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MINI REVIEW

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Catalytic Asymmetric Reductive Addition of Organic Electrophiles to Carbonyls and Beyond

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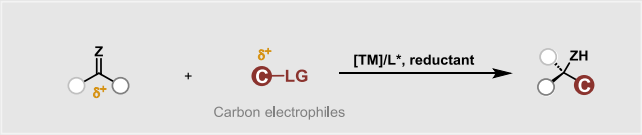
Stereoselective addition to carbonyls and imines constitutes a powerful synthetic strategy for constructing chiral alcohols and amines. Reductive additions, employing organic electrophiles under a terminal reductant, can circumvent the need for preformed organometallic reagents. This approach offers significant advantages over traditional nucleophilic additions, including improved functional group compatibility and broader substrate scope, and has consequently garnered substantial attention. Over the past decade, significant progress has been made in catalytic asymmetric reductive addition (CARA reaction) of carbonyl compounds enabled by a transition metal catalyst. This review provides a comprehensive summary of advances from the past decade in transition metal-catalyzed asymmetric reductive C–C bond formation with carbonyls and imines, including arylation, alkenylation, allylation, propargylation, and alkylation. Emphasis is placed on couplings of diverse carbon electrophiles with aldehydes, ketones, imines, isocyanates, and sulfinylimines to forge chiral C–C and C–S bonds. The scope of electrophilic reagents and related mechanistic insights is also discussed. Finally, this review outlines current challenges and emerging opportunities in this rapidly evolving field, offering perspectives on future research.



Keywords: **reductive addition, carbonyl compounds, organic electrophiles, transition metal, asymmetric catalysis**

Introduction

Carbonyls represent fundamental structural motifs that are extensively distributed throughout petrochemical feedstocks, bioactive molecules, and natural products. The oxygen atom's electronegativity polarizes the C=O bond, imparting substantial electrophilic character to the carbonyl carbon and rendering it a versatile linchpin for synthetically important C–C bond-forming reactions.[1] Among representative transformations, transition-metal-catalyzed carbonyl additions have emerged as a powerful strategy for constructing alcohol and amine scaffolds.[2] However, traditional approaches necessitate preformed organometallic reagents (e.g., organolithium

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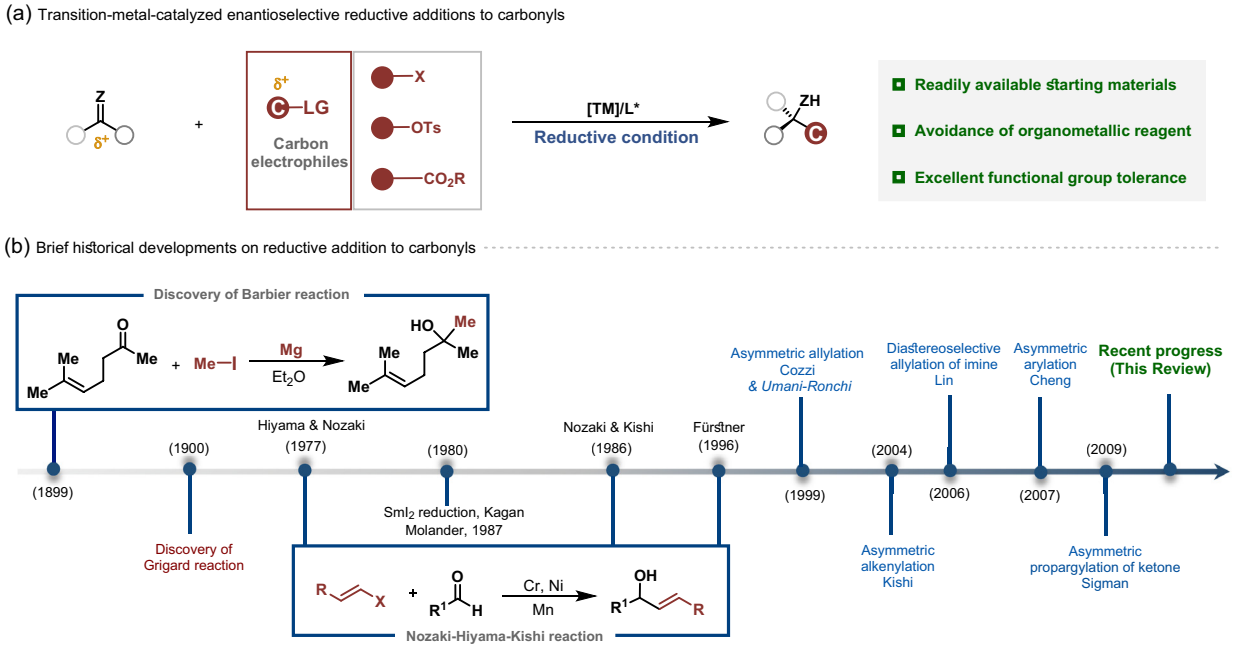

Scheme 1 | *Transition-metal-catalyzed asymmetric reductive addition to carbonyl compounds with carbon electrophiles.*

or Grignard reagents), which require stringent anhydrous conditions for preparation and storage.[3–7] Furthermore, these highly basic and strongly nucleophilic reagents exhibit limited functional group tolerance, significantly restricting their utility in late-stage molecular diversification and diminishing the general applicability of carbonyl additions in organic synthesis. In contrast, organic electrophiles, particularly halides, offer distinct advantages due to their inherent stability and ready accessibility. Reductive addition reactions employing these electrophiles with terminal reductant represent a highly attractive alternative, obviating the need for preformed organometallic reagents and enabling single-step construction of functionalized compounds with enhanced structural diversity (Scheme 1a).[8–11] The genesis of this approach traces back to Barbier's seminal work in 1899, in magnesium-mediated one-pot carbonyl additions of alkyl iodides (Scheme 1b).[12] Subsequent transformative breakthroughs, including the development of samarium (II) iodide-mediated reductive addition[13–16] and the establishment of Nozaki–Hiyama–Kishi (NHK) reaction,[17–20] dramatically enhanced the scope and usefulness of reductive addition chemistry. Notably, the NHK reaction has become an indispensable protocol for the facile assembly of chiral alcohols in complex natural products and pharmaceuticals, owing to its mild conditions, good chemoselectivity, and excellent functional group tolerance.[21] Given these distinctive merits, extensive efforts have been made in advancing catalytic asymmetric reductive addition (CARA) of carbonyls. In the last decades, rapid progress in innovation in chiral nitrogen and phosphorus ligands, and development of photoredox and electrocatalysis have facilitated remarkable developments in CARA enabled by transition metals.[22–24] This review provides a succinct overview and update on transition metal-catalyzed asymmetric reductive arylation, alkenylation, and alkylation reactions of carbonyl class of acceptors, including aldehydes, ketones, imines, and Michael acceptors. Notably, asymmetric reductive carbonyl couplings mediated by chiral Lewis acid or Brønsted acid catalysis have been extensively reviewed elsewhere[25,26] and fall beyond the scope of this review.

The mechanistic pathway of reductive addition typically begins with electrophile activation by a low-valent transition metal complex, requiring a reductant to provide electrons and drive the reaction forward; conventional reductants include the terminal metal species (e.g., Mn, Zn) or organic reductants (e.g., TDAE, B_2pin_2). This initiation step of activation can also be performed by photoredox and electrochemical means. Furthermore, asymmetric C(sp^3)–carbon bond construction can be classified into three types, depending on the pathways of electrophile activation and C–C bond formation, via polar addition of in situ-generated aryl/alkenyl-metal species, radical-polar crossover processes, or radical addition of alkyl radicals. In the first type of pathway, transition metal-catalyzed asymmetric arylation/alkenylation proceeds through oxidative addition of C(sp^2)-electrophiles to chiral low-valent metal complexes, followed by stereoselective nucleophilic addition to unsaturated C=O or C=N bonds (Scheme 2a). In the second pathway, C(sp^3)-electrophiles are activated via a

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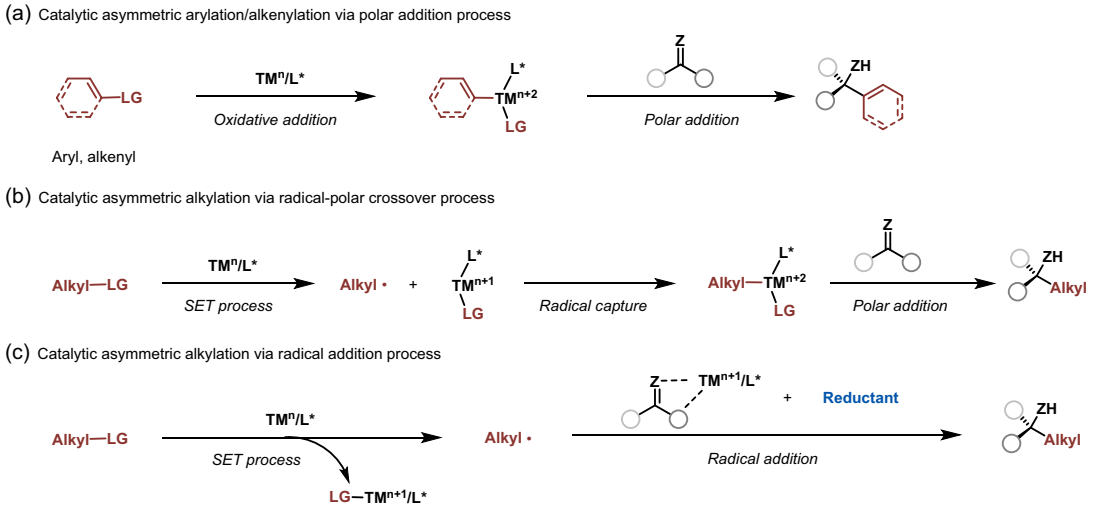


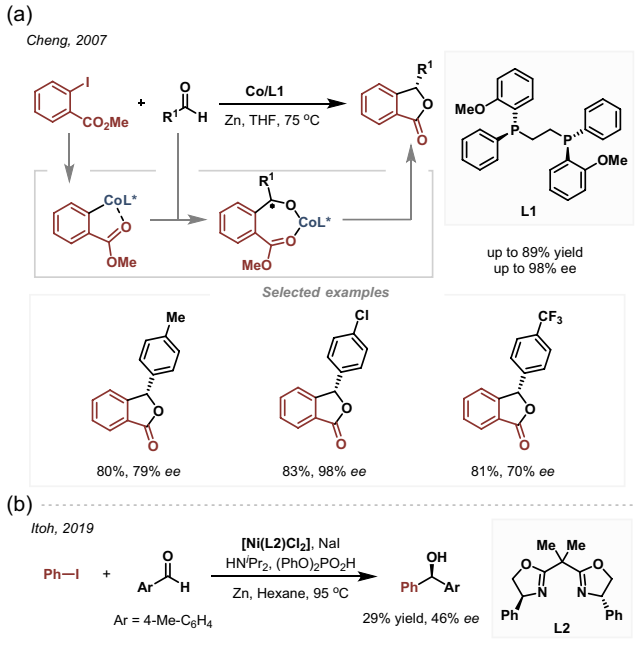
Scheme 2 | *Primary pathways for transition metal-catalyzed asymmetric reductive addition of electrophiles to carbonyls.*

single-electron transfer (SET) process to generate alkyl radicals that rapidly combine with the metal catalyst to form the nucleophilic alkyl-metal intermediate. Subsequent single-electron reduction and stereoselective addition to carbonyl compounds furnish the desired products while regenerating the chiral metal catalyst (Scheme 2b). The alkyl-metal intermediate species may also directly undergo asymmetric polar addition without requiring further single-electron reduction. In the third pathway, in situ-generated alkyl radicals from alkyl halides and low-valent metal catalysts may undergo stereoselective radical addition towards chelates formed by chiral metal complexes and carbonyl substrate to form new C(sp^3)–C(sp^3) bonds (Scheme 2c). Notably, alternative mechanisms like oxidative cyclization or radical–radical coupling between electrophiles and carbonyls may also afford chiral products.

Transition-Metal-Catalyzed Asymmetric Reductive Addition to Aldehydes

Asymmetric arylation with aryl electrophiles

The asymmetric reductive aryl addition of aldehydes has emerged as a preferred method for synthesizing chiral secondary benzylic alcohols, which are important structural motifs in numerous natural products and pharmaceuticals. An early work by Cheng's group[27] in 2000 disclosed a nickel-catalyzed reductive arylation of aldehydes with aryl halides using stoichiometric zinc. However, attempts to use chiral bisoxazoline ligands in this system afforded racemic products. A significant development came in 2007 when the same group achieved cobalt-catalyzed asymmetric aryl addition of *o*-iodobenzoates to aldehydes. Utilizing a bidentate *P*-chiral ligand, this transformation delivered arylated phthalides with high enantioselectivity (Scheme 3a).[28] Mechanistically, the reaction could proceed through oxidative addition of 2-iodobenzoate to cobalt, followed by aldehyde coordination/insertion to form a cobalt alkoxide, which underwent intramolecular esterification to produce the final product. In 2019, Itoh and coworkers[29] developed a nickel-catalyzed asymmetric reductive coupling of aryl iodides employing chiral bisoxazoline



Scheme 3 | *Early studies on cobalt/nickel-catalyzed asymmetric reductive addition of aldehydes.*

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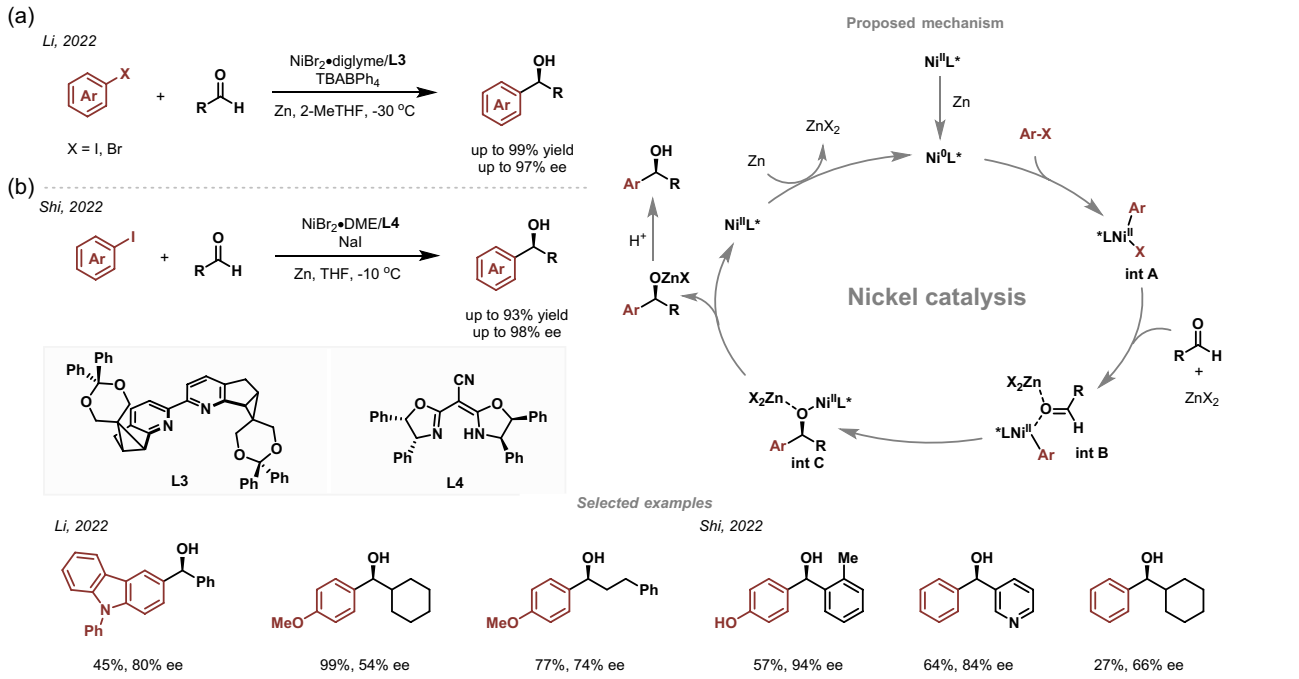

Scheme 4 | *Nickel-catalyzed asymmetric reductive addition of aryl halides with aldehydes.*

ligands, although only a moderate level of enantiocontrol was achieved (Scheme 3b).

