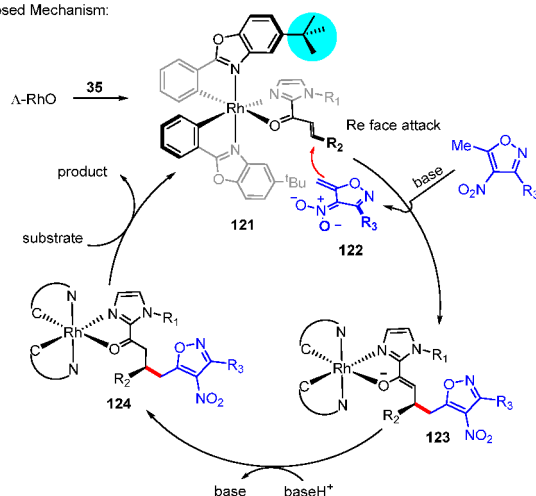
The asymmetric vinylogous Michael addition of carbon and heteroatom nucleophiles to Michael acceptors is a powerful tool for constructing highly functionalized synthetic building blocks. Notably, the nitroisoxazole derivatives as carbon nucleophiles have attracted considerable attention due to the prevalence of isoxazole-containing units in several drugs and bioactive compounds.[71,72] Recently, the chiral-at-rhodium complex **67** has successfully been employed for the catalytic asymmetric vinylogous Michael addition of 5-methyl 4-nitrosoxazoles **119** to α,β-unsaturated 2-acyl imidazoles **35** (Scheme 19).[73] A substoichiometric amount of diisopropylethylamine was used as a base to facilitate the deprotonation of the nucleophile. The C5-substituted chiral oxazoles derivatives **120** were isolated in high yields (80–96% yield) and excellent enantioselectivities (90–96% ee). The stereochemical outcome of the product can be explained by the substrate's activation via coordination with the Lewis acid catalyst and subsequent *Re*-face attack of the nucleophile.

However, when the chiral-at-rhodium complex **127** catalyzed vinylogy was applied for α,α-dicyanoolefin substrates to construct molecular skeletons possessing potential bioactivities, poor yields or stereoselectivities were obtained. To boost the catalysis, a chiral-at-rhodium complex **127** with a bulky electron-rich, naphthyl-containing ligand was developed.[74] The complex efficiently catalyzed the enantioselective

Scheme 19. Chiral-at-Rhodium Complex Catalyzed Enantioselective Synthesis of C5-Substituted Chiral Oxazole Derivatives
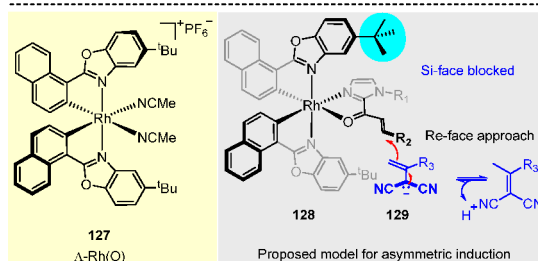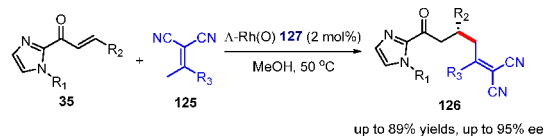

Scheme 20. Chiral-at-Rhodium Complex Catalyzed Enantioselective Michael Addition of α,α-Dicyanoolefins

Scheme 21. Enantioselective Hydroamination by a Chiral-at-Rhodium Catalyst

vinylogous Michael addition of α,α-dicyanoolefin **125** with α,β-unsaturated 2-acyl imidazoles **35** without the aid of a base (Scheme 20). The products **126** were obtained in high yields
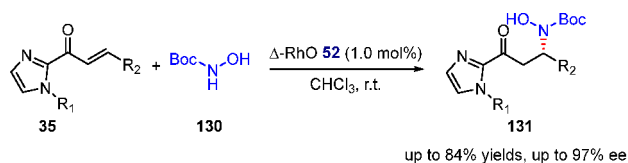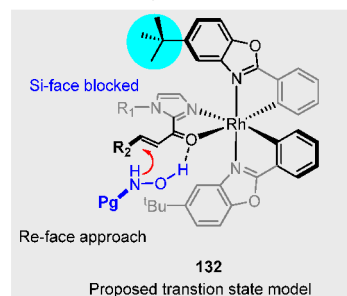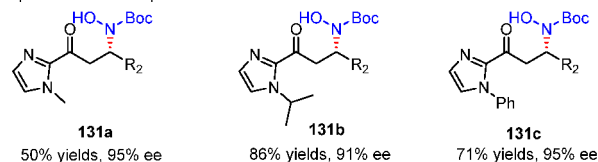
(up to 89%) and high enantioselectivities (up to 95%). A *Re*-face approach of the nucleophile **129** to the catalyst activated complex **128** explained the observed stereochemistry.

The Lewis acid catalyzed asymmetric aza-Michael reaction is a valuable synthetic tool for constructing nonracemic nitrogen-containing heterocycles.[75,76] In this context, the chiral-at-rhodium complex (Δ-RhO) **52** was found to be effective for catalyzing the enantioselective hydroamination of α,β-unsaturated 2-acyl imidazoles **35** with N-protected hydroxylamine **130** (Scheme 21).[77] Diverse N-protected β-amino acid derivatives **131** were isolated in up to 84% yields and up to 97% enantioselectivities. Among chiral-at-iridium and rhodium catalysts having a similar ligand framework, Δ-RhO displayed the best reactivity and selectivity. The bulkier N-substituent (*i*Pr, Ph vs Me) showed higher reactivity and selectivity. Based

on the observed stereochemistry of the product, the author proposed a transition state model **132**. The *Re*-face attack of the nitrogen center explains the observed stereochemistry.

A multifunctional catalytic system is one of the effective catalytic systems for double activation in metal-based or organocatalytic asymmetric reactions. In this case, two reacting substrates bind with the active sites already installed in the catalysts. This will make the two reacting substrates come close to each other in a disciplined manner, which increases the reaction rate and stereoselectivities. In this regard, Meggers and co-workers have reported inert octahedral 3-amino-pyrazolato iridium(III) complexes **139** and **140** for the highly efficient asymmetric sulfa-Michael and aza-Henry reaction (Scheme 22). In the sulfa-Michael addition reaction, α,β-unsaturated N-acyl pyrazole reacts with the aryl thiol to provide the desired product **135** with high yield and excellent enantioselectivities. The bifunctional approach can justify the iridium complex's role through the iridium catalyst's hydrogen bonding after the proton transfer from the thiol where the catalyst acts as a Brønsted base (Complex **141**, Scheme 22). Proton transfer from the thiol to the iridium complex makes an ion pair where the thiolate and cationic iridium complex are accumulated through a double hydrogen bond.

On the other hand, α,β-unsaturated N-acyl pyrazole forms a hydrogen bond with the hydroxymethyl substituent of the benzoxazole moiety. Thus, two reactants arrange themselves via hydrogen bonding and electrostatic attraction, which enables the Michael addition reaction. The aza-Henry reaction was then studied. Fortunately, nitromethane substituent **136** and N-Boc Schiff base **137** gave the desired product **138** with 98% yield and 98% ee. The previously reported Ir(III) catalysts could not provide the aza-Henry reaction's prime condition. However, the presence of an additional 3,5-*t*BuC6H3 group increases the steric demand of the catalyst, which leads to the highest enantiomeric excess.
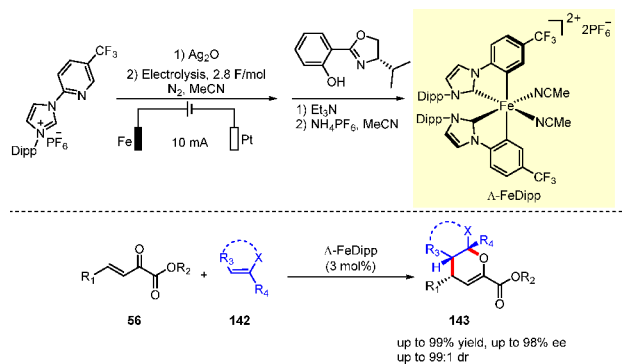
In this rapidly developing field, the Meggers group also developed a chiral-at-metal complex from earth-abundant iron

Scheme 22. Asymmetric Sulfa-metric Reaction and Aza-Henry Reaction by a Chiral-at-Iridium Catalyst

Scheme 23. Asymmetric Hetero-Diels−Alder Reaction by a Chiral-at-Iron Catalyst
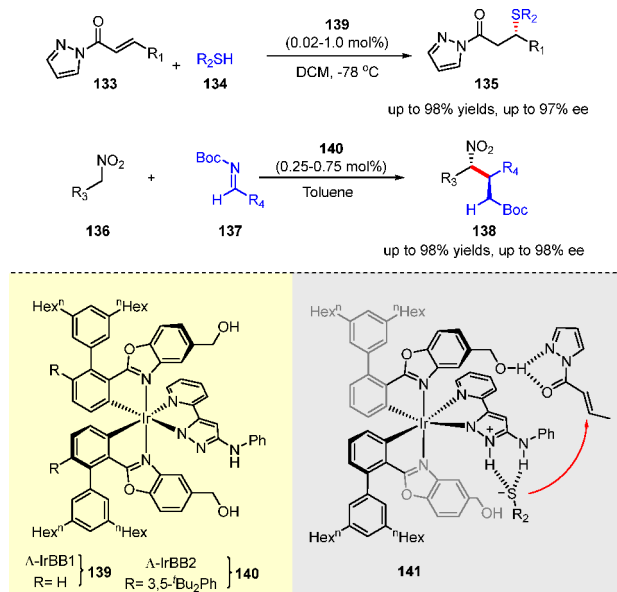
rather than a noble transition metal (Scheme 23).[78] This catalyst with two chelating *N*-(2-pyridyl)-substituted *N*-heterocyclic carbene (PyNHC) ligands coordinates Fe(II) in a C_2-symmetric fashion. Two labile acetonitrile ligands coordinatively saturate the Fe(II) center.

The helicity obtained due to the steric of the achiral PyNHC ligands provided the chiral induction around the Fe(II) complex. The chiral-at-iron complex is capable of catalyzing the inverse electron demand hetero-Diels−Alder reaction between β,γ-unsaturated α-carbonyl ester **56** and enol ethers **142** to deliver 3,4-dihydro-2*H*-pyrans **143** in high yield with excellent diastereoselectivities (up to 99:1) and magnificent enantioselectivities (up to 98%). Even though this is outside the scope of this Review, we discuss this significant development for the convenience of the reader.

3.1.4. Other Reactions. In developing new methods toward the asymmetric preparation of multisubstituted benzofuran derivatives, the Kang and the Du group collaboratively explored the chiral-at-rhodium complex **93** as a Lewis acid catalyst for the enantioselective C2-alkylation of 3-aminobenzofurans **144** with **35** (Scheme 24).[79] The C2-substituted benzofuran derivatives **145** were obtained in good

Scheme 24. Chiral-at-Rhodium Complex Catalyzed Synthesis of C2-Substituted Benzofuran Derivatives
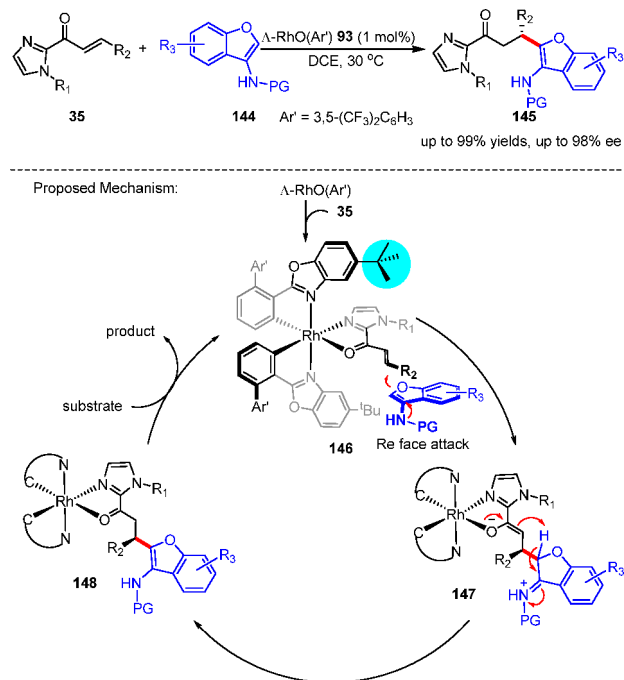
to excellent yields (76−99%) and excellent enantioselectivities (up to 98% ee). Even the reaction can be performed at the gram scale utilizing 0.5 mol % catalyst loading.
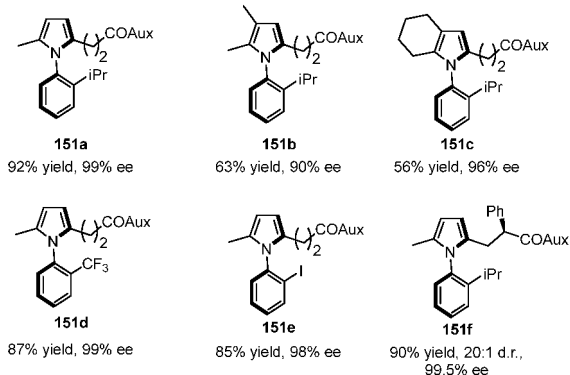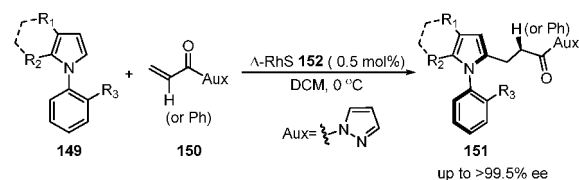
Optically active axially chiral molecules play a crucial role in organic chemistry as a chiral catalyst, building blocks of natural products, bioactive molecules, and functional materials.[80] *N*-Arylpyrroles molecules are important biaryl molecules due to their specific electronic and structural properties. However, the catalytic asymmetric synthesis of *N*-arylpyrroles remains a vigorous challenge for synthetic chemists. Tan and co-workers developed combined Lewis acid and chiral phosphoric acid catalyzed asymmetric synthesis of *N*-arylpyrroles by the Paal−Knorr method.[81] The same group reported the kinetic resolution of 2,5-disubstituted *N*-arylpyrroles to access highly enantioenriched products.[82] However, the requirement of bulky ketoamides at the 3,4-positions at the pyrrole moiety poised limitations. In this context, Meggers et al. synthesized highly enantioselective axially chiral *N*-arylpyrroles via a direct electrophilic aromatic substitution reaction using a rhodium-based chiral Lewis acid catalyst in up to >99.5% ee (Scheme 25).[83] A functional group at the α-position of the pyrrole ring controls the rotation along the C−N bond and configurational stability.

3.2. HOMO Activation

The chiral-at-metal complexes have also been utilized as Lewis acid catalysts for the HOMO activation strategy. The following section summarizes such reactions.

