Showcasing research from Professor Rakesh K. Saunthwal's laboratory, Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee, Uttarakhand, India.

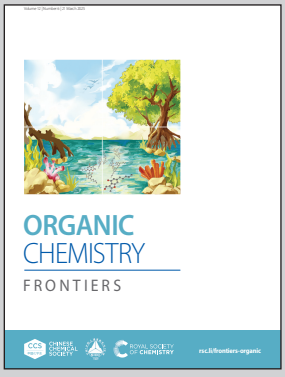
Cooperative iridium and organocatalysis: a new frontier in asymmetric chemistry

Cooperative iridium–organocatalysis has become an essential approach for synthesizing biologically active chiral molecules using readily available starting materials. Iridium metal catalysts have been effectively combined with a diverse range of organocatalysts, including Brønsted acids, Lewis bases, N-heterocyclic carbene catalysts, and even phase transfer catalysts.

Image reproduced by permission of Divakar Chaudhary, *Org. Chem. Front.*, 2025, **12**, 2025.

Photograph taken by Divakar Chaudhary.

As featured in:



See Divakar Chaudhary and Rakesh K. Saunthwal, *Org. Chem. Front.*, 2025, **12**, 2025.

CCS 中国化学会 CHINESE CHEMICAL SOCIETY
SIOC 1950
ROYAL SOCIETY OF CHEMISTRY
rsc.li/frontiers-organic

ORGANIC CHEMISTRY FRONTIERS

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2025, **12**, 2025

Cooperative iridium and organocatalysis: a new frontier in asymmetric chemistry

Divakar Chaudhary and Rakesh K. Saunthwal *

Received 27th December 2024,
Accepted 24th January 2025

DOI: 10.1039/d4qo02430c

rsc.li/frontiers-organic

The cooperative catalyst approach has become a significant and burgeoning area in synthetic organic chemistry, garnering substantial attention from the scientific community in recent years. Unlike single metal catalysts or organocatalysts, the cooperative catalysis strategy enables previously unattainable transformations to be accomplished in a stereocontrolled manner with high efficiency. In particular, cooperative iridium–organocatalysis has emerged as a valuable tool for producing biologically active chiral molecules from easily accessible starting materials. Iridium metal catalysts have been effectively combined with a diverse range of organocatalysts, including Brønsted acids, Lewis bases, N-heterocyclic carbene catalysts, and even phase transfer catalysts. This review provides a comprehensive overview of this evolving field, encompassing reaction advancements and mechanistic insights, to offer readers a better understanding of how metal–organic catalysts influence reaction mechanisms and the suitable starting materials for each catalytic process.

1. Introduction

The cooperative catalysis approach has advanced over the last two decades as an enabling strategy in chemical transformation.[1] Transition metal and organocatalysts work together to

Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee, Uttarakhand 247667, India. E-mail: rakesh.saunthwal@cy.iitr.ac.in

Divakar Chaudhary

Divakar Chaudhary was born in 1999 in Basti (UP), India. He completed his B.Sc. (Hons.) degree in chemistry from Banaras Hindu University, Varanasi, India and pursued his Master's degree in chemistry from the Indian Institute of Technology Kanpur, India. At present, he is a doctoral student in Prof. Rakesh Kumar Saunthwal's group at the Department of Chemistry, Indian Institute of Technology, Roorkee, India. His current research primarily centers on Asymmetric C–C bond formation by metal–organo cooperative catalysis.

Rakesh K. Saunthwal

Rakesh K. Saunthwal was born in Rooppura Sikar (Rajasthan), India. He completed his master's at the University of Rajasthan, India. Then, he pursued his doctoral studies at the University of Delhi (India) under the guidance of Prof. Akhilesh K. Verma. Following his Ph.D., he held positions as a SERB Overseas postdoctoral fellow and Marie Curie Postdoctoral fellow in Prof. Jonathan Clayden's Lab at the University of Bristol, U.K. Subsequently, he relocated to Illinois to join Professor Scott E. Denmark's group at the University of Illinois at Urbana Champaign, USA (UIUC), as a Postdoctoral Research Associate. In 2023, he returned to India and became an Assistant Professor at IIT (BHU). Currently, he serves as an Assistant Professor at the Department of Chemistry, Indian Institute of Technology Roorkee, India. His research interests encompass asymmetric synthesis, catalysis, and reaction methodology.

activate inert coupling partners, leading to the creation of a new compound class.[2,3] Recent advancements in this field highlight the use of dual catalysis,[4] where two different catalysts act on distinct substrates to enable a reaction between two activated intermediates.[5–7] Cooperative catalysis utilizes both single and dual catalytic cycles. Single-cycle activation involves two catalysts activating substrates A and B in one cycle to enhance the reaction rate. In the dual cycle, different catalysts simultaneously activate both substrates in separate catalytic cycles.[8]

In the dual catalysis approach, both catalysts are placed in close proximity to substrates to form active sites containing electrophilic and nucleophilic centers in the reaction system.[9,10] The collaboration of catalysts presents a perceived challenge in terms of kinetics. It might seem initially that the reaction between two catalytic intermediates present in low sub-stoichiometric concentrations would be inherently difficult. However, this assumption overlooks a crucial aspect of the rate equation – the rate constant k. In the case of the reaction between two activated intermediates, lowering the HOMO–LUMO gap in cooperative catalysis leads to a significant decrease in the activation energy. Consequently, this increase in the rate constant drives the desired pathway, favoring it over possible side reactions (Fig. 1).[8,11,12]

In the field of synthetic organic chemistry, organocatalysis has emerged as an innovative domain alongside transition metal catalysis for selectively building C–C and C–X bonds.[13–15] When transition metals are combined with organocatalysts, the resulting catalytic system becomes more reactive, leading to the formation of new C–C and C–X bonds.[16] In the past, transition metal–metal Lewis acids were used in the dual catalytic approach.[17–20] However, the combination of transition metal and organocatalysts gained more popularity in asymmetric synthesis compared to the combination of two different metal catalysts. This preference is attributed to the redox compatibility of different metal catalysts and the balanced kinetics of the two catalytic cycles.[2,21,22]

Previously, many researchers have explored the use of various chiral organocatalysts,[23] including Brønsted acids, Brønsted bases, Lewis bases, and phase transfer catalysts, in combination with different transition metals to collaboratively introduce a new chiral center at an achiral carbon. Cooperative catalysis offers several advantages over traditional catalytic approaches, such as improved selectivity, broader substrate applicability, cost reduction, and enhanced catalytic efficiency. As a result, it has been receiving increasing attention in the field.[21,24]

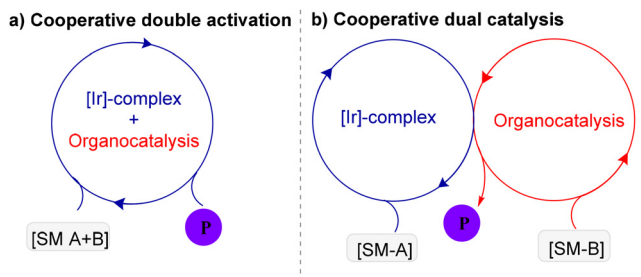


Fig. 1 Cooperative catalytic cycles.

In the early stages, the iridium catalyst was utilized in collaboration with a Brønsted acid. Later on, its application was extended to include cooperation with Lewis bases such as amino catalysts, N-heterocyclic carbenes, and isothiourea catalysts, as well as phase transfer catalysts. Over the past two decades, it has become widely utilized as a photocatalyst also.[25] For a successful cooperative catalytic cycle, iridium activates the [SM-**A**], and organocatalysts activate [SM-**B**] in a selective manner; otherwise, high reactivity and energy of the intermediate encourage the decomposition of the starting substrate or promote the side reaction, which diminishes the reaction efficacy and efficiency.[26]

In view of the significant role played by transition metal and organocatalysts in the context of synergistic catalysis, this review seeks to present an overview of the latest primary literature up until November 2024, focusing on the integration of synergistic dual catalysis and cooperative double activation, specifically involving iridium metal in combination with various organocatalysts. So far, all reviews have focused on either metal–metal cooperative catalysis or the use of specific organocatalysts alongside various metal catalysts for organic transformations. This review focuses specifically on one metal along with a selection of organocatalysts that remain to be explored. The emphasis will be on examining catalyst pairing, elucidating their proposed catalytic cycles, and highlighting notable instances of innovative transformation.

2. Combination of iridium and Brønsted acid

Brønsted acid catalysis has a rich history and remains one of the most widely utilized forms of catalysis in asymmetric organic transformations. It has been a cornerstone of the field for centuries, offering significant opportunities for advancing organic synthesis.[27–30] Over the past two decades, researchers have increasingly combined Brønsted acids and transition metals to activate different substrates[31] in organic synthesis. Notably, BINOL-derived Brønsted acid has been employed as a synergistic catalyst alongside metals such as Ag, Au, Pd, Rh, Ru, and Ir in asymmetric chemistry, yielding promising results in this field.[32]

In the realm of catalysts, the pairing of iridium catalyst with Brønsted acids, specifically BINOL phosphoric acid (**B*H-1** to **B*H-3** and **B*H-7**), spirocyclic phosphoric acid (**B*H-4** and **B*H-5**), and biphenyl phosphoric acid (**B*H-6**), has shown promise as a cooperative catalyst in driving asymmetric transformations (Fig. 2).

In 2008, the Xiao group initially investigated the use of an iridium catalyst in conjunction with a BINOL-phosphate anion as a synergistic catalyst for the asymmetric hydrogenation of acyclic amine,[33] by using chiral phosphate anion (1.0 mol%)

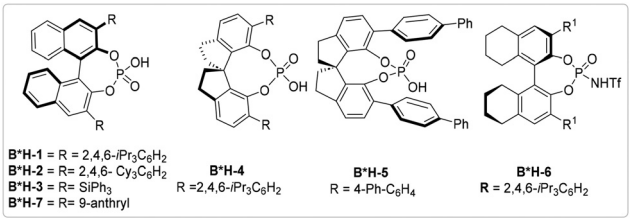
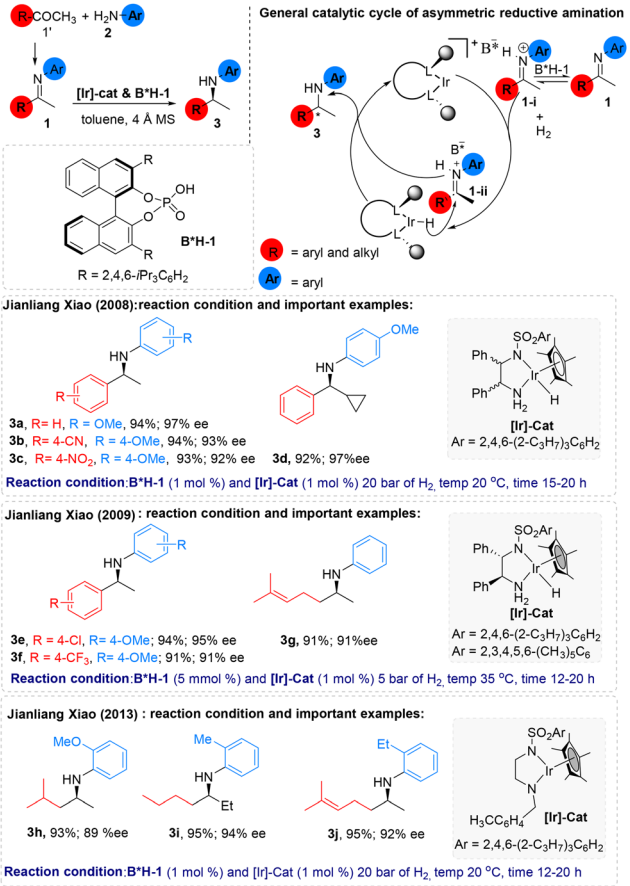


Fig. 2 Brønsted acid catalysts used with Ir-catalyst.

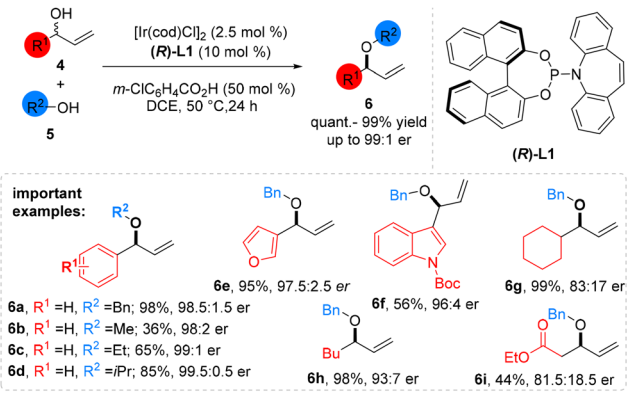
and diamine-ligated iridium catalyst in the presence of 20 bar H_2 pressure. By applying this protocol, a wide range of imines (**1**) can be efficiently hydrogenated, consistently yielding high product yields and impressive enantiomeric excess. In 2009, Xiao advanced the reductive amination approach by incorporating ketones (**1′**) and amines (**2**) as starting materials within a similar type of catalytic system.[34] A broad range of substituted aromatic and aliphatic ketones were rapidly aminated in this reaction, exhibiting high yields and enantiomeric excess. Mechanistically, imines are generated *in situ* or can be isolated from ketones **1′** and amines **2** by a condensation reaction; the reduction of imines **1** is initiated by an ionic pathway using chiral phosphoric acid to form transient iminium cation **1-ii**, which gives reduced amine product through enantioselective hydride transfer from iridium hydride complex by the facial attack. In 2013, the Xiao group built on the 2009 mechanistic hypothesis and revealed that combining an achiral [Ir]-catalyst with chiral phosphoric acid has produced a catalyst that enables highly enantioselective hydrogenation of both aliphatic and aromatic imines, achieving impressive enantiopurity.[35] These findings indicated that chiral phosphoric acids have the potential to induce high enantioselectivity through hydride transfer from achiral organo-hydride donors to imines (Scheme 1).

In a similar vein to Xiao's hypothesis, the Carreira group has developed an effective method for allylic etherification using a chiral ligand-enabled iridium complex and a Brønsted acid as a cooperative catalyst. This method demonstrates efficient coupling of two different alcohols in an enantioselective manner. By employing the widely available aliphatic alcohol **5** as the nucleophile and the branched allylic alcohol **4** as the electrophile, they achieved the asymmetric production of allylic ether **6** in high yield with up to 99% enantiomeric excess (Scheme 2).[36]

In 2014, Zhao's group explored the amination of alcohol by using iridium and chiral phosphoric acid catalysts. The amination of alcohols has been achieved by using the borrowing hydrogen methodology (also recognised as the hydrogen autotransfer process). In this methodology, enantioselective production of secondary amines occurs by alcohol (**7**) and aniline substrate (**2**) in the presence of cooperative iridium and chiral phosphoric acid catalyst (**B*H-1**). Three mechanistic steps are involved in this approach: dehydrogenation of alcohol (**7**) to the corresponding ketone (**1′**), followed by the keto-amine condensation to give iminium ion (**1-i**); in the final step, imine



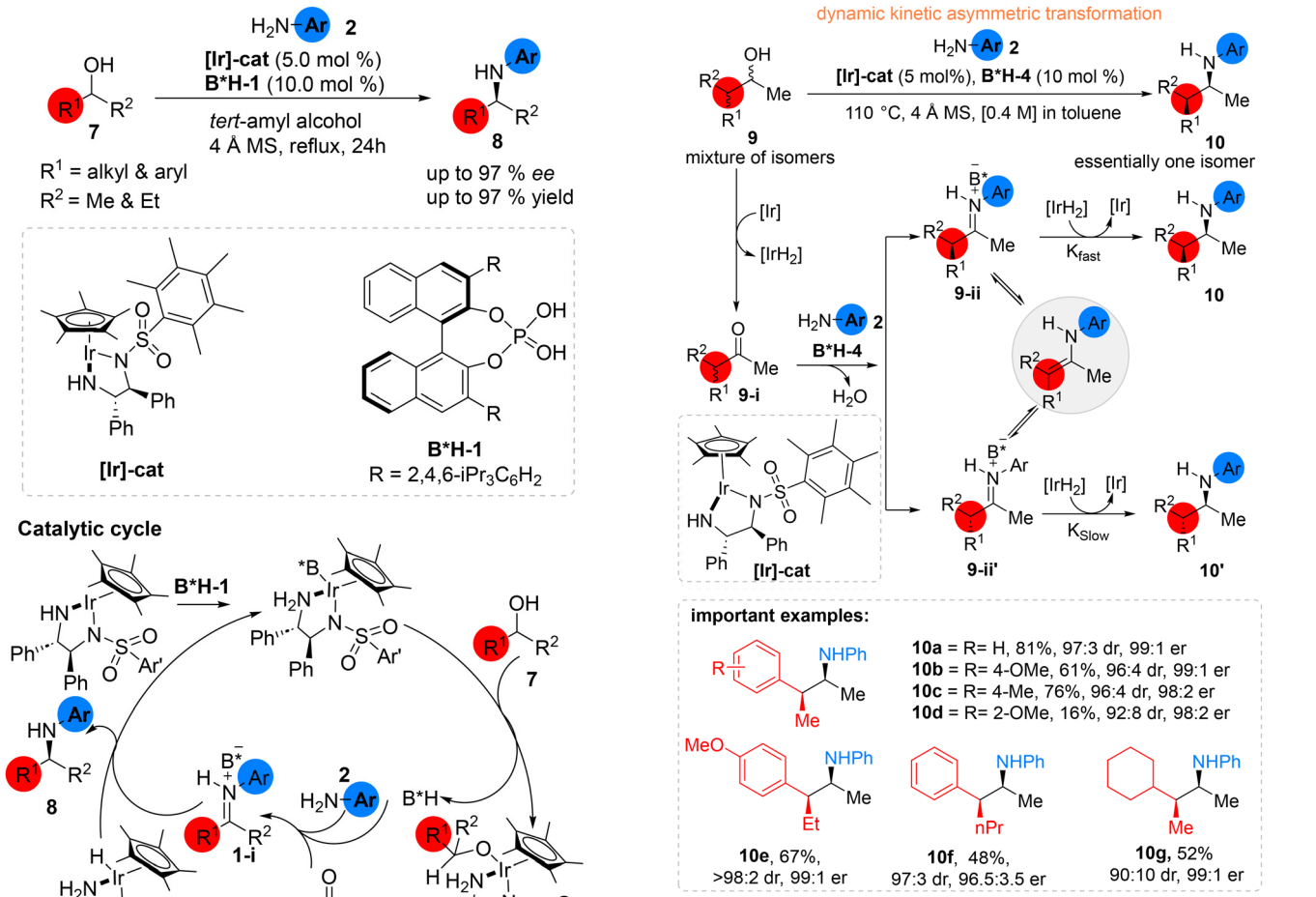
Scheme 1 Asymmetric reductive amination.



Scheme 2 Enantioselective allylic etherification.

hydrogenation and employing the alcohol as the H_2 donor. This method demonstrates good tolerance to electron-donating and withdrawing groups on various alcohols and aniline substrates (Scheme 3).[37]

Zhao group utilized a synergistic dual catalyst to expand the concept of amination for α-branched alcohols **9** through dynamic kinetic asymmetric transformation (DYKAT). The enantioenriched amine product **10** was obtained from both



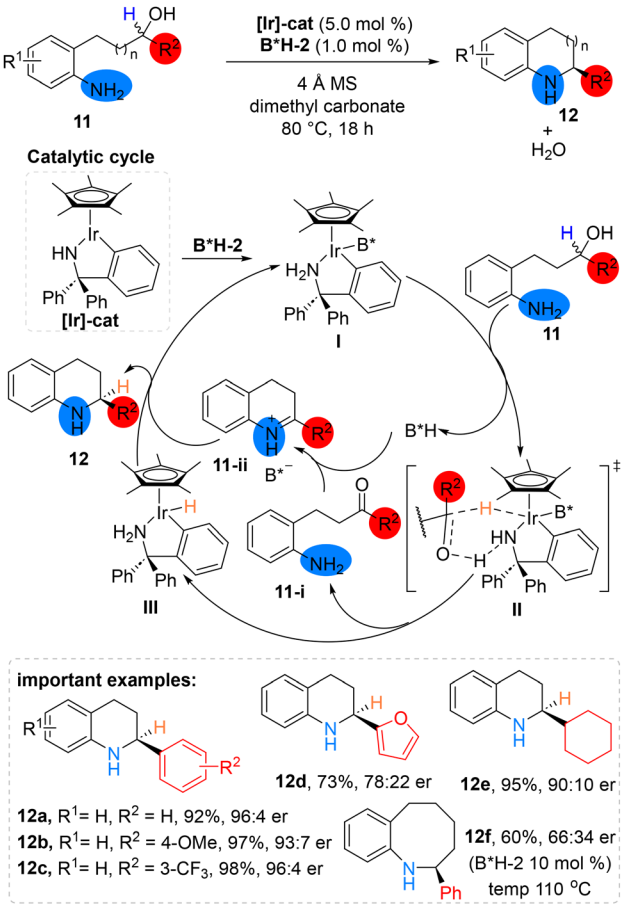
Scheme 4 Amination of α-branched alcohols by dynamic kinetic asymmetric transformation.