Subsequently, Li's group[30] designed a novel class of chiral 2,2′-bipyridine (bpy) ligands featuring minimized short-range steric hindrance, which enabled efficient nickel-catalyzed asymmetric reductive couplings of aryl halides with aldehydes (Scheme 4a). Mechanistic investigations identified that the π–π interaction between the phenyl group of benzaldehyde and a proximal phenyl substituent on the chiral ligand was crucial to achieving high enantioselectivity (up to 97% ee). Concurrently, Shi's group[31] reported a similar nickel-catalyzed enantioselective addition of aryl iodides using semicorrins as chiral ligands (Scheme 4b), which exhibited broad substrate scope and excellent functional group tolerance. It should be noted that both systems gave moderate enantioselectivity with aliphatic aldehydes. The general mechanism proceeded as follows: The Ni(II)/L* complex was reduced by Zn to afford active Ni(0)/L* species, which underwent oxidative addition into aryl iodide to afford Ar-Ni(II) **int A**. **int A** could interact with an aldehyde to generate reactive **int B**, followed by 1,2-migratory insertion, ligand exchange, and hydrolysis to yield a chiral alcohol.

Metallaphotoredox catalysis—combining transition-metal catalysis and photoredox processes—has emerged as a transformative strategy in reaction discovery over the past decade. It offers activation modes complementary to conventional thermal or reductive conditions while significantly expanding synthetic possibilities.[32] In 2022, Xiao and coworkers[33] reported a visible-light-driven cobalt-catalyzed asymmetric reductive addition of aryl halides using Hantzsch ester (HE) as the reductant and *N*,*N*-Diisopropylethylamine (DIPEA) as the proton acceptor (Scheme 5). The reaction accommodated both aromatic and aliphatic aldehydes with broad substrate scope, delivering products with excellent enantioselectivity (up to 99% ee). Kinetic studies identified the migratory insertion of aryl cobalt species into the aldehyde as the rate-determining step. Mechanistically, the dual photoredox/cobalt system substituted stoichiometric metal reductants with a photoexcited organic catalyst and an alkyl amine (Scheme 5, bottom). The catalytic cycle initiates with the reduction of the photoexcited photocatalyst (4CzIPN*) species by a terminal reductant (HE) to deliver 4CzIPN$^{\bullet-}$ species, which could reduce a Co(II) complex to catalytically active Co(I) species via SET. The latter undergoes oxidative addition with an aryl halide to form an aryl-Co(III) intermediate, followed by reduction to yield the aryl-Co(II) species, postulated to be the actual species for stereoselective carbonyl addition.

Building upon the aforementioned metallaphotoredox catalysis, the same group[34] subsequently extended the reactivity to asymmetric reductive couplings of biaryl dialdehydes with aryl iodides or alkynes (Scheme 6a, top). This desymmetrization reaction efficiently provided diverse axially chiral aldehydes with good functional group tolerance. It should be noted that the coupling between aldehydes and alkynes might proceed via elementary oxidative coupling. Recently, Xiao and coworkers[35] disclosed photoinduced cobalt-catalyzed

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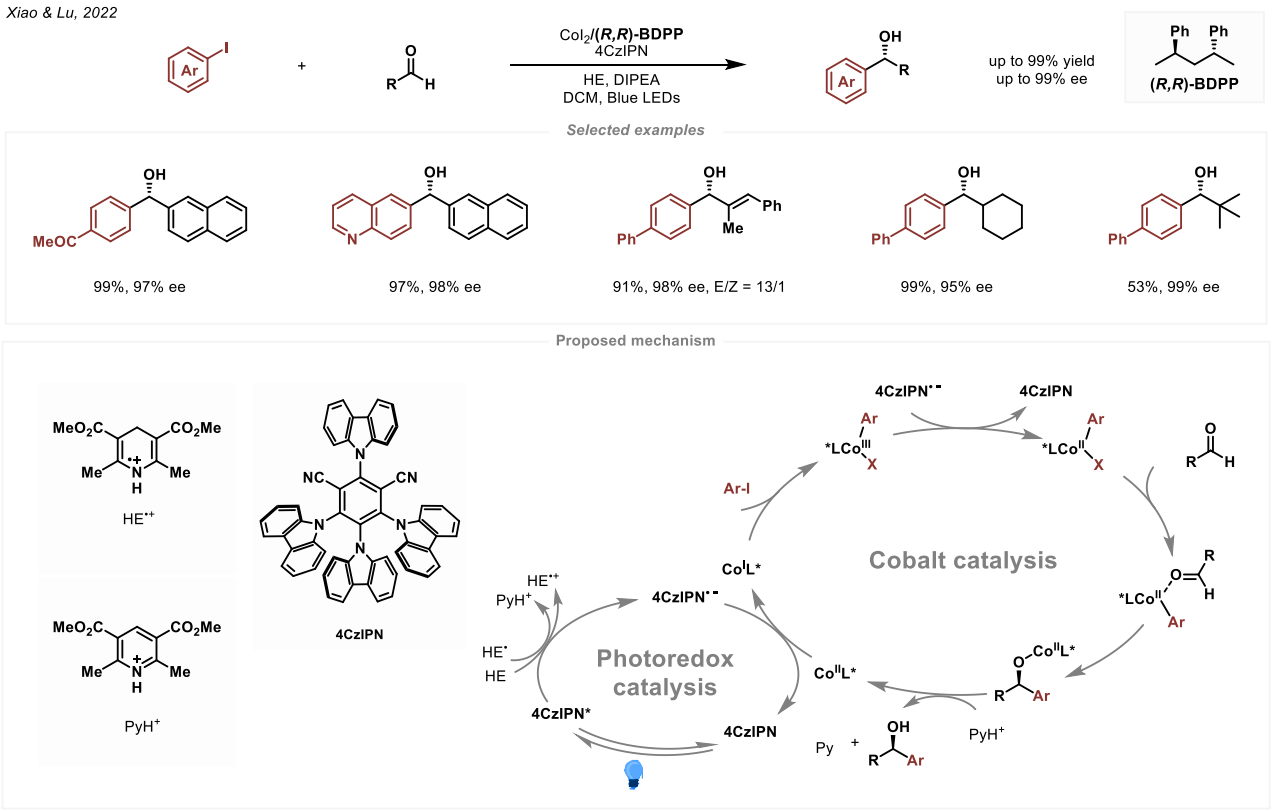
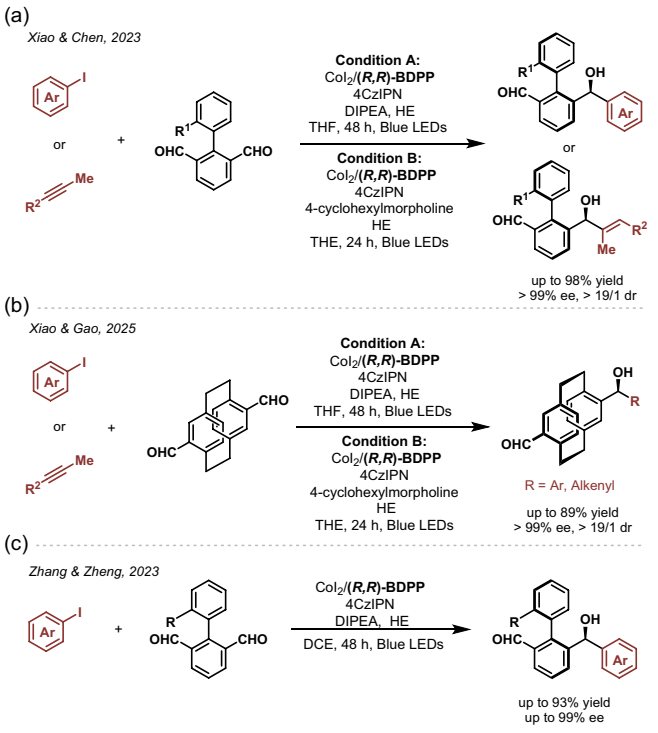


Scheme 5 | *Light-emitting diode (LED) light-induced cobalt-catalyzed asymmetric reductive addition of aryl iodides with aldehydes.*



Scheme 6 | *Cobalt-catalyzed asymmetric reductive arylation with aryl iodides to access axial chirality.*

desymmetric addition of paraphanes having two para-aldehydes with aryl iodides or alkynes (Scheme 6b). This method successfully afforded planar chiral [2,2] paracyclophane derivatives (up to 89% yield, >99% ee, and >19/1 dr). Additionally, a similar photoredox cobalt-catalyzed desymmetrization of prochiral biaryl dialdehydes via aryl addition was achieved by Zhang and coworkers in 2023 (Scheme 6c).[36] In contrast to Xiao's system, this approach was successfully applied to 2-methylated axially prochiral dialdehydes, in which methyl substituents effectively served as blocking groups. Preliminary mechanistic investigations suggested that the observed high stereocontrol might be attributed to a combination of an initial desymmetrization in the first arylation and kinetic resolution in the second arylation. Later, Liu and coworkers[37] employed DIPEA as the reductant to achieve a light-driven asymmetric coupling of aromatic aldehydes with aryl iodides. This approach circumvented the use of excess HE, thereby improving the atom economy of the transformation.

As illustrated in Scheme 4, the aromatic iodides and bromides were often used as electrophiles, whereas less reactive aryl chlorides rarely participate in reductive coupling reactions, owing to an inherently low reactivity of aryl chlorides toward oxidative addition with low-valent metal catalysts. Subsequent work in 2024 by Cao

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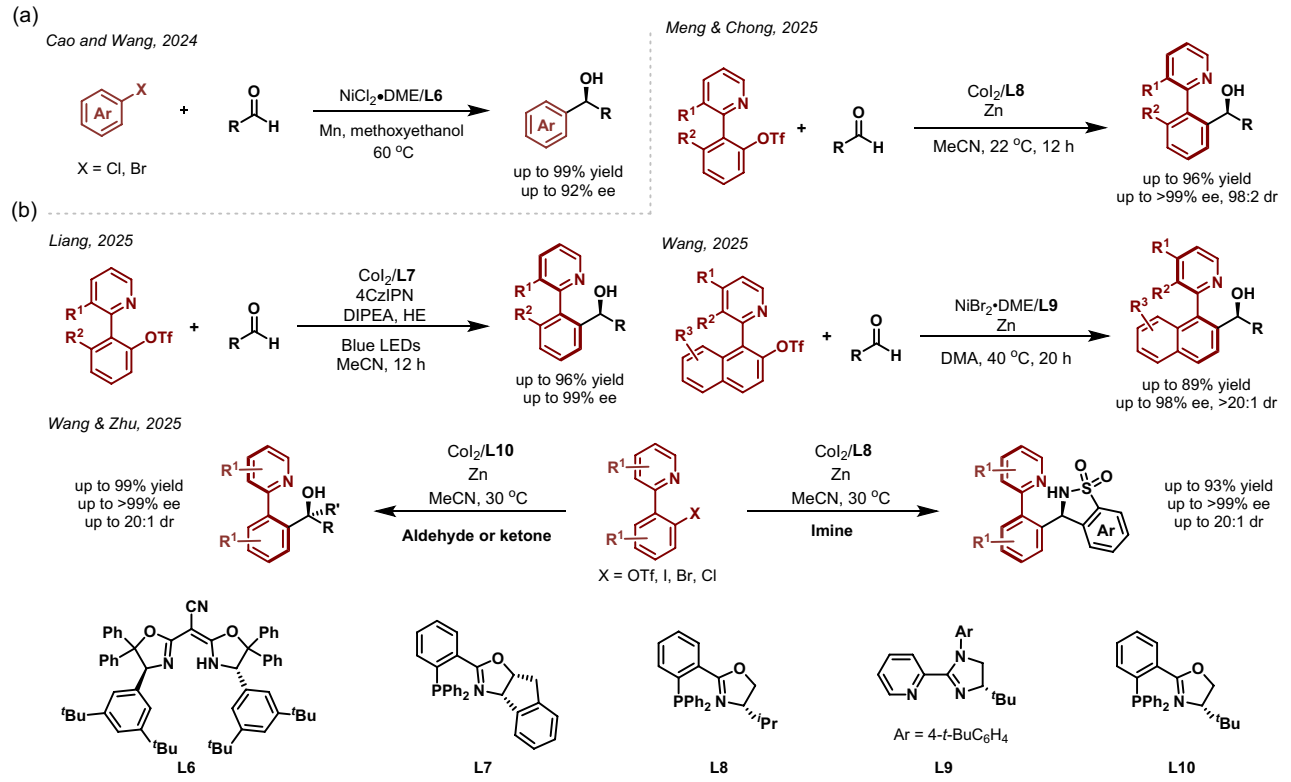
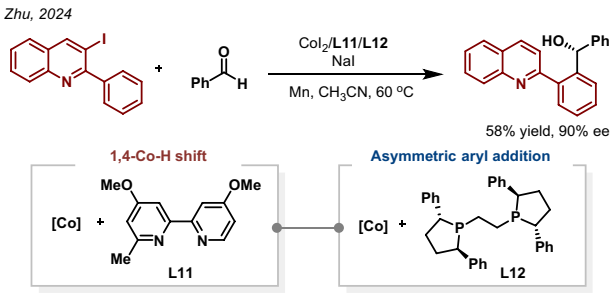


Scheme 7 | *Nickel/Cobalt-catalyzed asymmetric reductive addition of aryl chlorides and axially chiral aryl electrophiles with aldehydes.*

and coworkers[38] addressed this limitation by employing a new semicorrin ligand, which enabled nickel-catalyzed enantioselective carbonyl additions of both aryl chlorides and bromides (Scheme 7a). In addition, the groups of Liang,[39] Meng[40], and Wang[41] independently demonstrated asymmetric reductive aryl addition using racemic *N*-heterobiaryl triflates (Scheme 7b). This approach proceeded dynamic kinetic resolution of aryl nickel species after oxidative addition, providing access to optically pure heterobiaryl alcohols bearing both axial and central stereocenter with excellent diastereo- and enantioselectivity. Very recently, Wang and coworkers[42] also reported a similar arylation with racemic heterobiaryls using cobalt-catalysts (Scheme 7b, bottom). Notably, the authors successfully expanded the substrate scope of arylation from aldehydes to ketones and imines.

In the last decade, 3d metal-catalyzed catalytic reactions involving metal 1,4-shift have been increasingly reported.[43–45] In 2024, Zhu's group[46] disclosed cobalt-catalyzed asymmetric migratory reductive addition between aryl halides and aldehydes involving metal 1,4-migration (Scheme 8). Interestingly, the authors developed a ligand relay strategy involving two ligands of different types. The authors found that the bipy ligand facilitated 1,4-Co/H shift, while the other ligand of 1,2-bis (2,5-dialkylphospholano)ethane (BPE) was capable of promoting asymmetric reductive addition. A plausible mechanism for the migratory reductive addition is presented in Scheme 12.

C-Glycosides have garnered increasing attention due to their resistance to chemical and enzymatic degradation, different from natural *O*- and *N*-glycosides.[47–49] Recently, Zhu and colleagues[50] reported a photoinduced cobalt-catalyzed asymmetric reductive coupling between glycosyl aldehydes and aryl iodides, which provided efficient access to chiral hydroxymethine *C*-glycosides with excellent enantioselectivities and broad substrate scope (Scheme 9). In addition, using the enantiomer of the BDPP ligand led to the selective formation of the epimer of the



Scheme 8 | *Cobalt-catalyzed asymmetric aryl-to-heteroaryl migration and addition of aldehydes.*

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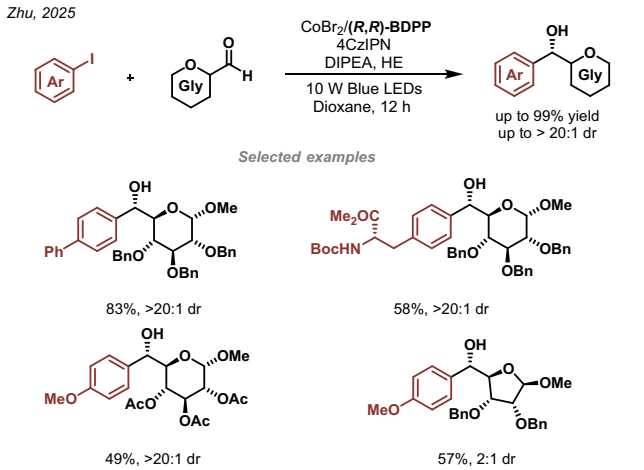
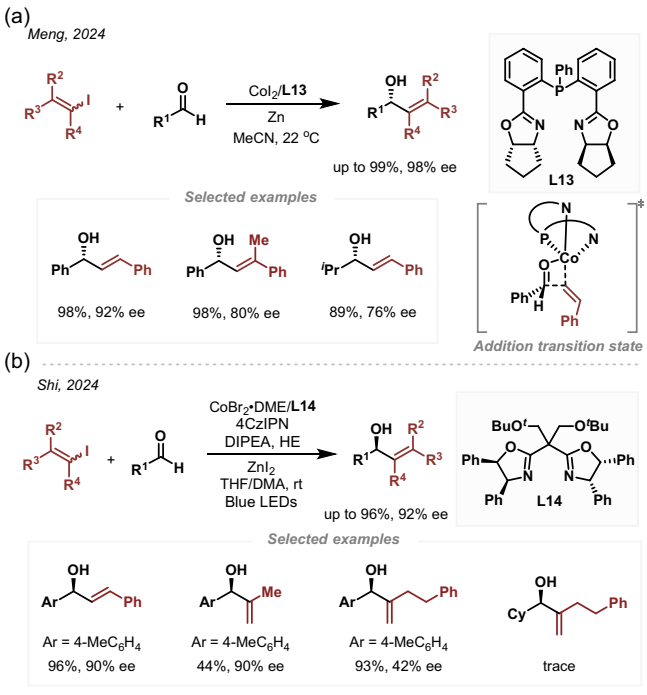


Scheme 9 | *Photoinduced cobalt-catalyzed asymmetric reductive addition of glycosyl C-aldehydes.*

C-glycoside diastereomers. Meanwhile, density functional theory (DFT) calculations provided mechanistic insights into the origin of the modulation of stereoselectivity in this transformation.