3.2.1. Transfer Hydrogenation of Carbonyls. Asymmetric transfer hydrogenation is a powerful approach to reduce organic compounds without using flammable hydrogen gas.[84] Notably, this field has made significant advances, and several new catalysts have been developed. In this regard, the Meggers group explored bis-cyclometalated chiral-at-iridium(III) complex Λ-IrS **41** for the enantioselective transfer hydrogenation of ketones using ammonium formate as the hydrogen source (Scheme 26).[85] The combination of Λ-IrS (0.002−1.0 mol %)

Scheme 25. Synthesis of Axially Chiral N-Arylpyrroles by Chiral-at-Rhodium Catalysts

151a
92% yield, 99% ee

151b
63% yield, 90% ee

151c
56% yield, 96% ee

151d
87% yield, 99% ee

151e
85% yield, 98% ee

151f
90% yield, 20:1 d.r., 99.5% ee

Scheme 26. Chiral-at-Iridium Complex Catalyzed Enantioselective Transfer Hydrogenation of Ketones
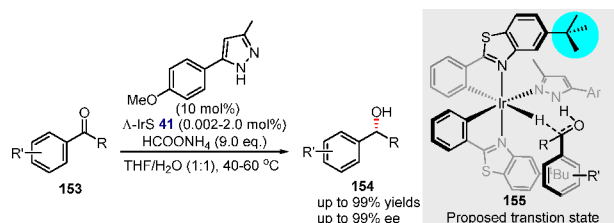
and pyrazole (10 mol %), as a coligand, in THF/H$_2$O (1:1) solvent delivered the reduced alcohol products **154** in high yields and excellent ee (up to 99% ee). Among the various coligands examined, 5-(4-methoxyphenyl)-3-methyl-1H-pyrazole markedly improved the yields and selectivities. The reaction was efficient even at low catalyst loading up to 0.002 mol % without significantly affecting the conversion and the selectivity. It was proposed that the labile acetonitrile group in Λ-IrS undergoes fast ligand exchange with the pyrazole. Then the active iridium hydride species is generated upon reaction with ammonium formate. In the transition state **155**, the aromatic ring of the ketone forms π−π stacking with the benzothiazole ligand of Λ-IrS (**41**). The N−H group of the ancillary pyrazole ligand plays a vital role by forming a hydrogen bond with the ketone oxygen.

3.2.2. Mannich Reaction. The Mannich reaction is one of the most fundamental and widely used reactions for constructing C−C and C−N bonds in organic synthesis, withstanding large varieties of functional groups. In this case, a chiral-at-metal Lewis acid catalyst was also found to be effective for the enantioselective Mannich reaction of 2-acyl imidazole **156** with 1,3,5-triaryl-1,3,5-triazines **157** (Scheme 27).[86] Using chiral-at-rhodium complex **101** as the catalyst (0.1−0.2 mol %), a variety of β-amino carbonyls **158** were obtained in high yields (up to 99%) and excellent enantioselectivities (up to >99%). The reaction can be performed at the gram scale using a 0.1 mol % catalyst loading, and the product was obtained in 95% yield without loss in enantioselectivity (95% ee). It was proposed that the

Scheme 27. Chiral-at-Rhodium Complex Catalyzed Enantioselective Mannich Reactions
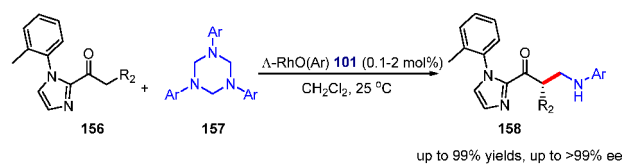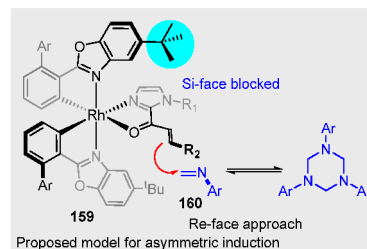
substrate **156** coordinates at the Lewis acidic rhodium center replacing the acetonitrile ligand. Subsequent deprotonation generates the rhodium enolate **159**, which attacks the imine **160** from the Re-face to yield enantioenriched β-amino carbonyls **158**.

The multicomponent Mannich reaction with aldehydes and amine derivatives provides facile access to β-amino carbonyl structures with two or more stereocenters.[87,88] Chiral-at-metal complexes have also been explored for the three-component Mannich reaction of N-acyl pyrazole **161**, aldehyde **162**, and primary or secondary amine **163** (Scheme 28).[89] The chiral-at-

Scheme 28. Chiral-at-Rhodium Complex Catalyzed Asymmetric Three-Component Mannich Reaction
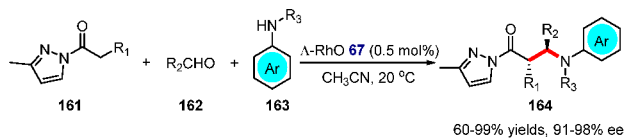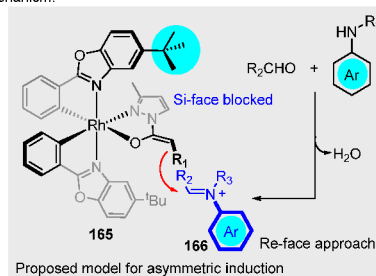
metal rhodium complex **67** operated at 0.5−1 mol % loading delivered the desired products in good yields of 60−90% and excellent enantioselectivities of 91−98% ee. The proposed reaction mechanism involved the in situ formations of an iminium intermediate **166** followed by its Re-face attack at the in situ generated rhodium enolate **165** to deliver products **164**.

The catalytic enantioselective oxidative Mannich reaction using molecular oxygen as a terminal oxidant was developed recently (Scheme 29).[90] The chiral-at-rhodium catalyst **67** combined with a catalytic amount of TFA enabled the C(sp³)−C(sp³) cross dehydrogenative coupling of 2-acyl imidazole **167** and imino ester **168**. Product **169** having two successive stereocenters was obtained in good yields (69−

Scheme 29. Chiral-at-Rhodium Complex Catalyzed Asymmetric Dehydrogenative Cross-Coupling

69-85% yields, 96-98% ee

Proposed mechanism:

Proposed model for asymmetric induction
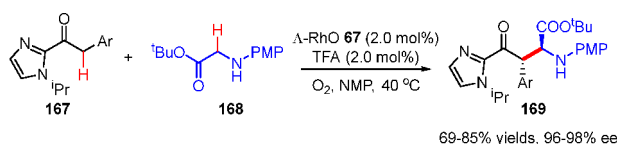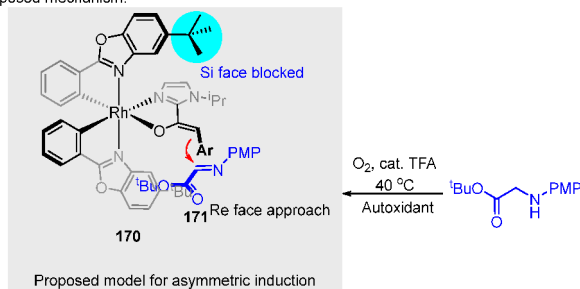
85%) and excellent enantioselectivities (96−98% ee). However, under the same reaction conditions, the analogous chiral-at-iridium catalyst fails to give the desired products. It is proposed that an in situ generated rhodium-enolate **170** reacts with the oxidatively generated carbon electrophiles **171** from the *Re*-face to yield the products in high selectivities.

3.2.3. Addition to Nitro Alkenes. The highly Lewis acidic chiral-at-rhodium complex **93** with a 3,5-ditrifluoromethyl phenyl group in the ligand backbone was also found to be effective for the enantioselective conjugate addition of 2-acyl imidazoles **171** to nitroalkenes **173** (Scheme 30).[91] The γ-nitro ketone derivatives **174** were synthesized in good yields (up to 99%) and excellent enantioselectivities (up to >99% ee). The stereoselectivity can similarly be assigned by the *Re*-face attack of the in situ rhodium enolate **175** to the nitroalkene electrophile **176**.

Scheme 30. Chiral-at-Rhodium Complex Catalyzed Asymmetric Conjugate Addition to Nitroalkenes

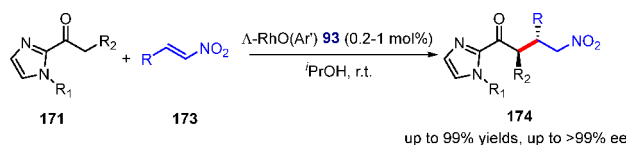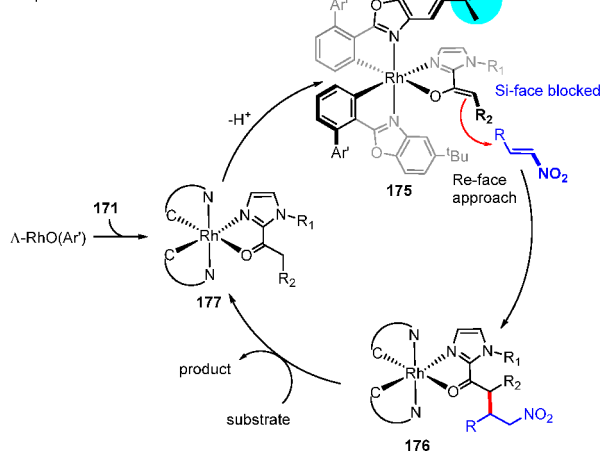up to 99% yields, up to >99% ee

Proposed mechanism:

3.2.4. α-Amination of Carbonyls. In 2015, the Meggers group disclosed chiral-at-rhodium complex **67** catalyzed α-amination of 2-acyl imidazoles **171a** using dibenzyl azodicarboxylate **178** as the electrophilic nitrogen source (Scheme 31).[92] The rhodium complex **67** displayed a better catalytic

Scheme 31. Chiral-at-Rhodium Complex Catalyzed Enantioselective α-Amination Reaction

64-95% yields, 90-97% ee

Proposed model for asymmetric induction
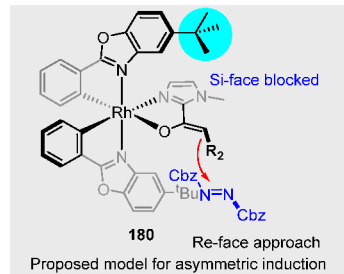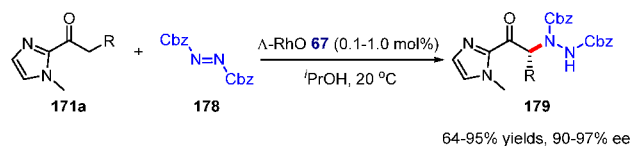
activity than the analogous iridium complex. The products **179** were isolated in high 64−95% yields and excellent enantioselectivities (90−97% ee). The *Re*-face attack of the in situ generated rhodium enolate **180** analogously explains the observed stereoselectivity.

3.2.5. α-Fluorination of carbonyls. The Xu group utilized a similar approach for the asymmetric α-fluorination of 2-acyl imidazoles **171** using selectfluor as the fluorinating agent (Scheme 32).[93] The chiral-at-iridium complex Δ-IrS **181** catalyzed the reaction in 4 mol % loading, delivering the α-fluorinated ketones **182** in good yields (60−97%) and excellent enantioselectivities (77−99% ee). The formation of N,O-coordinated Z-iridium enolate **183** and the attack from the *Si*-face were proposed to explain observed stereoselectivity.

Scheme 32. Chiral-at-Iridium Complex Catalyzed Enantioselective α-Fluorination Reaction

up to 97% yields
up to 99% ee
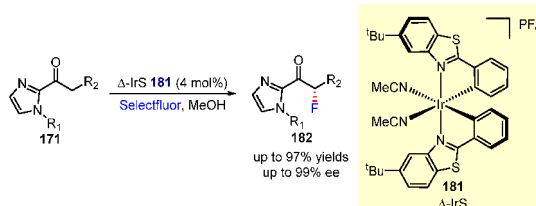
Proposed mechanism:
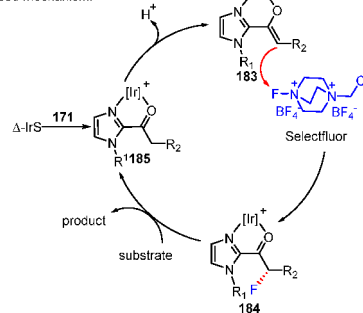
4. VISIBLE-LIGHT-INDUCED ASYMMETRIC CATALYSIS

In the past decade, visible-light-induced organic transformations have become a versatile synthetic tool for forging organic molecules in an environmentally benign way.[94,95] The enantioselective variant of such a reaction is in the developing phase. The progress is challenged by the requirement to combine the asymmetric catalysts with the photocatalytic process, which invariably involves short-lived reactive species, including excited state photocatalysts, radicals and radical anions, or cations.[96] Generally, the visible-light-induced asymmetric transformation employs a dual catalytic system where an achiral photocatalyst is accountable for the photochemistry and a chiral catalyst is responsible for the stereodifferentiation.[97] Moreover, there are single catalytic systems that can interface the visible-light photocatalysis and asymmetric catalysis. In such a case, a single catalyst would provide a new mechanistic pathway that can give control over the entire reaction pathway, especially at the most crucial stereocontrol step. The following section summarizes the chiral-at-metal complex catalyzed asymmetric photocatalysis.

4.1. Asymmetric Synthesis of α- and β-Functionalized Carbonyls

4.1.1. Alkyl Halide/Borate as an Alkyl Radical Precursor. Photocatalysis offers convenient access to radical intermediates from unconventional precursors R−X (R = alkyl group, X = I, Br) by breaking a relatively weak bond. In the initial stages of the investigation for asymmetric catalysis with chiral-at-metal complexes, Meggers and co-workers realized that an electrophilic alkyl radical could be generated from a benzyl bromide precursor **186** in the presence of a light source by the assistance of excited chiral-at-iridium catalyst **41** (Scheme 33a).[98] In this process, the sole chiral-at-iridium complex **41** simultaneously serves as the chiral Lewis acid and the photoredox catalyst. The electrophilic alkyl radical then combines with the enolate complex **188**, formed by the bidentate coordination of 2-acyl imidazole **171** with **41**. The reaction tolerates the electronically biased aryl bromide substituents, and the α-alkylated products **187** were obtained in up to 100% yield and up to 99% enantioselectivity in the presence of a weak base Na$_2$HPO$_4$.

A general mechanism is depicted in Scheme 33. The catalytic cycle started with the bidentate coordination of the substrate by replacing two labile acetonitrile groups of Λ-IrS complex. The α-deprotonation of the resultant intermediate **188** forms the iridium enolate complex **189**. The cyclo-voltammetry and photoluminescence study proved that the complex **189** acts as a photosensitizer in the reaction medium. Visible light irradiation excites the enolate complex **189**, enabling single-electron transfer (SET) to the electron-deficient halide substrate **186**. Mesolysis of the resultant radical anion yields an electron-deficient radical intercepted by the iridium enolate complex and generates the iridium ketyl radical complex **190**. The product was then ejected via SET and ligand exchange.

The strategy was further extended for the enantioselective trichloromethylation of 2-acyl imidazoles and 2-acylpyridines,[99] and α-perfluoroalkylation of 2-acyl imidazoles (Scheme 33b).[100]

The Xu group found that an iridium complex Ir-(ppy)$_2$(dtbbpy)PF$_6$ is necessary as a photosensitizer for the chiral-at-rhodium complex **152** catalyzed α-functionalization of acyl imidazole **171b** (Scheme 34).[101] Under these conditions, a variety of chiral gem-difluoroalkyl group containing γ-keto amides **196** and a series of fluorine-containing α,β-unsaturated-γ-keto esters **197** were afforded in excellent yields and excellent stereoselectivities. Experimentally, it was observed that the in situ formed Rh-enolate **198** is capable of reductively quenching the visible-light excited photocatalyst [{Ir(ppy)$_2$(dtbbpy)}$^+$]*.