Scheme 3 Enantioselective amination of alcohols using borrowing hydrogen methodology.

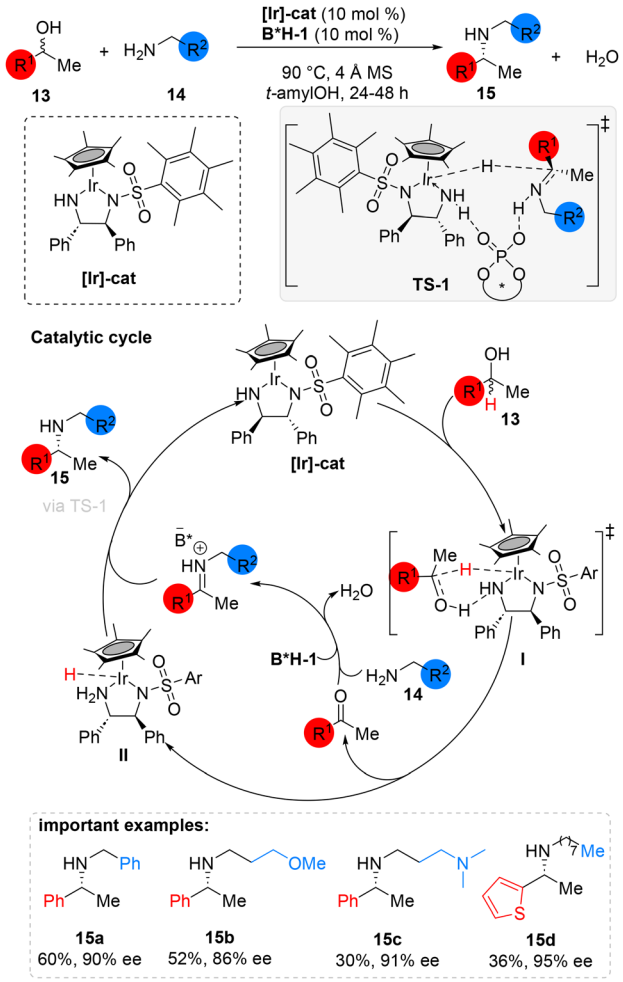
enantiomers of racemic branched alcohol through a series of steps: oxidation of the alcohol (**9-i**), iminium ion formation (**9-ii**) *via* keto-amine condensation, followed by the enantioselective reduction of the iminium ion (Scheme 4).[38]

In 2017, Zhao group further extended the borrowing hydrogen idea for enantioenriched tetrahydroquinolines **12** synthesis. In this procedure, chiral phosphoric acid (**B*H-2**) and Ir-complex are used as a cooperative catalyst to facilitate the enantioselective intramolecular cyclization of amino alcohol **11** in dimethyl carbonate solvent to afford the 2-substituted tetrahydroquinolines **12.** The interaction between the Ir-catalyst and chiral phosphoric acid **B*H-2** likely leads to the formation of complex **I.** This complex then reacts with the amino alcohol **11**, resulting in the production of the amino ketone intermediate **11-i** and iridium hydride **III** through a concerted transition state **11-i.** In this reaction, alcohol functions as the H_2 donor; this technique exploits three concurrent reactions: oxidation (**11-i**), condensation (**11-ii**), and reduction (**12**) without needing any additional reductant or oxidant. In this method, easily accessible racemic amino alcohols are transformed into tetrahydroquinolines in a redox-neutral manner, without requiring any stoichiometric reagents. Enantioselective hetero-cyclization reaction is well tolerated with electron-donating and electron-withdrawing groups with good yield and high enantioselectivity (Scheme 5).[39]

Following the amination of alcohol by aniline derivatives, the Zhao group further developed the hydrogen borrowing method by incorporating aliphatic amines **14.** This enantio-



Scheme 5 Enantioselective tetrahydroquinolines synthesis *via* intramolecular amination of alcohols.



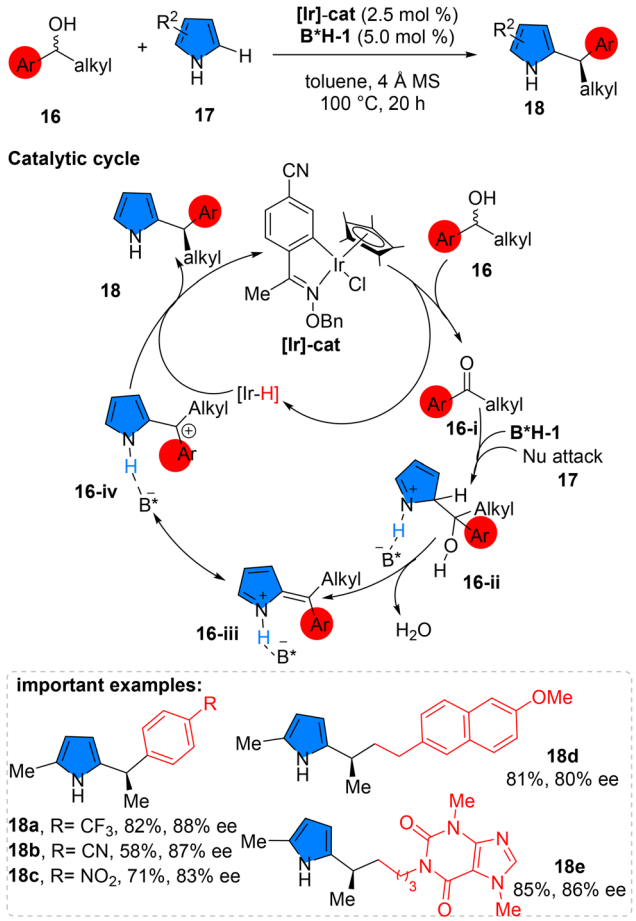
Scheme 6 Enantioconvergent amination of alcohols using aliphatic amines.

enriched amination reaction demonstrated remarkable versatility with both alcohols and aliphatic primary amines. Alongside the previously suggested mechanistic pathway for the amination reaction, a new transition state mode, **TS-1**, has been proposed to account for the stereochemical outcome of the reduction step of the iminium ion intermediate (Scheme 6).[40]

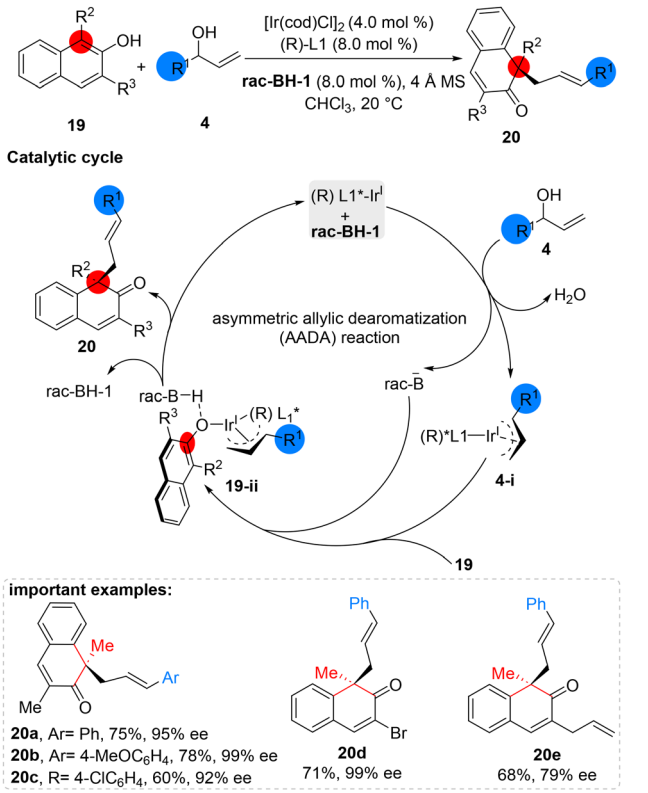
Upon investigating the potential of amines as a reactive nucleophile in conjunction with alcohols within the hydrogen borrowing technique, the Zhao group expanded this approach to enable the arylation of alcohols utilizing pyrrole **17** as a nucleophile. Similar to the amination process, the proposed mechanism commences with the dehydrogenation of alcohol **16**, generating ketone **16-i** and iridium hydride species. Subsequently, the acid-promoted nucleophilic addition of pyrrole results in the formation of the acid-bound tertiary alcohol **16-ii**, which further transforms into species **16-iii** through dehydration. Eventually, enantioselective hydride transfer from iridium hydride species produces the enantiopure arylated product **18**. Zhao's group investigated a cost-effective and redox-neutral process using various substituted pyrroles (**17**). They found that secondary aryl–alkyl alcohols with *ortho*-, *para*-, and *meta*-positions containing electron-donating and withdrawing groups were well-tolerated. This resulted in the production of products with high enantioselectivity and good yield (Scheme 7).[41]

In 2017, Zhong developed an extremely selective system for the allylic dearomatization of naphthol (**19**) by combining an Ir-catalyst and BINOL phosphoric acid (*rac*-**BH-1**). The system showed great tolerance towards aromatic groups with both electron-rich and electron-deficient substituents on the *ortho*-, *meta*-, or *para*-positions of the allyl alcohols, resulting in products with excellent enantioselectivities. The experimental results suggest that the chiral iridium complex and acid promoter *rac*-**BH-1** react with allylic alcohol **4** to produce an Ir-π-allyl intermediate (**4-i**), while naphthol deprotonation and naphtholate react with the Ir-allyl intermediate to form the key intermediate **19-ii**. Subsequently, the asymmetric allylic dearomatization proceeds through enantioselective nucleophilic addition of the allyl intermediate, ultimately yielding the desired products **20** (Scheme 8).[42]

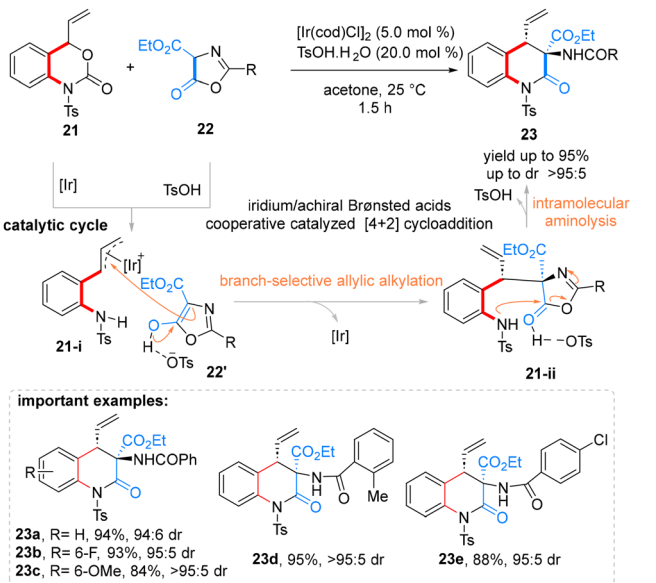
Over the past five years, researchers have not only employed chiral phosphoric acid as a cooperative catalyst with iridium



Scheme 7 Stereoconvergent heteroarylation of alcohols.



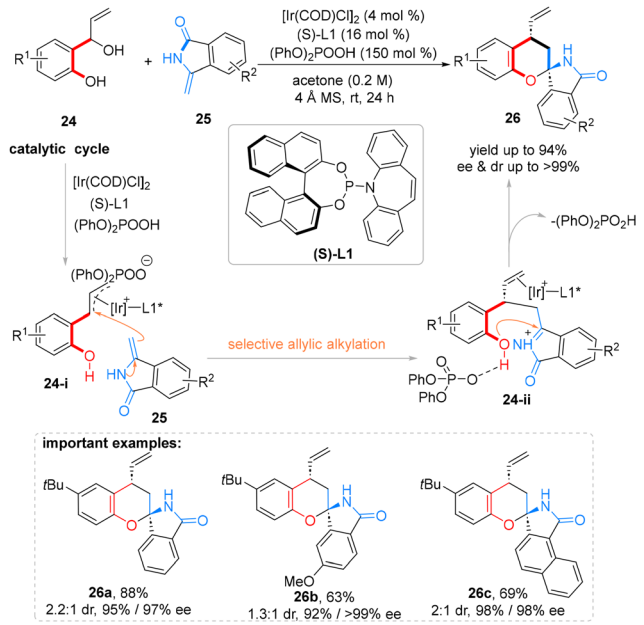
Scheme 8 Asymmetric allylic dearomatization of naphthol derivatives.



Scheme 9 Stereoselective reactions of vinyl benzoxazinones with azlactones.

but have also utilized achiral Brønsted acids in conjunction with iridium-catalysts for asymmetric synthesis. For instance, the Shi group has successfully used $[Ir(cod)Cl]_2$ and $TsOH{\cdot}H_2O$ Brønsted acid to achieve stereoselective reactions of vinyl benzoxazine **21** with azlactones **22**. In this process, the iridium catalyst promotes the decarboxylation of vinyl benzoxazinanones **21**, leading to the formation of π-allyl-Ir intermediate (**21-i**), while the Brønsted acid $TsOH{\cdot}H_2O$ triggers the enolization of azlactones (**22′**) *via* hydrogen bonding interaction. The combination of these two active species (**21-i** and **22′**) results in the production of the chiral 3,4-dihydroquinolin-2-one **23** through a [4 + 2] mode, regenerating the Ir-catalyst and TsOH acid in the process. This method has demonstrated high selectivity across a wide range of substituted azlactones and vinyl benzoxazinanones, yielding selectivity levels of up to 95 : 5 dr (Scheme 9).[43]

Following in the footsteps of Shi's work, Liu described a cooperative approach for producing enantioselective spiro-*N*,*O*-ketals by asymmetric [4 + 2] cycloaddition of 2-(1-hydroxyallyl) phenols and exocyclic enamides using $[Ir(cod)Cl]_2$ and $(PhO)_2POOH$. The formation of the Ir-π-allyl complex **24-i** by dehydration is the first step in the reaction mechanism. Nucleophilic enamine **25** then attacks the Ir-π-allyl complex to generate an iminium ion intermediate (**24-ii**). Eventually, the enantioenriched product **26** was produced by the spirocyclic ring closure. This strategy is shown for a wide class of enamides that have the phenyl moiety substituted at C2, C3, C4, or



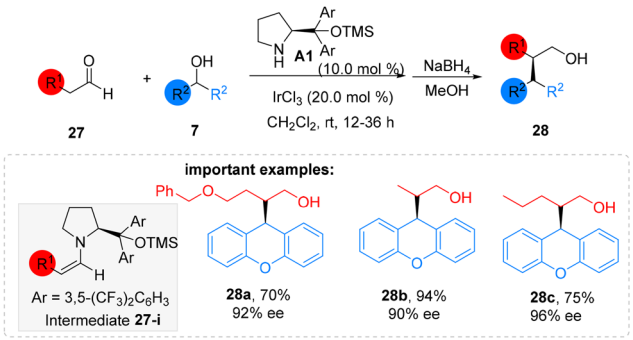
Scheme 10 Spiroketalization by cooperative catalysis.

C5 with groups that donate or withdraw electrons, as well as 2-(1-hydroxyallyl)phenols that have methoxy, bromo, and trifluoromethoxy groups at the C4 position of the aryl ring. This results in the production of distinct, well-yielding, high enantioenriched chromane-2,1′-isoindolins (Scheme 10).[44]

3. Combination of iridium and Lewis base

In recent decades, nucleophilic Lewis base organocatalysts have emerged as a promising and versatile tool in synthetic organic chemistry. N-heterocyclic carbene (NHC)[45,46] and tertiary amine[47] catalysts are commonly used examples, possessing a pair of nonbonding electrons.[48,49] Initially, the Cordova group[50] explored the use of a nucleophilic Lewis base catalyst in conjunction with palladium as a cooperative catalyst. Subsequently, various metals including Zn, Cu, Y, Au, In, Rh, Ru, and Ir have been employed with different Lewis bases.[51–54] In recent reports, authors used Brønsted acid with Lewis base catalyst as an additive to activate allyl substrate in the reaction process, which aids in the production of the Ir-π-allyl complex and its counter ion also aids in stabilizing the Ir-π-allyl complex. This section provides a summary of the recent applications of amine[6] and N-heterocyclic carbene (NHC) catalysts with iridium metal as a synergistic catalyst.

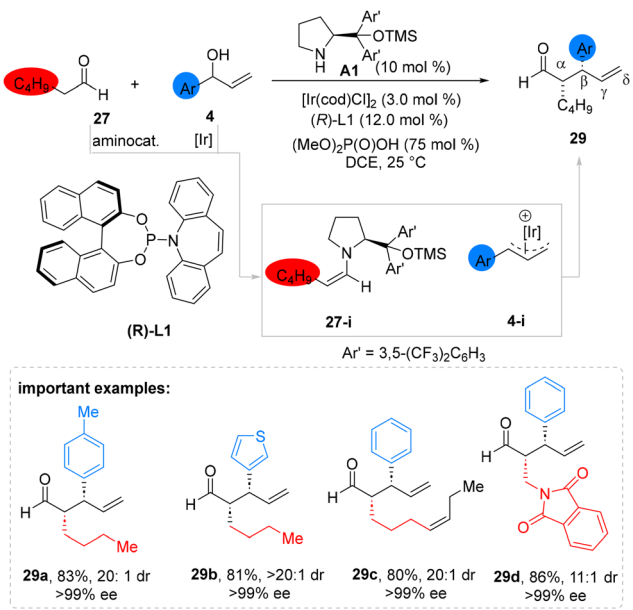
In 2012, Jian Xiao developed a highly selective method for combining $IrCl_3$ and a chiral diarylprolinol silyl ether catalyst **A1** to perform intermolecular α-alkylation of aldehydes **27**. This approach has proven effective for various bulky, linear aldehydes (**27**) and activated alcohols (**7**), consistently yielding high yield and excellent enantioselectivity (Scheme 11).[55]



Scheme 11 Stereoselective α-alkylation of aldehydes.