Asymmetric alkenylation with alkenyl electrophiles

In 2024, Meng's group[51] reported a cobalt-catalyzed asymmetric NHK reaction between aldehydes and alkenyl halides (Scheme 10a, top). A tridentate bisoxazolinephosphine **L13** proved crucial for achieving high stereoselectivity. Mechanistic investigations, including electron paramagnetic resonance (EPR) spectroscopy and reactions involving E/Z isomerization of alkenyl halides, revealed the involvement of alkenyl radicals as intermediates during the reaction. Subsequently, Shi's group[52] introduced a cobalt-catalyzed asymmetric NHK reaction under metallaphotoredox conditions (Scheme 10b, bottom). The authors also applied the reaction in late-stage modifications of complex molecules.



Scheme 10 | *Cobalt-catalyzed asymmetric NHK alkenylation of aldehydes.*

Electrochemical-organic synthesis has emerged as an environmentally benign and efficient alternative for constructing valuable molecules, replacing exogenous redox reagents with electric current.[53–55] In 2021, a collaborative work of Baran and coworkers[56] resulted in an electrochemical NHK coupling between alkyl aldehydes and alkenyl bromides via Ni/Cr cocatalysis. Here, it was demonstrated that low-valent nickel activates alkenyl halides to generate alkenyl-Ni(II) species. This intermediate undergoes transmetalation with chromium, followed by aldehyde addition and transmetalation from nickel to Cp_2ZrCl_2 to furnish the product (Scheme 11, bottom). Subsequent studies successfully extended this electrochemical method to the classic *asymmetric* NHK reaction with alkenyl halides,[57–61] which was first reported by Kishi et al. using chiral sulfonamide ligands with moderate-to-good enantioselectivity (Scheme 11, top). Crucially, unlike the classical NHK reaction, which was typically limited by the rate of Cr(III) to Cr(II) reduction, the electrochemical NHK (eNHK) enables direct modulation of reaction rates through current control.

In the previous section, Zhu's group[46] reported asymmetric reductive arylation relying on a key step of a 1,4-shift of cobalt. The same group extended the same strategy to asymmetric alkenylation of aldehydes (Scheme 12a). The reactions of employed *ortho*-halophenylethylenes proceeded through a novel aryl-to-alkenyl 1,4-cobalt shift to afford various chiral allylic alcohols. Mechanistic experiments with Co(I) complex indicated that the alkenyl cobalt(I) complex is likely the catalytic active species. Remarkably, the 1,4-shift of cobalt could be selectively switched on or off through judicious choice of ligands. Some aliphatic aldehydes were suitable substrates. In 2024, Shi's group[62] reported a nickel-catalyzed alkenylation with aldehydes under metallaphotoredox conditions (Scheme 12b). Kinetic isotope effect (KIE) studies suggested that 1,4-nickel migration might be turnover-limiting. Different from the work of Zhu's group,[46] aliphatic aldehydes were unsuitable substrates for this reaction system.

Xia's group[63] had made notable progress in achieving the first enantioselective reductive coupling between aldehydes and unsymmetrical internal alkynes via photoredox/cobalt catalysis (Scheme 13a). This system efficiently accessed diverse enantioenriched allylic alcohols with excellent regio- (>95:5) and stereoselectivity

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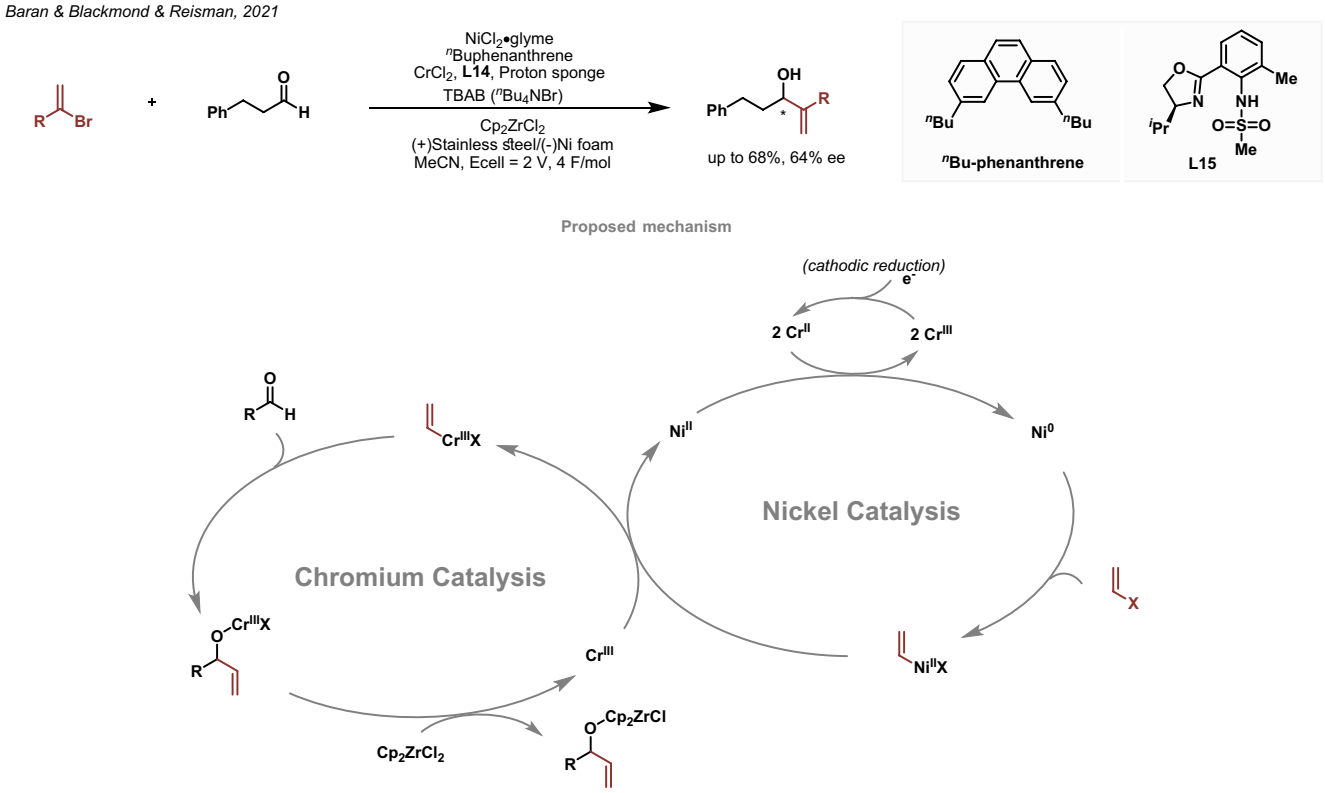
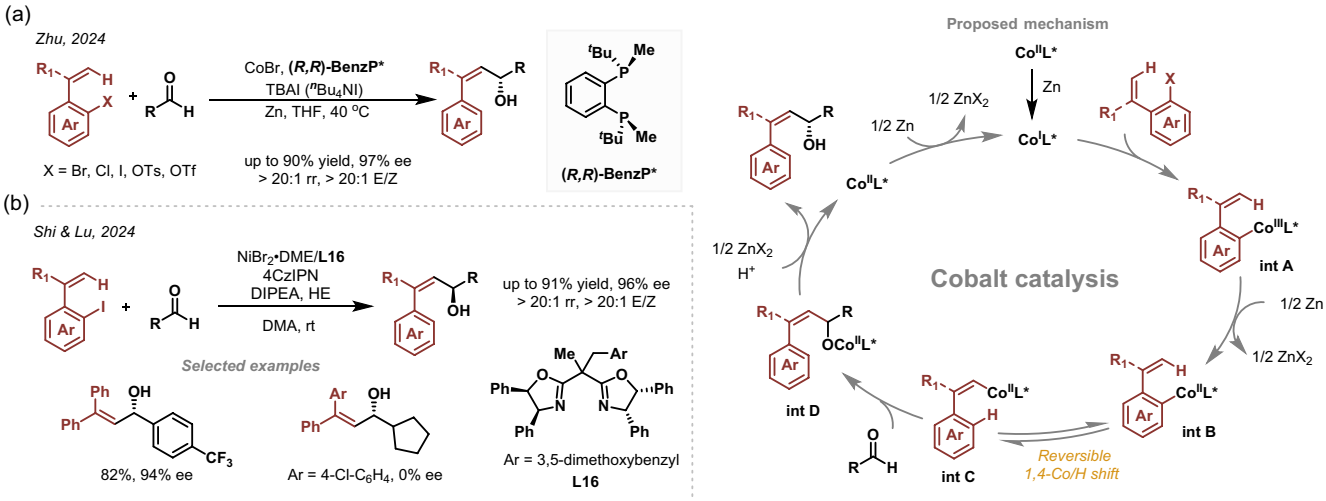


Scheme 11 | *Electro/Ni cocatalyzed asymmetric reductive alkenylation of aldehydes.*

(>95:5 E/Z, 99% ee). Mechanistic studies indicate that the single-electron reduction of Co(II) to active Co(I) initiated the oxidative cyclization with both alkyne and aldehyde bound to cobalt. Oxidative cyclization of the alkyne and aldehyde then formed a cobaltacycle (a cobalt-containing cyclic compound), and subsequent protonation, reduction, and final protonation afforded the product. However, an alternative pathway involving hydrometallation of alkynes by cobalt(III) hydride (generated via $HE^{\bullet+}$ oxidation) could not be ruled out. Subsequently, Xiao and colleagues disclosed a photoinduced cobalt-catalyzed desymmetric reductive coupling of dialdehydes with alkynes, enabling the synthesis of diverse chiral alcohols featuring central chirality in conjunction with axial or planar chirality (Scheme 13b).[34,35] In 2024, Li and Yu group[64] reported a reductive coupling of diaryl dialdehydes with alkynes by merging cobalt and photoredox catalysis (Scheme 13c). In the desymmetrization



Scheme 12 | *Cobalt-catalyzed asymmetric migratory NHK reaction.*

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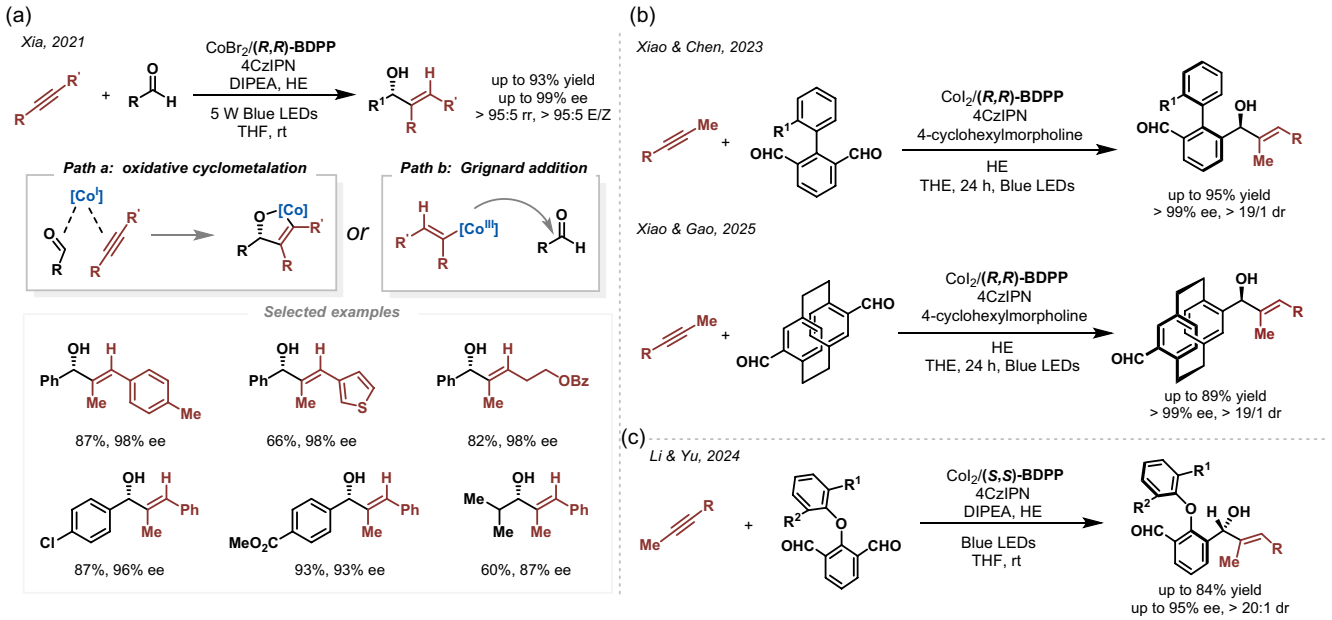


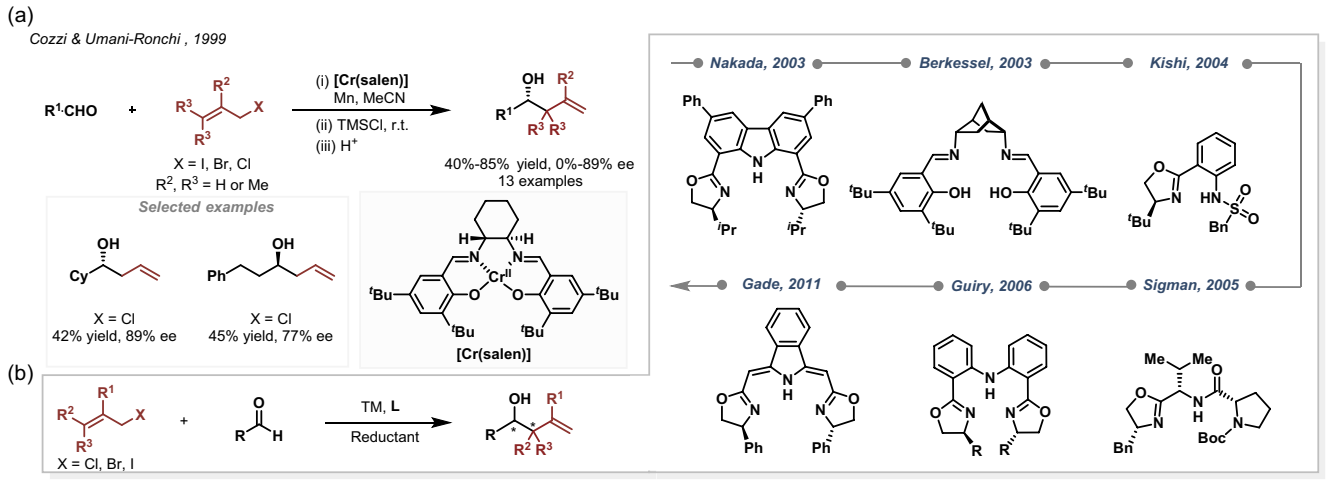
Scheme 13 | *Cobalt-catalyzed enantioselective reductive alkenylation of aldehydes with alkynes.*

strategy, a broad range of C–O axially chiral diaryl ether scaffolds were constructed with high diastereo- and enantioselectivities. The step of oxidative cyclization is probably a rate-limiting process according to KIE experiments.