Scheme 33. Enantioselective α-Alkylation Reactions
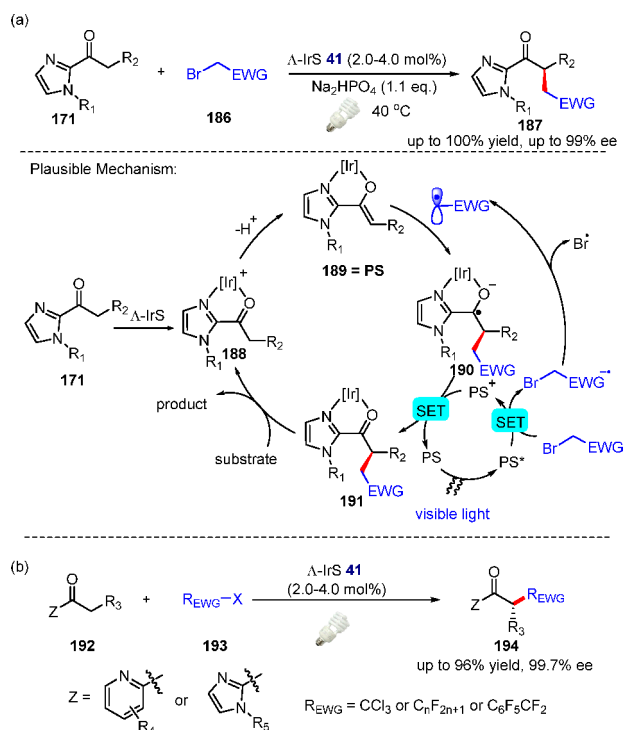
Scheme 34. Visible-Light-Mediated Enantioselective α-Amination and α-Alkylation Reaction Enabled by a Chiral-at-Rhodium(III) Catalyst
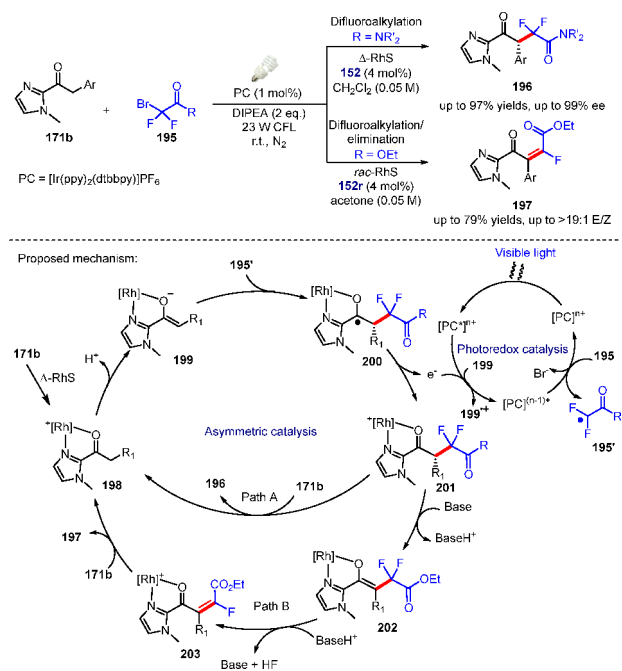
The reduced photocatalyst [PC]$^{(n-1)+}$ involved a single electron transfer with **195**, generating the difluoroacetyl radical, which subsequently combines with the electron-rich double bond of **199**. The generated intermediate **200** then quenched the excited photocatalyst [PC*]$^{n+}$ and produced **201** and the reduced photoredox sensitizer [PC]$^{(n-1)+}$. The ligand exchange via path A yields the difluoroalkylated product **196**. On the other hand, the α,β-unsaturated γ-keto ester **197** was formed via E1cB elimination and ligand exchange (path B). Further, the quantum yield of the difuoroalkylation reaction was determined as 2.00, suggesting the involvement of a radical chain process. Moreover, the chemoselectivity of this process was found to be dependent on the fluorine reagents besides the Lewis acid catalysts.

In 2016, the Meggers group utilized organotrifluoroborates **205** as the alkyl radical precursor for enantioselective alkyl radical addition into Michael acceptors (Scheme 35).[102] A

Scheme 35. Enantioselective Radical Addition to α,β-Unsaturated Carbonyls

chiral-at-rhodium Lewis acid catalyst **207** catalyzed the reaction in the presence of [Ir{dF(CF$_3$)ppy}$_2$(bpy)]PF$_6$ or [Acr-Mes]ClO$_4$ as a photoredox catalyst under visible-light irradiation. The enantioenriched β-alkylated carbonyl derivatives **206** w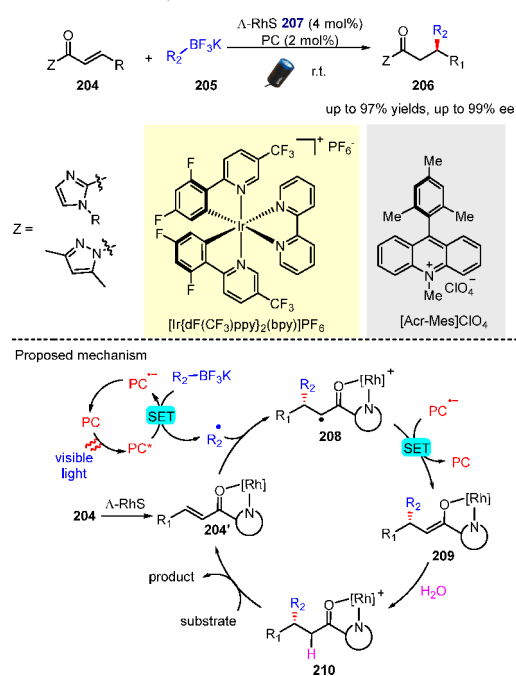ere generated in up to 97% yields and 99% ee. This reaction tolerates a wide range of substrates having diverse functionalities. By a competition experiment, the authors determined that the rhodium coordination increases the radical addition rate to the α,β-unsaturated electrophiles by a factor of at least 3 × 10^4. The observed high enantioselective radical addition at a low loading of the chiral Lewis acid can thus be explained. The postulated reaction mechanism involves a carbon-centered radical generation from **205** by a photoinduced single electron transfer mechanism. The coupling of the produced radical with N,O-rhodium coordinated α,β-unsaturated electrophile **204'** gives the intermediate **208**. A SET reduction produced the rhodium enolate **209**. Protonation and ligand exchange released product **206** and closed the cycle.

4.1.2. Alkyl Amine as α-Amino Radical Precursors.
In the past decade, α-amino radicals have been used as reactive open-shell intermediates, capable of engaging in a plethora of synthetic transformations providing amine-containing chemical motifs with a wide range of applications.[103,104] Classically, α-amino radicals can be derived from different pathways.[105,106] One such route involves leaving groups such as TMS (trimethylsilyl) in alkyl amine, which oxidatively generates the α-amino radical intermediates after photocatalytic C−Si bond cleavage. Meggers et al. exploited the enantioselective α-functionalization of acyl-imidazole **171c** using silyl amine **211** as an α-amino radical precursor using a chiral-at-iridium photosensitizer **34** and air as the terminal oxidant under visible-light irradiation (Scheme 36).[107] The enantioselective

Scheme 36. Visible-Light-Mediated Enantioselective Oxidative α-Amino Alkylation with a Single Chiral-at-Iridium(III) Catalyst
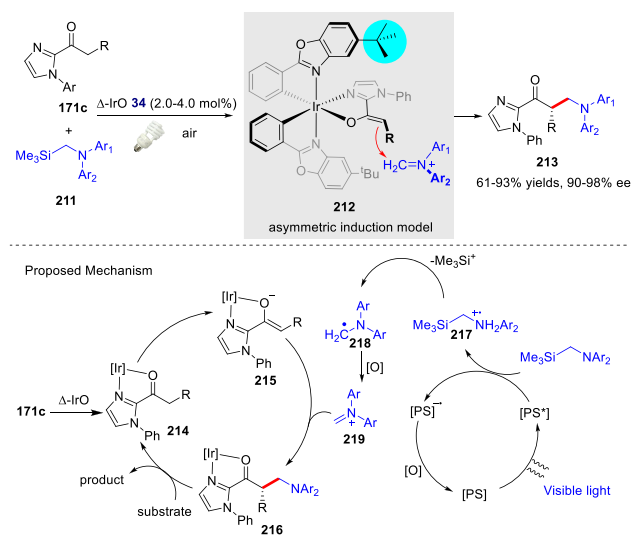
amino alkylation products were isolated in 61−93% yield and excellent 90−98% ee. The reductive quenching of the excited photocatalyst by **217** afforded the corresponding iminium ion **219** via photoinduced electron transfer, loss of Me$_3$Si$^+$, and oxidation. The iminium ion **219** was then trapped by the chiral enolate complex **215** and led to the formation of α-functionalized ketone **216**. Amazingly, the single iridium complex simultaneously serves three distinct functions: the exclusive source of chirality, the catalytically active Lewis acid, and a photoredox catalyst.

The Kang group utilized tetrahydroisoquinoline as the α-amino radical precursor for the chiral-at-rhodium complex Λ-RhO(Ar') **93** catalyzed enantioselective functionalization of α,β-unsaturated electrophile **35c** (Scheme 37).[108] The substrate-bound rhodium complex **222** served as a photoredox mediator (PS), which delivers the α-amino radical **226** after excitation, SET, and deprotonation processes. Subsequently, the radical **226** reacts with **222** to generate α-radical intermediate **223**. The SET process followed by protonation and ligand exchange liberated the product **221** and closed the cycle. The single chiral-at-rhodium complex served as the Lewis acid and the photoredox catalyst. The desired products **221** were isolated in 74−86% yields with 92−96% ee.

The enantioselective synthesis of α-amino carbonyls has also been achieved by the photoinduced stereocontrolled radical−

Scheme 37. Chiral-at-Rhodium Complex Catalyzed Enantioselective Conjugate Addition of α-Amino Radicals to Michael Acceptors

up to 96% yields, up to 99% ee
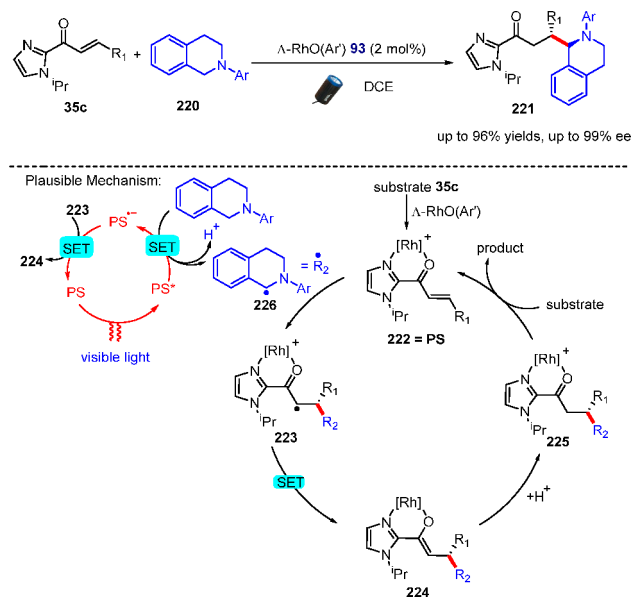
radical coupling between electron-deficient trifluoroacetyl imidazole **227** and amine derivatives **228** involving the same chiral-at-iridium complex **34** as a photocatalyst (Scheme 38).[109] It is proposed that, under visible-light irradiation, two substrates, one electron donor **228** and one electron acceptor **227**, are involved in electron exchange, creating two odd-electron species. The bidentate coordination of **227** with the iridium complex makes it a strong photo-oxidant. A single electron transfer from the amine donor **228** results in the ketyl

Scheme 38. Visible-Light-Mediated Enantioselective Radical–Radical Cross-Coupling Reaction Enabled by a Chiral-at-Iridium(III) Catalyst
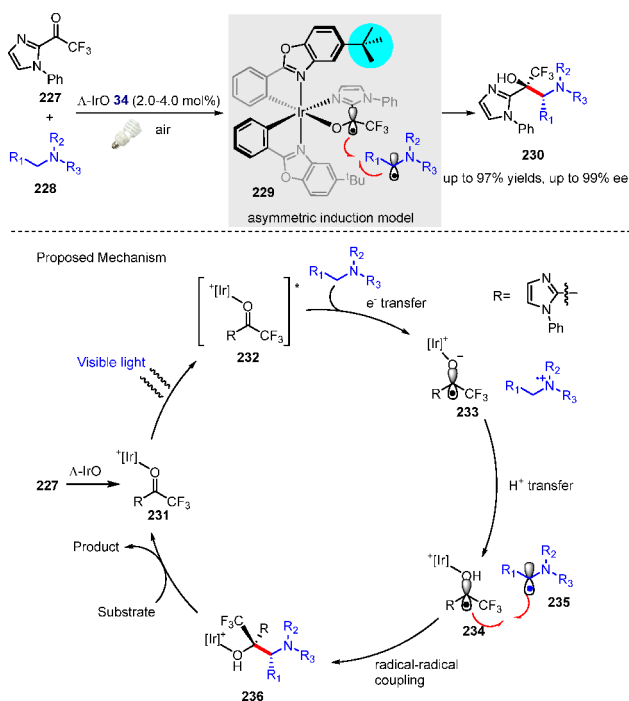

radical complex **234**. A radical—radical coupling and the ligand exchange delivered the desired products **230** in up to 97% yields and up to 99% ee. However, the less electron deficient 2-acetyl imidazole fails to give the desired products.

N-(Acyloxy)phthalimides are another class of precursors of α-aminoalkyl radical intermediates via photoinduced reductive decarboxylation.[110] The chiral-at-rhodium complex **207** was utilized for the visible-light-mediated β-aminoalkylations of α,β-unsaturated *N*-acylpyrazole **239** using glycine derived *N*-acyloxy phthalimides **237** as the precursor (Scheme 39).[111] The Hantzsch ester was used as a sacrificial reductant. Notably, complex **207** serves as both the photoredox catalyst and the chiral Lewis acid catalyst.

Scheme 39. Decarboxylative Conjugate Addition to Alkene through Enantioselective Photoredox Catalysis
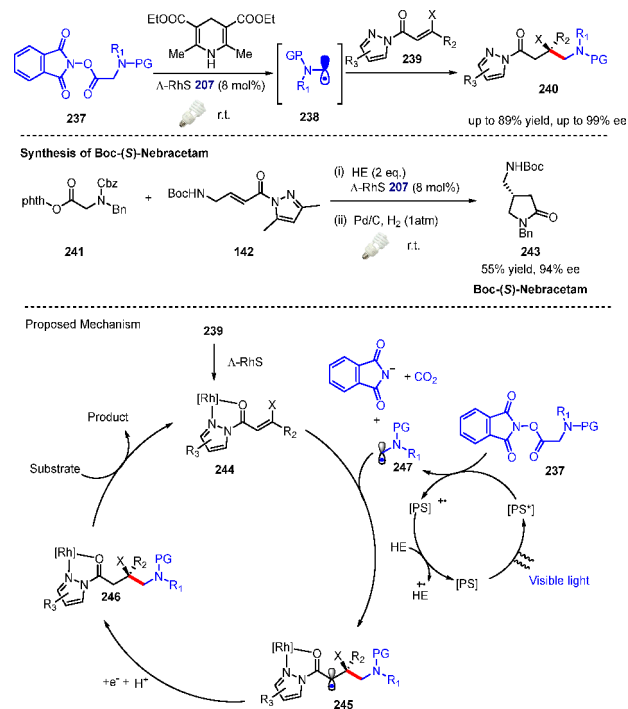
A wide range of β-substituted chiral γ-amino butyric acids **240** were synthesized in up to 89% yields and 99% ee. Using β-fluoro-α,β-unsaturated *N*-acylpyrazole substrate, a library of β-fluoro-β-aryl-γ-aminobutyric acid derivatives has also been synthesized under these conditions in up to 80% yields and 96% ee. The importance of this protocol is highlighted by synthesizing Boc-(*S*)-nebracetam **243** and β-substituted chiral γ-aminobutyric acids such as (*R*)-balcofen and (*R*)-rolipram derivatives. Mechanistically, the ground state N,O-coordinated rhodium complex **244** undergoes a photoinduced SET reduction of **237** to yield the α-aminoalkyl radical **247**, eliminating CO$_2$ and phthalimide. Adopting the unique property of **244**, the enantioselective addition of **247** takes place where the metal-centered chirality controls the selectivity.