Carreira group in 2014 devised a similar dual catalytic method for α-allylation of linear aldehydes by combining iridium catalysis with chiral diarylprolinol silyl ether **A1**, building on Xiao's stereoselective α-alkylation.[55] By reacting aryl vinyl carbinol **4** and hexanal **27** with dimethyl hydrogen phosphate as the promoter and chiral iridium complex and diaryl silyl prolinol ether as cooperative catalysts, excellent enantio- and diastereoselective γ,δ-unsaturated aldehyde (**29**) was produced. Phosphoric acid activates allyl alcohol in the reaction process, which aids in the production of the Ir-π-allyl complex. Phosphoric acid's counter ion also aids in stabilizing the Ir-π-allyl complex, and prolinol ether combines with the carbonyl group in a different pathway to generate an enamine intermediate. Synthesis of (−)-paroxetine demonstrated the synthetic utility of this method (Scheme 12).[56]

The α-allylation process of linear aldehydes with alcohols evolved, and in 2015, the Carreira group expanded this method to include the synthesis of protected α-amino- and α-hydroxy-acetaldehydes (**30** and **31**). With this approach, it is



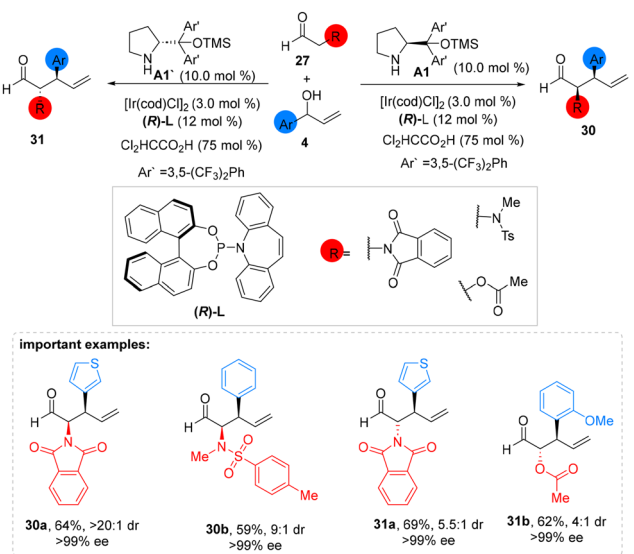
Scheme 12 Stereodivergent α-allylation of linear aldehydes.

also possible to achieve unsaturated product transformation in a stereodivergent way while maintaining the stereochemical integrity at the C-α location to show high selectivity. The reactivity of allylic alcohol **4** with electron-withdrawing substituents is aided by strong acid (trichloroacetic acid), producing compounds (**30** and **31**) with good diastereoselectivity and >99% ee (Scheme 13).[57]

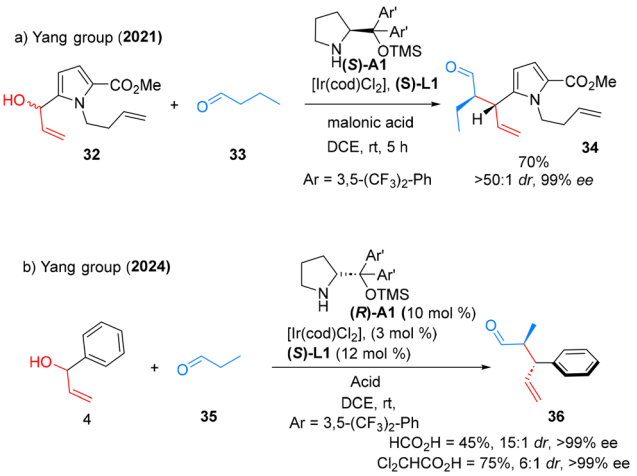
In continuation to Carreira's group, In 2021 Yang group employed Carreira's innovative stereodivergent Ir/amine dual catalysis method to couple pyrrole alcohol **32** and butanal **33**, leading to the intermediates **34** for the bisdehydrotuberostemonine **D** and bisdedydrotuberostemonine **E** synthesis.[58] Recently in 2024, the Yang group again incorporated the same method to develop a branched aldehyde intermediate **36** for (−)-daphenylline synthesis (Scheme 14).[59]

Recent investigations conducted by Carreira's group have successfully demonstrated the compatibility between amino and iridium catalysts. Following this confirmation, the Jørgensen group introduced the pioneering regio- and stereoselective γ-allylation of cyclic α,β-unsaturated aldehydes, achieved through the integration of aminocatalysis and [Ir(cod)Cl]$_2$ catalysis. This reaction proceeds *via* the formation of an enamine (**37-i**) and an Ir-π-allyl complex (**38-i**). Both electron-donating and electron-withdrawing groups having aldehyde and allylic alcohol exhibited favorable performance under standard reaction conditions (Scheme 15).[60]

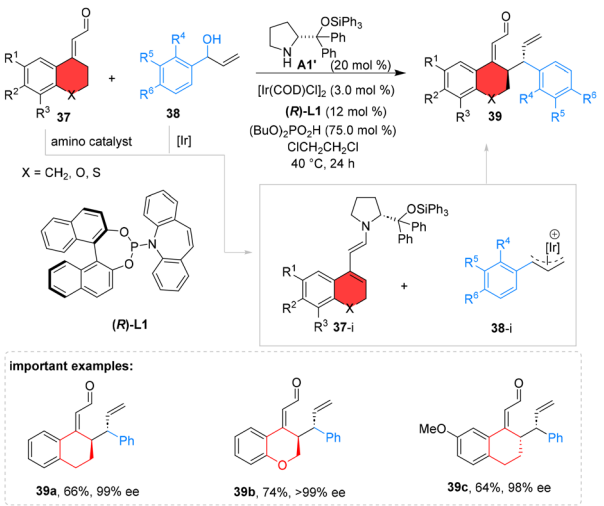
For the exploration of enamine intermediate in a multicomponent reaction (MCR), In 2016, Wenhao Hu revealed a three-component reaction of diazoacetates (**40**), indoles (**41**), and enals (**42**) by co-catalysis of iridium/chiral amine catalyst for the synthesis of the enantioselective 3-substituted indole derivative (**43**). This reaction involves the formation of an [Ir]-carbene intermediate (**40-i**), which then reacts with indole (**41**) to form a zwitterionic intermediate (**41-i**′).



Scheme 13 Stereodivergent α-allylation of protected α-amino- and α-hydroxyacetaldehydes.



Scheme 14 Stereodivergent coupling of alcohol and aldehyde.

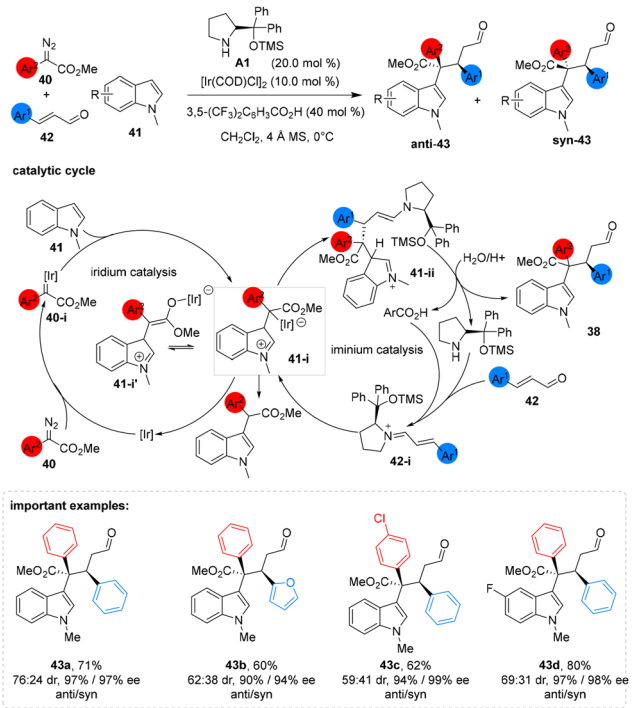


Scheme 15 γ-Allylation of α,β-unsaturated aldehydes.

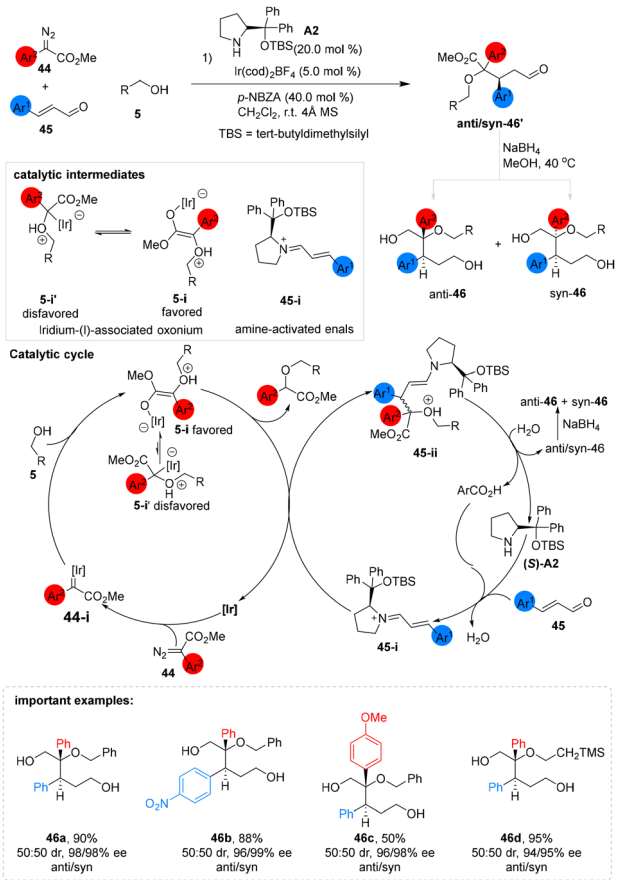
Concurrently, 3,5-bis(trifluoromethyl)benzoic acid accelerates the formation of an iminium ion **42-i**, capturing the zwitterionic intermediate (**41-i**) to produce the enamine **41-ii**. Finally, acidic hydrolysis leads to the desired products (*anti*-**43** and *syn*-**43**) with high diastereoselectivity (Scheme 16).[61]

Liu group successfully replaced the indole (**36**) nucleophile with alcohols (**5**) from Hu's work and developed a one-pot approach to the synthesis of enantioselective 1,2,5-triol (**46**) derivatives with vicinal chiral centers utilizing simple starting materials through the incorporation of a chiral secondary amine with an iridium(I) catalyst and a reducing agent. The reaction mechanism involves iridium-(I)-associated oxonium (**5-i**) and amine-activated enals intermediates (**45-i**) (Scheme 17).[62]

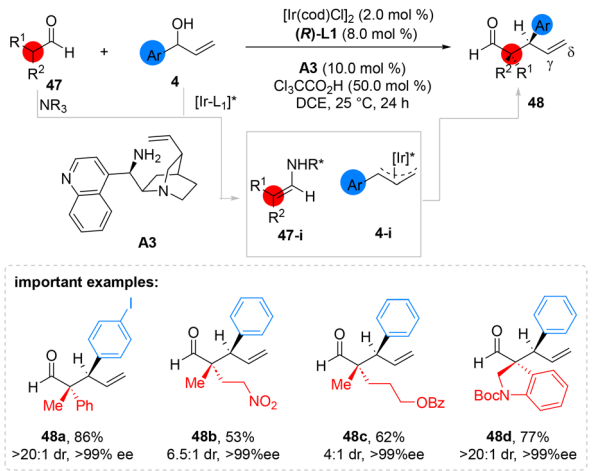
The Carreira group not only employed secondary amine catalysis but also made use of primary amine catalysts in tandem reactions. They successfully synthesized enantioselective γ,δ-unsaturated aldehydes (**48**) by combining allylic alcohol (**4**)



Scheme 16 Asymmetric three-component reaction of diazoacetates with indoles and enals.



Scheme 17 Vicinal chiral centers having 1,2,5-triol derivatives synthesis.

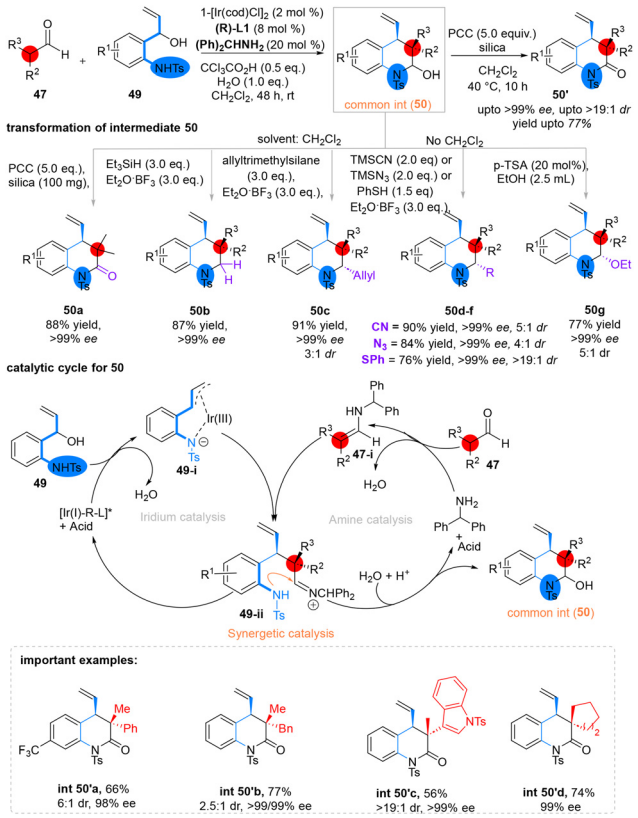


Scheme 18 α-Allylation of branched aldehydes by stereodivergent dual catalysis.

and aldehyde (**47**) using primary amine **A3** and a chiral iridium catalyst under acidic conditions. This approach involved the simultaneous activation of the aldehyde (**47**) and allylic alcohol (**4**) with primary amine and iridium catalysts, respectively, resulting in the formation of the enamine (**47-i**) and Ir-allyl-π complex (**4-i**) (Scheme 18).[63]

A combination of diphenylmethanamine and iridium catalyst enables the [4 + 2] cycloadditions of vinyl amino alcohols (**49**) with aldehydes (**47**) to produce enantioselective dihydroquinolone derivatives **50′** in good yield. Ir-catalyst forms Ir-allyl-π intermediate (**49-i**) by reacting with vinyl amino alcohol (**49**). The carbonyl compound and amine catalyst then condense to produce an enamine intermediate (**47-i**). The hemiacetal **50** is created when intermediate **49-i** and **47-i** are coupled in a [**4** + **2**] manner through intermediate **49-ii.** The Xiao group diversified the hemiaminal intermediate (**50**) into hydroquinolines (**50a**) by oxidation and tetrahydroquinolines (**50b**) by reduction in order to demonstrate the adaptability of the [4 + 2] cycloaddition reaction. Furthermore, the optically active 2-allyl (**50c**), 2-CN (**50d**), and 2-N_3 (**50e**) substituted tetrahydroquinolines could be produced by substituting the hydroxyl group with other organosilicon reagents. Likewise, nucleophiles ending in –SPh (**50f**) and –OEt (**50g**) can take the place of the OH-group (Scheme 19).[64]

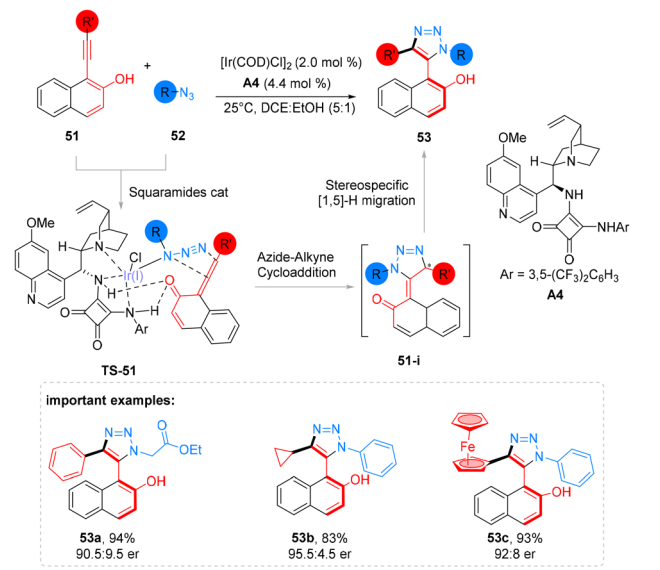
The Xu group used traditional click chemistry to combine the squaramides and Ir-catalysts for the synthesis of axially chiral aryl triazoles. In order to carry out the *atropo*-enantioselective azide–alkyne cycloaddition (AAC) reaction, naturally occurring squaraine organocatalyst and Ir(I) are combined with *ortho*-hydroxy alkenyl naphthalene (**51**) and benzyl azide (**52**). Examining experimental data closely revealed that the metal/organic catalyst combined with the starting materials to create a cycloaddition adduct (**Ts-51**) and then vinylidene



Scheme 19 Synergetic iridium/amine catalysis for the enantioconvergent [4 + 2] cycloadditions.

ortho-quinone methide (VQM) (**51-i**). The atrop-aryltriazoles **53** were then delivered by stereospecific [1,5]-H transfer (Scheme 20).[65]

Recently, the Yang group unveiled an innovative reaction that utilizes both Ir and Brønsted acid catalysis. This method

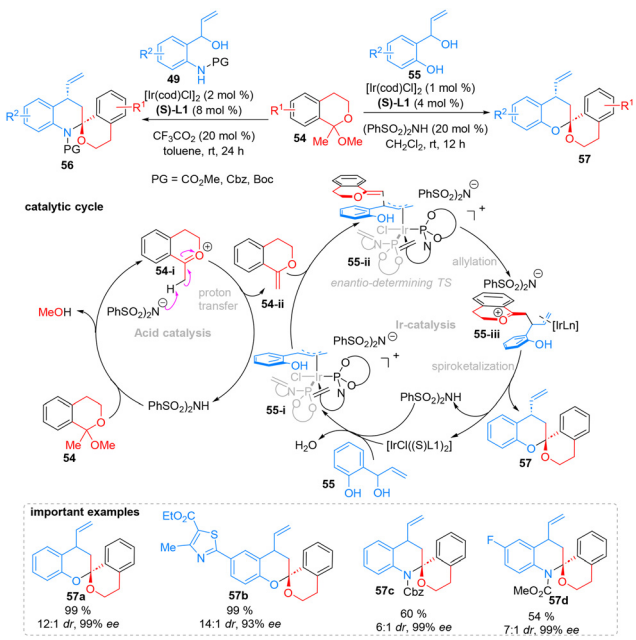


Scheme 20 Asymmetric azide–alkyne cycloaddition reaction for the synthesis of atrop-aryltriazoles.

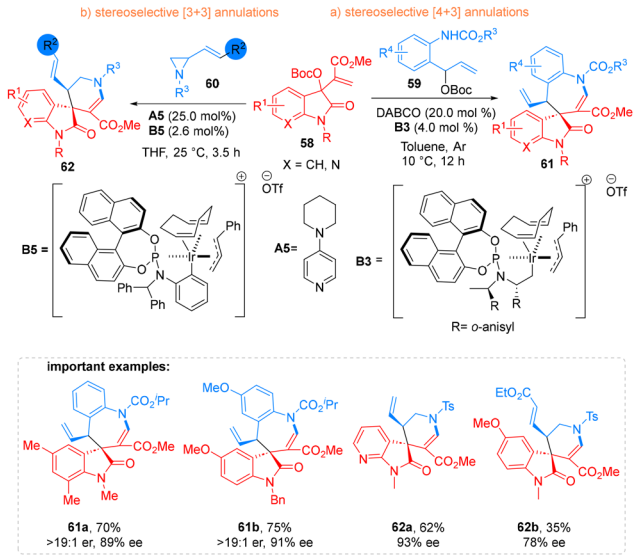
effectively transforms 2-(1-hydroxyallyl)-phenols **55** in conjunction with isochroman ketals **54** into bis-benzannulated spiroketals **57**, achieving remarkable efficiency and selectivity, with diastereomeric ratios reaching up to 17 : 1 and enantiomeric excess surpassing 99%. The process begins with the formation of exocyclic enol ethers (**54-ii**) from isochroman ketals **54**, driven by Brønsted acid catalysis, which is then followed by an Ir-catalyzed enantioselective allylation and spiroketalization of the 2-(1-hydroxyallyl)-phenols **55** (Scheme 21).[66]

Chen *et al.* combined achiral tertiary amine catalysts with iridium complexes to create a cooperative catalytic system in 2019. Stereoselective [4 + 3] annulated spiro compound (**61**) is formed by the chemoselective activation of Morita–Baylis–Hillman carbonate adduct (**58**) and carbamate-functionalized allylic carbonates (**59**) by the chiral iridium complex and DABCO, respectively. An essential development in stereoselective annulation chemistry is the independent activation by metal complexes and organocatalysts, leading to the emergence of two distinct dipole species. Apart from the [4 + 3] cycloaddition, Morita–Baylis–Hillman adducts (**58**) with vinyl aziridines (**60**) in the presence of iridium and tertiary amine catalysts **A5** were also used to demonstrate outstanding regio-, chemo-, and stereoselective [3 + 3] annulation (Scheme 22).[67]

Enantioselective coupling of the α,β-unsaturated carbonyl-derived latent enolate, and metal-induced electrophile discovered by Mukherjee group in 2021 by combining cinchonidine Lewis base **A6** with iridium metal catalyst. In this asymmetric procedure, an olefinic C(sp^2)–H bond is enantioselectively alkylated by linear allylic carbonate (**64**). The reaction is initiated by the activation of the olefinic C(sp^2)–H bond by the Iridium-Feringa's phosphoramidite ligand complex and cou-



Scheme 21 Asymmetric synthesis of bisbenzannulated spiroketals and spiroaminals.