Asymmetric alkylation with alkyl electrophiles

The pioneering work by Nozaki and Hiyama in 1977[17] established the first coupling protocol for allylic halides and aldehydes mediated by Cr(II). However, initial attempts still required stoichiometric chromium reagents until Fürstner's breakthrough catalytic system employing Mn as a reducing agent together with trimethylsilyl chloride (TMSCl).[20,65] Building upon these advances, Umani-Ronchi and coworkers[66] developed the first catalytic enantioselective variant using chiral [Cr(salen)] complexes, achieving up to 89% ee (Scheme 14a). Subsequent ligand design innovations have further refined the asymmetric NHK reaction, making it an indispensable tool for constructing complex chiral alcohols in natural product synthesis and pharmaceutical development (Scheme 14b).[67–78]

In 2015, Zhang's group[79] developed a chromium-catalyzed enantioselective lactone formation from carbonyl 2-(alkoxycarbonyl)allyl bromides and aldehydes (Scheme 15a). The additive CoPc likely mediated redox processes, in particular, the generation of reactive allylic



Scheme 14 | *Transition metal-catalyzed asymmetric NHK reaction of allyl halides to aldehydes.*

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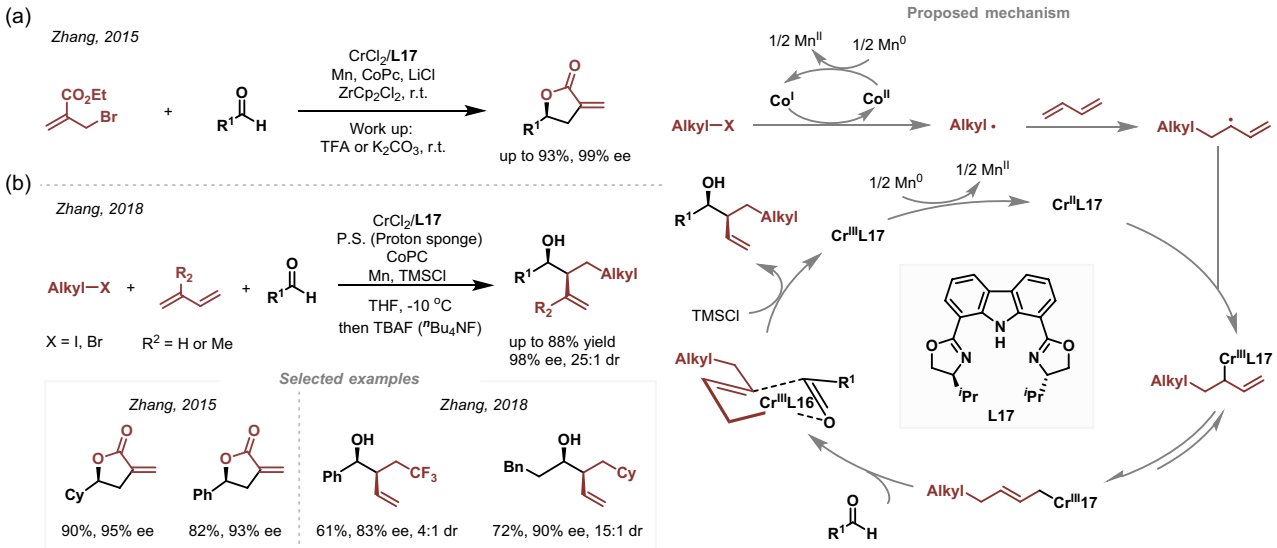

Scheme 15 | *Chromium-catalyzed enantioselective reductive allyl addition to aldehydes.*

intermediates. The reaction was utilized in an efficient synthesis of (+)-methylenolactocin without any erosion of enantioselectivity. The group subsequently extended this chromium-catalyzed reactivity to other classes of allylic electrophiles, such as halomethyl heteroarenes, γ-disubstituted allyl halides, (*E*)-4-bromobut-2-en-1-ol derivatives, and bromomethylnaphthalenes.[80–83] Meanwhile, Xiong and Zhang[84] extended the method to catalytic asymmetric three-component coupling through sequential alkylation of 1,3-dienes and alkyl halides and subsequent carbonyl allylation (Scheme 15b). The reaction was initiated from the SET generation of the alkyl radical mediated by CoPC. Subsequent radical addition of 1,3-butadiene formed π-allyl radical species, which then formed an allyl chromium complex. The latter added to aldehydes via a six-membered transition state to afford the desired product.

In 2021, Meng and coworkers[85] reported a cobalt-catalyzed method for a site-, diastereo-, and enantioselective reductive allylation of aldehydes using allylic alcohols (Scheme 16a). The transformation accommodated diverse structures of substrates, including racemic branched allylic carbonates or acetates, a *Z*,*E*-mixture of linear allylic carbonates or acetates, and unprotected allylic alcohols, as well as aryl and alkyl aldehydes. A wide array of enantioenriched homoallylic alcohols with contiguous stereocenters were successfully formed. Mechanistic studies revealed the possible formation of an allyl radical in equilibrium with an allyl cobalt species, while the chiral cobalt catalyst effectively controlled both the high stereoselectivity and chemoselectivity.

In recent years, transition metal and photoredox cocatalysis has proved to be a powerful strategy in Csp^3–Csp^3 bond formation.[86–91] For example, Liu's group[91] disclosed a diastereo- and enantioselective allylation of aldehydes by merging cobalt catalysis with photoexcitable HE, eliminating the need to add exogenous photocatalysts (Scheme 16b).

The stereoselective C–C bond formation between propargyl electrophiles and aldehydes proceeds via a six-membered cyclic transition state, wherein fine-tuning of steric repulsion between the catalyst and substrates might determine the divergent formation of either propargylation or allenylation products (Scheme 17a). In 2023, Meng's group[92] accomplished a photoredox/cobalt dual-catalyzed propargylation of aldehydes with excellent regio-, diastereo-, and enantioselectivity (Scheme 17b). This protocol efficiently constructs highly functionalized homopropargyl alcohols featuring two contiguous stereogenic centers using commercially available bidentate phosphine ligands. The mechanism involved reversible propargyl radical recombination to form allenyl-Co(III), its single-electron reduction to reactive allenyl-Co(II), and rate-limiting nucleophilic addition to aldehydes, as suggested by DFT calculations and experimental results.

In contrast, Wang and coworkers[93] disclosed a chromium-catalyzed enantioconvergent allenylation of aldehydes using racemic propargyl halides (Scheme 17c). Employing a semicorrin, this method provided efficiently optically pure α-allenols featuring adjacent axial and central chirality. Mechanistic studies suggested the generation of a propargyl radical, which was captured by a chromium catalyst. The resulting propargylic chromium complexes preferentially added to aldehydes via a six-membered transition state, affording α-allenols. Afterward, a chromium-catalyzed enantioconvergent coupling of racemic propargylic halides was developed

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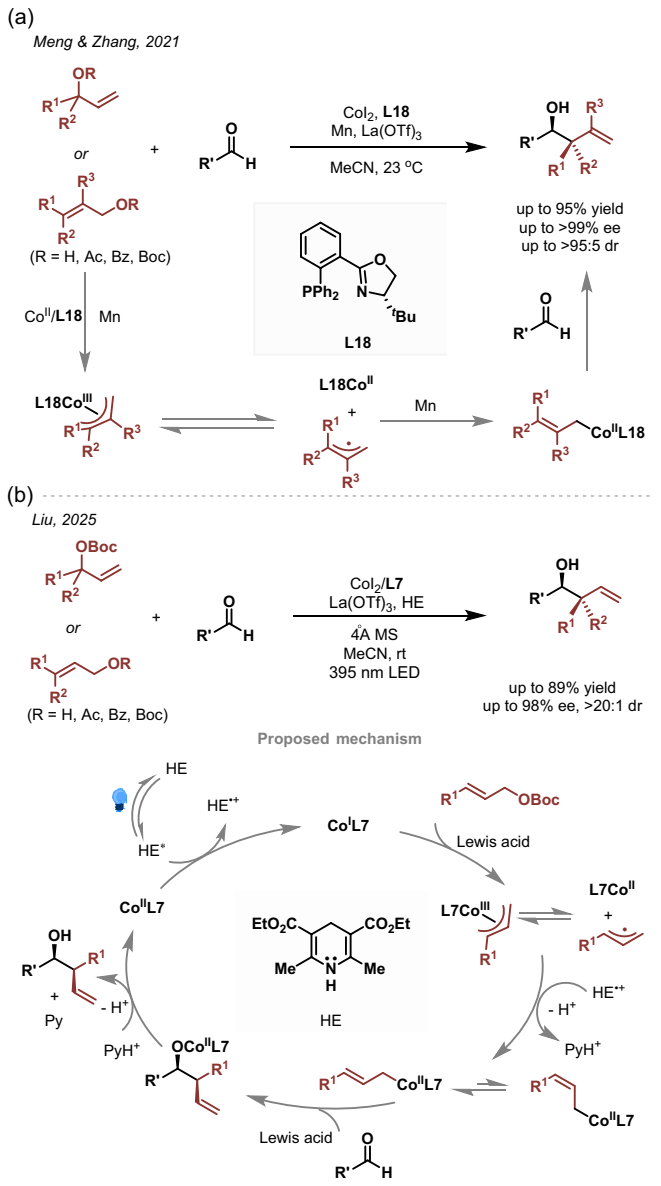

Scheme 16 | *Cobalt-catalyzed asymmetric reductive allyl additions to aldehydes.*

to access chiral 2,3-allenones, featuring a key step of radical-polar crossover/Oppenauer oxidation cascade.[94] In addition, the same group has developed a domino reaction of 4-alkyl-1,4-dihydropyridines (alkyl-DHPs) as radical precursors, enynes and aldehydes, via a key step of radical addition to 1,3-enynes under cooperative photoredox/chromium catalysis (Scheme 17d).[95]

The Reformatsky reaction typically involves zinc-mediated reductive addition of α-halocarbonyl compounds to aldehydes or ketones, and it has emerged as a powerful method for asymmetric C–C bond formation.[96–99] Thus, considerable efforts have been devoted to developing a catalytic asymmetric Reformatsky reaction, with one such example employing a chiral chromium/diarylamine bis(oxazoline) catalyst (Scheme 18).[100] This method provided a diverse array of chiral β-hydroxy carbonyl derivatives from α-chloro- or α-bromo-substituted esters and amides with excellent enantioselectivities. Notably, the reaction proceeded via a radical-polar crossover mechanism and exhibited high efficiency under both classical catalytic and photoredox conditions. Wang's group has also reported other coupling partners with aldehydes via radical-polar crossover process, such as α-boronate alkyl chlorides, *N*-sulfonyl imines, benzylamines, internal 1,3-dienes, and alkenes.[101–105]

Despite significant advances in reactions involving activated alkyl electrophiles, asymmetric reductive additions of unactivated alkyl groups to C=X bonds remain underdeveloped. This limitation primarily stems from challenges in effectively differentiating the enantiotopic faces of transient free alkyl radicals. In a joint study, Baran and coworkers[56] reported a Cr-electrocatalytic decarboxylative alkylations using redox-active esters, producing only racemic carbinols. In 2024, the same group[106] reported an asymmetric variant of this decarboxylative addition under electrochemical conditions (Scheme 19). The authors identified tetrakis(dimethylamino)ethylene (TDAE) as a critical mediator for reducing the Cr^{III}/L catalyst and optimized conditions using sulfonamide ligand **L22**. Thus, chiral secondary alcohols were produced with high enantiomeric excess (~90% ee) and moderate yields.

Transition-Metal-Catalyzed Asymmetric Reductive Addition of Ketones

Asymmetric arylation with aryl electrophiles

The development of asymmetric reductive additions to ketones lagged behind the transformations with aldehydes, primarily due to inherently reduced electrophilicity and difficulty in facial differentiation of unactivated ketones. In 2016, Liu's group[107] achieved catalytic enantioselective arylation of ketones utilizing a chromium catalyst with oxazoline/sulfonamide **L15** (Scheme 20a). The protocol proved effective for both aliphatic and arylaliphatic ketones, providing access to chiral tetrahydronaphthalen-1-ols with good enantioselectivities. Later, Zhou and Xu[108] reported nickel-catalyzed asymmetric intramolecular desymmetrization of 1,3-diketones via the addition of aryl halides (Scheme 20b). This method afforded bicyclic[4.3.0] skeleton bearing vicinal stereogenic centers with moderate enantioselectivities and excellent diastereoselectivities. Lv and coworkers[109] developed a nickel/bisoxazoline-catalyzed intramolecular asymmetric cyclization of aryl halides to unactivated ketones, affording chiral 3-hydroxy-2,3-dihydrobenzofurans in excellent stereocontrol (Scheme 20c). In 2023, Mei's group[110] developed an analogous enantioselective

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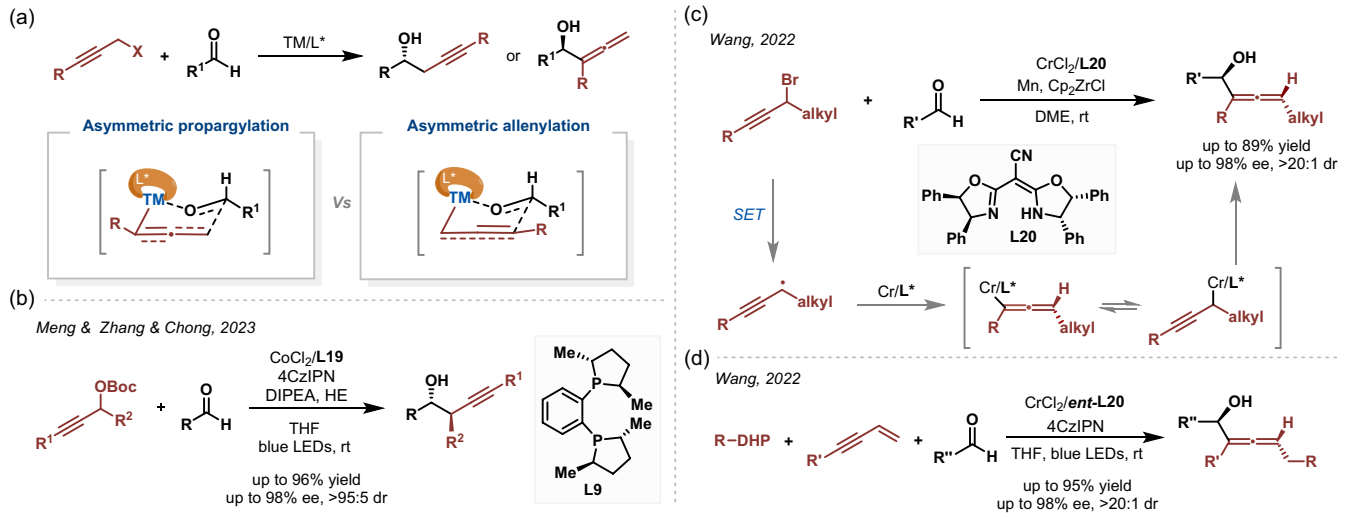
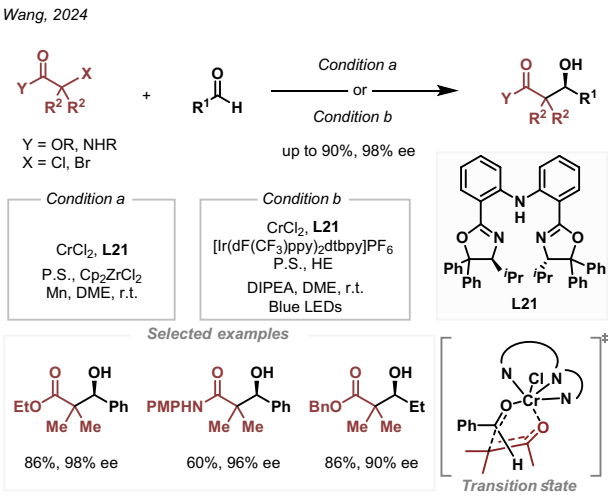


Scheme 17 | *Cobalt/chromium-catalyzed enantioconvergent coupling between (racemic) propargyl electrophiles and aldehydes.*

cyclization of aryl bromides under electrochemical conditions (Scheme 20d).

The above examples were limited to intermolecular addition of common ketones. A significant advancement was achieved by Zhou's group,[111] who developed the first intermolecular examples in enantioselective reductive arylation and alkenylation of common ketones (Scheme 20e). One reaction was scaled up to 10 mmol using 0.1 mol % nickel, yielding 1.95 g of the alcohol. Optically pure tertiary alcohols were synthesized efficiently via nickel catalysis of bisoxazoline Bn-Box L25. Notably, the desired product formation was assisted by in situ-generated mixed titanium alkoxides from Ti(Oi-Pr)$_4$ and hexafluoroisopropanol (HFIP). Stoichiometric studies employing an isolated complex Ni^{II}L(Ar)Br demonstrated that Mn-mediated reduction of the aryl nickel^{II} intermediate was not necessary for ketone insertion. The mixed titanium(IV) alkoxide was proposed to abstract halide to create cationic aryl nickel complexes for facilitating asymmetric aryl insertion. Wang and coworkers[112] have reported another example of catalytic enantioselective intermolecular addition of aryl iodides to isatins, using chiral cobalt complexes and bis(neopentylglycolato)diboron (B_2nep_2) as the stoichiometric reductant (Scheme 20f).