4.1.3. Nitrogen-Centered Radicals (NCRs). Nitrogen-centered radicals (NCRs) are a versatile class of highly reactive species. A wide variety of methods can generate NCRs via a SET reduction pathway or the energy transfer pathway under mild conditions.[112,113] Depending on the hybridization and substitution patterns, NCRs can serve as electrophiles or

nucleophiles.[114] In this context, the Meggers group highlighted the use of (ODN)-*N*-functionalized carbamates **248** (ODN = 2,4-dinitrophenylsulfonyloxy) to access the corresponding NCRs and their enantioselective coupling with 2-acyl imidazole **171c** (Scheme 40).[115] A chiral-at-rhodium complex

Scheme 40. Visible-Light-Mediated Enantioselective α-Amination Reaction Enabled by a Chiral-at-Rhodium(III) Catalyst

Scheme 41. Visible-Light-Mediated Enantioselective α-Amination and α-Alkylation Reaction Enabled by a Chiral-at-Rhodium(III) Catalyst
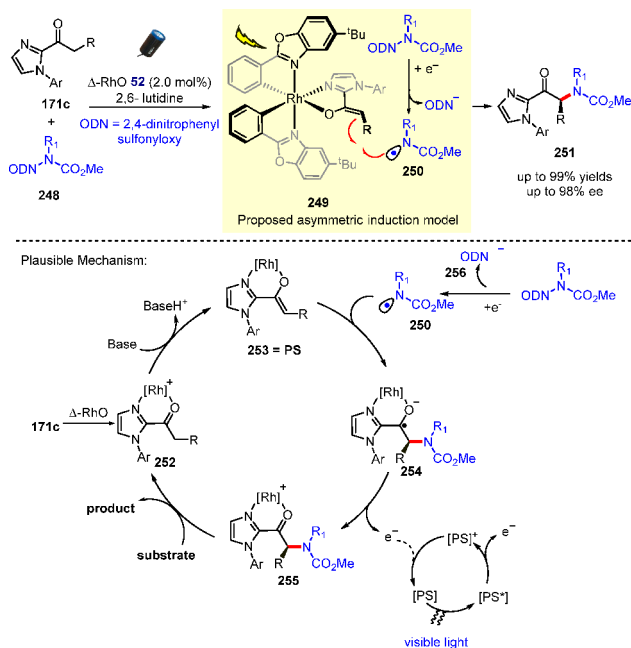
at 2 mol % loadings catalyzed the reaction in the presence of 2,6-lutidine. The products **251** were isolated in up to 99% yields and 98% ee in a short reaction time under visible-light irradiation. It was proposed that, upon photoactivation, the in situ generated rhodium enolate complex **253** underwent efficient SET to **248**. Subsequent fragmentation generates a sulfonate anion **256** and the electrophilic aminyl radical **250**, which then is successively intercepted by the enolate **253**. It is worth mentioning that a chiral-at-iridium complex with an identical ligand environment fails to catalyze the reaction. The authors attributed the preferences for rhodium over iridium to the much faster ligand exchange kinetics of the rhodium complexes, which is crucial to control the highly reactive and short-lived nitrogen-centered radical intermediates.
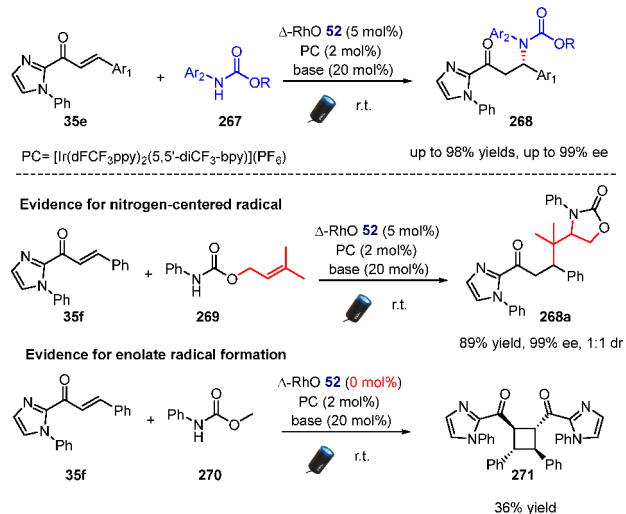
Organic azides have long been known as versatile and valuable precursors for the NCRs via the extrusion of molecular N₂. The resulting reactive intermediates can be conveniently employed to synthesize various cyclic and acyclic nitrogen-containing compounds. In this regard, the asymmetric α-aminations of 2-acyl imidazoles **171** using organic azides **257** have recently been obtained via a combination of chiral-at-rhodium(III) Lewis acid **207** and a secondary photosensitizer such as Ru(bpy)₃PF₆ (Scheme 41).[116] The latter has been used to counterbalance the restricted photochemical properties of the in situ generated rhodium enolate **262**. The products **260** were isolated in good yields up to 90% and 99% ee, tolerating different substituents in the aryl azide **257** coupling partners. It was proposed that, upon visible-light irradiation, the nitrogen-centered radicals are generated via SET from strongly reducing [Ru(bpy)₃]⁺ to the organic azide substrate, followed by N₂
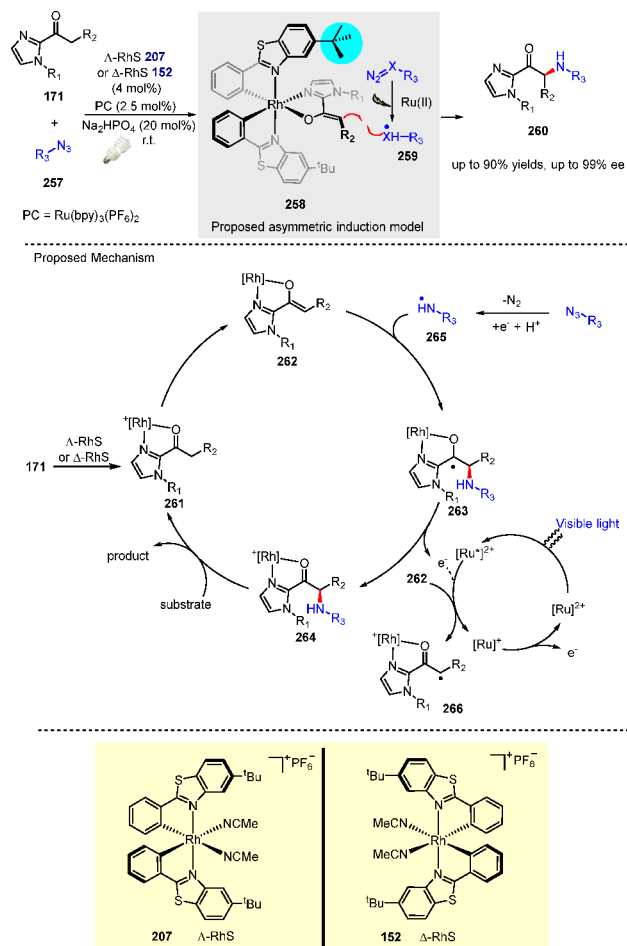
extrusion and protonation. The subsequent stereoselective addition of these electron-deficient radicals to the electron-rich double bond of the rhodium enolate **262** constitutes the chirality generating step and provides the Rh-coordinated ketyl radical **263**. The oxidation of ketyl radical leads to a Rh-coordinated product, which engages in a new catalytic cycle after product elimination.

The proton-coupled electron transfer (PCET) is another innovative strategy to convert N−H into NCRs.[117,118] Recently, in the presence of a mild phosphate base, the PCET strategy was devised for the photoinduced enantioselective β-amination of α,β-unsaturated 2-acyl imidazoles **35e** with the aid of **267** as the photoredox catalyst (PC) and chiral-at-rhodium complex **52** as a Lewis acid catalyst (Scheme 42).[119] The desired products **268** were obtained in excellent yields (up to 98%) and enantioselectivities (up to 99% ee), tolerating a wide range of electron-rich and electron-deficient functionalities in both coupling partners. The intermediate N-centered radical formation was verified by an intramolecular radical trapping to an alkene **270** followed by the reaction of the formed carbon-centered radical with the unsaturated 2-acyl imidazole **35e**. In addition, the formation of the enolate radical **273** is experimentally evidenced by the appearance of cyclobutane **271** in the absence of the Rh catalyst. The construction of **271** is viable by photoredox-mediated [2 + 2] cycloaddition through the single electron reduction of **35f**.

Scheme 42. Enantioselective Catalytic β-Amination through Proton-Coupled Electron Transfer

Scheme 43. Enantioselective Translocated Radical Addition to Alkene via Visible-light Photoredox Catalysis with a Chiral-at-Rhodium(III) Complex

The Meggers group reported the chiral-at-rhodium complex catalyzed asymmetric photorearrangement of 3-(2-formylphenyl)-1-pyrazol-1-yl-propenone substrate **283** (Scheme 44).[122]

Scheme 44. Photoinduced Asymmetric Intramolecular HAT Reaction

4.1.4. Via 1,5 Hydrogen Atom Transfer.

Hydrogen atom transfer (HAT) often enables selective generation of R$^{\bullet}$ via the direct activation of R−H bonds. In recent years, photocatalysis has contributed to developing this field boosted by the visible-light absorbing transition metal complexes[120] and organic dyes.[95] It is well-known that the alkoxy radical is susceptible for the hydrogen atom abstraction from the δ-carbon atom via a 1,5-HAT process. Recently, a combination of a chiral-at-rhodium Lewis acid catalyst and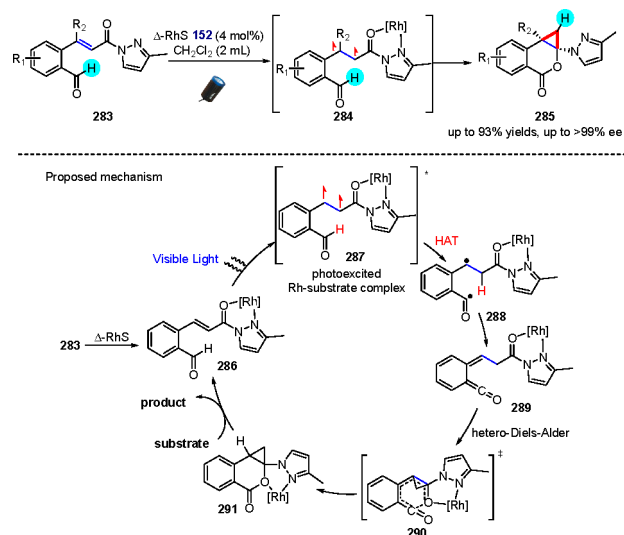 *fac*-[Ir(ppy)$_3$] as a photoredox catalyst has been applied for the enantioselective C(sp^3)−H functionalization of N-alkoxy phthalimides **278** via a 1,5-HAT process (Scheme 43).[121] α,β-Unsaturated N-acyl pyrazoles **279** acts as the radical acceptor and a Hantzsch ester is used as the terminal reductant. Following the absorption of visible light, the excited state *fac*-[Ir(ppy)$_3$]* is reductively quenched by the Hantzsch ester. The generated reduced state of the photocatalyst then transfers a single electron to N-alkoxyphthalimide substrate **280**. It triggers a homolytic N−O bond cleavage, yielding an alkoxy radical **281**, which then undergoes intramolecular 1,5-HAT. The formed C-centered radical **282** then adds to the rhodium-activated enone substrates in an asymmetric fashion that delivers the desired product **280** in 49−85% yields and 82−97% ee.

Mechanistic experiments and DFT computations suggest that, upon visible-light absorption, the rhodium bound α,β-unsaturated N-acyl pyrazole complex **283** undergoes a π−π* photoexcited state and generates the diradical rhodium complex **287**. The aldehyde moiety present nearby suffers a HAT process. The resultant intermediate **289** then undergoes an intramolecular hetero-Diels−Alder reaction, and the product **285** is liberated after ligand exchange. The synthetic utility of this methodology was further demonstrated by gram scale reactions that afforded the product with an improved yield of 90% and 99% ee. The chiral-at-rhodium complex can be recovered in 86% yield. Further, the deuterium-labeling experiment varifies the HAT process where the deuterium in aldehydic position ended up forming a deuterated cyclopropane ring in 78%.

4.1.5. Visible-Light Mediated β-Functionalization of Carbonyls.

Allyl sulfones are versatile radical acceptors for allylation reactions. However, the fragmented sulfonyl radicals are often discarded as waste. The Meggers group demonstrated reductive β-allylation of α,β-unsaturated 2-acyl-pyrazole **292** with allyl sulfones **293** as the allylating agent, and simultaneously, the generated waste sulfonyl radicals were used via a radical addition for the synthesis of nonracemic β-sulfonyl carbonyls (Scheme 45).[123] A chiral-at-rhodium

Scheme 45. Enantioselective C−C Bond Formation via Stereocontrolled Coupling

precursor (Scheme 46).[126] The rhodium complex **152** performed a dual role in this reaction as a visible-light-absorbing unit after substrate binding and as the sole source of chirality.

Scheme 46. Asymmetric β-Alkylation of α,β-Unsaturated Acyl Imidazole
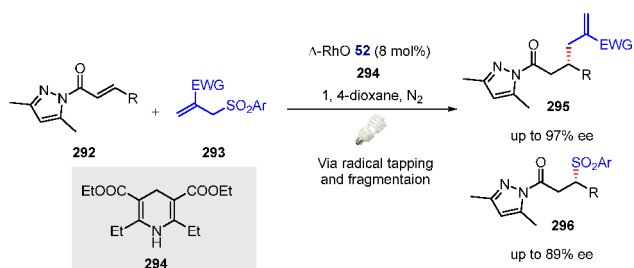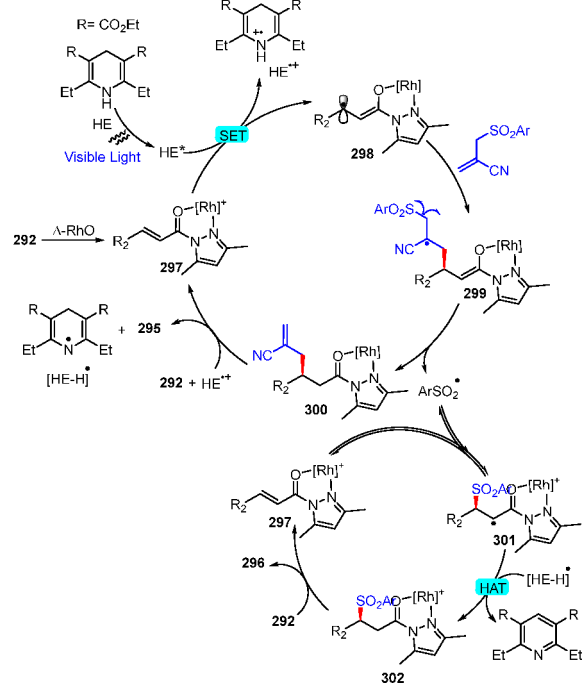
complex catalyzed the reaction, efficiently controlling the stereochemistry in the visible-light-generated prochiral radical addition for the allylation reaction and the asymmetric sulfonyl addition reaction. A stoichiometric amount of Hantzsch ester **294** served as a sacrificial reductant. The author suggested that the visible-light-activated Hantzsch ester $[E^{(HE^{\bullet+}/HE*)} = -2.23$ V vs Fc/Fc$^+]$ can efficiently reduce the Rh-coordinated substrate RhO-**297** (-1.62 V vs Fc/Fc$^+$) to form rhodium enolate radical **298**. The free substrates (-2.59 V vs Fc/Fc$^+$ for **292**) could not efficiently quench the luminescence of HE. The generated Rh-coordinated radical intermediate **298** can be trapped by allyl sulfone and produce the chiral β-substituted product **295** in high yields and up to 97% ee. Successive fragmentation of **299** would result in a sulfonyl radical that can efficiently trap RhO-**297** to yield **296** in high yields and up to 89% ee.