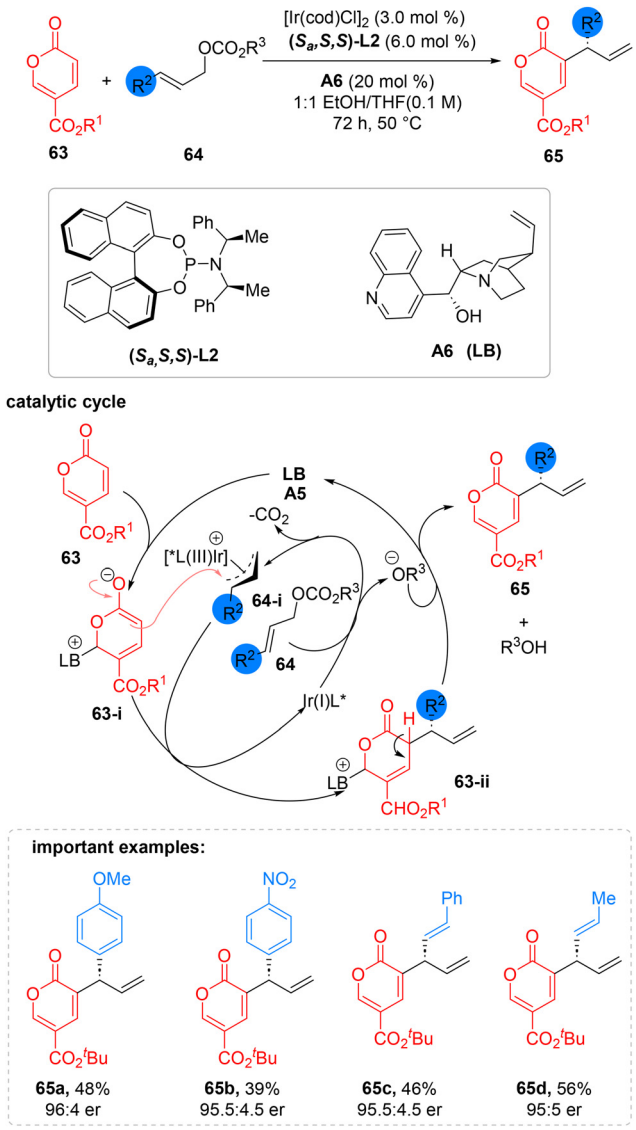
Scheme 22 Regio-, chemo-, and stereoselective [4 + 3] and [3 + 3] cycloaddition reactions.

malate ester (**63**) activated by the cinchonidine catalyst in a cooperative fashion. This method yields cinnamyl carbonates with a wide range of electrically biased substrate compatibility at various aryl ring locations. Without sacrificing enantioselectivity, a relatively reduced yield was seen by lengthening the ester's carbon chain. Enantioenriched α-allylic coumalate ester derivatives (**65**) can be functionalized as crucial synthetic building blocks for various reactions, including retro-cycloaddition, cascade reactions, and decarboxylation (Scheme 23).[68]

A key obstacle in asymmetric catalysis is the generation of all possible stereoisomers of a given chiral molecule carrying multiple stereocenters using a straightforward and unified method. In 2017, Hartwig devised a protocol for stereodivergent substitution using allylic *t*-butyl carbonates (**67**) and aryl acetic acid ester (**66**) catalyzed cooperatively by iridium complex and benzotetramisole **A7** in the presence of diisopropyl ethyl amine as a base. In this catalytic cycle, the iridium and Lewis base catalysts react with the allylic precursor (**67**) and the aryl acetic acid ester (**66**) cooperatively to produce Ir-allyl-π complex (**67-ii**) and C1-ammonium enolates (**66-ii**) respectively. Both intermediates react with high facial selectivity to yield stereo-divergent products (**68**). This dual catalytic cycle allows access to four stereoisomers by permutations of the enantiomers of the two chiral catalysts with high diastereo and enantioselectivity (Scheme 24).[69]

Snaddon's team further investigated this chemical reaction to produce varied homoallylic amine compounds, using the allylic substitution protocol and sequential Hofmann rearrangement strategy to synthesize branched homoallylic amine **69** (Scheme 25).[70]

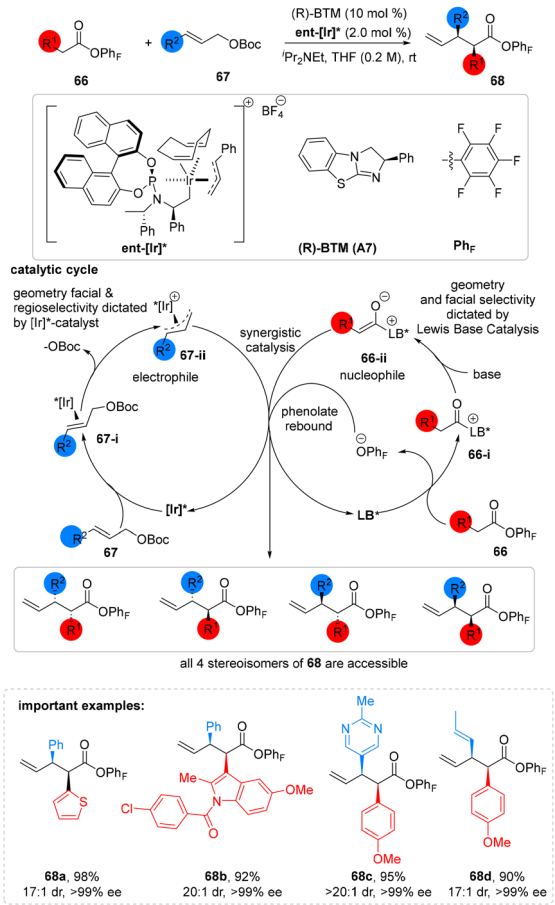
Following in the footsteps of Hartwig and Snaddon, the Deng group revealed that iridium and isothiourea Lewis base catalyzed vinyl indoloxazolidones (**70**) and acid anhydrides



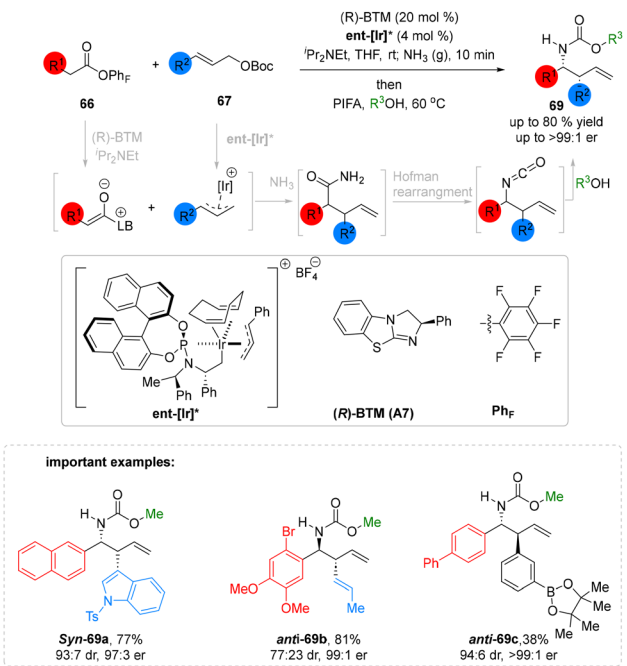
Scheme 23 α-C(sp^2)–H allylic alkylation of coumalates.

(**71**) in a synergistic manner to produce Ir-π-allyl intermediate and C1 ammonium enolate for the enantioselective [3 + 2] cycloaddition chiral polycyclic indoles **72**. The technique demonstrates a wide range of substrates, including substituted vinyl indoloxazolidones and anhydrides with various electron-donating and withdrawing groups at different positions. The result is the formation of asymmetric cyclic indoles **72** with high yield and excellent enantioselectivity (Scheme 26).[71]

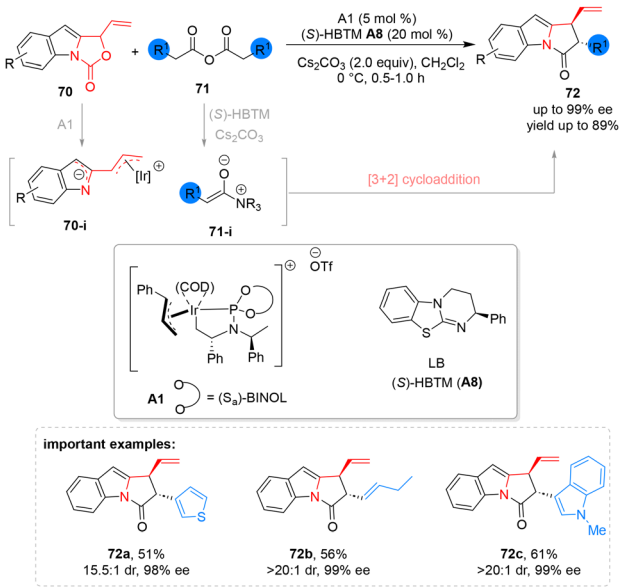
The γ-lactam moiety plays a crucial role in various bioactive substances, serving as a fundamental framework in pharmaceuticals, natural products, and bioactive molecules. Recently, the Song group introduced a comprehensive and adaptable approach for synthesizing chiral γ-lactam compounds (**74**). This involved a chiral isothiourea **A7** and [Ir(COD)Cl]$_2$ cooperatively catalyzed [3 + 2] asymmetric annulation reaction among vinyl aziridines (**73**), pentafluorophenyl esters (**66**), and a base at room temperature. The cooperative catalytic framework



Scheme 24 Stereodivergent allylic substitutions of aryl acetic acid esters.



Scheme 25 Regio- and stereodivergent synthesis of branched homoallylic amines.

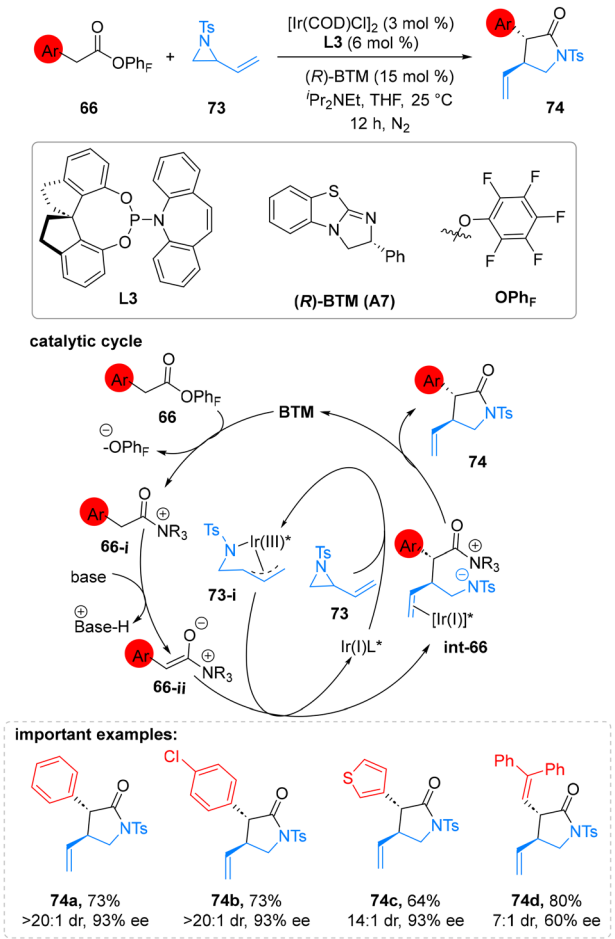


Scheme 26 Asymmetric [3 + 2] cycloaddition reaction.

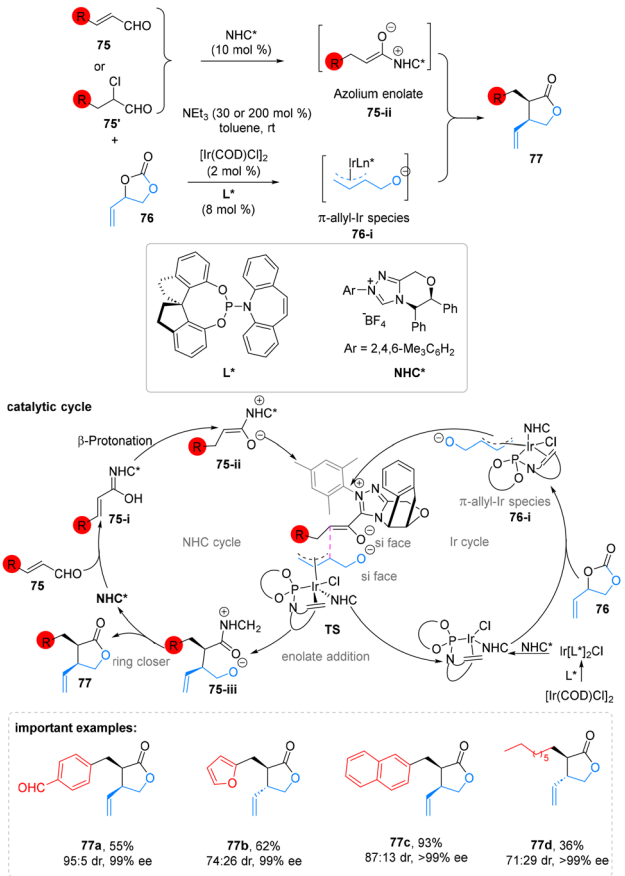
resulted in the production of a wide range of optically active γ-lactams with excellent yield and high chiral induction. The catalytic cycle involved various steps, such as the reaction of isothiourea Lewis base with aryl acetic acid ester, leading to the formation of reactive C1-ammonium enolate. Additionally, co-catalytic cycles involving [Ir(I)]* complex resulted in the production of key intermediate (**int-66**) through intermolecular asymmetric allylic alkylation. Subsequently, the ring closure of the intermediate **int-66** led to the final [3 + 2] ring expansion product **74** (Scheme 27).[72]

In 2019, the Glorius group successfully developed a new method for synthesizing α,β-disubstituted γ-butyrolactones (**77**) using *trans*-cinnamaldehyde **75** and vinylethylene carbonate **76** through a dual catalysis approach involving iridium and N-heterocyclic carbene (NHC). This innovative process enables enantio- and diastereodivergent [3 + 2] annulation reactions. The catalytic cycle commences with the formation of *Z*-enol intermediate (**75-ii**) from α,β-unsaturated aldehyde *via* homoenolate formation, followed by facile β-protonation or base-mediated elimination of chloride in α-chloroaldehydes. In the co-catalytic cycle, an Ir-π-allyl intermediate (**76-i**) is formed from vinylethylene carbonate (**76**) *via* decarboxylation. The Sunoj group's[73] DFT analogy demonstrates that the *Si*-face of both species **75-ii** and **76-i** come closer to form a new C–C bond (**75-iii**) and subsequently ring closer to produce the desired product **77** with high selectivity (Scheme 28).[74]

The remarkable effectiveness of switchable homoenolate and enolate intermediates derived from common enal precursors has been demonstrated through the use of the (NHC)/iridium catalyst system, enabling stereoselective and regiodivergent [3 + 2] and [3 + 3] annulation reactions. In 2021, the Wei-Ping Deng group published a study on a switchable annulation reaction of enals and 2-indolyl allyl carbonates **78** using



Scheme 27 Asymmetric [3 + 2] annulation for γ-lactam synthesis.



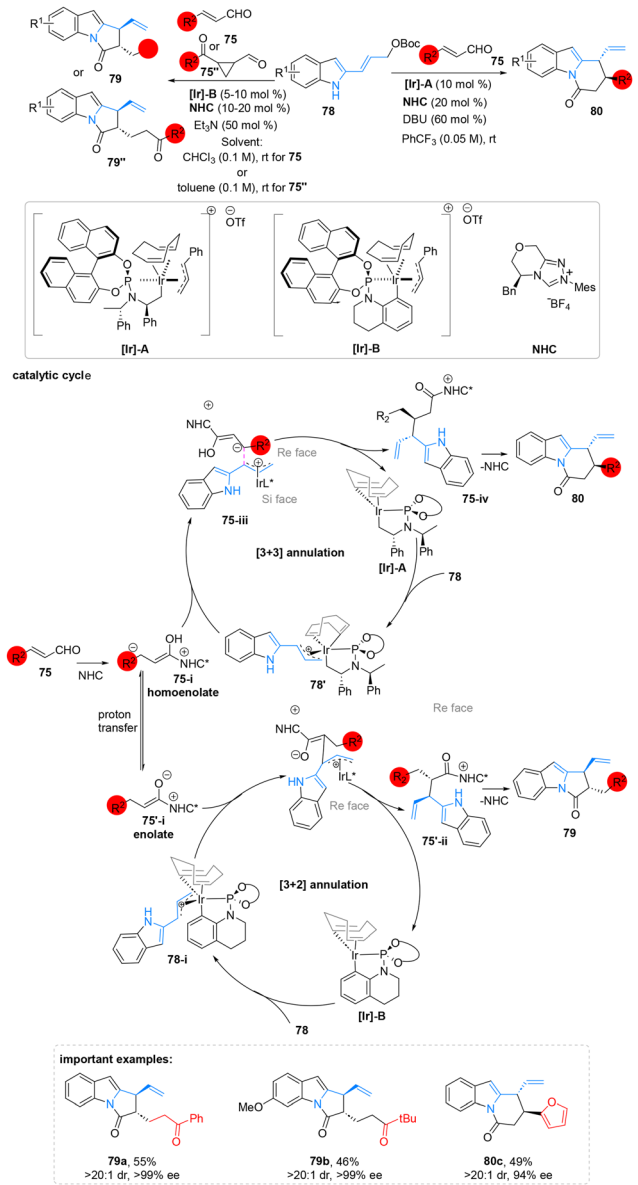
Scheme 28 Diastereodivergent [3 + 2] annulation reaction for α,β-disubstituted γ-butyrolactones synthesis.

NHC/iridium catalysis. The reaction, carried out in the presence of two different bases (triethyl amine and DBU), resulted in regiodivergent pyridine[1,2-*a*]indoles **80** and pyrrolo[1,2-*a*]indoles **79** derivatives with high diastereo- and enantioselectivity. A mechanistic study reveals that the NHC catalyst has the ability to activate cinnamaldehyde **75** or **75′**, resulting in the formation of homoenolate intermediate **75-i**. When weak base Et_3N is present, homoenolate **75-i** undergoes a quick proton transfer to yield enolate intermediate **75′-i**. In the co-catalytic cycle, 2-indolyl π-allyl-iridium intermediate **78-i** is formed from substrate **78**. The enolate attacks the *Re*-face of the π-allyl-iridium intermediate. Ultimately, the catalytic cycle concludes with the lactamization of intermediate **75′-ii**, producing product **79** with high selectivity. The use of DBU halts the proton transfer, leading to the predominance of homoenolate **75-i** reactivity. As a result, the [3 + 3] annulation reaction proceeds through the *Re–Si* face attack of homoenolate **75-i** to the π-allyl-iridium species **75-iii**, ultimately leading to the synthesis of pyridine[1,2-*a*]indoles (**80**) (Scheme 29).[75]

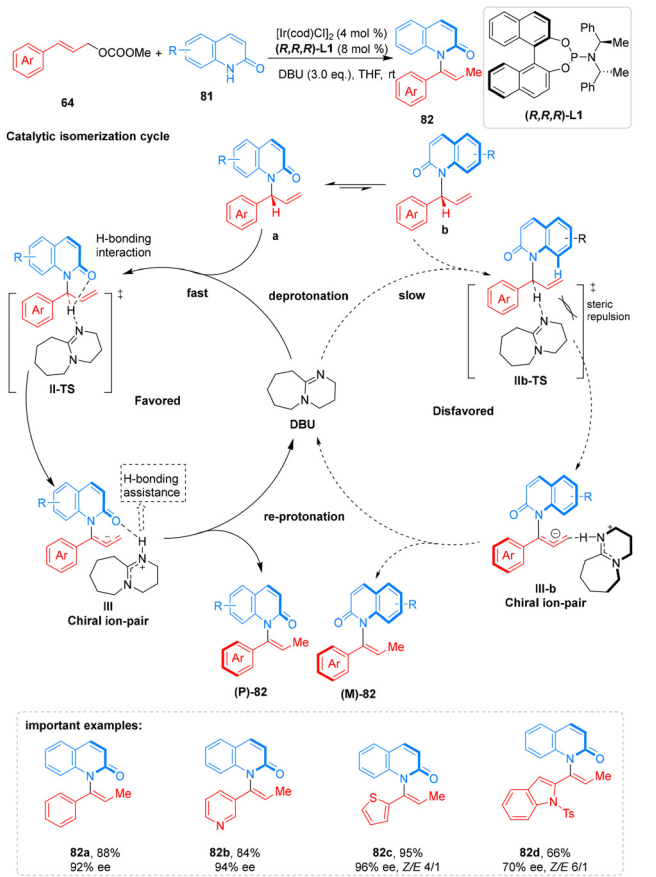
Using an extremely efficient catalytic process, He group recently achieved a significant breakthrough with the first enantioselective creation of axially chiral enamides **82** with an N–C axis as a chiral component. With the aid of an iridacycle catalyst, they carried out an enantioselective allylation to form the C(sp^2)–N link between 2-quinolinol **81** and cinnamyl carbonates **64**. The final enamides product **82** was then created by *in situ* isomerizing the allylation product *via* a 1,3-H transfer that was made possible by the base diazabicycloundecene (DBU). This allowed the chirality to shift from central to axial. The corresponding axially chiral product is produced in a high yield with good enantiomeric excess by this reaction, which exhibits excellent functional group compatibility with both cinnamyl carbonates **64** and 2-quinolinol **81** analogs bearing electron-rich, electron-neutral, and electron-deficient substituents (Scheme 30).[76]

4. Combination of iridium and phase-transfer catalyst

Over the past 30 years, asymmetric phase-transfer catalysis has proven to be a highly versatile method for organic synthesis.[77,78] Recently, researchers have been exploring the combined use of phase-transfer catalysts and transition metal catalysts to activate normally inert C–C and C–H bonds. Notably, the Takemoto group was the first to demonstrate the



Scheme 29 Regiodivergent [3 + 2] and [3 + 3] annulation reaction.