Scheme 18 | *Chromium-catalyzed asymmetric Reformatsky reaction with α-halo esters and amides.*

The asymmetric reductive conjugate addition of Michael acceptors is considered to be one of the most useful methods for C–C bond formation. In 2022, Zhou and coworkers[113] reported nickel-catalyzed enantioselective reductive conjugate addition of enones with aryl and heteroaryl halides (Scheme 21a). The method was successfully employed in the efficient synthesis of ar-turmerone and the core structures of (+)-tolterodine and AZD5672. Combining mechanistic studies and theoretical calculations, Zhou et al.[114] suggested that the key species responsible for the insertion was the aryl nickel (I) complex of L26 int B. The intermediate is inserted into the enone via a new mechanism of "elementary 1,4-addition" involving a nonplanar 6-membered cyclic transition state, affording a nickel *O*-enolate int C. The nickel catalyst facilitates elementary 1,4-addition to α,β-unsaturated carbonyls instead of classic 1,2-migratory insertion seen on rhodium and palladium. The author proposed that the different reactivity originates from a smaller covalent radius, lower orbital energy, and greater oxophilicity of nickel than 4d metals, rhodium, and palladium. In 2024, the same group also reported reductive alkenylation of α,β-unsaturated ketones and amides with alkenyl bromides, triflates, and tosylates using nickel catalysts of chiral quinox (Scheme 21b).[114]

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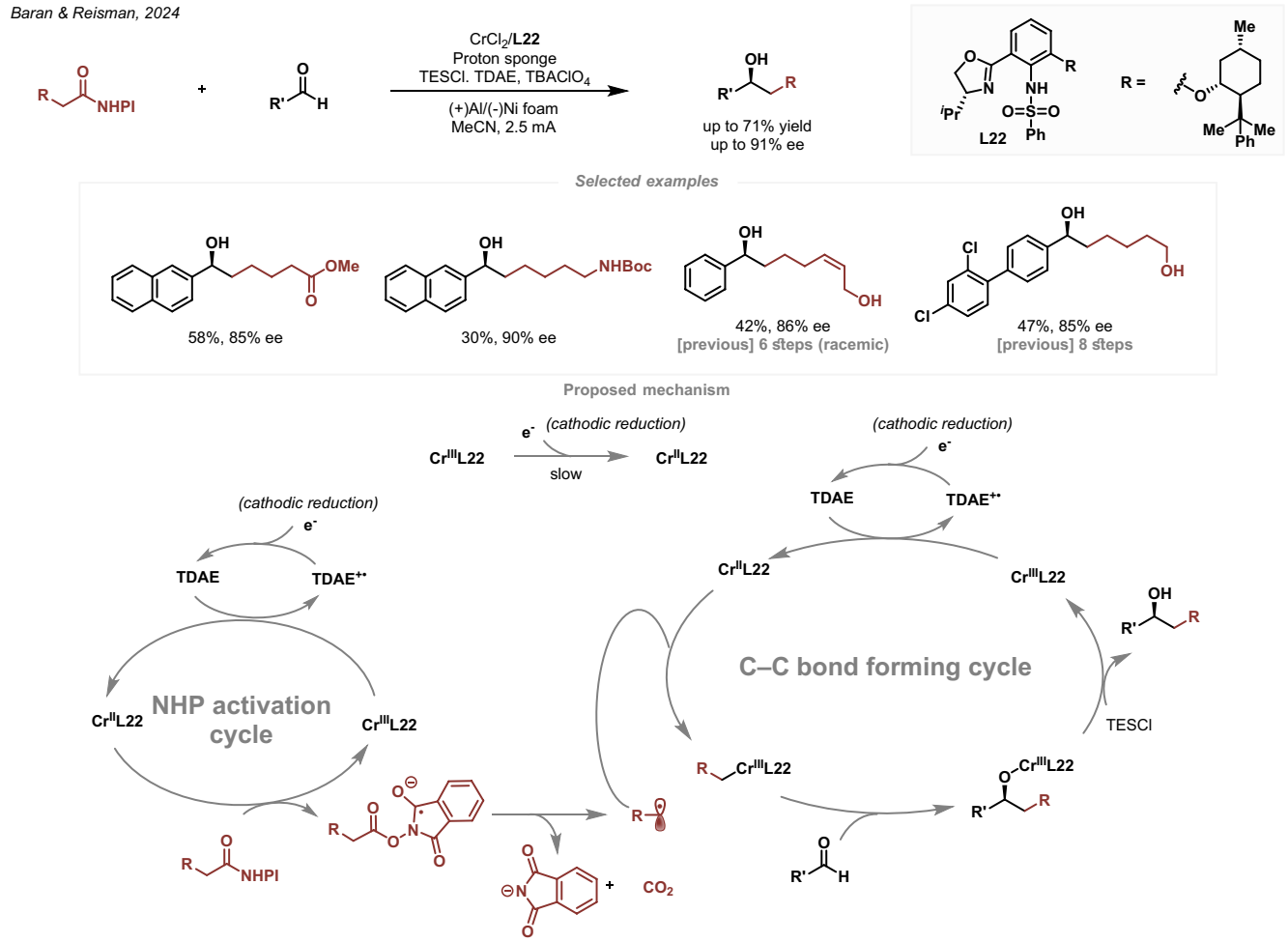

Scheme 19 | *Chromium-electrocatalytic asymmetric decarboxylative alkylation with aliphatic redox-active esters.*

In the catalytic cycles, Zhou et al.[115] originally proposed oxidative addition of (L)nickel(0) and aryl and alkenyl halides. However, according to current knowledge, the peak reduction potentials of nickel(I) bipy-type complexes are more negative than –2.0 V, which is beyond the reducing power of zinc and manganese powder (peak reduction potentials around –1.3 and 1.5 V in organic solvents).[115] Thus, oxidative addition of aryl and alkenyl halides should have occurred on nickel(I) complexes instead.[116,117]

Using chiral cobalt catalysis, Zhou and coworkers[118] subsequently developed enantioselective reductive aryl/alkenyl addition of Michael acceptors (Scheme 21c). Similarly, the authors use experiments and DFT calculations to establish that the active species for the insertion of enone was the aryl cobalt(I) complex of quinox. The insertion also proceeded via a step of "elementary 1,4-addition." In addition, α,β-unsaturated amides served as suitable substrates when strongly donating diphosphine BenzP* was used as a chiral ligand, affording the corresponding arylation and alkenylation products with excellent enantioselectivity. In particular, the addition of aryl halides and alkenyl triflates to *N*-indolyl enones proceeded very efficiently with low loadings of cobalt (0.5 mol %), and the reactions were scalable. The solid products of *N*-indolyl enones were formed in exceptionally high ees, and their ees can be improved via simple recrystallization. Additionally, the products can be readily converted to other chiral building blocks such as ketones, carboxylic acids, esters, and alcohols.

In 2023, Xiao and coworkers[119] disclosed enantioselective reductive conjugate addition of heterobiaryl triflates via cooperative photoredox/cobalt catalysis (Scheme 22). A series of axially chiral heterobiaryl compounds were synthesized in high yields and excellent enantiocontrol via dynamic kinetic resolution. In the proposed mechanism, chelation of pendant pyridine to the aryl cobalt center helps to reduce the rotational barrier of the putative axially chiral cobalt complex, thereby facilitating the interconversion of *(S)-int* to *(R)-int*. Subsequently, the groups of Zhang[120] and Harutyunyan[121] independently developed nickel-catalyzed reductive conjugate arylations/alkenylations of α,β-unsaturated ketones by merging electrochemistry and chiral nickel catalysis.

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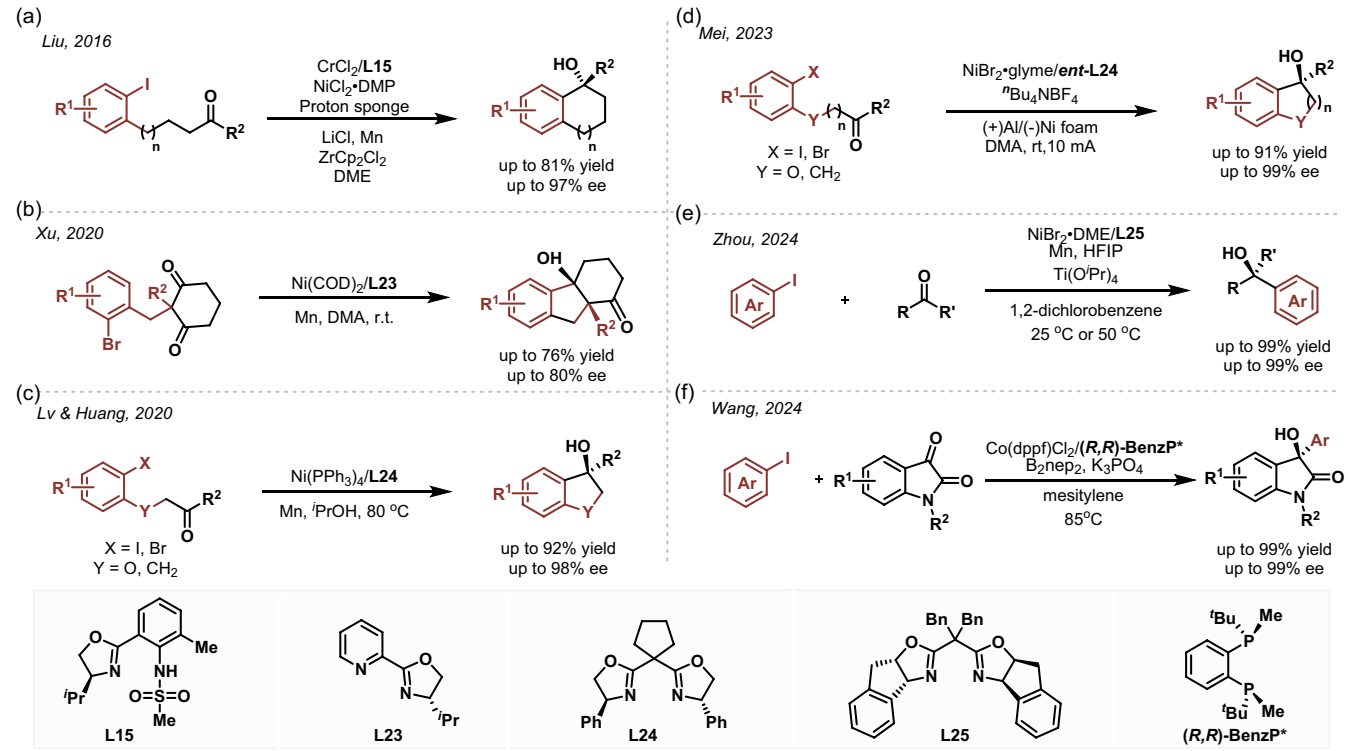
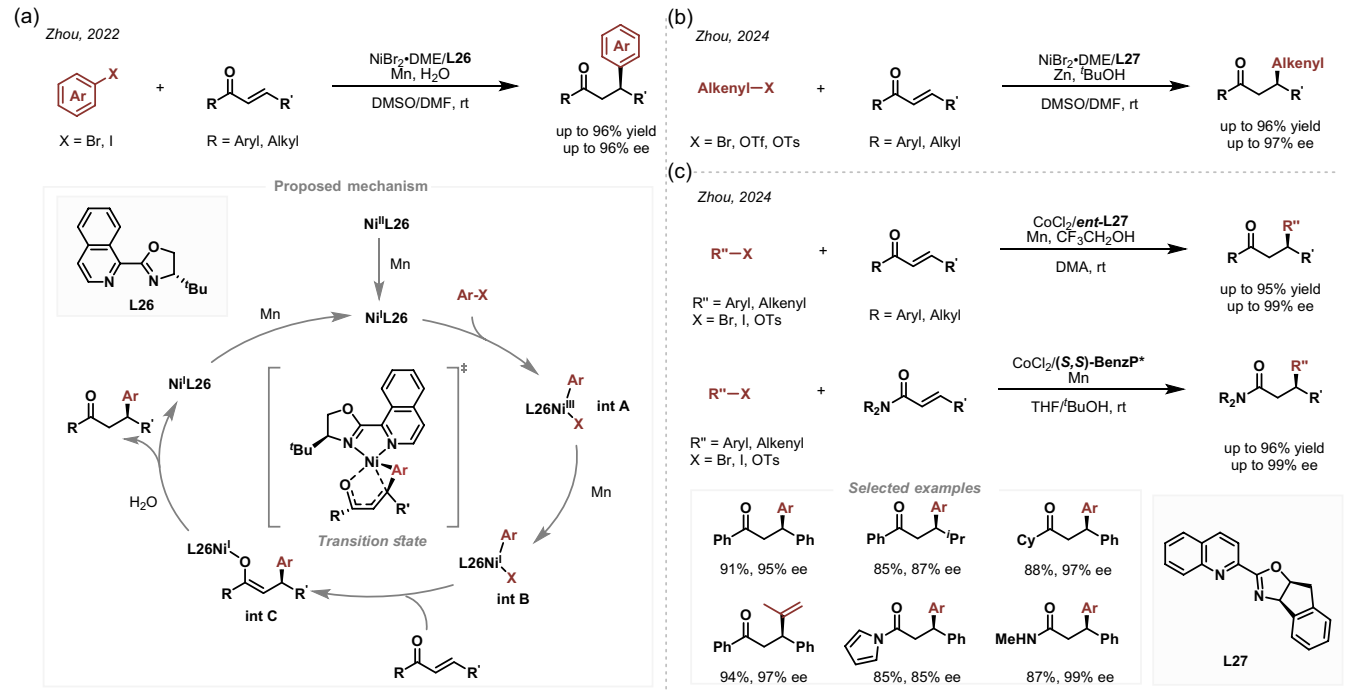


Scheme 20 | *Chromium/nickel/cobalt-catalyzed asymmetric reductive aryl addition to ketones.*

The development of catalytic deoxygenative C–C coupling reactions utilizing alcohols and their derivatives has attracted increasing attention in recent years.[122–125] In 2024, Shu group[126] employed easily accessible β-keto alkenyl acetates to achieve enantioselective reductive conjugate addition of α,β-enones (Scheme 23, top). The enone groups in products can be readily transformed into diverse complex structures, thereby significantly



Scheme 21 | *Nickel/cobalt-catalyzed enantioselective reductive arylation/alkenylation of enones.*

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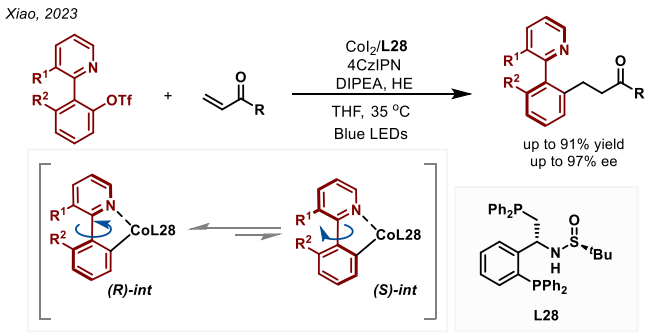
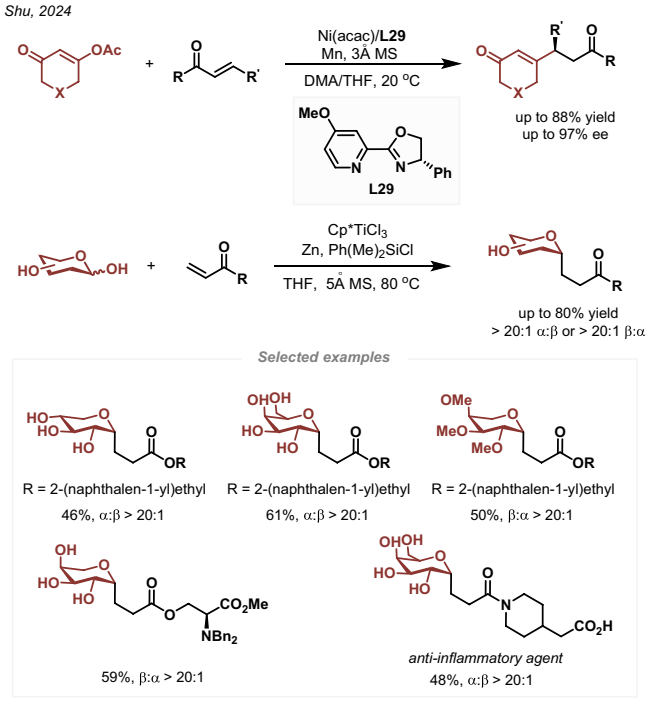


Scheme 22 | *Photoinduced cobalt-catalyzed enantioselective reductive arylation of enones.*

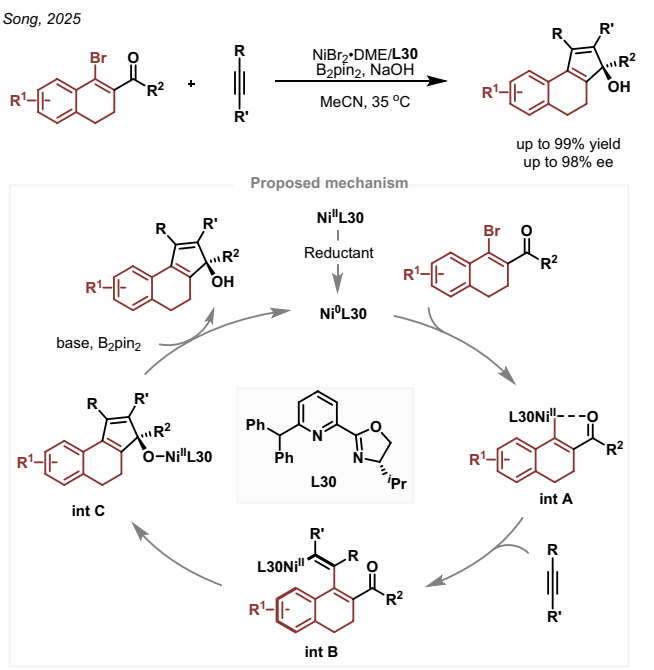
expanding the accessible chemical space. Later, the same group[127] developed a stereoselective deoxygenative reductive addition of enones with native saccharides utilizing a titanium catalyst (Scheme 23, bottom). This method delivered *C*-glycosylation products with high α or β selectivity from monosaccharides and oligosaccharides. The transformation proceeded through a stereoselective Giese-type radical addition to form a new C–C bond.