In recent years, it has been found that 4-alkyl substituted Hantzsch ester (HE) derivatives are excellent precursors for alkyl radicals under photocatalytic conditions.[124,125] In the presence of a photoredox catalyst, it undergoes single-electron oxidation, which homolytically cleaves the C−C bond of the 4-position of the HE to generate free alkyl radicals. The Meggers group developed a systematic and feasible catalytic asymmetric Giese reaction using a rhodium-based chiral Lewis acid catalyst and 4-alkyl substituted Hantzsch ester as a reasonable radical
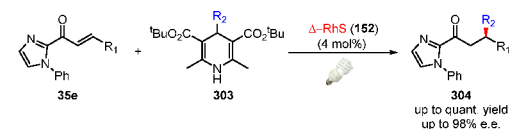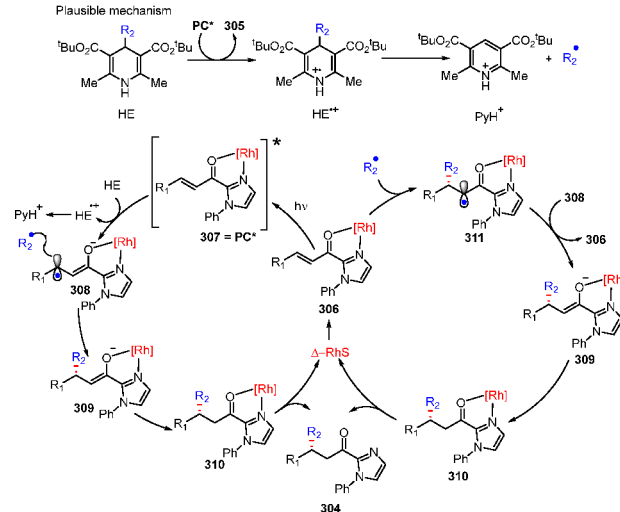
This procedure provides β-functionalized 2-acyl imidazole derivatives **304** in quantitative yields and excellent enantioselectivities (up to 98%). The substrate-bound rhodium complex **306** absorbs in the visible region. The photoexcited rhodium complex acts as a strong oxidant ($E^{red}* = +0.88$ V Fc/Fc$^+$) and transfers a single electron to the HE derivative ($E_p{}^{Ox} = +1.03$ V Ag/AgCl) and forms HE$^{\bullet+}$, which undergoes C−C bond fragmentation to generate the free alkyl radical. Now, the radical can react in two ways. The radical can be captured by the reduced rhodium bound substrates (enolate radical anion **308**) to form intermediate **309** that, after protonation and ligand exchange, gives the desired product **304**. Alternatively, the radicals generated from the HE derivative can engage in radical addition reactions with **306** to form intermediate **311**. Subsequent SET reduction, protonation, followed by ligand exchange liberated the desired product **304**.

The enantioselective synthesis of β-dicarbonyls **314** has been achieved by merging the neutral eosin-Y as a HAT catalyst and Λ-RhS complex **207** as a chiral Lewis acid catalyst (Scheme 47).[127] The protocol tolerates a variety of primary aliphatic aldehydes **313** at a lower temperature, delivering the enantioenriched products **314** in moderate yields (23−60%) and moderate to excellent ee (61−94% ee). The aryl aldehydes displayed a lower reactivity, and the reactions had to be conducted at 30 °C to achieve synthetically useful conversions. Under these conditions, electron-neutral, electron-rich, and electron-deficient aryl aldehydes reacted to afford the desired products in moderate yields (32−46%) and good to excellent enantioselectivities (76−99% ee). The direct oxidation of **313** to an acyl radical by the neutral eosin-Y is not possible ($E^{S*/S-} = +0.83$ V vs SCE in CH$_3$CN/H$_2$O). The author described acyl radical generation via polarity matching a HAT process

Scheme 47. Asymmetric synthesis of 1,4-Dicarbonyls via the Merging of HAT Catalysis with Chiral Lewis Acid Catalysis

Scheme 48. Enantioselective β-C−H Functionalization of Acceptor Substituted Ketones with 1,2-Dicarbonyl Compounds
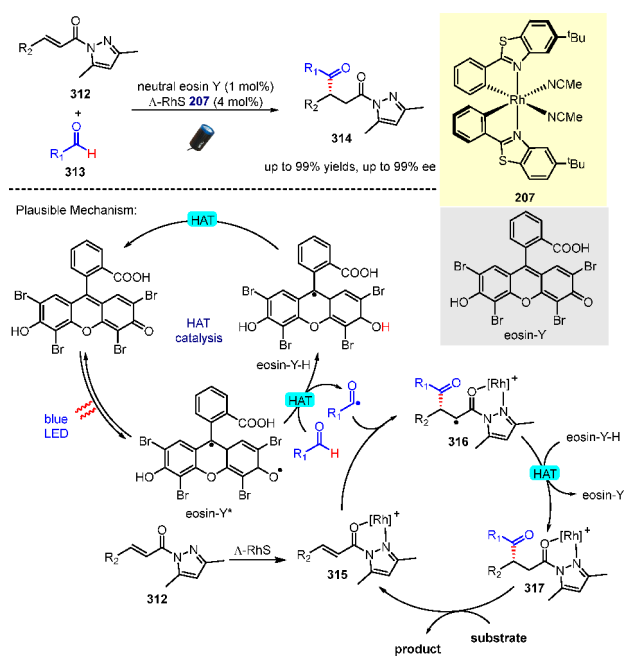
with the photoexcited eosin-Y. The N,O-coordinated Rh-complex **315** then intercepts the acyl radical to deliver the intermediate **316**. A reverse HAT reaction with eosin−Y-H completes the HAT catalytic cycle and generates the Rh-coordinated product **317**, which upon ligand exchange liberates the product **314**.

While different methods are available for introducing functionalities at the β-position of the carbonyls with soft nucleophiles, β-functionalization via direct activation of the β-C(sp3)−H bond is challenging. Recently, chiral-at-rhodium complex **321** catalyzed asymmetric β-C(sp³)−H functionalization of α,β-unsaturated carbonyls **318** with 1,2-dicarbonyls **319** has been accomplished (Scheme 48).[128] Under visible-light irradiation, the ketyl radical **325** is generated from photoexcitation of the rhodium enolate complex **323** via SET. The resultant radicals **324** and **325** subsequently combine to deliver the intermediate **326**. The protonation and ligand exchange then liberate the products **320**. Notably, a related iridium complex (Δ-IrS, **41**) failed to promote this transformation. Further, the control experiments with the radical trapping agent indicate the intermediacy of β-carbon radical enolate intermediate **324**.

4.2. Photocycloaddition Reaction

The photoinduced cycloaddition reaction is one of the frequently used chemical reactions to construct ring systems.[129] In this context, Meggers et al. explored the chiral-at-rhodium complex **152** catalyzed visible-light-mediated [2 + 2]-cycloaddition reaction for the catalytic asymmetric dearomatization of benzofuran **331** and benzothiophene **332** derivatives (Scheme 49a).[130] The reaction presumably proceeds through the association of N-acyl pyrazolyl substrate **328** with the rhodium complex **152**. After absorbing blue light, the latter gets excited to its singlet excited state **334**. The highly reactive diradical **335** is then generated after intersystem crossing (ISC). An olefin then stereoselectively combines with **335** to create 1,4-diradical **336**. Subsequent recombination
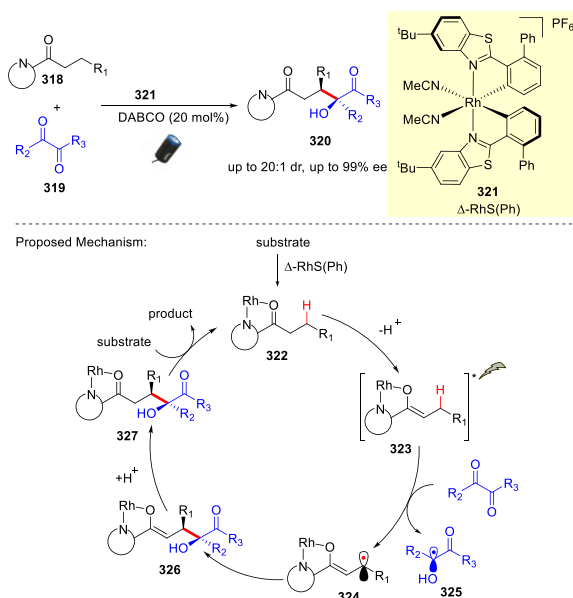
results in the products **331** and **332** in high yields with excellent ee (up to 99%) and dr (up to 20:1).

Similarly, under visible-light irradiation, the chiral-at-rhodium complex **152** catalyzed the asymmetric [2 + 2][20] and [2 + 3][131] photocycloaddition reactions of α,β-unsaturated 2-acyl imidazoles **338** with alkene **339** and vinyl azide **340**, respectively (Scheme 49b). The enantioenriched cyclobutanes **341** and 1-pyrrolines **342** were synthesized in high yields with broad substrate scope and excellent enantiomeric and diastereomeric ratios.

The chiral-at-rhodium complex **207** catalyzed enantioselective [3 + 2] photocycloaddition of acyl cyclopropane **343** with alkene **344** and alkyne **345** was accomplished under visible-light irradiation with an aliphatic amine as a sacrificial reductant (Scheme 50).[132] Previously inaccessible chiral cyclopentanes **346** and cyclopentenes **347** were isolated in up to 99% yields with excellent enantioselectivities of up to >99% ee. The authors indicated that the substrate coordination to the Lewis acid catalyst lowers the reduction potential, creating a strongly oxidizing excited state that a mild reducing agent can reduce. The resulting reduced complex **350** then opens the cyclopropane ring to yield **351** that consecutively reacts with alkene **344** and alkyne **345**, leading to the formation of chiral cyclopentane **346** and cyclopentene **347** derivatives, respectively.

4.3. Multicomponent Coupling Reaction

The multicomponent reaction is an attractive strategy for constructing two or more new chemical bonds that generate molecular complexity from simple substrates.[133] Meggers et al. reported an exciting application of a chiral-at-rhodium Lewis acid catalyst **133** and 4,4′-difluorobenzil **341** photoredox mediator for the asymmetric three-component fluoroalkylation reaction generating a diverse library of fluoroalkyl-containing chiral compounds (Scheme 51).[134]

Under visible-light irradiation, the photoredox mediator enabled the SET oxidation of perfluoroalkylsulfinate **353** substrates. The generated perfluoroalkyl radicals R$_F^•$ are

Scheme 49. Chiral-at-Rhodium Complex Catalyzed Asymmetric [2 + 2] and [2 + 3] Cycloaddition Reactions under Visible-Light Irradiation

Scheme 50. Visible-Light-Induced [3 + 2] Cycloaddition Reactions
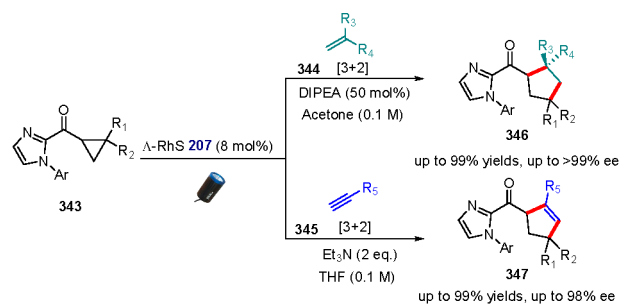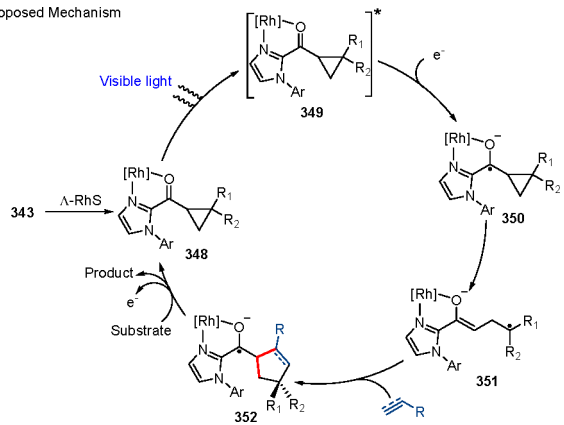
Scheme 51. Visible-Light-Mediated Three-Component Asymmetric Fluoroalkylation Reaction

trapped by the electron-rich vinyl ether **354** to deliver α-oxy carbon-centered radicals **359**. The latter was subsequently intercepted by the rhodium-coordinated α,β-unsaturated N-acyl pyrazoles **360** in a stereocontrolled fashion. The nonracemic fluoroalkyl containing products **356** were isolated in high yields (up to 98% yields) and excellent selectivities (up to 98% ee and up to 6:1 dr).

4.4. Other Reactions

Recently, Meggers and co-workers described the catalytic α-deracemization of ketones **363** having a stereocenter at the α-position of the pyridylketones via deprotonation/enantioselective protonation induced by the chiral-at-metal Λ-RhInd to obtain the nonracemic pyridylketone **364** up to 97% ee (Scheme 52).[135] Here, the chiral-at-metal Rh(III) complex not only creates the chiral environment during deracemization but also instigates the redox process. Notably, a tertiary amine serves as the electron donor, HAT reagent, and proton source. The proposed mechanism of photo-deracemization of the pyridylketone is described. A mixture of two diastereomeric configurations [(R)-**365** and (S)-**365**] is formed when the racemic pyridylketone substrate undergoes bidentate N,O-coordination with the chiral-at-rhodium complex. The Rh(III) complex **365** is excited under visible-light irradiation to

generate **366**. The latter undergoes SET with the tertiary amine to form rhodium ketyl radical complex **367**, which experiences HAT from the radical cation of the tertiary amine to give rise to rhodium enolate complex **368**. Diastereoselective proton transfer from the protonated amine to the rhodium enolate complex forms rhodium coordinated ketone **365** as a single diastereomer. Detachment of the nonracemic ketone leads to a new catalytic cycle.