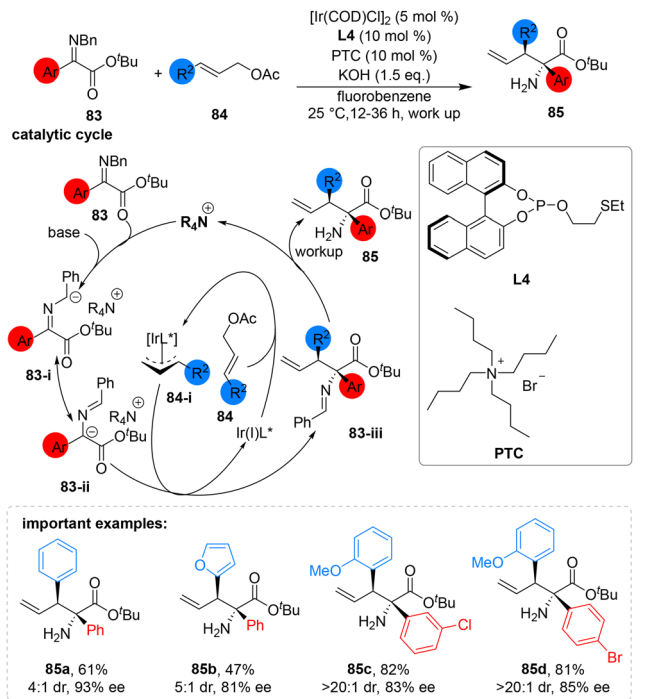


Scheme 30 Enantioselective allylic substitution–isomerization of axially chiral enamides.

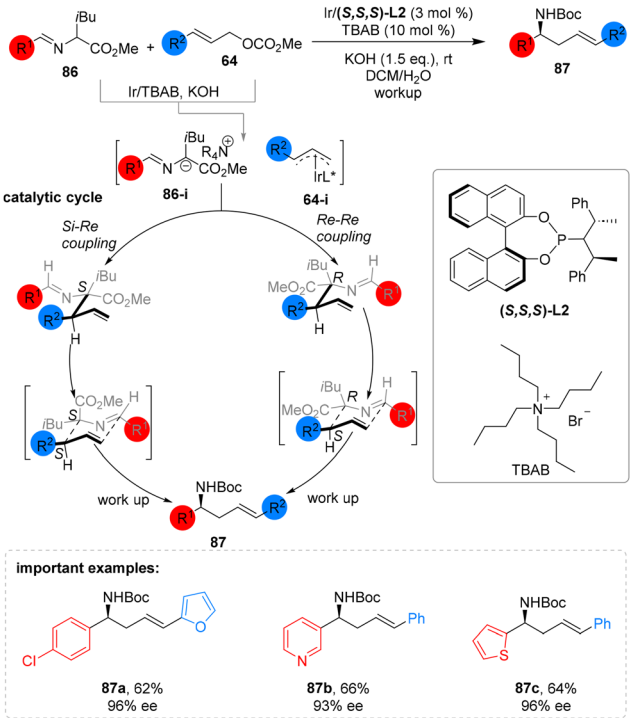
synergistic effect of phase-transfer catalysis and palladium metal in facilitating asymmetric allylic alkylation of allylic acetates.[79,80]

In 2017, Han and colleagues developed an innovative method to produce α-quaternary amino acid (**85**) with two vicinal stereocenters from α-imino esters **83** and allyl acetates **84**. It was achieved by employing cooperative iridium and phase-transfer catalyst (PTC). During the process, the activation of α-imino esters by PTC (tetra butyl ammonium bromide) led to the formation of the 2-azallyl anion intermediate **83-ii**, which then combined with the η^3-π-allyliridium intermediate **84-i** to generate the asymmetric final product **85** (Scheme 31).[81]

Wang's 2019 publication introduces a practical and cost-effective approach for producing enantioselective homoallylic



Scheme 31 α-Imino ester synthesis by Ir/PTC cooperative catalysis.



Scheme 32 Asymmetric allylation/2-aza Cope rearrangement by Ir/PTC cooperative catalysis.

amines (**87**). This method involves the cooperative activation of substituted cinnamyl carbonate **64** and leucine-derived aldimine esters **86** by iridium, in combination with a phase-transfer catalyst (PTC), to create a diverse range of homoallylic amines **87**. These amines exhibit outstanding enantioselectivity with yields ranging from moderate to good. The reaction is compatible with various allylic carbonates and aldimine esters featuring electron-donating, withdrawing, and neutral substituents (Scheme 32).[82]

5. Cooperative iridium photocatalysis

Over the past two decades, there has been notable progress in contemporary organic synthesis, largely attributed to the integration of visible light photocatalysis and organocatalysis.[83,84] Visible light-induced cooperative iridium photocatalysis has emerged as a key tool in the cooperative catalysis regime for designing a stereoselective radical reaction to create site-selective carbon–carbon bonds under benign reaction conditions.[85–87] Therefore, our goal in this section on cooperative photoredox is to present a particular perspective on current advancements through in-depth mechanistic analyses of cooperative organocatalyst/Ir-photocatalysis.

Combination of iridium photocatalyst and amine catalyst

In the cooperative Iridium photocatalyst and amine catalyst reaction, the amino catalysts interacted with a carbonyl compound to produce a chiral enamine intermediate. Simultaneously, the Ir-photocatalyst engaged with an electrophile, leading to the formation of highly reactive electrophilic radical species. It's worth noting that both processes occurred in an overall redox-neutral manner.[88]

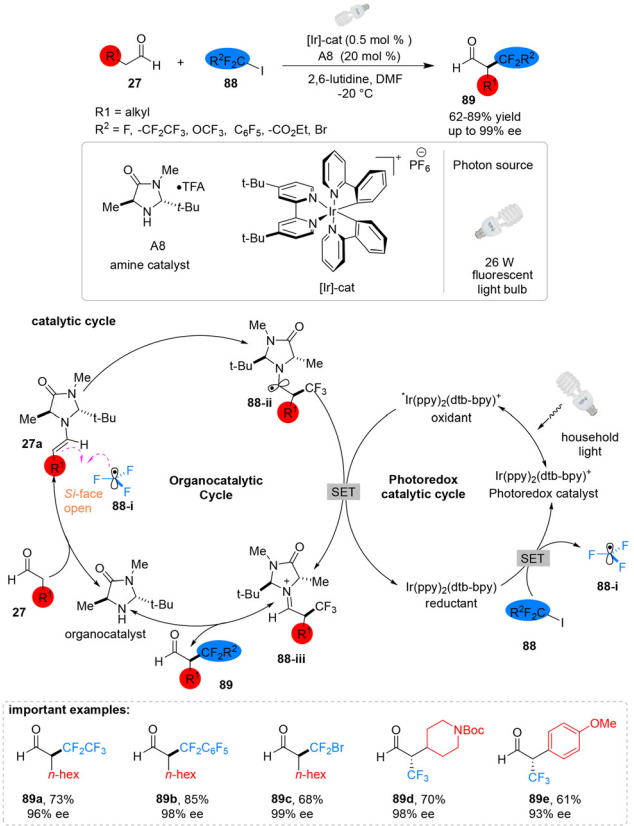
The MacMillan research team developed a new method to achieve the first asymmetric α-trifluoromethylation and α-perfluoroalkylation of aldehydes **27** using a combination of cooperative iridium photocatalyst and imidazolidinone **A8** organocatalyst under white light irradiation. This approach successfully allowed for a wide range of functional groups, including ethers, esters, amines, carbamates, and aromatic rings, to be compatible with the protocol. The resulting α-trifluoromethyl aldehyde **89** has the potential to be utilized in the synthesis of various organofluorine-containing compounds. Upon combination with the enamine **27a** intermediate, the trifluoromethyl radical **88-i** resulted in the α-trifluoromethylation of aldehyde **27**. This method is applicable to aldehydes **27** with diverse functional groups like ethers, esters, amines, carbamates, and aromatic rings. Using α-trifluoromethyl aldehyde **89**, a broad spectrum of valuable organofluorine-containing compounds can be synthesized. The MacMillan group expected[89] that $Ir^*(ppy)_2(dtb\text{-}bpy)^+$ would easily accept a single electron from enamine to create a potent reductant $Ir(ppy)_2(dtbbpy)$ (−1.51 V *vs.* SCE in CH_3CN), with the electron-rich iridium system playing a crucial role in single electron transfer (SET) with trifluoromethyl iodide **88**. This process generates the electrophilic radical **88-i** and regenerates the photoredox catalyst (Scheme 33).[90]

In 2010, the MacMillan group further developed the α-trifluoromethylation mechanism to enable the enantioselective α-benzylation of aldehydes **27**. This α-benzylation was achieved by employing an iridium photo-redox catalyst in combination with an imidazolidinone **A8** organocatalyst under white light. The protocol proved effective for various substituted aldehydes containing functional groups like ethers, amines, and carbamates. Notably, the reaction process exhibited broad functional group resilience, even with benzyl bromide **90** substituents, consistently yielding the desired enantioselective product (Scheme 34).[91]

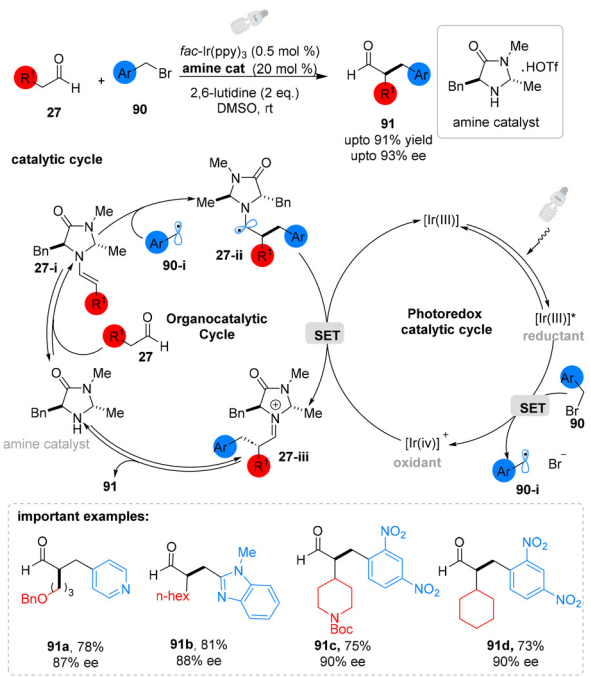
Combination of iridium photocatalyst and Brønsted acid catalyst

Over the past twenty years, Brønsted acid has been widely utilized as a co-catalyst alongside iridium photocatalyst in C–C bond formation reactions similar to the use of Lewis acids. It is suggested that Brønsted acid might catalysed the reaction through a proton-coupled electron transfer mechanism.[10]

Knowles group successfully developed a groundbreaking enantioselective intramolecular aza-pinacol cyclization reaction in 2013. This innovative reaction, catalyzed by a Ir $(ppy)_2(dtbpy)PF_6$ photo-redox catalyst and aryl phosphoric acids, creates highly enantioselective products through a proton-coupled electron transfer (PCET) mechanism. Chiral phosphoric acid and an iridium photo redox catalyst facilitated this proton-coupled electron transfer (PCET) reaction in the presence of a blue LED, resulting in the intramolecular reduc-



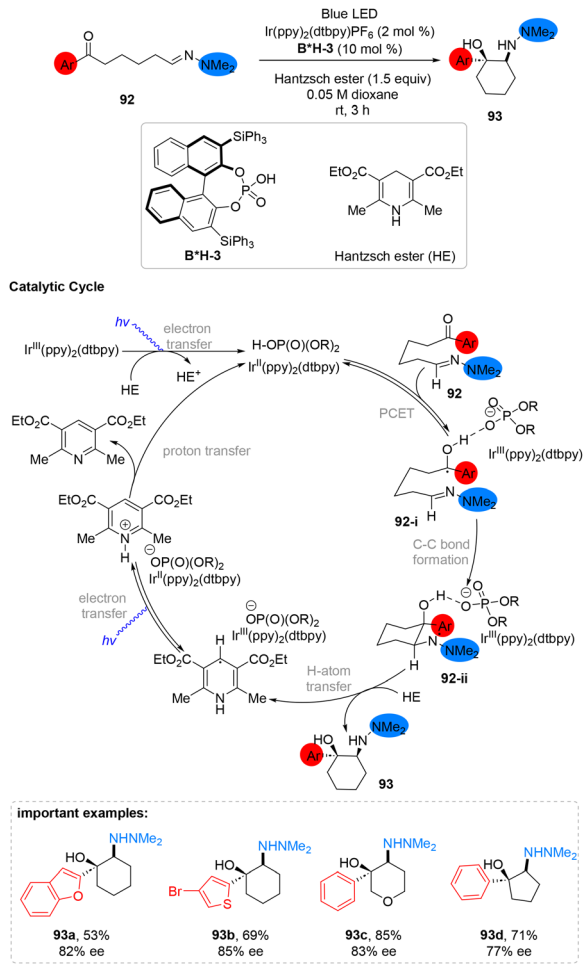
Scheme 33 Enantioselective α-trifluoromethylation of aldehydes.



Scheme 34 Enantioselective α-benzylation of aldehydes.

tive coupling of ketones and hydrazones to produce a highly enantioselective product *via* the formation of ketyl radical intermediates (**92**). The process is suitable for aryl ketones with various substituents and consistently delivers *syn*-1,2-amino alcohol-derived molecules **93** with high yield and enantioselectivity (Scheme 35).[92]

In 2018, Phipps and colleagues successfully developed a highly selective method for synthesizing α-heterocycle amines **96** utilizing a well-established minisci-type approach. The process involved the use of a chiral Brønsted acid catalyst (**B*H-1** and **B*H-2**) along with an iridium photocatalyst to generate prochiral free radical **95-i** from amino acid derivatives (**95**) using blue LED and [Ir]-photocatalyst. Radical **95-i** was then added at the 2-position of a hydrogen-bonded pyridinium counterion (**94-i**) to form the aminium ion intermediate (**94-ii**). In the next step, the aminium ion undergoes deprotonation to form species (**94-iii**). This species could potentially yield the enantioenriched product **96** through rapid single-electron oxidation. In this reaction, the iridium photocatalyst facilitates the electron transfer process, while the chiral Brønsted acid plays a dual role by activating the substrate and inducing asymmetry. This approach demonstrates efficacy across a range of substituted amines, pyridines, and quinolines, consistently delivering



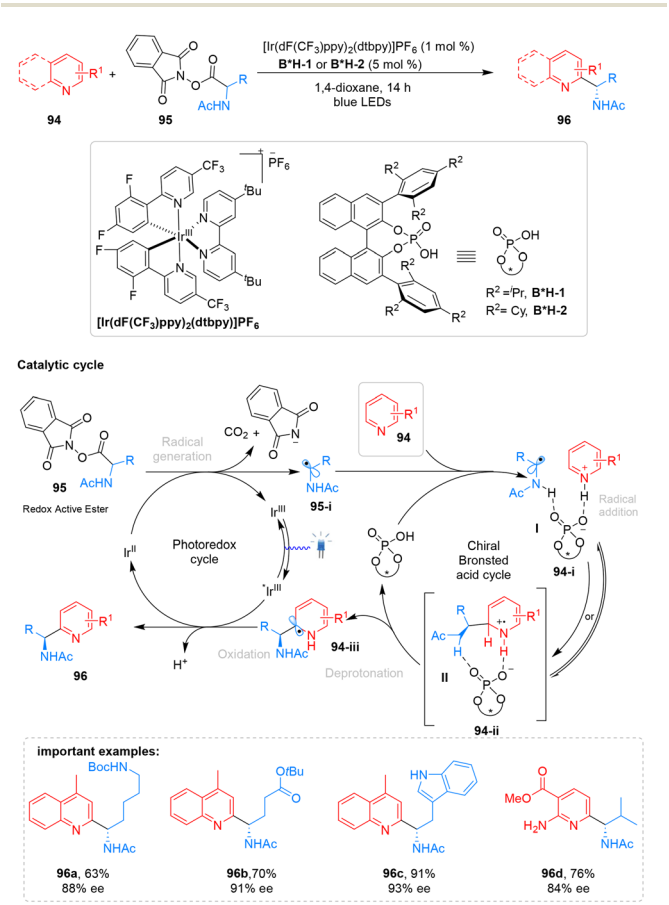
Scheme 35 Enantioselective intramolecular aza-pinacol cyclization of keto-hydrazone.

highly enantioselective and regioselective α-heterocycle amines (Scheme 36).[93]

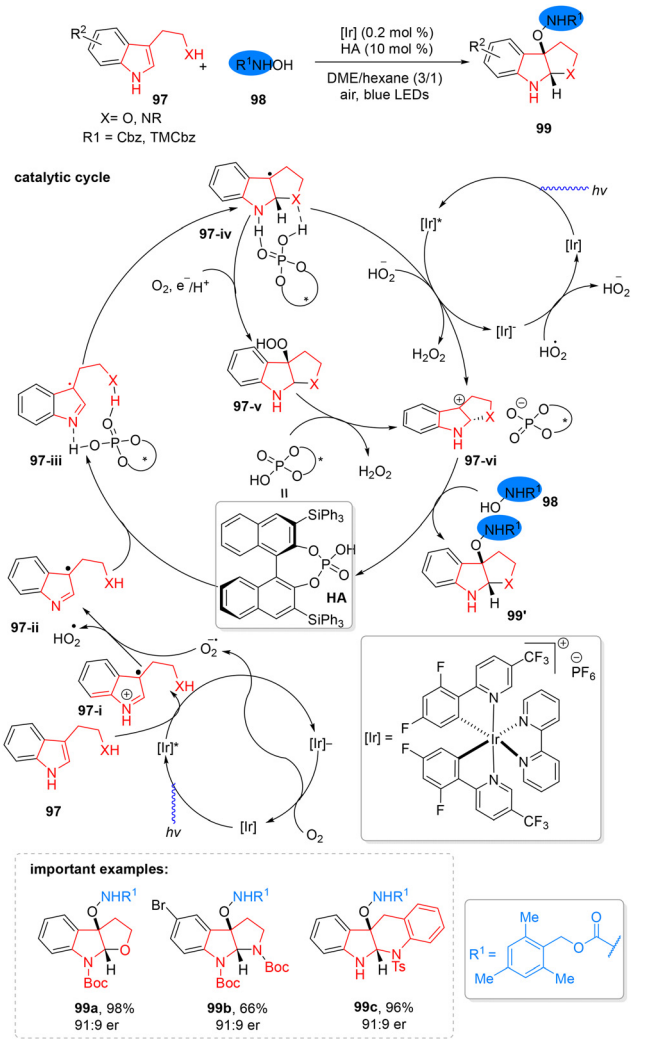
You *et al.* identified a fascinating example of the cooperatively catalyzed synthesis of an indoline derivative by using the umpolung chemistry of indole (**97**). Oxy-amine, tethered indoline derivatives (**99**) were produced using chiral phosphoric acid as a co-catalyst with iridium photocatalyst *via* an enantioselective dearomatization reaction of electrophilic indoles **97**. This method is thoroughly investigated across a large range of substituted indoles **97**, and it is discovered that introducing groups that withdraw electrons (–F, –Cl, –Br) into the indole moiety improves enantioselectivity when compared to groups that give electrons. The catalytic cycle begins with the activation of the Ir-photocatalyst using blue LED light. Once activated, the photoexcited [Ir]* assists in the initial SET oxidation of **97** to produce the indole radical cation intermediate (**97-i**). Following this, the [Ir]-photocatalyst is regenerated by molecular oxygen, and the indole radical cation intermediate is deprotonated by the oxygen anion radical. The deprotonated indole radical (**97-iii**) then undergoes ring closure through **B*H-3** mediation, and the second SET oxidation takes place in the presence of [Ir]* to create the configurationally biased tertiary pyrroloindoline carbocation intermediate (**97-vi**), which is stabilized by electrostatic interactions with the chiral phosphate anion. Finally, the pyrroloindoline carbocation (**97-vi**) is trapped by a hydroxyl amine nucleophile to produce the optically enriched indoline derivatives **99** (Scheme 37).[94]

Yoon introduced a pioneering method for producing highly enantioselective pyridine-substituted cyclobutene **102** through a [2 + 2] cycloaddition reaction between vinyl pyridines **100** and a styrene derivative (**101**). This innovative approach involved the use of an iridium photocatalyst and chiral phosphoric acid (**B*H-5**) as a Brønsted acid catalyst. Yoon proposed that during a transient excited state, matched chiral catalyst pairs interact to generate an enantioenriched [2 + 2] photocycloaddition product **102**, paving the way for the development of synergistic stereoinduction. Additionally, the authors noted that electron-rich styrenes (**101**) resulted in higher enantiomeric excess compared to electron-deficient styrene (Scheme 38).[95]

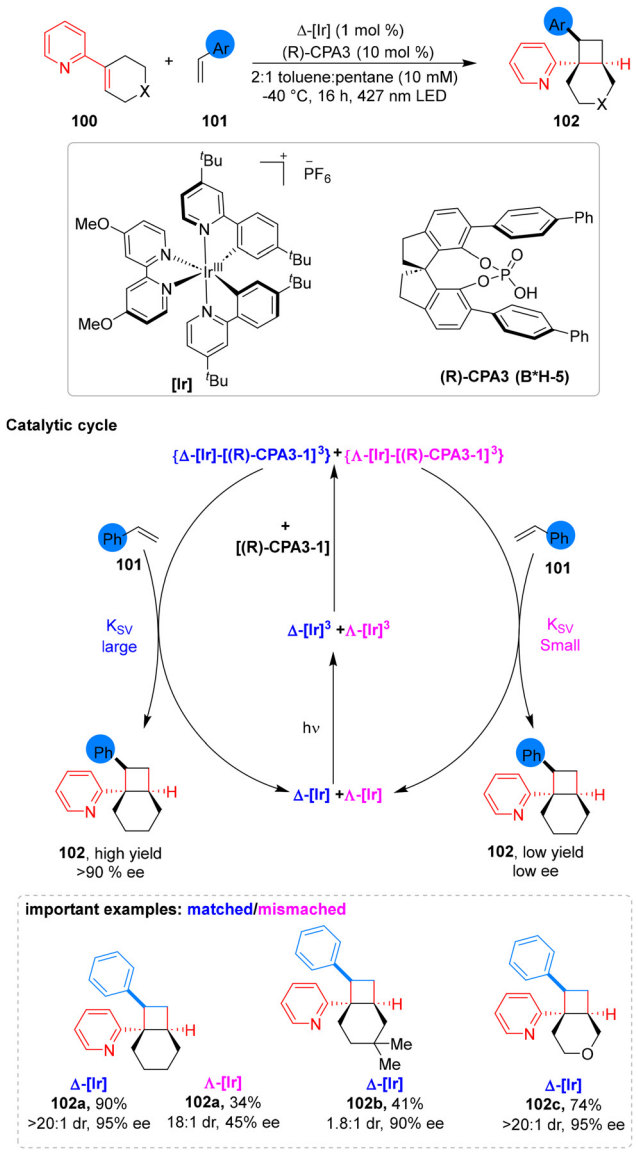
An enantioselective three-component method for the synthesis of enantioenriched keto alkyl-functionalized 4-amino



Scheme 36 Enantioselective Minisci-type addition to N-heterocycles.