Asymmetric alkenylation with alkenyl electrophiles

Recently, Song's group[128] introduced a regio- and enantioselective reductive [3 + 2] annulation of



Scheme 23 | *Stereoselective deoxygenative reductive addition with alcohols and their derivatives.*



Scheme 24 | *Nickel-catalyzed regio- and enantioselective reductive [3 + 2] annulations.*

β-bromoenones with alkynes (Scheme 24). With the assistance of reductant B_2pin_2 and Ni catalyst of chiral ligand **L30**, the asymmetric cyclization proceeded smoothly to afford versatile chiral five-membered cyclic tertiary alcohols with excellent yields and enantioselectivities. The chirality of the axially chiral 1,3-diene intermediate originated from regio- and enantioselective migration insertion of alkynes with alkenyl Ni(II) intermediate. Mechanistic experiments revealed the specific function of B_2pin_2 in the mononuclear nickel-catalyzed system. Subsequent DFT calculations clarified that the observed regio- and enantioselectivity arises from a synergistic interplay of electronic and steric effects.

Asymmetric alkylation with alkyl electrophiles

The evolution of chiral catalysts has driven notable advancements in the asymmetric NHK reaction of ketones, despite inherent challenges in reduced reactivity and enantiofacial differentiation of ketones compared to aldehydes. In 2007, Miller and Sigman[129] disclosed an enantioselective addition of aryl ketones with allylic halides enabled by a chromium catalyst with a chiral truncated oxazoline ligand (Scheme 25a). However, aliphatic ketones exhibited significantly lower enantioselectivity under the standard conditions. Four years later, Sigman[130] established three-dimensional correlation of steric and electronic free energy relationships, which facilitated the achievement of enantioselective propargylation of aryl ketones or aliphatic ketones

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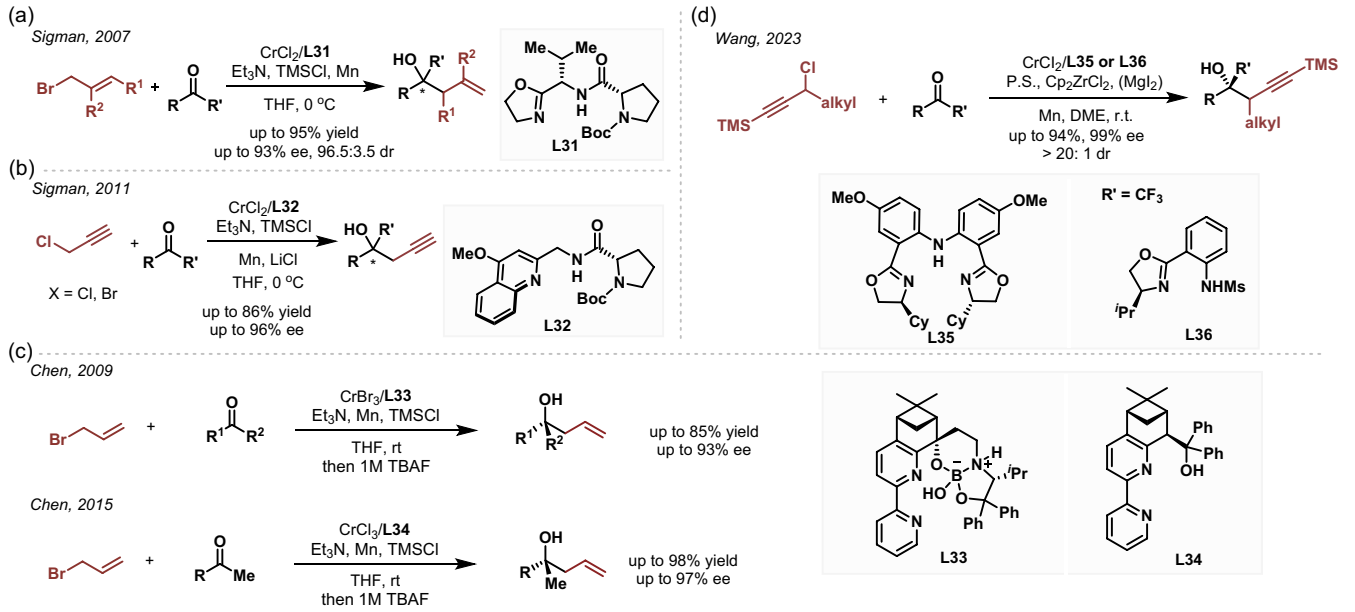
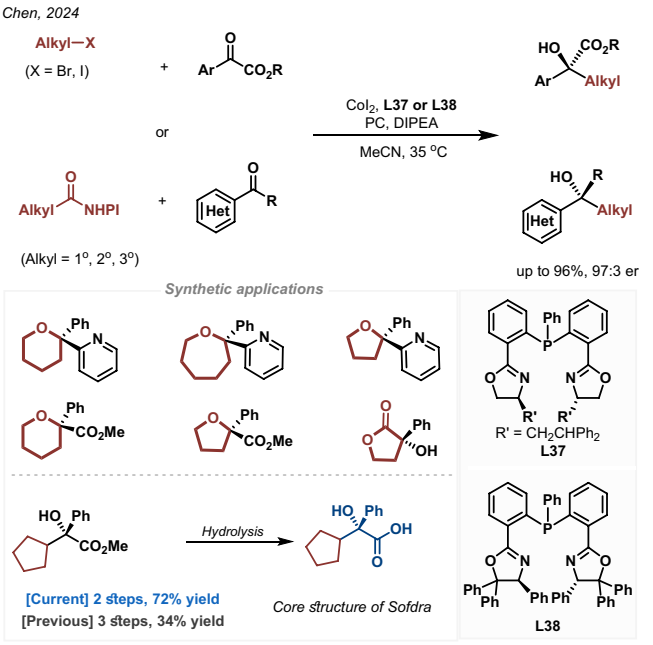


Scheme 25 | *Chromium-catalyzed enantioselective allylation and propargylation of ketones.*

(Scheme 25b). The resultant mathematical model provided guidance for catalytic system optimization. In 2009, Chen and coworkers[131] developed a new chiral spirocyclic borate ligand that effectively promoted the enantioselective allylation of ketones with allyl bromides (Scheme 25c, top). In this reaction, the rigid framework of the ligand was essential for achieving high stereoselectivity, while the presence of the borate ring influenced the stereochemical outcome of the product. Subsequently, a class of bipyridyl alcohol ligands was developed by the same group to achieve chromium-catalyzed enantioselective allylation (Scheme 25c, bottom).[132] This reaction also demonstrated broad substrate scopes and excellent enantioselectivities. In 2023, Wang's group[133] reported an efficient reductive coupling of racemic secondary propargylic chlorides and ketones (Scheme 25d). Under the catalysis of chromium complexes of diarylamine bis(oxazoline) **L35** or Kishi-type ligand **L36**, a series of chiral tertiary alcohols bearing vicinal stereocenters were successfully obtained with good regio-, diastereo-, and enantioselectivity. The authors proposed that the regio- and stereoselectivity of this transformation was governed by a Zimmerman-Traxler-type six-membered transition state during nucleophilic addition of an allenyl-Cr intermediate to 1-indanone.

In 2024, Chen and coworkers[134] reported a photoredox/cobalt-catalyzed asymmetric Barbier-type addition reaction of unactivated alkyl electrophiles to ketones, for efficient construction of highly congested tetrasubstituted stereocenters (Scheme 26). This protocol has a broad substrate scope, encompassing primary, secondary, and tertiary alkyl halides as well as redox-active esters as alkyl radical precursors, while α-ketoesters and chelating aza-aromatic ketones were suitable radical acceptors. High enantioselectivity was achieved through the sterically bulky tridentate, nitrogen-phosphorus-nitrogen (NPN) ligand **L37** and **L38**. A subsequent application study highlighted the method's synthetic utility in the facile synthesis of bioactive molecules and structurally diverse chiral saturated heterocycles.



Scheme 26 | *Photoredox cobalt-catalyzed asymmetric reductive alkylative reaction of ketones with unactivated alkyl electrophiles.*

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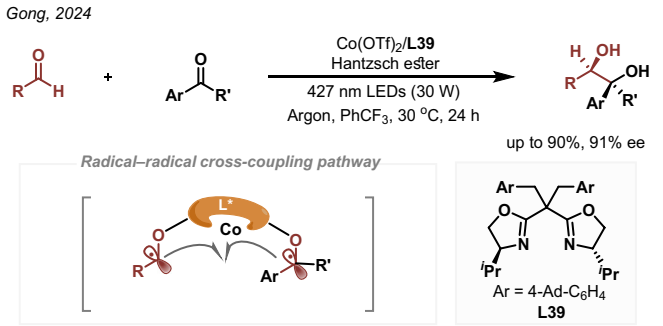


Scheme 27 | *Photoredox cobalt-catalyzed asymmetric reductive cross-coupling of aldehydes with ketones.*

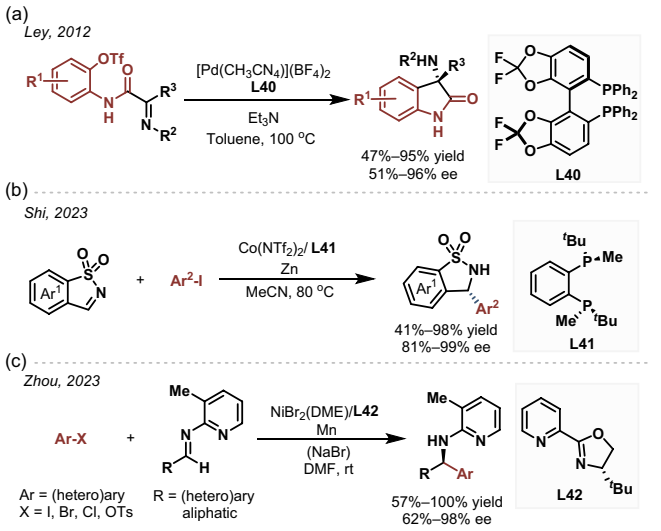
Beyond conventional alkyl halides as radical precursors, aryl aldehydes and α,β-unsaturated aldehydes may also serve as radical coupling partners in asymmetric cross-coupling, disclosed by Gong's group in 2024 (Scheme 27).[135] This photoredox-mediated cobalt-catalyzed reductive cross-coupling proceeded smoothly without the requirement of external photosensitizers, primarily due to the inherent photoactivity of aryl ketones, together with the potential contribution of the HE and photochemical reactivity of the cobalt catalyst. Mechanistic studies revealed a stereoselective pathway of radical–radical cross-coupling, enabling stereoselective synthesis of diverse optically pure unsymmetrical 1,2-diols.

Transition-Metal-Catalyzed Asymmetric Reductive Addition of Imines

Asymmetric arylation with aryl electrophiles

Imines are readily accessible through the condensation of aldehydes/ketones with various amines, serve as versatile synthetic intermediates in asymmetric transformations to efficiently construct enantioenriched alkyl amines.[136–141] In 2012, Ley's group[142] achieved palladium-mediated enantioselective intramolecular arylation of α-ketimino amides utilizing (*R*)-Difluorphos **L40** as a chiral ligand to enantioenriched to access 3-amino-2-oxindole compounds (Scheme 28a).

In 2024, cobalt-catalyzed enantioselective reductive (hetero)arylations of cyclic *N*-sulfonyl imines with aryl and heteroaryl halides were developed by Shi and coworkers (Scheme 28b).[143] They employed $Co(NTf_2)_2$ as a catalyst, chiral bisphosphine ligand **L41** as the chiral ligand, and zinc powder to provide optically active diarylmethylamines. In the proposed mechanism, the enantioselectivity of this transformation was dictated by steric interactions and hydrogen bonding in the transition state.



Scheme 28 | *Palladium/cobalt/nickel-catalyzed catalytic enantioselective reductive arylation of imines.*

Zhou's group[144] has reported an enantioselective reductive arylation and heteroarylation of aldimines to construct chiral benzylic amines employing a nickel/^{t}Bu-Pyrox (**L42**) as catalyst (Scheme 28c). Organic halides were used directly, including aryl iodides, bromides, and some aryl chlorides and sulfonates. In some cases, NaBr was added to accelerate Mn reduction, probably via ligand exchange of nickel complexes on the surface of Mn. Additionally, crude aldimines (prepared from refluxing toluene with $MgSO_4$) were used without purification, thereby improving both practicality and operational simplicity of the procedure. The nitrogen atom of the *N*-pyridyl group can coordinate to nickel and support the "elementary 1,4-addition" of aryl nickel(I) species, which was supported by experiments using an isolated complex (L)Ni(Ar)Br and calculations of the insertion step.

Asymmetric alkenylation

In 2022, Jia's group[145] performed cobalt-catalyzed enantioselective [3+2] umpolung annulation of *o*-halophenylated *N*-heteroarenes (such as quinolines, isoquinolines, quinoxalines, and pyridines) and both internal and terminal alkynes (Scheme 29a). Chiral *N*-heterocyclic compounds bearing spiro quaternary stereocenters were produced in high ees. Importantly, the coordination of alkenyl-Co species, generated after insertion, to the nitrogen atom of heteroarenes is crucial for this transformation, as evidenced by the lack of reactivity of methylquinolinium iodide. Very recently, Xiao's group[146] developed asymmetric [3+2] annulation of *N*-sulfonyl ketimines and alkynes under photoredox/cobalt catalysis to construct benzosultams (Scheme 29b). It is noted

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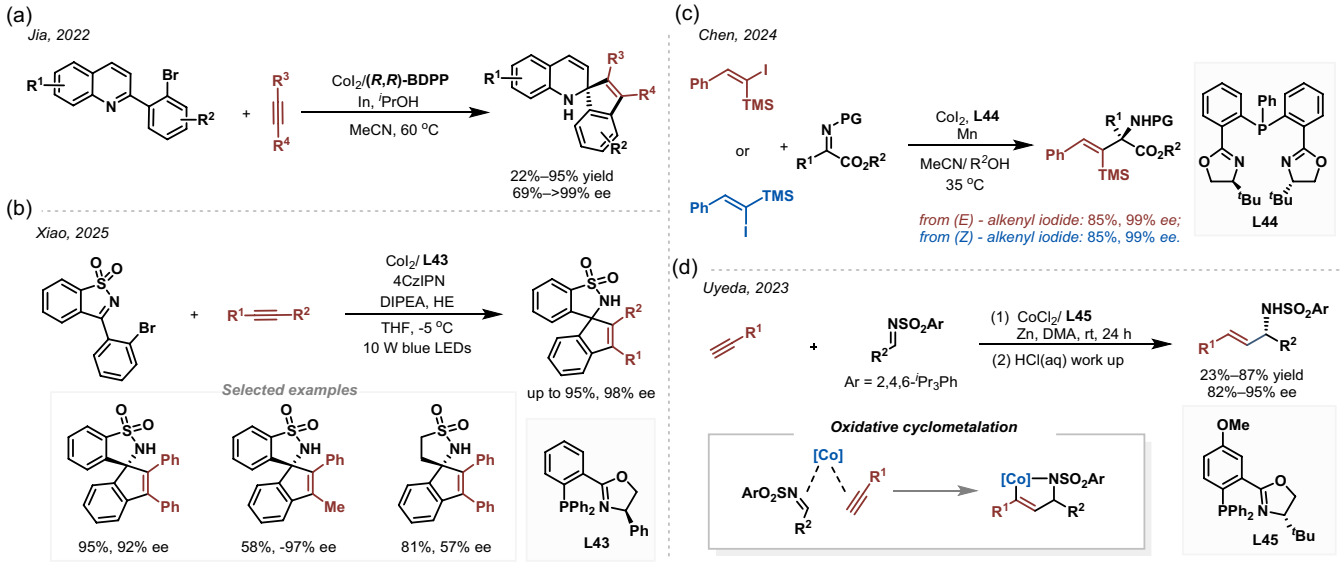


Scheme 29 | *Cobalt-catalyzed asymmetric alkenylation of imines with alkynes and alkenyl halides.*

that aliphatic cyclic imines showed significantly reduced enantioselectivity, indicating the critical role of aromatic rings of imines for high reactivity and stereocontrol.