Cyclic imines are present in a wide range of natural products and synthetically useful organic molecules.[136] Among those, pyrroline moieties are even more important because of their diverse biological activities.[137] Over the last decades, significant progress has been made in photoredox catalysis for the synthesis of racemic pyrroline.[138,139] In 2020, the Alemán

Scheme 52. α-Deracemization of Ketone Enabled by a Chiral-at-Rhodium Catalyst

Scheme 53. Enantioselective Synthesis of Pyrroline Derivatives via a Radical Polar Cascade Reaction
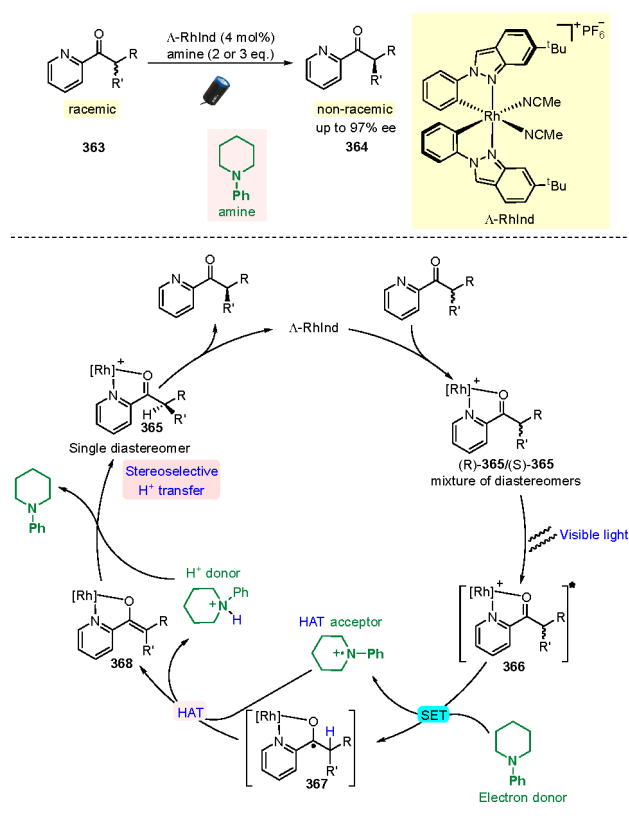
group synthesized optically active substituted cyclic imines by a photoredox/chiral-at-rhodium(III) dual catalytic strategy (Scheme 53).[140] This procedure requires acyl imidazole **369** and ketimines **370** to provide the substituted cyclic imines **371** via a HAT, radical coupling, and cyclization process. The desired products were obtained in high yields and excellent enantioselectivities, tolerating a broad range of functional groups. Scheme 53 illustrates the proposed mechanism. The Λ-RhS complex was coordinated with the acyl imidazole substrate to form intermediate **372**. At the same time, the excited photocatalyst *Ir(III) oxidizes DABCO to form a radical cation, which abstracts the hydrogen atom from intermediate **372** to generate radical intermediate **373**. In another cycle, the reduced photocatalyst Ir(II) reduces the ketimines to **A/B** and regenerates the photocatalyst. After that, α-amino radical **A** reacts with the alkyl radical in an enantiocontrolled fashion to provide intermediate **374**. The intramolecular cyclization process delivers intermediate **375**, which releases water to yield the enantioenriched cyclic imines.

5. ELECTRICITY DRIVEN ASYMMETRIC CATALYSIS

Electricity-driven organic synthesis avoiding the stoichiometric amount of chemical oxidant or reductant has become a rapidly growing field in the last decades.[141−146] However, due to the presence of highly reactive radicals and ionic intermediates on the catalyst surface, it is very challenging to merge asymmetric catalysis with organic electrosynthesis, and limited success is achieved.[147,148] In this regard, the Meggers group has utilized a chiral-at-rhodium complex **378** as a Lewis acid catalyst for the electricity-driven oxidative cross-coupling of 2-acyl imidazoles **376** with silyl enol ethers **377** (Scheme 54).[149] The resulting nonracemic 1,4-dicarbonyl compounds **379** were isolated in up
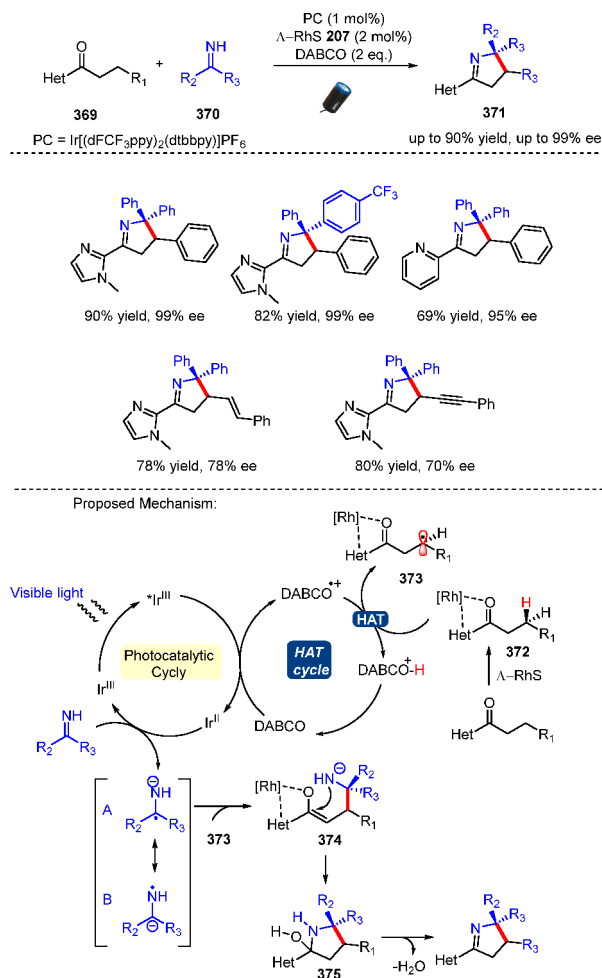
Scheme 54. Electricity-Driven Asymmetric Reaction Using Chiral Lewis Acid Catalyst
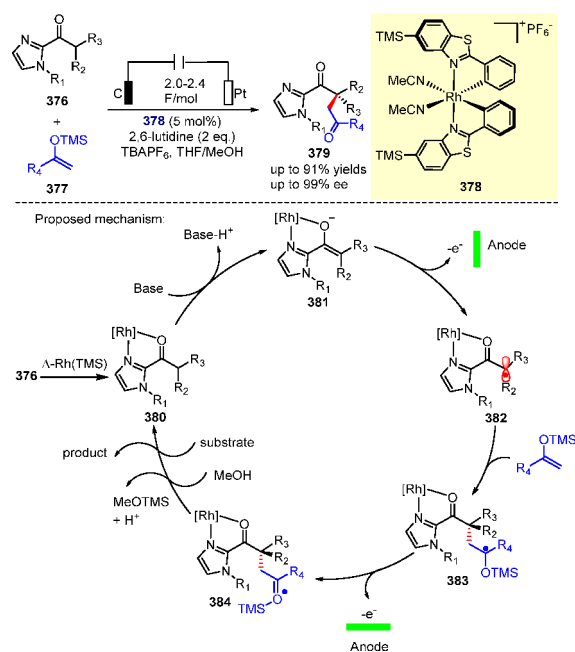
to 91% yields and up to 99% ee with excellent functional group tolerance. It was proposed that the in situ generated rhodium-enolate complex **381** (oxidation potential +0.52 V vs Ag/AgCl) undergoes anodic oxidation to generate α-radical Rh-complex **382**. After combining with the silyl enol ether **377** and another anodic oxidation, the desired product **379** was formed without forming a homocoupling partner. Free acyl imidazole and silyl enol ether could not oxidize during the catalytic cycle as both have an oxidation potential of greater than +2.0 and +1.72 V vs Ag/AgCl, respectively.

6. CONCLUSION AND OUTLOOK

Recent developments in chiral-at-metal catalysis in nucleophilic, electrophilic, photochemical, and electrochemical reactions have revolutionized the field of asymmetric catalysis. The strategy stands out with evident advantages desired in modern synthetic chemistry without using chiral ligands or chiral auxiliaries. The complexes are easy to synthesize in an enantiopure manner and are structurally manipulable. Additionally, the complexes are thermally and configurationally stable, even in the presence of assessable labile ligands. Moreover, the photochemical and redox characteristics of the in situ produced substrate-activated complex enabled their use in photoredox and electrocatalysis.

Despite recent advances in this field, there is still potential for improvement in the novel applications in asymmetric catalysis with broader substrates. For example, the developed reactions have intensively explored utilizing substrates with two coordination sites, such as an acyl imidazole or acyl pyrazole, that bind with the chiral-at-metal catalyst in a bidentate manner. On the other hand, various substrates with or without two coordination sites have yet to be studied. Moreover, the catalyst design could be improved with modulated stereoelectronics with easy synthesis and resolution. Additionally, the catalyst design solely concentrated on the octahedral space. The chemistry buried in other geometrical environments is largely unexplored. Further mechanistic exploration and synthetic applications are yet to be investigated to achieve novel asymmetric transformations, particularly the development of sustainable processes.

■ AUTHOR INFORMATION

Corresponding Author

Biplab Maji − *Department of Chemical Sciences, Indian Institute of Science Education and Research Kolkata, Mohanpur 741246, India;* ⓘ orcid.org/0000-0001-5034-423X; Email: bm@iiserkol.ac.in

Authors

Purusattam Dey − *Department of Chemical Sciences, Indian Institute of Science Education and Research Kolkata, Mohanpur 741246, India*

Pramod Rai − *Department of Chemical Sciences, Indian Institute of Science Education and Research Kolkata, Mohanpur 741246, India*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acsorginorgau.1c00032

Author Contributions

‡P.D. and P.R. contributed equally to this work.

Biographies

Purusattam Dey was born in West Bengal, India. He did B.Sc. chemistry at Midnapore College (Autonomous) and M.Sc. chemistry at Indian Institute of Technology, Madras. Since 2019 he has been doing his Ph.D. under the supervision of Dr. Biplab Maji at IISER Kolkata. His current research focuses on photoredox catalysis and asymmetric synthesis.

Pramod Rai was born in 1993 in West Bengal (India). After completing his B.Sc. at North Bengal University and M.Sc. at Sikkim University, he joined the research group of Dr. Biplab Maji as a Ph.D. student at IISER Kolkata. His research interest is the development of a new methodology in asymmetric photoredox catalysis.

Biplab Maji was born in 1987 in West Bengal (India). He obtained his M.Sc. from IIT Kanpur in 2009 (thesis supervisor: Prof. Dr. Manas K. Ghorai) and Ph.D. from Ludwig-Maximilians-Universität Munich in

2012 (thesis supervisor: Prof. Dr. Herbert Mayr). He did postdoctoral studies with Prof. Dr. Hisashi Yamamoto at Chubu University, Japan, and Prof. Dr. Frank Glorious at Westfälische Wilhelms-Universität Münster, Germany (as an Alexander von Humboldt fellow). In 2016, he joined the Department of Chemical Sciences, IISER Kolkata as an assistant professor, and in 2021 he was promoted to associate professor in the same department. His research focuses on organic synthesis, catalysis, and mechanistic studies.

◼ REFERENCES

(1) Halpern, J.; Trost, B. M. Asymmetric catalysis. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5347−5347.

(2) Mikami, K.; Lautens, M. *New frontiers in asymmetric catalysis*; John Wiley & Sons: 2007.

(3) Yamamoto, H.; Carreira, E. M. *Comprehensive Chirality: Online*; Elsevier Science: 2012.

(4) Zhou, Q.-L. *Privileged chiral ligands and catalysts*; John Wiley & Sons: 2011.

(5) Zhou, Q. L. Transition-Metal Catalysis and Organocatalysis: Where Can Progress Be Expected? *Angew. Chem., Int. Ed.* **2016**, *55*, 5352−5353.

(6) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. A powerful chiral counterion strategy for asymmetric transition metal catalysis. *Science* **2007**, *317*, 496−499.

(7) Fu, G. Asymmetric Catalysis with "Planar-Chiral" Derivatives of 4-(Dimethylamino)pyridine. *Acc. Chem. Res.* **2004**, *37*, 542−547.

(8) Werner, A. Zur kenntnis des asymmetrischen kobaltatoms. I. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1887−1898.

(9) Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. Highly efficient molybdenum-based catalysts for enantioselective alkene metathesis. *Nature* **2008**, *456*, 933−937.

(10) Busch, D. H. The stereochemistry of complex inorganic compounds. *J. Chem. Educ.* **1964**, *41*, 77−85.

(11) Constable, E. C. Stereogenic metal centres−from Werner to supramolecular chemistry. *Chem. Soc. Rev.* **2013**, *42*, 1637−1651.

(12) Fontecave, M.; Hamelin, O.; Menage, S. Chiral-at-metal complexes as asymmetric catalysts. In *Chiral Diazaligands for Asymmetric Synthesis*; Springer: 2005; Vol. 15, pp 271−288.

(13) Bailar, J. C., Jr The numbers and structures of isomers of hexacovalent complexes. *J. Chem. Educ.* **1957**, *34*, 334−338.

(14) Knight, P. D.; Scott, P. Predetermination of chirality at octahedral centres with tetradentate ligands: prospects for enantioselective catalysis. *Coord. Chem. Rev.* **2003**, *242*, 125−143.

(15) Bauer, E. B. Chiral-at-metal complexes and their catalytic applications in organic synthesis. *Chem. Soc. Rev.* **2012**, *41*, 3153−3167.

(16) Cao, Z.-Y.; Brittain, W. D.; Fossey, J. S.; Zhou, F. Recent advances in the use of chiral metal complexes with achiral ligands for application in asymmetric catalysis. *Catal. Sci. Technol.* **2015**, *5*, 3441−3451.

(17) Crassous, J. Transfer of chirality from ligands to metal centers: recent examples. *Chem. Commun.* **2012**, *48*, 9684.

(18) Huang, X.; Meggers, E. Asymmetric photocatalysis with bis-cyclometalated rhodium complexes. *Acc. Chem. Res.* **2019**, *52*, 833−847.

(19) Lacour, J.; Hebbe-Viton, V. Recent developments in chiral anion mediated asymmetric chemistry. *Chem. Soc. Rev.* **2003**, *32*, 373−382.

(20) Huang, X.; Quinn, T. R.; Harms, K.; Webster, R. D.; Zhang, L.; Wiest, O.; Meggers, E. Direct visible-light-excited asymmetric Lewis acid catalysis of intermolecular [2+ 2] photocycloadditions. *J. Am. Chem. Soc.* **2017**, *139*, 9120−9123.

(21) Meggers, E. Asymmetric synthesis of octahedral coordination complexes. *Eur. J. Inorg. Chem.* **2011**, *2011*, 2911−2926.

(22) Hamada, T.; Ishida, H.; Usui, S.; Tsumura, K.; Ohkubo, K. Enantioselective and photocatalytic oxidation of 1, 1′-bi-2-naphthol with a chiral ruthenium complex which includes molecular helicity. *J. Mol. Catal.* **1994**, *88*, L1−L5.

(23) Sato, I.; Kadowaki, K.; Ohgo, Y.; Soai, K.; Ogino, H. Highly enantioselective asymmetric autocatalysis induced by chiral cobalt complexes due to the topology of the coordination of achiral ligands. *Chem. Commun.* **2001**, 1022−1023.

(24) Chavarot, M.; Ménage, S.; Hamelin, O.; Charnay, F.; Pécaut, J.; Fontecave, M. "Chiral-at-metal" octahedral ruthenium (II) complexes with achiral ligands: a new type of enantioselective catalyst. *Inorg. Chem.* **2003**, *42*, 4810−4816.

(25) Hamelin, O.; Rimboud, M.; Pécaut, J.; Fontecave, M. Chiral-at-metal ruthenium complex as a metalloligand for asymmetric catalysis. *Inorg. Chem.* **2007**, *46*, 5354−5360.

(26) Ganzmann, C.; Gladysz, J. A. Phase transfer of enantiopure Werner cations into organic solvents: an overlooked family of chiral hydrogen bond donors for enantioselective catalysis. *Chem. - Eur. J.* **2008**, *14*, 5397−5400.

(27) Chen, L.-A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. Asymmetric catalysis with an inert chiral-at-metal iridium complex. *J. Am. Chem. Soc.* **2013**, *135*, 10598−10601.