Scheme 37 Asymmetric photoredox dearomatization of indole derivatives.

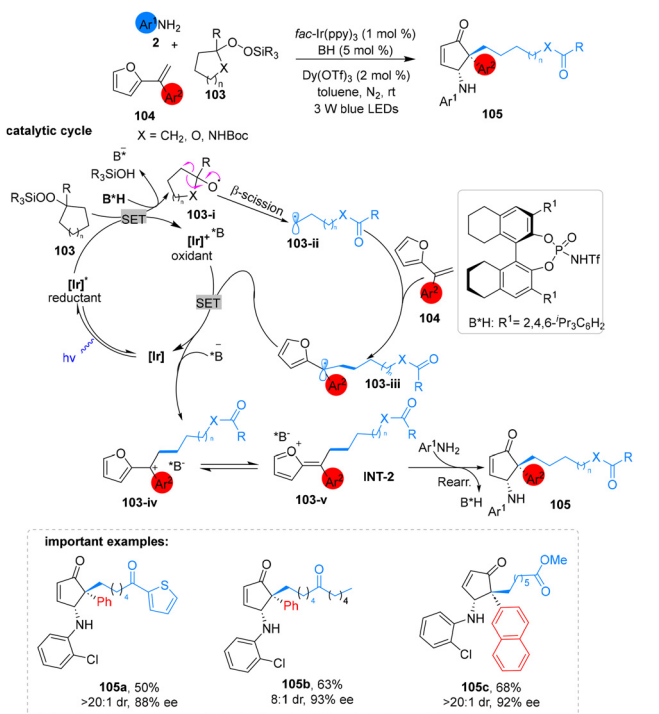


Scheme 38 Enantioselective [2 + 2] photo cycloaddition of vinylpyridines.

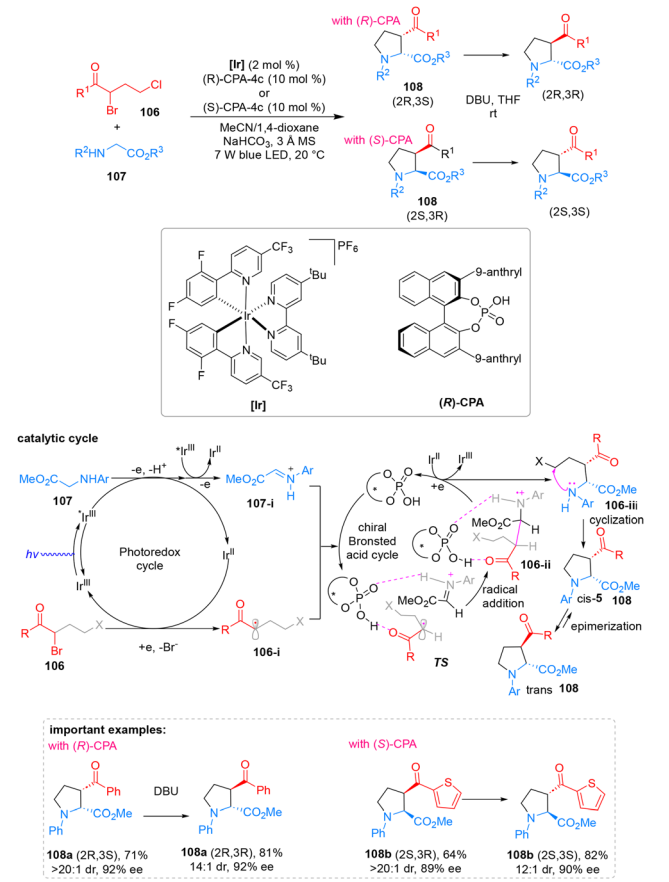
cyclopentenone was employed by the Cai group, using cooperative chiral Brønsted acid and iridium photocatalyst. In this process, the [Ir]-photocatalyst and chiral Brønsted acid catalyst (**B*H**) facilitated the creation of ketoalkyl radical (**103-ii**) from cycloalkyl silyl peroxide **103**. The keto alkyl radical then attacked alkenyl furan **104**, resulting in single-electron oxidation and the formation of a chiral-anion-stabilized keto-alkyl functionalized furan oxonium ion (**103-iii**). Subsequently, aryl amine **2** sequential nucleophilic attack on the furan ring led to ring opening and chiral anion-controlled asymmetric 4π-electrocyclization, producing the desired enantioenriched product **105**. Extensive investigation revealed that the approach yielded highly enantioselective products in most cases, with moderate to good yield. This protocol enables the synthesis of various essential chiral cyclopentenone motifs with different functional groups (Scheme 39).[96]

In 2023, Wang's research group achieved the asymmetric synthesis of 3-substituted proline derivative (**108**) through a *de novo* approach, using a cascade radical addition/cyclization of racemic α-bromo γ-chloro ketone **106** and *N*-aryl glycine ester **107**, facilitated by cooperative iridium photoredox/Chiral phosphoric acid catalysis. This reaction also demonstrated the broad applicability of the protocol, showing that both *N*-arylated glycinate methyl esters **107** and α-bromo γ-chloro aryl ketones **106**, with electron-withdrawing and electron-donating substituents, yield exceptional enantio- and diastereoselectivity. However, this reaction does not work well with linear aliphatic dihalide ketones (Scheme 40).[97]

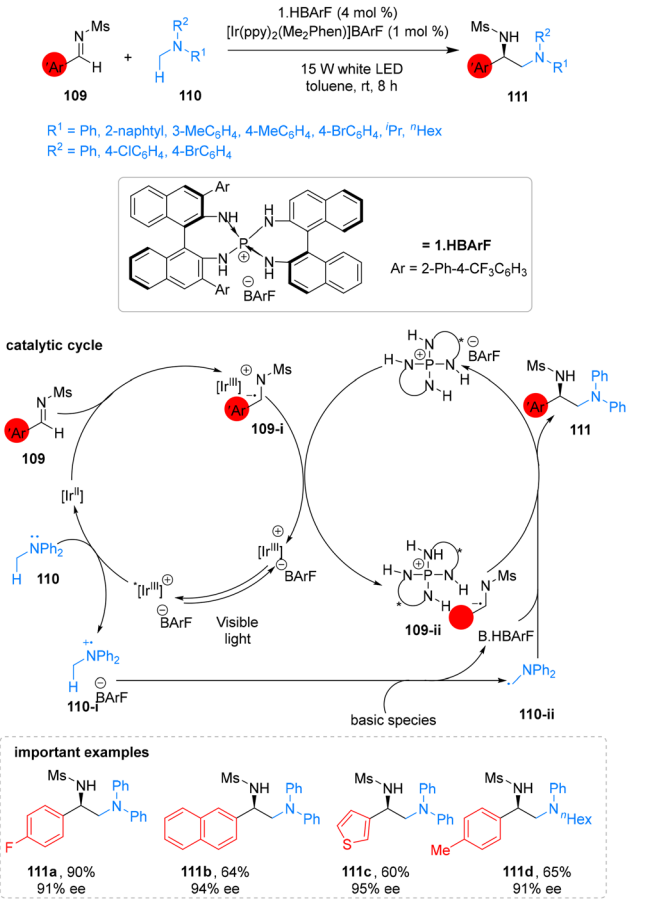
A spectacular demonstration of the enantioselective α-coupling between *N*-arylaminomethanes **110** and *N*-sulfonyl imines **109** was carried out in 2015 by Takashi Ooi and co-workers. Chiral arylaminophosphonium barfate (HBArF) and iridium metal photosensitizer were used in cooperative style with exposure to visible light to produce an enantioenriched coupled product between *N*-sulfonyl aldimines **109** and *N*-arylaminomethanes **110**. The catalytic cycle commences with the excitation of the [Ir(ppy)$_2$(bpy)]BArF complex under visible light irradiation, followed by the reductive quenching of *Ir(III) to form a neutral Ir(II) complex. This complex then transfers an electron to the imine to create an anion–radical. The anion–radical pairs with a positively charged Ir(III) complex (**109-i**) and then reacts with chiral arylamino phosphonium barfate to produce a crucial chiral ion pair (**109-ii**)



Scheme 39 Asymmetric ketoalkylation/rearrangement of alkyenlfurans.



Scheme 40 Asymmetric *de novo* synthesis of 3-substituted proline derivatives.



Scheme 41 Redox neutral asymmetric α-coupling of *N*-arylaminomethanes with aldimines.

while regenerating the parent photosensitizer. Simultaneously, an aminomethyl radical is formed through the deprotonation of the Ph_2NMe **110** cation–radical species. Ultimately, the imine anion–radical and aminomethyl radicals are coupled to yield an enantioenriched 1,2-diamine derivative **111**. A wide range of *N*-substituted aminomethane and aromatic *N*-sulfonyl imines (**109**) with electron-rich and electron-deficient substituents produced α-coupled products (**111**) with a high degree of enantiomeric excess (Scheme 41).[98]

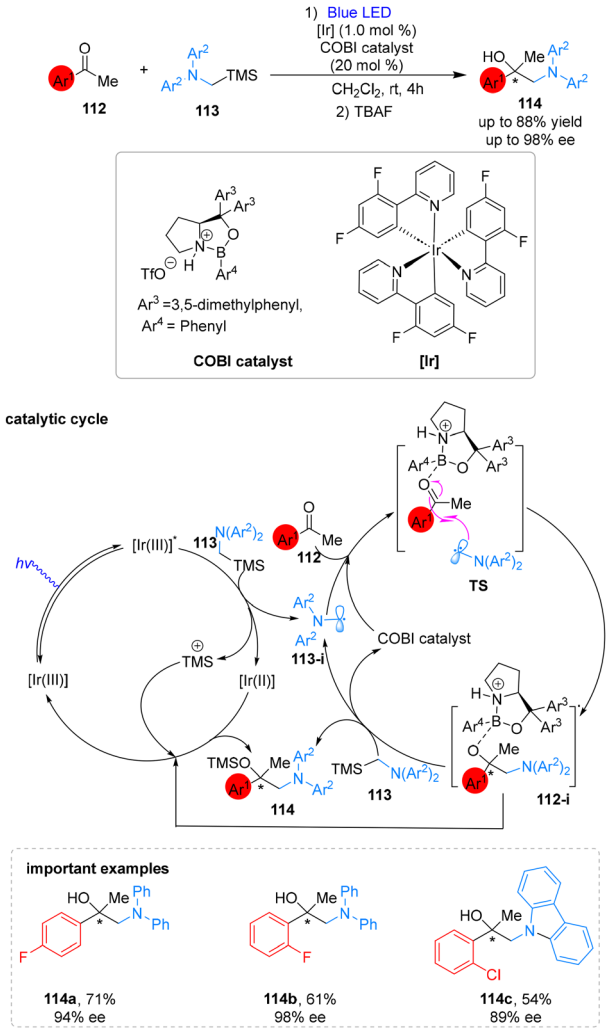
Combination of iridium photocatalyst and Lewis acid catalyst

Synthesis of highly enantioenriched 1,2-amino tertiary alcohols (**114**) was reported by the Ryu group by employing chiral oxazaborolidinium ion organocatalyst and iridium photocatalyst. This protocol produces asymmetric amino tertiary alcohols (**114**) with high yield (up to 88%) and excellent enantioselectivity (up to 98%). This process involves the generation of α-amino alkyl radical (**113-i**) through visible light irradiation of α-silyl amine **113** using a single-electron transfer mechanism. The radical then undergoes an enantioselective attack on the COBI-activated aryl methyl ketone (**TS**). The reaction is concluded by a second single-electron transfer using α-silyl amine. The research also involved a thorough investigation of acetophenone derivatives with different substitution patterns on the phenyl ring, revealing that electron-donating substituents led to decreased selectivity and reactivity (Scheme 42).[99]

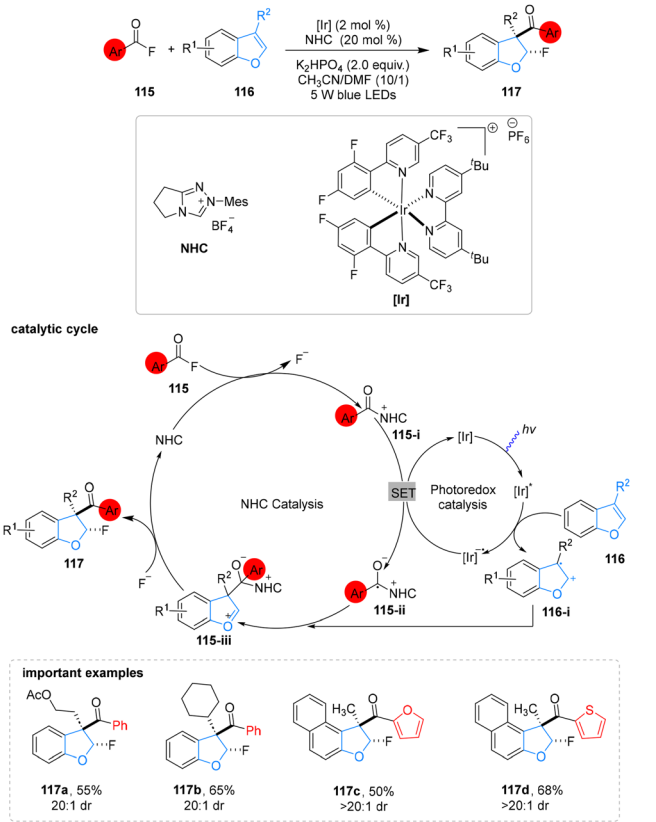
Combination of iridium photocatalyst and N-heterocyclic carbene

In 2022, Armido Studer discovered a method for synthesizing 2,3-difunctionalized dihydrobenzofurans (**117**) by utilizing a combination of N-heterocycle carbene (NHC) and iridium photoredox mediated reaction to form C–C and C–F bonds. This process involves the use of aroyl fluorides **115** as dual-purpose reagents in the presence of K_2HPO_4 base and 5 W blue LEDs, resulting in the conversion of benzofurans **116** into 3-aroyl-2-fluoro-2,3-dihydrobenzofurans **117** through dearomatizing fluoroaroylation.

The mechanistic cycle commences with the oxidation of benzofuran **116** to its radical cation (**116-i**) by photoexcited Ir(III)*. Simultaneously, NHC generates acyl azonium ion (**115-i**) from acyl fluoride **115** in the co-catalytic cycle. The acyl azonium ion is then reduced by Ir(II) to regenerate Ir(III), leading to the formation of the persistent ketyl radical (**115-ii**). The subsequent merge of the benzofuran radical cation (**116-i**) with the ketyl radical (**115-ii**) results in the formation of the



Scheme 42 Enantioselective addition of α-aminoalkyl radicals to ketones.



Scheme 43 Photoredox dearomatizing fluoroaroylation of benzofurans.