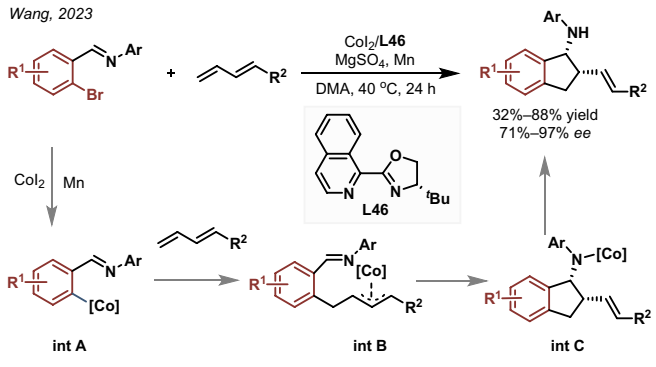
For enantioselective reductive alkenylation of ketimines with alkenyl halides, Chen and coworkers[147] employed CoI_2/bisoxazolinephosphine **L44** as a chiral catalyst to access diverse tetrasubstituted α-vinylic amino acid derivatives with excellent enantioselectivity (Scheme 29c). The authors found that different E/Z isomers of the alkenyl halide yielded an identical product with the same absolute configuration. Experiments demonstrated that the geoemetric isomerization of alkenyl iodide was initiated by a low-valent cobalt catalyst.

Asymmetric reductive coupling reactions of the π system are an efficient alternative approach for constructing the C–C bond. In 2023, Uyeda group[148] published a cobalt-catalyzed enantioselective reductive coupling of alkynes and aldimines to furnish highly enantioenriched allylic amines (Scheme 29d). A series of terminal alkynes and aryl imines participated successfully in the reaction, while internal alkynes and alkyl imines did not give good results. The proposed mechanism involves oxidative cyclization of the alkyne and imine on the low-valent cobalt catalyst, generating a key metallacycle intermediate.

Asymmetric alkylation

In 2023, Wang and coworkers[149] developed asymmetric reductive annulation of 1,3-dienes and bromoaryl imines via cobalt catalysis (Scheme 30). The [3+2] annulation provided disubstituted *cis*-indanes with excellent diastereo- and enantioselectivities under mild conditions. In contrast to aryl-substituted diene substrates, alkyl-substituted 1,3-dienes exhibited significantly lower reactivity and enantioselectivity. The proposed mechanism featured two key steps of enantioselective intermolecular migratory insertion of 1,3-dienes followed by diastereoselective intramolecular allylation of the imine, which collectively determined the high stereoselectivity of the reductive coupling.

Chen's group[150] has achieved cobalt-catalyzed asymmetric reductive addition of α-chloro carbonyl compounds to α-ketimines, delivering expedient access to a range of chiral β-quaternary amino acid derivatives in excellent yields and enantioselectivities (Scheme 31). The reaction can use a diverse set of α-chloro carbonyl compounds, including amides, esters, and ketones, as well as sulfonamides. The method can be used for constructing iterative α-amino acid units and oligopeptides. Mechanistic investigations excluded a Reformatsky-type pathway and confirmed the involvement of α-carbonyl radical in the catalytic addition.



Scheme 30 | *Cobalt-catalyzed enantioselective reductive annulation of o-bromoaryl imines and 1,3-dienes.*

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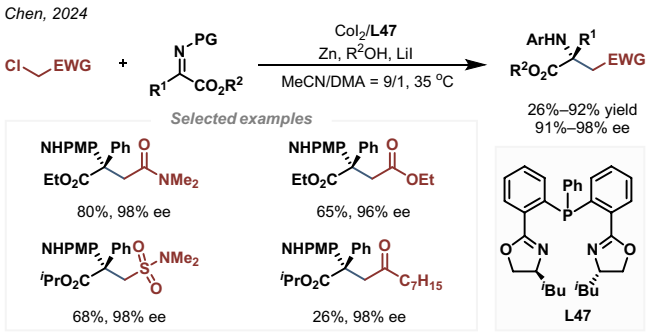
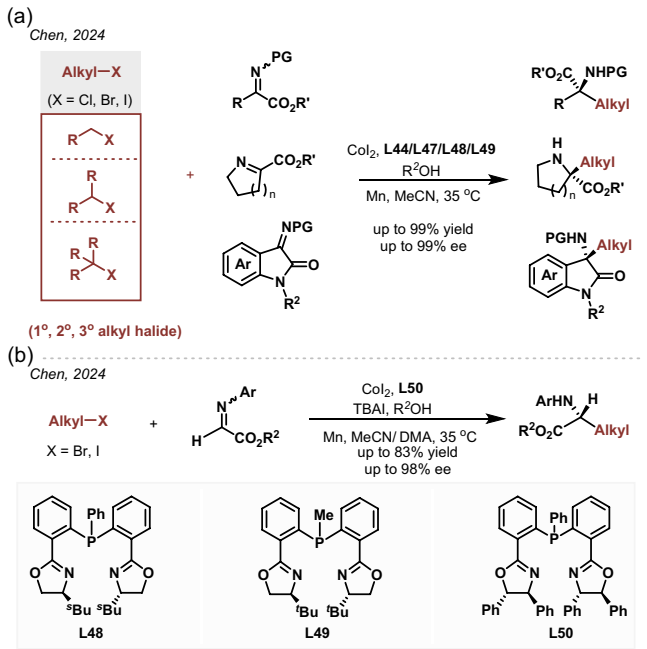


Scheme 31 | *Cobalt-catalyzed enantioselective reductive alkylation of α-iminoesters with α-chloro carbonyl compounds.*

The asymmetric alkylation of imines using unactivated alkyl electrophiles presents a significant challenge, primarily owing to the difficulty in controlling stereoselectivity. Baran and Reisman independently developed reductive alkylation protocols for imines using redox-active esters and alkyl halides, respectively.[151–153] Specifically, Baran's group achieved a diastereoselective reductive addition through a chiral auxiliary-mediated strategy using chiral sulfinyl imines. Nevertheless, a general catalytic asymmetric approach for the alkylation of imines remains elusive. In 2024, Chen group[154] disclosed an efficient cobalt-catalyzed enantioselective aza-Barbier reaction, employing a CoI_2/NPN catalyst with manganese reductant (Scheme 32a). This asymmetric process has a broad scope of unactivated alkyl halides, including primary, secondary, and tertiary alkyl iodides, bromides, and even chlorides. Notably, suitable ketimine substrates included α-imino esters, cyclic iminoesters, and iminooxindoles. The method can be amenable for sequential asymmetric reductive addition/intramolecular substitution for the construction of sterically congested *N*-heterocycles with α-tetrasubstituted stereocenters. Stoichiometric reactions with different amounts of Mn indicated that an alkyl-cobalt(II) species was the reactive Co species in the catalytic cycle. Subsequently, the same group[155] extended the asymmetric aza-Barbier reaction to dehydroglycine derivatives, giving chiral α-alkyl amino acid esters (Scheme 32b). Based on the current mechanistic investigations, the authors proposed that the reaction proceeded through a radical addition to form the C–C bond. Later, Chen's group reported[156] cobalt-catalyzed asymmetric reductive addition of cyclopropyl chlorides to α-iminoesters for the efficient construction of chiral amino acid derivatives containing cyclopropyl fragments.



Scheme 32 | *Cobalt-catalyzed asymmetric reductive alkylation of α-iminoesters and iminooxindoles with unactivated alkyl halides.*

Catalytic Asymmetric Reductive Addition of Electrophiles to Other Unsaturated Compounds

Chiral organosulfur compounds featuring stereogenic sulfur centers are useful structural motifs in pharmaceuticals, and they are also used as chiral ligands and organocatalysts in asymmetric catalytic transformations.[157–159] In particular, enantioenriched *S*-stereogenic sulfinamides can act as chiral auxiliaries/ligands in asymmetric metal catalysis and serve as key precursors in the synthesis of compounds containing sulfur-stereogenic centers.[160] In 2025, Shi group[161] reported nickel-/cobalt-catalyzed enantioselective reductive arylation and alkenylation of sulfinylamines using aryl or alkenyl halides (Scheme 33a). This protocol obviated the requirement for preformed organometallic reagents, enabling direct synthesis of *S*-chiral sulfinamides in high yields with excellent enantioselectivities. Nonlinear effect experiments involving a chiral ligand indicated that active catalytic species exist as a monomeric nickel complex bearing a single chiral ligand. In a proposed mechanism, the aryl insertion of the S = N bond determined the enantioselectivity. Shortly after, Yang and coworkers[162] also reported a similar reductive addition to access enantiopure sulfinamides using cobalt complexes of chiral diphosphine or tridentate NPN ligands (Scheme 33b). The addition of NaI and 3 Å molecular sieves improved reaction efficiency and enantioselectivity. Mechanistic investigations indicated that oxidative addition of aryl iodide to the Co^{I} complex formed aryl-Co^{III} **int A**, which was then reduced to generate aryl-Co^{II} **int B**. Migratory insertion of the

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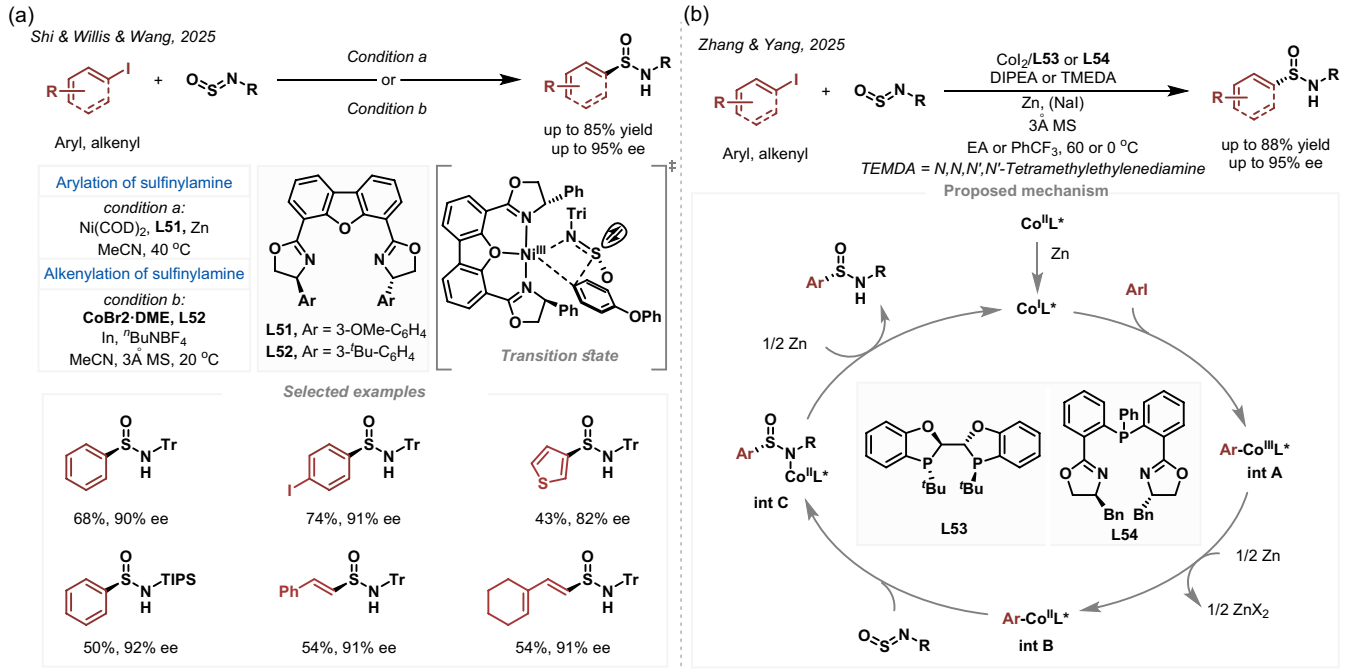


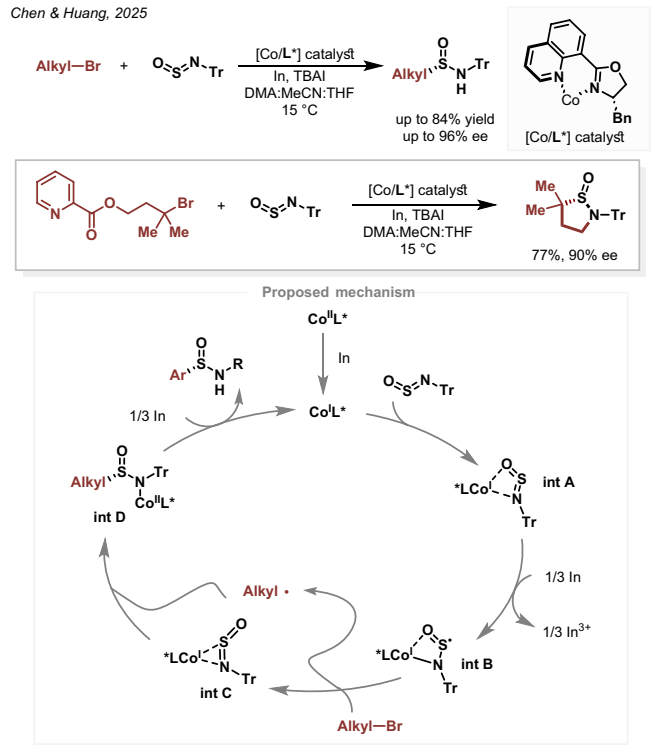
Scheme 33 | *Nickel/cobalt-catalyzed asymmetric reductive arylation and alkenylation of sulfinylamines.*

sulfinylimine followed by transmetalation with ZnI_2 delivered the desired product.

The reductive addition also proves equally useful for the construction of challenging C(sp^3)–S stereocenters from TrNSO and unactivated alkyl halides. Very recently, Chen and coworkers[163] disclosed reductive alkylation of sulfinylamines employing a cobalt/quinox catalyst (Scheme 34). A diverse array of alkyl-substituted sulfinamides was synthesized with excellent enantioselectivities, and the reaction tolerated ester, aldehyde, and heteroaromatic rings. Remarkably, the methodology was adapted to a sequential addition/cyclization, giving directly enantioenriched sultims. Based on mechanistic experiments and DFT calculations, a plausible catalytic cycle was proposed: sulfinylamine-Co(I) **int A** was reduced by indium to generate **int B**, which underwent a halogen-atom transfer (XAT) with the alkyl halide, producing an alkyl radical and **int C**. Subsequent stereoselective radical addition to sulfinylamine formed **int D**, followed by reduction and protonation to deliver the final product.

Concurrently, Shi's group[164] accomplished an enantio- and diastereoselective reductive propargylic sulfinamidation of racemic propargyl acetates, utilizing nickel/copper dual catalysts (Scheme 35). This method can use primary, secondary, and tertiary propargyl acetates as substrates for the efficient construction of *S*-propargyl sulfinamides containing carbon and sulfur stereocenters. Racemic secondary propargylic acetates can also be used. Control experiments suggested that chiral induction was predominantly governed by the nickel/**L55** catalyst, while the copper/**L56** catalyst served as a crucial auxiliary.