(28) Xu, W.; Arieno, M.; Löw, H.; Huang, K.; Xie, X.; Cruchter, T.; Ma, Q.; Xi, J.; Huang, B.; Wiest, O.; Gong, L.; Meggers, E. Metal-Templated Design: Enantioselective Hydrogen-Bond-Driven Catalysis Requiring Only Parts-per-Million Catalyst Loading. *J. Am. Chem. Soc.* **2016**, *138*, 8774−8780.

(29) Chen, L. A.; Tang, X.; Xi, J.; Xu, W.; Gong, L.; Meggers, E. *Angew. Chem., Int. Ed.* **2013**, *52*, 14021−14025.

(30) Skubi, K. L.; Kidd, J. B.; Jung, H.; Guzei, I. A.; Baik, M.-H.; Yoon, T. P. Enantioselective Excited-State Photoreactions Controlled by a Chiral Hydrogen-Bonding Iridium Sensitizer. *J. Am. Chem. Soc.* **2017**, *139*, 17186−17192.

(31) Ma, J.; Zhang, X.; Huang, X.; Luo, S.; Meggers, E. Preparation of chiral-at-metal catalysts and their use in asymmetric photoredox chemistry. *Nat. Protoc.* **2018**, *13*, 605−632.

(32) Yamamoto, H. *Lewis acids in organic synthesis*; Wiley-VCH Verlag GmbH: 2000; Vol. *1*.

(33) Heravi, M. M.; Zadsirjan, V.; Saedi, P.; Momeni, T. Applications of Friedel−Crafts reactions in total synthesis of natural products. *RSC Adv.* **2018**, *8*, 40061−40163.

(34) Rueping, M.; Nachtsheim, B. J. A review of new developments in the Friedel−Crafts alkylation − From green chemistry to asymmetric catalysis. *Beilstein J. Org. Chem.* **2010**, *6*, 6−30.

(35) Huo, H.; Fu, C.; Harms, K.; Meggers, E. Asymmetric catalysis with substitutionally labile yet stereochemically stable chiral-at-metal iridium (III) complex. *J. Am. Chem. Soc.* **2014**, *136*, 2990−2993.

(36) Shen, X.; Huo, H.; Wang, C.; Zhang, B.; Harms, K.; Meggers, E. Octahedral Chiral-at-Metal Iridium Catalysts: Versatile Chiral Lewis Acids for Asymmetric Conjugate Additions. *Chem. - Eur. J.* **2015**, *21*, 9720−9726.

(37) Ma, J.; Shen, X.; Harms, K.; Meggers, E. Expanding the family of bis-cyclometalated chiral-at-metal rhodium(iii) catalysts with a benzothiazole derivative. *Dalton Trans.* **2016**, *45*, 8320−8323.

(38) Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. Recent Advances in the Synthesis of Cyclobutanes by Olefin [2 + 2] Photo-cycloaddition Reactions. *Chem. Rev.* **2016**, *116*, 9748−9815.

(39) Domínguez, G.; Pérez-Castells, J. Recent advances in [2 + 2+2] cycloaddition reactions. *Chem. Soc. Rev.* **2011**, *40*, 3430−3444.

(40) Shen, X.; Huo, H.; Wang, C.; Zhang, B.; Harms, K.; Meggers, E. Octahedral Chiral-at-Metal Iridium Catalysts: Versatile Chiral Lewis Acids for Asymmetric Conjugate Additions. *Chem. - Eur. J.* **2015**, *21*, 9720−9726.

(41) Sun, G.-J.; Gong, J.; Kang, Q. Chiral rhodium (III) complex-catalyzed cascade Michael-alkylation reactions: enantioselective synthesis of cyclopropanes. *J. Org. Chem.* **2017**, *82*, 796−803.

(42) Li, J.; Lin, L.; Hu, B.; Zhou, P.; Huang, T.; Liu, X.; Feng, X. Gold(I)/Chiral N,N'-Dioxide-Nickel(II) Relay Catalysis for Asymmetric Tandem Intermolecular Hydroalkoxylation/Claisen Rearrangement. *Angew. Chem., Int. Ed.* 2017, 56, 885−888.

(43) Li, J.; Lin, L.; Hu, B.; Lian, X.; Wang, G.; Liu, X.; Feng, X. Bimetallic Gold(I)/Chiral N,N′-Dioxide Nickel(II) Asymmetric Relay Catalysis: Chemo- and Enantioselective Synthesis of Spiroketals and Spiroaminals. *Angew. Chem., Int. Ed.* 2016, 55, 6075−6078.

(44) Gong, J.; Wan, Q.; Kang, Q. Gold (I)/chiral Rh (III) Lewis acid relay catalysis enables asymmetric synthesis of spiroketals and spiroaminals. *Adv. Synth. Catal.* 2018, 360, 4031−4036.

(45) Adrio, J.; Carretero, J. C. Recent advances in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. *Chem. Commun.* 2014, 50, 12434−12446.

(46) Nájera, C.; Sansano, J. M. Catalytic Enantioselective 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides and Alkenes: The Direct Strategy To Prepare Enantioenriched Highly Substituted Proline Derivatives. *Angew. Chem., Int. Ed.* 2005, 44, 6272−6276.

(47) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. New Strategies for Organic Catalysis: The First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition. *J. Am. Chem. Soc.* 2000, 122, 9874−9875.

(48) Kano, T.; Hashimoto, T.; Maruoka, K. Asymmetric 1,3-Dipolar Cycloaddition Reaction of Nitrones and Acrolein with a Bis-Titanium Catalyst as Chiral Lewis Acid. *J. Am. Chem. Soc.* 2005, 127, 11926−11927.

(49) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. An Entry to a Chiral Dihydropyrazole Scaffold: Enantioselective [3 + 2] Cycloaddition of Nitrile Imines. *J. Am. Chem. Soc.* 2005, 127, 8276−8277.

(50) Sibi, M. P.; Itoh, K.; Jasperse, C. P. Chiral Lewis Acid Catalysis in Nitrile Oxide Cycloadditions. *J. Am. Chem. Soc.* 2004, 126, 5366−5367.

(51) Gong, J.; Wan, Q.; Kang, Q. Asymmetric [3+ 2] Cycloaddition Employing N, N′-Cyclic Azomethine Imines Catalyzed by Chiral-at-Metal Rhodium Complex. *Org. Lett.* 2018, 20, 3354−3357.

(52) Galliford, C. V.; Scheidt, K. A. Pyrrolidinyl-Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents. *Angew. Chem., Int. Ed.* 2007, 46, 8748−8758.

(53) Singh, G. S.; Desta, Z. Y. Isatins As Privileged Molecules in Design and Synthesis of Spiro-Fused Cyclic Frameworks. *Chem. Rev.* 2012, 112, 6104−6155.

(54) Xiao, J.-A.; Li, Y.-C.; Luo, Z.-J.; Cheng, X.-L.; Deng, Z.-X.; Chen, W.-Q.; Su, W.; Yang, H. Construction of Bispirooxindole Heterocycles via Palladium-Catalyzed Ring-Opening Formal [3 + 2]-Cycloaddition of Spirovinylcyclopropyl Oxindole and 3-Oxindole Derivatives. *J. Org. Chem.* 2019, 84, 2297−2306.

(55) Wan, Q.; Chen, L.; Li, S.; Kang, Q.; Yuan, Y.; Du, Y. Enantioselective Synthesis of Multisubstituted Spirocyclopentane Oxindoles Enabled by Pd/Chiral Rh(III) Complex Synergistic Catalysis. *Org. Lett.* 2020, 22, 9539−9544.

(56) Ming, S.; Qurban, S.; Du, Y.; Su, W. Asymmetric Synthesis of Multi-Substituted Tetrahydrofurans via Palladium/Rhodium Synergistic Catalyzed [3 + 2] Decarboxylative Cycloaddition of Vinylethylene Carbonates. *Chem. - Eur. J.* 2021, 27, 12742−12746.

(57) Gutiérrez-Jiménez, M. I.; Aydillo, C.; Navo, C. D.; Avenoza, A.; Corzana, F.; Jiménez-Osés, G.; Zurbano, M. M.; Busto, J. H.; Peregrina, J. M. Bifunctional Chiral Dehydroalanines for Peptide Coupling and Stereoselective S-Michael Addition. *Org. Lett.* 2016, 18, 2796−2799.

(58) Samoilichenko, Y.; Kondratenko, V.; Ezernitskaya, M.; Lyssenko, K.; Peregudov, A.; Khrustalev, V.; Maleev, V.; Moskalenko, M.; North, M.; Tsaloev, A.; Gugkaeva, Z. T.; Belokon, Y. A mechanistic study of the Lewis acid−Brønsted base−Brønsted acid catalysed asymmetric Michael addition of diethyl malonate to cyclohexenone. *Catal. Sci. Technol.* 2017, 7, 90−101.

(59) Subramaniapillai, S. G. Mannich reaction: A versatile and convenient approach to bioactive skeletons. *J. Chem. Sci.* 2013, 125, 467−482.

(60) Kang, T.; Hou, L.; Ruan, S.; Cao, W.; Liu, X.; Feng, X. Lewis acid-catalyzed asymmetric reactions of β,γ-unsaturated 2-acyl imidazoles. *Nat. Commun.* 2020, 11, 3869−3878.

(61) Song, L.; Gong, L.; Meggers, E. Asymmetric dual catalysis via fragmentation of a single rhodium precursor complex. *Chem. Commun.* 2016, 52, 7699−7702.

(62) Gong, J.; Li, K.; Qurban, S.; Kang, Q. Rhodium (III)/Amine Synergistically Catalyzed Enantioselective Alkylation of Aldehydes with α, β-Unsaturated 2-Acyl Imidazoles. *Chin. J. Chem.* 2016, 34, 1225−1235.

(63) Li, K.; Wan, Q.; Kang, Q. Chiral-at-metal Rh (III) complex catalyzed asymmetric conjugate addition of unactivated alkenes with α, β-unsaturated 2-acyl imidazoles. *Org. Lett.* 2017, 19, 3299−3302.

(64) Wang, Z.-L. Recent Advances in Catalytic Asymmetric Decarboxylative Addition Reactions. *Adv. Synth. Catal.* 2013, 355, 2745−2755.

(65) Lubkoll, J.; Wennemers, H. Mimicry of Polyketide Synthases— Enantioselective 1,4-Addition Reactions of Malonic Acid Half-Thioesters to Nitroolefins. *Angew. Chem., Int. Ed.* 2007, 46, 6841−6844.

(66) Evans, D. A.; Mito, S.; Seidel, D. Scope and Mechanism of Enantioselective Michael Additions of 1,3-Dicarbonyl Compounds to Nitroalkenes Catalyzed by Nickel(II)−Diamine Complexes. *J. Am. Chem. Soc.* 2007, 129, 11583−11592.

(67) Li, S.-W.; Gong, J.; Kang, Q. Chiral-at-metal Rh (III) complex-catalyzed decarboxylative Michael addition of β-keto acids with α, β-unsaturated 2-acyl imidazoles or pyridine. *Org. Lett.* 2017, 19, 1350−1353.

(68) Li, S.-W.; Wan, Q.; Kang, Q. Chiral-at-Metal Rh (III) Complex-Catalyzed Michael Addition of Pyrazolones with α, β-Unsaturated 2-Acyl Imidazoles. *Org. Lett.* 2018, 20, 1312−1315.

(69) Wan, Q.; Li, S.; Kang, Q.; Yuan, Y.; Du, Y. Chiral-at-Metal Rh (III) Complex Catalyzed Cascade Reduction-Michael Addition Reaction. *J. Org. Chem.* 2019, 84, 15201−15211.

(70) Rai, P.; Waiba, S.; Maji, K.; Sahoo, D.; Maji, B. Cooperative Lewis Acid Catalysis for the Enantioselective C(sp3)−H Bond Functionalizations of 2-Alkyl Azaarenes. *Org. Lett.* 2021, 23, 8888.

(71) Ran, X.; Zhao, Y.; Liu, L.; Bai, L.; Yang, C.-Y.; Zhou, B.; Meagher, J. L.; Chinnaswamy, K.; Stuckey, J. A.; Wang, S. Structure-Based Design of γ-Carboline Analogues as Potent and Specific BET Bromodomain Inhibitors. *J. Med. Chem.* 2015, 58, 4927−4939.

(72) Kaur, K.; Kumar, V.; Sharma, A. K.; Gupta, G. K. Isoxazoline containing natural products as anticancer agents: A review. *Eur. J. Med. Chem.* 2014, 77, 121−133.

(73) Li, S.-W.; Du, Y.; Kang, Q. A chiral-at-metal asymmetric catalyzed vinylogous Michael addition of ortho-methyl aromatic nitro compounds for isoxazole derivative synthesis. *Org. Chem. Front.* 2019, 6, 2775−2779.

(74) Hu, L.; Lin, S.; Li, S.; Kang, Q.; Du, Y. Chiral-at-Metal Rhodium (III) Complex Catalyzed Enantioselective Vinylogous Michael Addition of α, α-Dicyanoolefins with α, β-Unsaturated 2-Acyl Imidazoles. *ChemCatChem* 2020, 12, 118−121.

(75) Guerin, D. J.; Miller, S. J. Asymmetric Azidation−Cycloaddition with Open-Chain Peptide-Based Catalysts. A Sequential Enantioselective Route to Triazoles. *J. Am. Chem. Soc.* 2002, 124, 2134−2136.

(76) Cai, Y.; Liu, X.; Jiang, J.; Chen, W.; Lin, L.; Feng, X. Catalytic Asymmetric Chloroamination Reaction of α,β-Unsaturated γ-Keto Esters and Chalcones. *J. Am. Chem. Soc.* 2011, 133, 5636−5639.

(77) Deng, T.; Thota, G. K.; Li, Y.; Kang, Q. Enantioselective conjugate addition of hydroxylamines to α, β-unsaturated 2-acyl imidazoles catalyzed by a chiral-at-metal Rh (III) complex. *Org. Chem. Front.* 2017, 4, 573−577.

(78) Hong, Y.; Cui, T.; Ivlev, S.; Xie, X.; Meggers, E. Chiral-at-Iron Catalyst for Highly Enantioselective and Diastereoselective Hetero-Diels-Alder Reaction. *Chem. - Eur. J.* 2021, 27, 8557−8563.

(79) Zhang, H.; Li, S.; Kang, Q.; Du, Y. Chiral-at-metal rhodium (iii) complex catalyzed enantioselective synthesis of C2-substituted benzofuran derivatives. *Org. Chem. Front.* 2019, 6, 3683−3687.

(80) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384−5427.

(81) Zhang, L.; Zhang, J.; Ma, J.; Cheng, D.-J.; Tan, B. Highly Atroposelective Synthesis of Arylpyrroles by Catalytic Asymmetric Paal−Knorr Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 1714−1717.

(82) Zhang, L.; Xiang, S.-H.; Wang, J.; Xiao, J.; Wang, J.-Q.; Tan, B. Phosphoric acid-catalyzed atroposelective construction of axially chiral arylpyrroles. *Nat. Commun.* **2019**, *10*, 566−576.

(83) Ye, C.-X.; Chen, S.; Han, F.; Xie, X.; Ivlev, S.; Houk, K. N.; Meggers, E. Atroposelective Synthesis of Axially Chiral N-Arylpyrroles by Chiral-at-Rhodium Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 13552−13556.

(84) Gladiali, S.; Alberico, E. Asymmetric transfer hydrogenation: chiral ligands and applications. *Chem. Soc. Rev.* **2006**, *35*, 226−236.

(85) Tian, C.; Gong, L.; Meggers, E. Chiral-at-metal iridium complex for efficient enantioselective transfer hydrogenation of ketones. *Chem. Commun.* **2016**, *52*, 4207−4210.