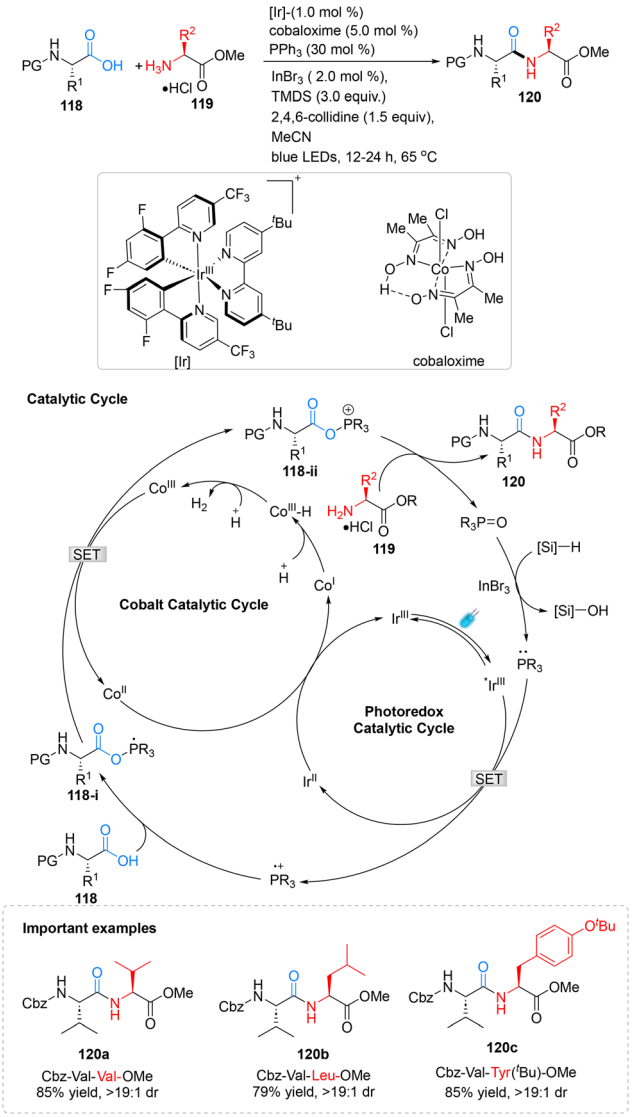
oxocarbenium ion (**115-iii**). Finally, the oxocarbenium ion is diastereoselectively trapped by F-anion in trans to the bulky alcoholate moiety, and NHC-regeneration produces product **117** in good yield. This photocatalytic protocol has been extensively studied for aroyl fluoride with *para*-position substituents that either donate or withdraw electrons from the aryl ring. Furthermore, benzofurans with various substituents at the aromatic ring have shown high tolerance, yielding acceptable yields with significant diastereoselectivity (Scheme 43).[100a]

Recently, the Zhao group made an interesting breakthrough in the diastereoselective synthesis of oligopeptides by using a combination of synergistic photoredox, cobaloxime, and organophosphorus triple catalysis. This process creates a phosphine radical cation that engages in nucleophilic addition with a carboxylate, leading to the formation of the phosphoranyl radical (**118-i**). Further electron transfer between **118-i** and a cobaloxime catalyst (Co^{III}) is expected to occur easily, leading to the formation of an oligopeptide **120** *via* aminolysis, while also producing a phosphine oxide. Finally, the *in situ* reduction of $P^{V}{=}O$ by silanes and $InBr_3$ completes the catalytic cycle (Scheme 44).[100b]

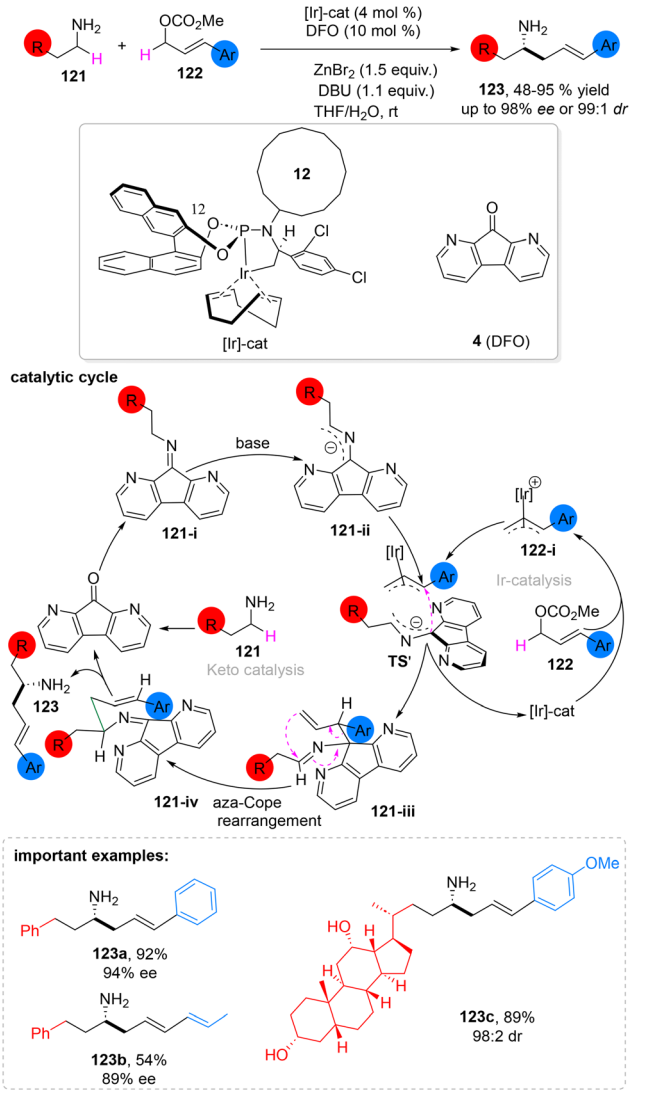
Miscellaneous

Baoguo Zhao and his colleagues very recently released a study detailing how 1,8-diaza-fluoren-9-one (DFO) was able to activate the normally inactive α-C–H bond of an unprotected primary amine by increasing its acidity by an impressive 10^{44} times.

By harnessing the excellent cooperative nature of Diazafluorenone with an Ir-catalyst, successfully crafted the chiral homoallylic amine **123** building block. This was achieved through an asymmetric allylic substitution, followed by *in situ* 2-aza-cope rearrangement using primary alkyl amine **121** and allylic carbonates **122** in the presence of $ZnBr_2$ and DBU in THF/H_2O solvent at room temperature. The reaction began with the condensation of alkyl amine **121** with diazafluorenone, resulting in the formation of imine **121-i**. Following this, the delocalized carbanion **121-ii** underwent an asymmetric addition to π-allyl-Ir species **122-i**, generating a branched aza cope intermediate **121-iii** *via* **TS′**. Species **122-i** is generated from the iridium catalyst and allylic carbonate **122**. Subsequently, compound **121-iii** undergoes 2-aza-Cope rearrangement to form species **121-iv**, followed by hydrolysis, leading to the production of α-C–H allylic alkylation product



Scheme 44 Diastereoselective oligopeptide synthesis.



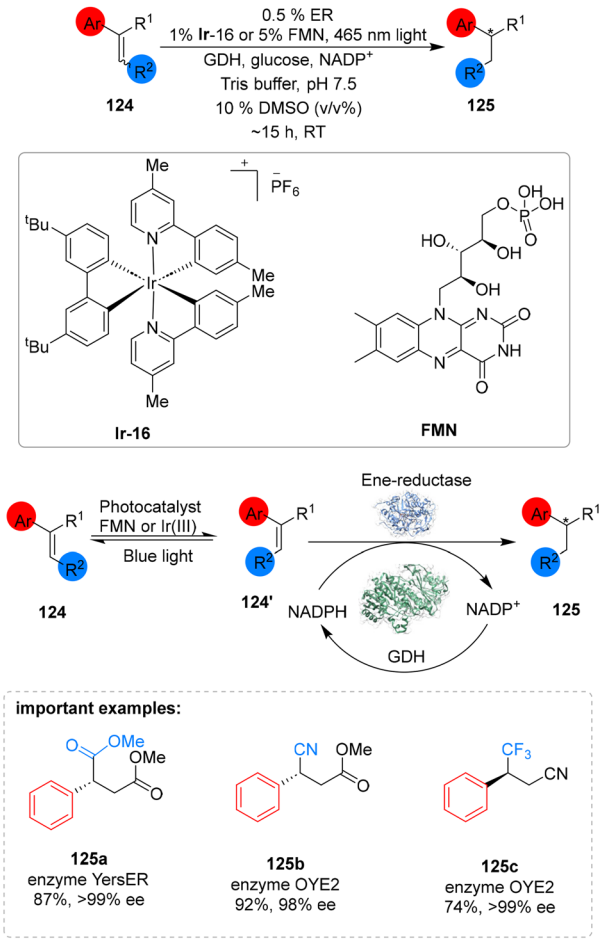
Scheme 45 Chiral homoallylic amine synthesis by keto-iridium dual catalysis.

123 and the regeneration of the diazafluorenone (Scheme 45).[101]

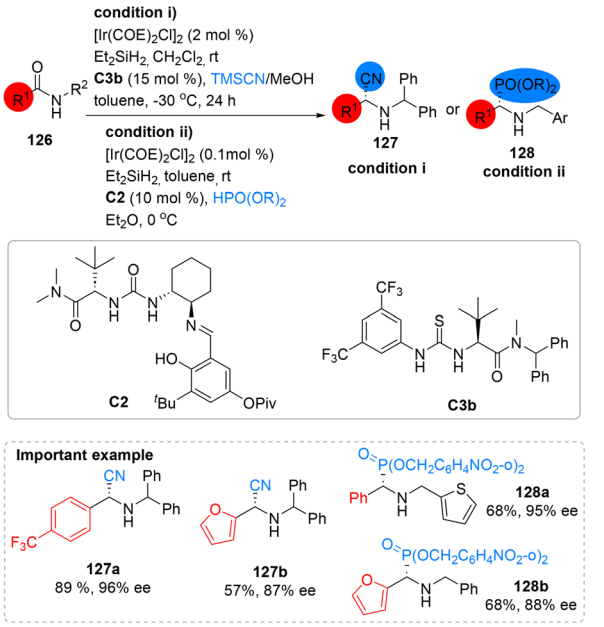
A straightforward and effective method for the asymmetric reduction of the C–C double bond to produce a highly enantioselective product in the presence of photocatalysis and enzymatic catalysis was established by Hartwig in 2018. The reaction is driven by a combination of photocatalysis and enzymatic catalysis, resulting in higher yield and enantiomeric excess. Utilizing blue light and a series of synergistic chemoenzymatic reactions, the reduction of the *E*/*Z* mixture of alkene **124** to the highly enantiopure product **125** is achieved. This process involves an iridium photocatalyst combined with an ene-reductase enzyme, resulting in the desired **125** products with high yield and high enantioselectivity (Scheme 46).[102]

Direct conversion of secondary amides **126** to chiral α-amino-nitriles **127** and α-aminophosphonates **128** can be accomplished through a one-pot process involving enantioselective reductive cyanation and phosphonylation. This approach utilizes a combination of iridium and chiral thiourea catalysis. During the catalytic cycle, the amides **126** undergo reduction in the iridium-catalyzed step, leading to the formation of imine intermediates. These intermediates are subsequently transformed into chiral α-functionalized amines through the action of the thiourea catalyst (Scheme 47).[103]

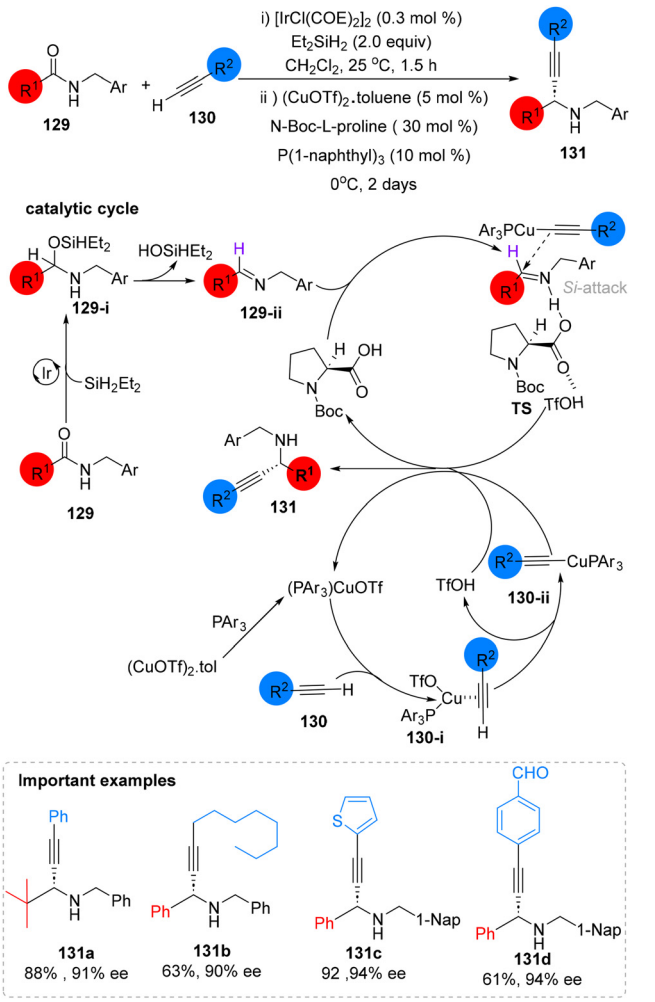
In 2022, Huang reported a novel method for the catalytic asymmetric reductive/deoxygenative alkynylation of secondary amides. This approach employs a multi-catalysis strategy, combining iridium and copper relay catalysis with cooperative catalysis from Cu and N-protected L-proline. The process involves three catalytic cycles: first, the Ir-catalyzed hydrosilylation of a secondary amide **129** using diethylsilane leads to the formation of an *O*-silyl hemi-aminal intermediate (**129-i**). This



Scheme 46 Asymmetric reduction by combining photocatalysis and enzymatic catalysis.



Scheme 47 Asymmetric reductive cyanation and phosphonylation of secondary amides.



Scheme 48 Enantioselective reductive alkynylation of secondary amides.

intermediate then undergoes a transformation by eliminating diethylsilanol, resulting in an imine intermediate (**129-ii**). Next, copper catalyzes the *in situ* formation of a nucleophilic Cu-alkynylide species (**130-ii**). Finally, the reaction proceeds with the *N*-Boc L-proline-catalyzed asymmetric alkynylation of the imine. Here, *N*-Boc L-proline acts both as a Brønsted acid, activating the relatively unreactive imine *via* hydrogen bonding, and as an asymmetric inducer, selectively blocking the *Re*-face approach. Consequently, the Cu-alkynylide (**130-ii**) preferentially adds to the reactive intermediate (**TS**) from the *Si*-face, yielding (*R*)-propargylamine **131** (Scheme 48).[104]

6. Conclusions

The development of a cooperative catalysis strategy using organocatalysts and transition metals in combination is heavily reliant on catalyst compatibility and the balanced kinetics of selective substrate activation in the reaction system. The coupling of metal and organocatalysis creates new reactivity

and diverse applications for catalytic systems in the pharmaceutical, agrochemical, and fine chemical industries. Cooperative catalysis enables difficult chemical reactions that were not possible with either the organocatalyst or the metal catalyst alone.

In the realm of asymmetric dual catalysis, chirality arises from either the ligand on the metal or from the chiral counter ion of an organic catalyst. Even though cooperative catalysis has become a highly effective approach for achieving high selective and complex functionality, however, it does have some synthetic limitations to consider. Issues often arise when iridium and organocatalysts disrupt the properties of each other. This incompatibility can compromise the effectiveness of the catalytic cycle, so it's essential to choose catalysts carefully to ensure a successful dual catalytic system. To make significant strides in cooperative catalysis, a deeper understanding of how catalysts interact both mechanistically and theoretically is crucial. Another notable limitation relates to organocatalysts, which have been used in conjunction with iridium metal. Specifically, various types of organocatalysts have been explored in cooperative catalysis along with iridium, including BINOL phosphoric acid-based catalysts, different Lewis bases like NHC, tertiary amines, and proline-based catalysts, as well as a few phase transfer catalysts. This dependency on delicate and costly organocatalysts underscores the importance of seeking alternatives that are more economical, readily accessible, and robust, in order to enhance the versatility of this process. The current obstacles in iridium–organo cooperative catalysis are sure to spark new innovations, paving the way for the development of novel synergistic catalytic systems.

This review offers a thorough examination of advanced strategies and foundational research in iridium–organo cooperative catalysis. Its goal is to provide a comprehensive insight into innovative techniques and potential pathways for synthesizing crucial pharmaceutical compounds, while also inspiring new discoveries and promoting the progress of novel cooperative catalytic processes.

Author contributions

D. C. and R. K. S. contributed to the writing and editing of the manuscript. All authors have given their approval for the final version.

Data availability

No original research findings or new data were produced or examined in the course of this review.

Conflicts of interest

There are no conflicts to report.

Acknowledgements

We acknowledge financial support from the Science and Engineering Research Board (SERB), India (SRG/2023/000581), and the IIT Roorkee FIG-101034 grant. Divakar Chaudhary is thankful to the PMRF Foundation for the fellowship. We thank Sumit Kumar for his help in the literature search.

References

1 U. Bin Kim, D. J. Jung, H. J. Jeon, K. Rathwell and S. G. Lee, Synergistic Dual Transition Metal Catalysis, *Chem. Rev.*, 2020, **120**, 13382–13433.
2 (*a*) Z. Shao and H. Zhang, Combining transition metal catalysis and organocatalysis: A broad new concept for catalysis, *Chem. Soc. Rev.*, 2009, **38**, 2745–2755; (*b*) B. A. Arndtsen and L. Z. Gong, *Asymmetric Organocatalysis Combined with Metal Catalysis*, Springer International Publishing, 2020.
3 (*a*) D. S. Kim, W. J. Park and C. H. Jun, Metal-Organic Cooperative Catalysis in C-H and C-C Bond Activation, *Chem. Rev.*, 2017, **117**, 8977–9015; (*b*) R. Peters, *Cooperative Catalysis. Designing Efficient Catalysts for Synthesis*, Wiley-VCH, Weinheim, 2015, pp. 1–427.
4 J. Park and S. Hong, Cooperative bimetallic catalysis in asymmetric transformations, *Chem. Soc. Rev.*, 2012, **41**, 6931–6943.
5 A. Sinibaldi, V. Nori, A. Baschieri, F. Fini, A. Arcadi and A. Carlone, Organocatalysis and beyond: Activating reactions with two catalytic species, *Catalysts*, 2019, **9**, 928.
6 C. D. T. Nielsen, J. D. Linfoot, A. F. Williams and A. C. Spivey, Recent progress in asymmetric synergistic catalysis – the judicious combination of selected chiral aminocatalysts with achiral metal catalysts, *Org. Biomol. Chem.*, 2022, **20**, 2764–2778.
7 X. Liang, T. Y. Zhang, X. Y. Zeng, Y. Zheng, K. Wei and Y. R. Yang, Ir-Catalyzed Asymmetric Total Synthesis of (−)-Communesin F, *J. Am. Chem. Soc.*, 2017, **139**, 3364–3367.
8 S. Afewerki and A. Córdova, Combinations of Aminocatalysts and Metal Catalysts: A Powerful Cooperative Approach in Selective Organic Synthesis, *Chem. Rev.*, 2016, **116**, 13512–13570.
9 Y. Kuang, J. Lai and J. P. Reid, Transferrable selectivity profiles enable prediction in synergistic catalyst space, *Chem. Sci.*, 2023, **14**, 1885–1895.
10 K. L. Skubi, T. R. Blum and T. P. Yoon, Dual Catalysis Strategies in Photochemical Synthesis, *Chem. Rev.*, 2016, **116**, 10035–10074.
11 A. E. Allen and D. W. C. MacMillan, Synergistic catalysis: A powerful synthetic strategy for new reaction development, *Chem. Sci.*, 2012, **3**, 633–658.
12 A. Del Vecchio, A. Sinibaldi, V. Nori, G. Giorgianni, G. Di Carmine and F. Pesciaioli, Synergistic Strategies in Aminocatalysis, *Chem. – Eur. J.*, 2022, **28**, e202200818.