(86) Gong, J.; Li, S.-W.; Qurban, S.; Kang, Q. Enantioselective Mannich Reaction Employing 1,3,5-Triaryl-1,3,5-triazinanes Catalyzed by Chiral-at-Metal Rhodium Complexes. *Eur. J. Org. Chem.* **2017**, *2017*, 3584−3593.

(87) Paul, J.; Presset, M.; Le Gall, E. Multicomponent Mannich-Like Reactions of Organometallic Species. *Eur. J. Org. Chem.* **2017**, *2017*, 2386−2406.

(88) Filho, J. F. A.; Lemos, B. C.; de Souza, A. S.; Pinheiro, S.; Greco, S. J. Multicomponent Mannich reactions: General aspects, methodologies and applications. *Tetrahedron* **2017**, *73*, 6977−7004.

(89) Feng, L.; Dai, X.; Meggers, E.; Gong, L. Three-Component Asymmetric Mannich Reaction Catalyzed by a Lewis Acid with Rhodium-Centered Chirality. *Chem. - Asian J.* **2017**, *12*, 963−967.

(90) Tan, Y.; Yuan, W.; Gong, L.; Meggers, E. Aerobic Asymmetric Dehydrogenative Cross-Coupling between Two C-H Groups Catalyzed by a Chiral-at-Metal Rhodium Complex. *Angew. Chem.* **2015**, *127*, 13237−13240.

(91) Thota, G. K.; Sun, G. J.; Deng, T.; Li, Y.; Kang, Q. Enantioselective Conjugate Addition of 2-Acylimidazoles with Nitroalkenes Promoted by Chiral-at-Metal Rhodium (III) Complexes. *Adv. Synth. Catal.* **2018**, *360*, 1094−1098.

(92) Wang, C.; Chen, L.-A.; Huo, H.; Shen, X.; Harms, K.; Gong, L.; Meggers, E. Asymmetric Lewis acid catalysis directed by octahedral rhodium centrochirality. *Chem. Sci.* **2015**, *6*, 1094−1100.

(93) Xu, G. Q.; Liang, H.; Fang, J.; Jia, Z. L.; Chen, J. Q.; Xu, P. F. Catalytic Enantioselective α-Fluorination of 2-Acyl Imidazoles via Iridium Complexes. *Chem. - Asian J.* **2016**, *11*, 3355−3358.

(94) Shaw, M. H.; Twilton, J.; MacMillan, D. W. Photoredox catalysis in organic chemistry. *J. Org. Chem.* **2016**, *81*, 6898−6926.

(95) Romero, N. A.; Nicewicz, D. A. Organic photoredox catalysis. *Chem. Rev.* **2016**, *116*, 10075−10166.

(96) Schmittel, M.; Burghart, A. Understanding reactivity patterns of radical cations. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550−2589.

(97) Lipp, A.; Badir, S. O.; Molander, G. A. Stereoinduction in Metallaphotoredox Catalysis. *Angew. Chem., Int. Ed.* **2021**, *60*, 1714−1726.

(98) Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.-A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. Asymmetric photoredox transition-metal catalysis activated by visible light. *Nature* **2014**, *515*, 100−103.

(99) Huo, H.; Wang, C.; Harms, K.; Meggers, E. Enantioselective, catalytic trichloromethylation through visible-light-activated photoredox catalysis with a chiral iridium complex. *J. Am. Chem. Soc.* **2015**, *137*, 9551−9554.

(100) Huo, H.; Huang, X.; Shen, X.; Harms, K.; Meggers, E. Visible-light-activated enantioselective perfluoroalkylation with a chiral iridium photoredox catalyst. *Synlett* **2016**, *27*, 749−753.

(101) Liang, H.; Xu, G.-Q.; Feng, Z.-T.; Wang, Z.-Y.; Xu, P.-F. Dual catalytic switchable divergent synthesis: An asymmetric visible-light photocatalytic approach to fluorine-containing γ-keto acid frameworks. *J. Org. Chem.* **2019**, *84*, 60−72.

(102) Huo, H.; Harms, K.; Meggers, E. Catalytic, enantioselective addition of alkyl radicals to alkenes via visible-light-activated photoredox catalysis with a chiral rhodium complex. *J. Am. Chem. Soc.* **2016**, *138*, 6936−6939.

(103) Taylor, R. D.; MacCoss, M.; Lawson, A. D. Combining Molecular Scaffolds from FDA Approved Drugs: Application to Drug Discovery. *J. Med. Chem.* **2017**, *60*, 1638−1647.

(104) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87*, 1348−1349.

(105) Zuo, Z.; MacMillan, D. W. C. Decarboxylative Arylation of α-Amino Acids via Photoredox Catalysis: A One-Step Conversion of Biomass to Drug Pharmacophore. *J. Am. Chem. Soc.* **2014**, *136*, 5257−5260.

(106) McManus, J. B.; Onuska, N. P. R.; Nicewicz, D. A. Generation and Alkylation of α-Carbamyl Radicals via Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 9056−9060.

(107) Wang, C.; Zheng, Y.; Huo, H.; Röse, P.; Zhang, L.; Harms, K.; Hilt, G.; Meggers, E. Merger of visible light induced oxidation and enantioselective alkylation with a chiral iridium catalyst. *Chem. - Eur. J.* **2015**, *21*, 7355−7359.

(108) Lin, S.-X.; Sun, G.-J.; Kang, Q. A visible-light-activated rhodium complex in enantioselective conjugate addition of α-amino radicals with Michael acceptors. *Chem. Commun.* **2017**, *53*, 7665−7668.

(109) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. Asymmetric Radical−Radical Cross-Coupling through Visible-Light-Activated Iridium Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 685−688.

(110) Xuan, J.; Zhang, Z.-G.; Xiao, W.-J. Visible-Light-Induced Decarboxylative Functionalization of Carboxylic Acids and Their Derivatives. *Angew. Chem., Int. Ed.* **2015**, *54*, 15632−15641.

(111) Ma, J.; Lin, J.; Zhao, L.; Harms, K.; Marsch, M.; Xie, X.; Meggers, E. Synthesis of β-Substituted γ-Aminobutyric Acid Derivatives through Enantioselective Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2018**, *57*, 11193−11197.

(112) Kärkäs, M. D. Photochemical Generation of Nitrogen-Centered Amidyl, Hydrazonyl, and Imidyl Radicals: Methodology Developments and Catalytic Applications. *ACS Catal.* **2017**, *7*, 4999−5022.

(113) Davies, J.; Morcillo, S. P.; Douglas, J. J.; Leonori, D. Hydroxylamine Derivatives as Nitrogen-Radical Precursors in Visible-Light Photochemistry. *Chem. - Eur. J.* **2018**, *24*, 12154−12163.

(114) Joule, J. A.; Mills, K. Applications and Occurrences of Heterocycles in Everyday Life. In *Heterocyclic Chemistry at a Glance*; Wiley: 2012; pp 180−194.

(115) Shen, X.; Harms, K.; Marsch, M.; Meggers, E. A rhodium catalyst superior to iridium congeners for enantioselective radical amination activated by visible light. *Chem. - Eur. J.* **2016**, *22*, 9102−9105.

(116) Huang, X.; Webster, R. D.; Harms, K.; Meggers, E. Asymmetric catalysis with organic azides and diazo compounds initiated by photoinduced electron transfer. *J. Am. Chem. Soc.* **2016**, *138*, 12636−12642.

(117) Wenger, O. S. Proton-Coupled Electron Transfer with Photoexcited Metal Complexes. *Acc. Chem. Res.* **2013**, *46*, 1517−1526.

(118) Gentry, E. C.; Knowles, R. R. Synthetic Applications of Proton-Coupled Electron Transfer. *Acc. Chem. Res.* **2016**, *49*, 1546−1556.

(119) Zhou, Z.; Li, Y.; Han, B.; Gong, L.; Meggers, E. Enantioselective catalytic β-amination through proton-coupled electron transfer followed by stereocontrolled radical−radical coupling. *Chem. Sci.* **2017**, *8*, 5757−5763.

(120) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 2056−2071.

(121) Wang, C.; Harms, K.; Meggers, E. Catalytic asymmetric C− H functionalization under photoredox conditions by radical trans-

location and stereocontrolled alkene addition. *Angew. Chem., Int. Ed.* **2016**, *55*, 13495−13498.

(122) Zhang, C.; Chen, S.; Ye, C. X.; Harms, K.; Zhang, L.; Houk, K.; Meggers, E. Asymmetric Photocatalysis by Intramolecular Hydrogen-Atom Transfer in Photoexcited Catalyst−Substrate Complex. *Angew. Chem.* **2019**, *131*, 14604−14608.

(123) Huang, X.; Luo, S.; Burghaus, O.; Webster, R. D.; Harms, K.; Meggers, E. J. C. s. Combining the catalytic enantioselective reaction of visible-light-generated radicals with a by-product utilization system. *Chem. Sci.* **2017**, *8*, 7126−7131.

(124) Chen, W.; Liu, Z.; Tian, J.; Li, J.; Ma, J.; Cheng, X.; Li, G. Building Congested Ketone: Substituted Hantzsch Ester and Nitrile as Alkylation Reagents in Photoredox Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 12312−12315.

(125) Nakajima, K.; Nojima, S.; Nishibayashi, Y. Nickel- and Photoredox-Catalyzed Cross-Coupling Reactions of Aryl Halides with 4-Alkyl-1,4-dihydropyridines as Formal Nucleophilic Alkylation Reagents. *Angew. Chem., Int. Ed.* **2016**, *55*, 14106−14110.

(126) de Assis, F. F.; Huang, X.; Akiyama, M.; Pilli, R. A.; Meggers, E. Visible-Light-Activated Catalytic Enantioselective *β*-Alkylation of *α,β*-Unsaturated 2-Acyl Imidazoles Using Hantzsch Esters as Radical Reservoirs. *J. Org. Chem.* **2018**, *83*, 10922−10932.

(127) Kuang, Y.; Wang, K.; Shi, X.; Huang, X.; Meggers, E.; Wu, J. Asymmetric Synthesis of 1, 4-Dicarbonyl Compounds from Aldehydes by Hydrogen Atom Transfer Photocatalysis and Chiral Lewis Acid Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 16859−16863.

(128) Ma, J.; Rosales, A. R.; Huang, X.; Harms, K.; Riedel, R.; Wiest, O.; Meggers, E. Visible-light-activated asymmetric *β*-C−H functionalization of acceptor-substituted ketones with 1, 2-dicarbonyl compounds. *J. Am. Chem. Soc.* **2017**, *139*, 17245−17248.

(129) Sarkar, D.; Bera, N.; Ghosh, S. [2 + 2] Photochemical Cycloaddition in Organic Synthesis. *Eur. J. Org. Chem.* **2020**, *2020*, 1310−1326.

(130) Hu, N.; Jung, H.; Zheng, Y.; Lee, J.; Zhang, L.; Ullah, Z.; Xie, X.; Harms, K.; Baik, M. H.; Meggers, E. Catalytic Asymmetric Dearomatization by Visible-Light-Activated [2+ 2] Photocycloaddition. *Angew. Chem., Int. Ed.* **2018**, *57*, 6242−6246.

(131) Huang, X.; Li, X.; Xie, X.; Harms, K.; Riedel, R.; Meggers, E. Catalytic asymmetric synthesis of a nitrogen heterocycle through stereocontrolled direct photoreaction from electronically excited state. *Nat. Commun.* **2017**, *8*, 2245.

(132) Huang, X.; Lin, J.; Shen, T.; Harms, K.; Marchini, M.; Ceroni, P.; Meggers, E. Asymmetric [3+ 2] Photocycloadditions of Cyclopropanes with Alkenes or Alkynes through Visible-Light Excitation of Catalyst-Bound Substrates. *Angew. Chem., Int. Ed.* **2018**, *57*, 5454−5458.

(133) Muller, T. J. J.; Arevalo, M. J.; Alavijeh, N. S. *Science of synthesis*; Georg Thieme Verlag KG: Stuttgart, 2014.

(134) Ma, J.; Xie, X.; Meggers, E. Catalytic Asymmetric Synthesis of Fluoroalkyl-Containing Compounds by Three-Component Photoredox Chemistry. *Chem. - Eur. J.* **2018**, *24*, 259−265.

(135) Zhang, C.; Gao, A. Z.; Nie, X.; Ye, C.-X.; Ivlev, S. I.; Chen, S.; Meggers, E. Catalytic *α*-Deracemization of Ketones Enabled by Photoredox Deprotonation and Enantioselective Protonation. *J. Am. Chem. Soc.* **2021**, *143*, 13393−13400.

(136) Saha, D.; Bagchi, S.; Sharma, A. Metal-catalyzed synthesis of cyclic imines: a versatile scaffold in organic synthesis. *Chem. Heterocycl. Compd.* **2018**, *54*, 302−313.

(137) Iwanejko, J.; Wojaczyńska, E. Cyclic imines − preparation and application in synthesis. *Org. Biomol. Chem.* **2018**, *16*, 7296−7314.

(138) Davies, J.; Booth, S. G.; Essafi, S.; Dryfe, R. A. W.; Leonori, D. Visible-Light-Mediated Generation of Nitrogen-Centered Radicals: Metal-Free Hydroimination and Iminohydroxylation Cyclization Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 14017−14021.

(139) Jiang, H.; Studer, A. Iminyl-Radicals by Oxidation of *α*-Iminooxy Acids: Photoredox-Neutral Alkene Carboimination for the Synthesis of Pyrrolines. *Angew. Chem., Int. Ed.* **2017**, *56*, 12273−12276.

(140) Rodríguez, R. I.; Mollari, L.; Alemán, J. Light-Driven Enantioselective Synthesis of Pyrroline Derivatives by a Radical/Polar Cascade Reaction. *Angew. Chem., Int. Ed.* **2021**, *60*, 4555−4560.

(141) Francke, R.; Little, R. D. Redox catalysis in organic electrosynthesis: basic principles and recent developments. *Chem. Soc. Rev.* **2014**, *43*, 2492−2521.

(142) Jiang, Y.; Xu, K.; Zeng, C. Use of electrochemistry in the synthesis of heterocyclic structures. *Chem. Rev.* **2018**, *118*, 4485−4540.

(143) Waldvogel, S. R.; Lips, S.; Selt, M.; Riehl, B.; Kampf, C. J. Electrochemical arylation reaction. *Chem. Rev.* **2018**, *118*, 6706−6765.

(144) Wiebe, A.; Gieshoff, T.; Möhle, S.; Rodrigo, E.; Zirbes, M.; Waldvogel, S. R. Electrifying organic synthesis. *Angew. Chem., Int. Ed.* **2018**, *57*, 5594−5619.

(145) Yoshida, J.-i.; Kataoka, K.; Horcajada, R.; Nagaki, A. Modern strategies in electroorganic synthesis. *Chem. Rev.* **2008**, *108*, 2265−2299.

(146) Sauermann, N.; Meyer, T. H.; Qiu, Y.; Ackermann, L. Electrocatalytic C−H Activation. *ACS Catal.* **2018**, *8*, 7086−7103.

(147) Ghosh, M.; Shinde, V. S.; Rueping, M. A review of asymmetric synthetic organic electrochemistry and electrocatalysis: concepts, applications, recent developments and future directions. *Beilstein J. Org. Chem.* **2019**, *15*, 2710−2746.

(148) Chang, X.; Zhang, Q.; Guo, C. Asymmetric Electrochemical Transformations. *Angew. Chem., Int. Ed.* **2020**, *59*, 12612−12622.

(149) Huang, X.; Zhang, Q.; Lin, J.; Harms, K.; Meggers, E. Electricity-driven asymmetric Lewis acid catalysis. *Nat. Catal.* **2019**, *2*, 34−40.