13 Y. Qin, L. Zhu and S. Luo, Organocatalysis in Inert C-H Bond Functionalization, *Chem. Rev.*, 2017, **117**, 9433–9520.
14 R. Parella, S. Jakkampudi and J. C. G. Zhao, Recent Applications of Asymmetric Organocatalytic Methods in Total Synthesis, *ChemistrySelect*, 2021, **6**, 2252–2280.
15 R. Mitra and J. Niemeyer, Dual Brønsted-acid Organocatalysis: Cooperative Asymmetric Catalysis with Combined Phosphoric and Carboxylic Acids, *ChemCatChem*, 2018, **10**, 1221–1234.
16 D. F. Chen, Z. Y. Han, X. Le Zhou and L. Z. Gong, Asymmetric organocatalysis combined with metal catalysis: Concept, proof of concept, and beyond, *Acc. Chem. Res.*, 2014, **47**, 2365–2377.
17 J. Becica and G. E. Dobereiner, The roles of Lewis acidic additives in organotransition metal catalysis, *Org. Biomol. Chem.*, 2019, **17**, 2055–2069.
18 X. Liang, S. Z. Jiang, K. Wei and Y. R. Yang, Enantioselective Total Synthesis of (-)-Alstoscholarisine A, *J. Am. Chem. Soc.*, 2016, **138**, 2560–2562.
19 S. Zhou, H. Chen, Y. Luo, W. Zhang and A. Li, Asymmetric total synthesis of mycoleptodiscin A, *Angew. Chem., Int. Ed.*, 2015, **54**, 6878–6882.
20 S. Z. Jiang, X. Y. Zeng, X. Liang, T. Lei, K. Wei and Y. R. Yang, Iridium-Catalyzed Enantioselective Indole Cyclization: Application to the Total Synthesis and Absolute Stereochemical Assignment of (-)-Aspidophylline A, *Angew. Chem., Int. Ed.*, 2016, **55**, 4044–4048.
21 C. C. Malakar, L. Dell'Amico and W. Zhang, Dual Catalysis in Organic Synthesis: Current Challenges and New Trends, *Eur. J. Org. Chem.*, 2023, **26**, e202201114.
22 N. Chakraborty, B. Das, K. K. Rajbongshi and B. K. Patel, Combined Power of Organo- and Transition Metal Catalysis in Organic Synthesis, *Eur. J. Org. Chem.*, 2022, **2022**, e202200273.
23 C. Zhong and X. Shi, When organocatalysis meets transition-metal catalysis, *Eur. J. Org. Chem.*, 2010, 2999–3025.
24 J. M. Lee, Y. Na, H. Han and S. Chang, Cooperative multi-catalyst systems for one-pot organic transformations, *Chem. Soc. Rev.*, 2004, **33**, 302–312.
25 S. H. Xiang and B. Tan, Advances in asymmetric organocatalysis over the last 10 years, *Nat. Commun.*, 2020, **11**, 3786.
26 E. Weis, *Iridium-Catalyzed C–H Activation Methods for Late-Stage Functionalization of Pharmaceuticals*, University, Stockholm, 2022.
27 C. Min and D. Seidel, Asymmetric Brønsted acid catalysis with chiral carboxylic acids, *Chem. Soc. Rev.*, 2017, **46**, 5889–5902.
28 M. H. Aukland and B. List, Organocatalysis emerging as a technology, *Pure Appl. Chem.*, 2021, **93**, 1371–1381.
29 T. Akiyama, J. Itoh and K. Fuchibe, Recent progress in chiral Brønsted acid catalysis, *Adv. Synth. Catal.*, 2006, **348**, 999–1010.
30 A. Zamfir, S. Schenker, M. Freund and S. B. Tsogoeva, Chiral BINOL-derived phosphoric acids: Privileged Brønsted acid organocatalysts for C-C bond formation reactions, *Org. Biomol. Chem.*, 2010, **8**, 5262–5276.
31 M. Rueping, R. M. Koenigs and I. Atodiresei, Unifying metal and Brønsted acid catalysis-concepts, mechanisms, and classifications, *Chem. – Eur. J.*, 2010, **16**, 9350–9365.
32 D. Parmar, E. Sugiono, S. Raja and M. Rueping, Complete field guide to asymmetric BINOL-phosphate derived Brønsted acid and metal catalysis: History and classification by mode of activation; Brønsted acidity, hydrogen bonding, ion pairing, and metal phosphates, *Chem. Rev.*, 2014, **114**, 9047–9153.
33 C. Li, C. Wang, B. Villa-Marcos and J. Xiao, Chiral counter-anion-aided asymmetric hydrogenation of acyclic imines, *J. Am. Chem. Soc.*, 2008, **130**, 14450–14451.
34 C. Li, B. Villa-Marcos and J. Xiao, Metal-bronsted acid cooperative catalysis for asymmetric reductive amination, *J. Am. Chem. Soc.*, 2009, **131**, 6967–6969.
35 W. Tang, S. Johnston, C. Li, J. A. Iggo, J. Bacsa and J. Xiao, Cooperative catalysis: Combining an achiral metal catalyst with a chiral Brønsted acid enables highly enantioselective hydrogenation of imines, *Chem. – Eur. J.*, 2013, **19**, 14187–14193.
36 M. Roggen and E. M. Carreira, Enantioselective allylic etherification: Selective coupling of two unactivated alcohols, *Angew. Chem., Int. Ed.*, 2011, **50**, 5568–5571.
37 Y. Zhang, C. Lim, D. S. B. Sim, H. Pan and Y. Zhao, Catalytic Enantioselective Amination of Alcohols by the Use of Borrowing Hydrogen Methodology: Cooperative Catalysis by Iridium and a Chiral Phosphoric Acid, *Angew. Chem., Int. Ed.*, 2014, **53**, 1399–1403.
38 Z. Q. Rong, Y. Zhang, R. H. B. Chua, H. J. Pan and Y. Zhao, Dynamic kinetic asymmetric amination of alcohols: From a mixture of four isomers to diastereo- and enantiopure α-branched amines, *J. Am. Chem. Soc.*, 2015, **137**, 4944–4947.
39 C. S. Lim, T. T. Quach and Y. Zhao, Enantioselective Synthesis of Tetrahydroquinolines by Borrowing Hydrogen Methodology: Cooperative Catalysis by an Achiral Iridacycle and a Chiral Phosphoric Acid, *Angew. Chem., Int. Ed.*, 2017, **56**, 7176–7180.
40 X. Q. Ng, C. S. Lim, M. W. Liaw, T. T. Quach, B. M. Yang, V. Isoni, J. Wu and Y. Zhao, Direct access to chiral aliphatic amines by catalytic enantioconvergent redox-neutral amination of alcohols, *Nat. Synth.*, 2023, **2**, 572–580.
41 Y. Liu, R. Tao, Z. K. Lin, G. Yang and Y. Zhao, Redox-enabled direct stereoconvergent heteroarylation of simple alcohols, *Nat. Commun.*, 2021, **12**, 5035.
42 D. Shen, Q. Chen, P. Yan, X. Zeng and G. Zhong, Enantioselective Dearomatization of Naphthol Derivatives with Allylic Alcohols by Cooperative Iridium and Brønsted Acid Catalysis, *Angew. Chem., Int. Ed.*, 2017, **56**, 3242–3246.
43 M. Sun, X. Wan, S. J. Zhou, G. J. Mei and F. Shi, Iridium and a Brønsted acid cooperatively catalyzed chemodivergent and stereoselective reactions of vinyl benzoxazinones with azlactones, *Chem. Commun.*, 2019, **55**, 1283–1286.

44 X. Q. Xie, X. Li and P. N. Liu, Enantioselective synthesis of spiro-N,O-ketals via iridium and Brønsted acid co-catalyzed asymmetric formal [4 + 2] cycloaddition, *Chem. Commun.*, 2024, **60**, 1448–1451.
45 D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes, *Chem. Rev.*, 2015, **115**, 9307–9387.
46 C. De Risi, A. Brandolese, G. Di Carmine, D. Ragno, A. Massi and O. Bortolini, Oxidative N-Heterocyclic Carbene Catalysis, *Chem. – Eur. J.*, 2023, **29**, e202202467.
47 G. J. Knox, L. S. Hutchings-Goetz, C. M. Pearson and T. N. Snaddon, *Tertiary Amine Lewis Base Catalysis in Combination with Transition Metal Catalysis*, Springer International Publishing, 2020, vol. 378.
48 K. Liu, I. Khan, J. Cheng, Y. J. Hsueh and Y. J. Zhang, Asymmetric Decarboxylative Cycloaddition of Vinylethylene Carbonates with β-Nitroolefins by Cooperative Catalysis of Palladium Complex and Squaramide, *ACS Catal.*, 2018, **8**, 11600–11604.
49 S. E. Denmark and G. L. Beutner, Lewis base catalysis in organic synthesis, *Angew. Chem., Int. Ed.*, 2008, **47**, 1560–1638.
50 I. Ibrahem and A. Córdova, Direct catalytic intermolecular α-allylic alkylation of aldehydes by combination of transition-metal and organocatalysis, *Angew. Chem., Int. Ed.*, 2006, **45**, 1952–1956.
51 M. H. Wang and K. A. Scheidt, Cooperative Catalysis and Activation with N-Heterocyclic Carbenes, *Angew. Chem., Int. Ed.*, 2016, **55**, 14912–14922.
52 K. Nagao and H. Ohmiya, N-Heterocyclic Carbene (NHC)/Metal Cooperative Catalysis, *Top. Curr. Chem.*, 2019, **377**, 1–15.
53 Q. Jia, Y. Li, Y. Lin and Q. Ren, The combination of lewis acid with N-heterocyclic carbene (NHC) catalysis, *Catalysts*, 2019, **9**, 863–886.
54 T. Kurihara, M. Kojima, T. Yoshino and S. Matsunaga, Achiral Cp*Rh(III)/Chiral Lewis Base Cooperative Catalysis for Enantioselective Cyclization via C-H Activation, *J. Am. Chem. Soc.*, 2022, **144**, 7058–7065.
55 J. Xiao, Merging organocatalysis with transition metal catalysis: Highly stereoselective α-alkylation of aldehydes, *Org. Lett.*, 2012, **14**, 1716–1719.
56 S. Krautwald, M. A. Schafroth, D. Sarlah and E. M. Carreira, Stereodivergent α-allylation of linear aldehydes with dual iridium and amine catalysis, *J. Am. Chem. Soc.*, 2014, **136**, 3020–3023.
57 T. Sandmeier, S. Krautwald, H. F. Zipfel and E. M. Carreira, Stereodivergent Dual Catalytic α–Allylation of Protected α–Amino– and α–Hydroxyacetaldehydes, *Angew. Chem., Int. Ed.*, 2015, **54**, 14363–14367.
58 Y. Deng, X. Liang, K. Wei and Y. R. Yang, Ir-Catalyzed Asymmetric Total Syntheses of Bisdehydrotuberostemonine D, Putative Bisdehydrotuberostemonine e and Structural Revision of the Latter, *J. Am. Chem. Soc.*, 2021, **143**, 20622–20627.
59 B. L. Wu, J. N. Yao, X. X. Long, Z. Q. Tan, X. Liang, L. Feng, K. Wei and Y. R. Yang, Enantioselective Total Synthesis of (−)-Daphenylline, *J. Am. Chem. Soc.*, 2024, **146**, 1262–1268.
60 L. Næsborg, K. S. Halskov, F. Tur, S. M. N. Mønsted and K. A. Jørgensen, Asymmetric γ-Allylation of α,β-Unsaturated Aldehydes by Combined Organocatalysis and Transition-Metal Catalysis, *Angew. Chem., Int. Ed.*, 2015, **54**, 10193–10197.
61 M. Li, X. Guo, W. Jin, Q. Zheng, S. Liu and W. Hu, An enantioselective three-component reaction of diazoacetates with indoles and enals by iridium/iminium co-catalysis, *Chem. Commun.*, 2016, **52**, 2736–2739.
62 M. Li, X. Guo, Q. Zheng, W. Hu and S. Liu, Enantioselective Multicomponent Reaction for Rapid Construction of 1,2,5-Triol Derivatives with Vicinal Chiral Centers, *J. Org. Chem.*, 2017, **82**, 5212–5221.
63 S. Krautwald, D. Sarlah, M. A. Schafroth and E. M. Carreira, Enantio- and diastereodivergent dual catalysis: α-Allylation of branched aldehydes, *Science*, 2013, **340**, 1065–1068.
64 M. M. Zhang, Y. N. Wang, B. C. Wang, X. W. Chen, L. Q. Lu and W. J. Xiao, Synergetic iridium and amine catalysis enables asymmetric [4 + 2] cycloadditions of vinyl aminoalcohols with carbonyls, *Nat. Commun.*, 2019, **10**, 2716.
65 X. Zhang, S. Li, W. Yu, Y. Xie, C. H. Tung and Z. Xu, Asymmetric Azide-Alkyne Cycloaddition with Ir(I)/Squaramide Cooperative Catalysis: Atroposelective Synthesis of Axially Chiral Aryltriazoles, *J. Am. Chem. Soc.*, 2022, **144**, 6200–6207.
66 Y. Chen, H. Yan, H. Zheng, W. P. Deng, Z. Li and W. L. Yang, Ir/Brønsted acid dual-catalyzed asymmetric synthesis of bisbenzannulated spiroketals and spiroaminals from isochroman ketals, *Org. Chem. Front.*, 2024, **11**, 5831–5840.
67 Z. Chen, Z. Chen, Z. Yang, L. Guo, W. Du and Y. Chen, Cooperative Tertiary Amine/Chiral Iridium Complex Catalyzed Asymmetric [4 + 3] and [3 + 3] Annulation Reactions, *Angew. Chem., Int. Ed.*, 2019, **58**, 15021–15025.
68 R. Sarkar and S. Mukherjee, Erratum: Iridium-catalyzed enantioselective olefinic C(sp2)-H allylic alkylation, *Chem. Sci.*, 2021, **12**, 3076.
69 X. Jiang, J. J. Beiger and J. F. Hartwig, Stereodivergent allylic substitutions with aryl acetic acid esters by synergistic iridium and lewis base catalysis, *J. Am. Chem. Soc.*, 2017, **139**, 87–90.
70 C. M. Pearson, J. W. B. Fyfe and T. N. Snaddon, A Regio– and Stereodivergent Synthesis of Homoallylic Amines by a One–Pot Cooperative–Catalysis–Based Allylic Alkylation/Hofmann Rearrangement Strategy, *Angew. Chem., Int. Ed.*, 2019, **58**, 10521–10527.
71 F. Tian, W. L. Yang, T. Ni, J. Zhang and W. P. Deng, Catalytic asymmetric dipolar cycloadditions of indolyl delocalized metal-allyl species for the enantioselective synthesis of cyclopenta [b]indoles and pyrrolo[1,2-a] indoles, *Sci. China: Chem.*, 2021, **64**, 34–40.

72 Q. Wang, T. Fan and J. Song, Cooperative Isothiourea/Iridium-Catalyzed Asymmetric Annulation Reactions of Vinyl Aziridines with Pentafluorophenyl Esters, *Org. Lett.*, 2023, **25**, 1246–1251.
73 B. Bhaskararao and R. B. Sunoj, Origin of Stereodivergence in Cooperative Asymmetric Catalysis with Simultaneous Involvement of Two Chiral Catalysts, *J. Am. Chem. Soc.*, 2015, **137**, 15712–15722.
74 S. Singha, E. Serrano, S. Mondal, C. G. Daniliuc and F. Glorius, Diastereodivergent synthesis of enantio-enriched α,β-disubstituted γ-butyrolactones via cooperative N-heterocyclic carbene and Ir catalysis, *Nat. Catal.*, 2020, **3**, 48–54.
75 J. Zhang, Y. S. Gao, B. M. Gu, W. L. Yang, B. X. Tian and W. P. Deng, Cooperative N-heterocyclic Carbene and Iridium Catalysis Enables Stereoselective and Regiodivergent [3 + 2] and [3 + 3] Annulation Reactions, *ACS Catal.*, 2021, **11**, 3810–3821.
76 C. Sun, X. Qi, X. L. Min, X. D. Bai, P. Liu and Y. He, Asymmetric allylic substitution-isomerization to axially chiral enamides: Via hydrogen-bonding assisted central-to-axial chirality transfer, *Chem. Sci.*, 2020, **11**, 10119–10126.
77 T. Hashimoto and K. Maruoka, Recent development and application of chiral phase-transfer catalysts, *Chem. Rev.*, 2007, **107**, 5656–5682.
78 S. Shirakawa and K. Maruoka, Recent developments in asymmetric phase-transfer reactions, *Angew. Chem., Int. Ed.*, 2013, **52**, 4312–4348.
79 M. Nakoji, T. Kanayama, T. Okino and Y. Takemoto, Chiral phosphine-free Pd-mediated asymmetric allylation of prochiral enolate with a chiral phase-transfer catalyst, *Org. Lett.*, 2001, **3**, 3329–3331.
80 M. Nakoji, T. Kanayama, T. Okino and Y. Takemoto, Pd-catalyzed asymmetric allylic alkylation of glycine imino ester using a chiral phase-transfer catalyst, *J. Org. Chem.*, 2002, **67**, 7418–7423.
81 Y. L. Su, Y. H. Li, Y. G. Chen and Z. Y. Han, Ir/PTC cooperatively catalyzed asymmetric umpolung allylation of α-imino ester enabled synthesis of α-quaternary amino acid derivatives bearing two vicinal stereocenters, *Chem. Commun.*, 2017, **53**, 1985–1988.
82 L. Wei, L. Xiao, Z. F. Wang, H. Y. Tao and C. J. Wang, Ir/Phase-Transfer-Catalysis Cooperatively Catalyzed Asymmetric Cascade Allylation/2-aza-Cope Rearrangement: An Efficient Route to Homoallylic Amines from Aldimine Esters, *Chin. J. Chem.*, 2020, **38**, 82–86.
83 N. A. Romero and D. A. Nicewicz, Organic Photoredox Catalysis, *Chem. Rev.*, 2016, **116**, 10075–10166.
84 A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, L. I. Frye, O. L. Garry, M. N. Lavagnino, B. X. Li, Y. Liang, E. Mao, A. Millet, J. V. Oakley, N. L. Reed, H. A. Sakai, C. P. Seath and D. W. C. MacMillan, Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis, *Chem. Rev.*, 2022, **122**, 1485–1542.
85 J. H. Shen, M. Shi and Y. Wei, Synergistic Visible Light Photocatalysis with Organocatalysis, *Chem. – Eur. J.*, 2023, **29**, e202301157.
86 W. Yao, E. A. Bazan-Bergamino and M. Y. Ngai, Asymmetric Photocatalysis Enabled by Chiral Organocatalysts, *ChemCatChem*, 2022, **14**, e202101292.
87 Y. Y. Liu, J. Liu, L. Q. Lu and W. J. Xiao, Organocatalysis Combined with Photocatalysis, *Top. Curr. Chem.*, 2019, **377**, 1–15.
88 M. H. Shaw, J. Twilton and D. W. C. MacMillan, Photoredox Catalysis in Organic Chemistry, *J. Org. Chem.*, 2016, **81**, 6898–6926.
89 J. D. Slinker, A. A. Gorodetsky, M. S. Lowry, J. Wang, S. Parker, R. Rohl, S. Bernhard and G. G. Malliaras, Efficient Yellow Electroluminescence from a Single Layer of a Cyclometalated Iridium Complex, *J. Am. Chem. Soc.*, 2004, **126**, 2763–2767.
90 D. A. Nagib, M. E. Scott and D. W. C. MacMillan, Enantioselective α-trifluoromethylation of aldehydes via photoredox organocatalysis, *J. Am. Chem. Soc.*, 2009, **131**, 10875–10877.
91 H. W. Shih, M. N. Vander Wal, R. L. Grange and D. W. C. MacMillan, Enantioselective α-benzylation of aldehydes via photoredox organocatalysis, *J. Am. Chem. Soc.*, 2010, **132**, 13600–13603.
92 L. J. Rono, H. G. Yayla, D. Y. Wang, M. F. Armstrong and R. R. Knowles, Enantioselective photoredox catalysis enabled by proton-coupled electron transfer: Development of an asymmetric aza-pinacol cyclization, *J. Am. Chem. Soc.*, 2013, **135**, 17735–17738.
93 R. S. J. Proctor, H. J. Davis and R. J. Phipps, Catalytic enantioselective Minisci-type addition to heteroarenes, *Science*, 2018, **360**, 419–422.
94 Y. Cheng, Q. Zhao, X. Zhang and S. You, Asymmetric Dearomatization of Indole Derivatives with N–Hydroxycarbamates Enabled by Photoredox Catalysis, *Angew. Chem., Int. Ed*, 2019, **58**, 18069–18074.
95 S. J. Chapman, W. B. Swords, C. M. Le, I. A. Guzei, F. D. Toste and T. P. Yoon, Cooperative Stereoinduction in Asymmetric Photocatalysis, *J. Am. Chem. Soc.*, 2022, **144**, 4206–4213.
96 J. Wei, Y. Tang, Q. Yang, H. Li, D. He and Y. Cai, Asymmetric Ketoalkylation/Rearrangement of Alkyenlfurans via Synergistic Photoredox/Brønsted Acid Catalysis, *Org. Lett.*, 2022, **24**, 7928–7933.
97 C. Che, Y. N. Lu and C. J. Wang, Enantio- and Diastereoselective De Novo Synthesis of 3-Substituted Proline Derivatives via Cooperative Photoredox/Brønsted Acid Catalysis and Epimerization, *J. Am. Chem. Soc.*, 2023, **145**, 2779–2786.
98 D. Uraguchi, N. Kinoshita, T. Kizu and T. Ooi, Synergistic Catalysis of Ionic Brønsted Acid and Photosensitizer for a Redox Neutral Asymmetric α-Coupling of N-Arylaminomethanes with Aldimines, *J. Am. Chem. Soc.*, 2015, **137**, 13768–13771.

99 S. M. Cho, J. Y. Kim, S. Han and D. H. Ryu, Visible Light-Mediated Enantioselective Addition of α-Aminoalkyl Radicals to Ketones Catalyzed by Chiral Oxazaborolidinium Ion, *J. Org. Chem.*, 2022, **87**, 11196–11203.

100 (*a*) X. Yu, Q. Y. Meng, C. G. Daniliuc and A. Studer, Aroyl Fluorides as Bifunctional Reagents for Dearomatizing Fluoroaroylation of Benzofurans, *J. Am. Chem. Soc.*, 2022, **144**, 7072–7079; (*b*) J. Su, J.-N. Mo, G. Zhang, Z. Jiang and J. Zhao, A practical approach for oligopeptide synthesis via synergistic photoredox, cobaloxime and organophosphorus triple catalysis, *Org. Chem. Front.*, 2023, **10**, 4895–4904.

101 J. Li, S. Gong, S. Gao, J. Chen, W. W. Chen and B. Zhao, Asymmetric α-C(sp3)–H allylic alkylation of primary alkylamines by synergistic Ir/ketone catalysis, *Nat. Commun.*, 2024, **15**, 939.

102 Z. C. Litman, Y. Wang, H. Zhao and J. F. Hartwig, Cooperative asymmetric reactions combining photocatalysis and enzymatic catalysis, *Nature*, 2018, **560**, 355–359.

103 D. H. Chen, W. T. Sun, C. J. Zhu, G. S. Lu, D. P. Wu, A. E. Wang and P. Q. Huang, Enantioselective Reductive Cyanation and Phosphonylation of Secondary Amides by Iridium and Chiral Thiourea Sequential Catalysis, *Angew. Chem., Int. Ed.*, 2021, **60**, 8827–8831.

104 H. Chen, Z. Z. Wu, D. Y. Shao and P. Q. Huang, Multicatalysis protocol enables direct and versatile enantioselective reductive transformations of secondary amides, *Sci. Adv.*, 2022, **8**, eade3431.