Isocyanates can serve as versatile building blocks in amide synthesis due to bench stability, commercial



Scheme 34 | *Cobalt-catalyzed enantioselective reductive alkylation of sulfinylamines.*

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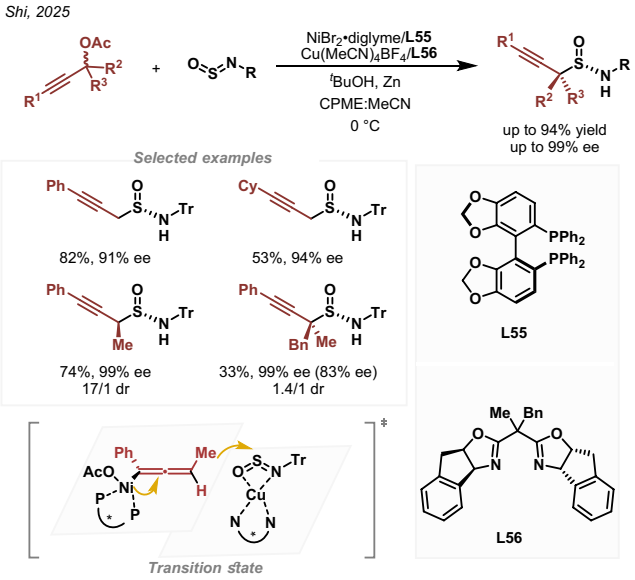


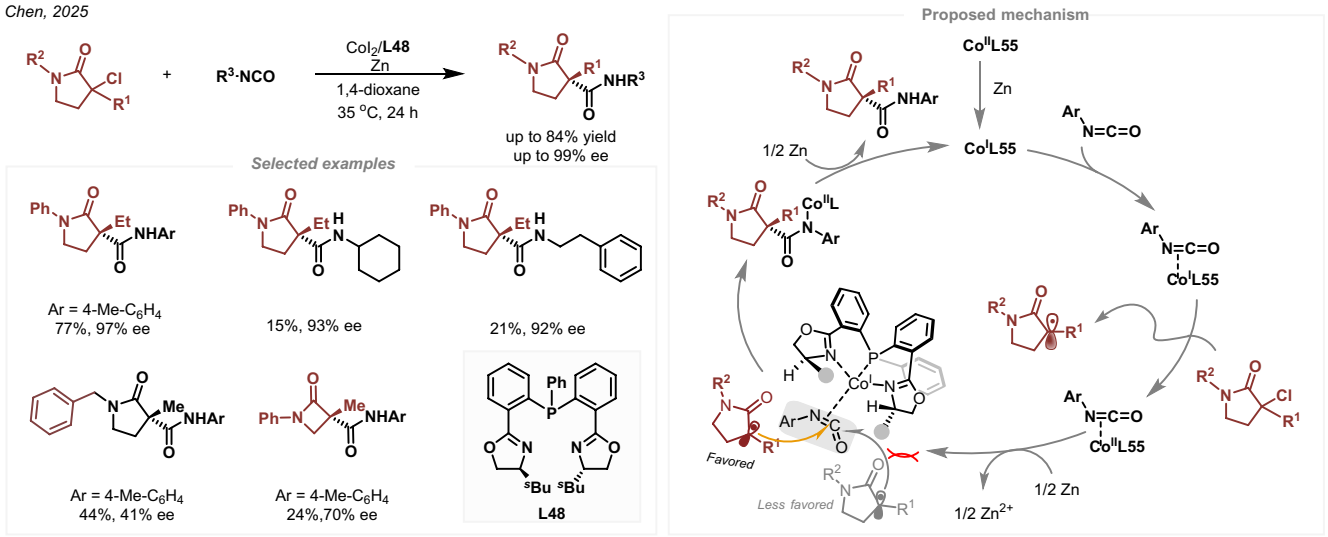
Scheme 35 | *Ni/Cu cocatalyzed asymmetric reductive propargylation of sulfinylamines.*

availability, and high electrophilicity. Generally, amide bonds can be constructed via an addition reaction between isocyanates and carbon nucleophiles.[165,166] However, the utility of this method was limited due to poor functional group compatibility of organometallic reagents. Recently, Chen group[167] reported a cobalt-catalyzed asymmetric reductive addition of tertiary α-halolactams to isocyanates (Scheme 36). The transformation successfully constructed α-tetrasubstituted lactams in up to 99% ee. However, the method showed significantly reduced enantioselectivity in catalytic reactions of *N*-benzyl pyrrolidinone or α-halo-β-lactams.

Summary and Outlook

CARA reactions to carbonyls have emerged as a powerful strategy to construct a new C–C bond in modern organic synthesis. By directly coupling readily available electrophiles with carbonyl compounds, this approach circumvents the requirement for sensitive organometallic reagents while offering exceptional functional group tolerance and substrate generality. These advantages establish reductive carbonyl additions as a privileged protocol for efficient construction of enantioenriched alcohols and amines, particularly demonstrating broad application potential in natural product synthesis. This mini-review highlights recent advances in transition-metal-catalyzed asymmetric reductive additions to carbonyls (aldehydes, ketones, imines, and sulfinylimines), covering asymmetric arylation, alkenylation, and alkylation.

Despite significant advances in recent years, several challenges remain to be addressed to expand the synthetic utility of the CARA reactions: (1) Current methods predominantly employ functionalized and reactive carbonyl compounds. Unactivated alkyl ketones and imines present formidable challenges, primarily owing to their inherently low reactivity and difficulty in achieving stereodiscrimination. Meanwhile, extending the reactivity to other π-unsaturated substrates, including nitriles and nitrones, can broaden the synthetic utility of the method; (2) Catalytic enantioconvergent catalysis[168–170] provides a novel opportunity for asymmetric reductive additions, which utilizes racemic alkyl halides for efficient construction of contiguous stereocenters. However, achieving simultaneous control of both enantioselectivity and diastereoselectivity remains a significant



Scheme 36 | *Cobalt-catalyzed asymmetric reductive addition of tertiary alkyl halides to isocyanates.*

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challenge. (3) In the last decade, metallaphotoredox catalysis and metallaelectrocatalysis have emerged as powerful strategies for rapid assembly of structurally complex molecules. They eliminate the use of stoichiometric amounts of metal reductants and also offer a new dimension of tunability through adjusting light intensity, spectral width of light, or reduction potentials.

While the new reductive addition reactions showed promise in the synthesis of complex bioactive molecules, scale-up applications still lag due to high catalyst loadings and slow reaction kinetics in many cases. Future efforts in new catalyst design and development of more practical and cost-effective reductants or catalytic systems will pave the way to practical large-scale applications. Furthermore, reaction engineering, such as catalyst immobilization on solid supports and continuous flow synthesis, will help the separation of products and facilitate the recycling and reuse of catalysts.

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References

1. Knochel, P., Molander, G. A., Eds. *Comprehensive Organic Synthesis*, 2nd ed.; Elsevier: Amsterdam, **2014**.
2. Molnár, Á., Olah, G. A., Prakash, G. K. S., Eds. Addition Reactions. In *Hydrocarbon Chemistry*; JohnWiley & Sons: Hoboken, **2017**.
3. Knochel, P. Organomagnesium and Organozinc Chemistry. In *Organometallics in Synthesis*; Schlosser, M., Ed.; JohnWiley & Sons: Hoboken, **2013**.
4. Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. Catalytic Asymmetric Conjugate Addition and Allylic Alkylation with Grignard Reagents. *Chem. Rev.* **2008**, *108*, 2824–2852.
5. Jumde, R. P.; Lanza, F.; Veenstra, M. J.; Harutyunyan, S. R. Catalytic Asymmetric Addition of Grignard Reagents to Alkenyl-Substituted Aromatic *N*-Heterocycles. *Science* **2016**, *352*, 433–437.
6. Luo, W.; Zhang, L.-M.; Zhang, Z.-M.; Zhang, J. Synthesis of W-Phos Ligand and its Application in the Copper-Catalyzed Enantioselective Addition of Linear Grignard Reagents to Ketones. *Angew. Chem. Int. Ed.* **2022**, *61*, e202204443.
7. Zhang, L.-M.; Luo, W.; Fu, J.; Liu, Y.; Zhang, J. W-Phos Ligand Enables Copper-Catalyzed Enantioselective Alkylation of *N*-Sulfonyl Ketimines with Grignard Reagents. *ACS Catal.* **2023**, *13*, 8830–8837.
8. Blomberg, C. *The Barbier Reaction and Related One-Step Processes*; Springer Berlin: Heidelberg, **1993**.
9. Moragas, T.; Correa, A.; Martin, R. Metal-Catalyzed Reductive Coupling Reactions of Organic Halides with Carbonyl-Type Compounds. *Chem. Eur. J.* **2014**, *20*, 8242–8258.
10. Presset, M.; Paul, J.; Cherif, G. N.; Ratnam, N.; Laloi, N.; Léonel, E.; Gosmini, C.; Gall, E. L. CoI-Catalyzed Barbier Reactions of Aromatic Halides with Aromatic Aldehydes and Imines. *Chem. Eur. J.* **2019**, *25*, 4491–4495.
11. Kumar, R.; Flodén, N. J.; Whitehurst, W. G.; Gaunt, M. J. A General Carbonyl Alkylative Amination for Tertiary Amine Synthesis. *Nature* **2020**, *581*, 415–420.
12. Barbier, P. C. R. Synthèse du dimethylheptenol. *Hebd. Seances Acad. Sci.* **1899**, *128*, 110–111.
13. Namy, J. L.; Girard, P.; Kagan, H. B. ChemInform Abstract: A New Preparation of Some Divalent Lanthanide Iodides and Their Usefulness in Organic Synthesis. *Nouv. J. Chim.* **1977**, *1*, 5–7.
14. Girard, P.; Namy, J. L.; Kagan, H. B. Divalent Lanthanide Derivatives in Organic Synthesis. 1. Mild Preparation of Samarium Iodide and Ytterbium Iodide and Their Use as Reducing or Coupling Agents. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.
15. Molander, G. A.; Etter, J. B.; Zinke, P. W. Stereocontrolled Cyclization Reactions Mediated by Samarium Diiodide. *J. Am. Chem. Soc.* **1987**, *109*, 453–463.
16. Krief, A.; Laval, A.-M. Coupling of Organic Halides with Carbonyl Compounds Promoted by SmI_2, the Kagan Reagent. *Chem. Rev.* **1999**, *99*, 745–778.
17. Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. Grignard-Type Carbonyl Addition of Allyl Halides by Means of Chromous Salt. A Chemospecific Synthesis of Homoallyl Alcohols. *J. Am. Chem. Soc.* **1977**, *99*, 3179–3181.
18. Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. Catalytic Effect of Nickel(II) Chloride and Palladium(II) Acetate on Chromium(II)-Mediated Coupling Reaction of Iodo Olefins with Aldehydes. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646.
19. Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. Reactions of Alkenylchromium Reagents Prepared from Alkenyl Trifluoromethanesulfonates (Triflates) with Chromium(II) Chloride Under Nickel Catalysis. *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050.
20. Fürstner, A.; Shi, N. Nozaki–Hiyama–Kishi Reactions Catalytic in Chromium. *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357.
21. Gil, A.; Albericio, F.; Álvarez, M. Role of the Nozaki–Hiyama–Takai–Kishi Reaction in the Synthesis of Natural Products. *Chem. Rev.* **2017**, *117*, 8420–8446.
22. Kokić, B.; Vulović, B.; Jović, M.; Andrijević, A.; Ajdacić, V.; Opsenica, I. M. Strategies for Carbon Electrophile Addition to Carbonyls and Imines by Cobalt Catalysis. *Eur. J. Org. Chem.* **2023**, *26*, e202300997.
23. Xia, T.; Yu, Z.; Wu, X.; Qu, J.; Chen, Y. Catalytic Reductive Addition of Imine for Chiral Amine Synthesis: Recent Advances and Future Perspectives. *ChemCatChem* **2025**, *17*, e202401407.
24. Tian, J.; Li, C.; Chen, J.; Lv, H. Nickel and Cobalt-Catalyzed Asymmetric Reductive Coupling of Halides with Aldehydes, Ketones and Imines. *Chin. J. Org. Chem.* **2025**, *45*, 1946–1960.

Citation: *CCS Chem.* **2025**, Just Published. DOI: 10.31635/ccschem.025.202506433
Link to VoR: https://doi.org/10.31635/ccschem.025.202506433

25. Hou, L.; Liu, X.; Cao, W.; Feng, X. Recent Advances in Visible Light-Induced Asymmetric Transformations of Carbonyl Compounds into Chiral Alcohols. *ChemCatChem* **2023**, *15*, e202300893.
26. Cao, W.; Liu, X.; Feng, X. Asymmetric Catalytic Radical Reactions Enabled by Chiral *N,N'*-Dioxide–Metal Complexes. *Acc. Chem. Res.* **2025**, *58*, 2496–2510.
27. Majumdar, K. K.; Cheng, C.-H. Ni(II)/Zn-Mediated Chemoselective Arylation of Aromatic Aldehydes: Facile Synthesis of Diaryl Carbinols. *Org. Lett.* **2000**, *2*, 2295–2298.
28. Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. Highly Efficient Cyclization of *o*-Iodobenzoates with Aldehydes Catalyzed by Cobalt Bidentate Phosphine Complexes: A Novel Entry to Chiral Phthalides. *Chem. Eur. J.* **2007**, *13*, 4356–4363.
29. Ishida, S.; Suzuki, H.; Uchida, S.; Yamaguchi, E.; Itoh, A. Nickel-Catalyzed Intermolecular Carbonyl Addition of Aryl Halide. *Eur. J. Org. Chem.* **2019**, *2019*, 7483–7487.
30. Zhang, S.; Perveen, S.; Ouyang, Y.; Xu, L.; Yu, T.; Zhao, M.; Wang, L.; Song, P.; Li, P. Design and Synthesis of Tunable Chiral 2,2-Bipyridine Ligands: Application to the Enantioselective Nickel-Catalyzed Reductive Arylation of Aldehydes. *Angew. Chem. Int. Ed.* **2022**, *61*, e202117843.
31. Zhu, Z.; Xiao, J.; Li, M.; Shi, Z. Nickel-Catalyzed Intermolecular Asymmetric Addition of Aryl Iodides Across Aldehydes. *Angew. Chem. Int. Ed.* **2022**, *61*, e202201370.
32. Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis. *Chem. Rev.* **2022**, *122*, 1485–1542.
33. Jiang, X.; Jiang, H.; Yang, Q.; Cheng, Y.; Lu, L.-Q.; Tunge, J. A.; Xiao, W.-J. Photoassisted Cobalt-Catalyzed Asymmetric Reductive Grignard-Type Addition of Aryl Iodides. *J. Am. Chem. Soc.* **2022**, *144*, 8347–8354.
34. Jiang, H.; He, X.-K.; Jiang, X.; Zhao, W.; Lu, L.-Q.; Cheng, Y.; Xiao, W.-J. Photoinduced Cobalt-Catalyzed Desymmetrization of Dialdehydes to Access Axial Chirality. *J. Am. Chem. Soc.* **2023**, *145*, 6944–6952.
35. Liu, S.-Q.; Xiong, W.; Huang, J.-C.; Jiang, X.; Xu, W.; Zhang, Z.; Cheng, Y.; Lu, L.-Q.; Gao, K.; Xiao, X.-J. Construction of Planar Chiral [2,2] Paracyclophanes via Photoinduced Cobalt-Catalyzed Desymmetric Addition. *Nat. Commun.* **2025**, *16*, 4012–4024.
36. Liang, T.; Wu, Y.; Sun, J.; Li, M.; Zhao, H.; Zhang, J.; Zheng, G.; Zhang, Q. Visible Light-Mediated Cobalt and Photoredox Dual-Catalyzed Asymmetric Reductive Coupling for Axially Chiral Secondary Alcohols. *Chin. J. Chem.* **2023**, *41*, 3253–3260.
37. Han, T.; Mou, Q.; Lv, Y.; Liu, M. Light-Driven Asymmetric Coupling of Aromatic Aldehydes and Aryl Iodides Using a Simple Amine Reductant. *Green Chem.* **2024**, *26*, 1370–1374.
38. Jiang, M.; Yu, L.; Zou, C.; Yuan, H.; Xu, M.; Chen, B.; Hu, P.; Wang, B.-Q.; Cao, P. Nickel-Catalyzed Enantioselective Carbonyl Addition of Aryl Chlorides and Bromides to Aldehydes. *Chem. Eur. J.* **2024**, *30*, e202401591.
39. Shao, Y.-P.; Liang, Y.-M. Dynamic Kinetic Reductive Grignard-Type Addition for the Construction of Axial and Central Chirality. *ACS Catal.* **2025**, *15*, 1147–1157.
40. Lin, C.; Xu, X.; Chong, Q.; Meng, F. Simultaneous Construction of Axial and Central Stereogenicity by Cobalt-Catalyzed Stereoconvergent Reductive Coupling of Heterobiaryl Triflates and Aldehydes. *Chem. Eur. J.* **2025**, *31*, e202500248.
41. Ding, X.; Wang, C. Nickel-Catalyzed Dynamic Kinetic Asymmetric Reductive Arylation of Aldehydes with Heterobiaryl Triflates. *Org. Lett.* **2025**, *27*, 2897–2901.
42. Wu, L.; Li, X.; Xu, H.; Sheng, F.-T.; Zhu, S.; Wang, Y. Linking Dynamic Kinetic Resolution of Racemic Heterobiaryls with Asymmetric NHK and Aza-NHK Couplings via Cobalt Catalysis. *Sci. China Chem.* **2025**. DOI: https://doi.org/10.1007/s11426-025-2801-y
43. Sommer, H.; Juliá-Hernández, F.; Martin, R.; Marek, I. Walking Metals for Remote Functionalization. *ACS Cent. Sci.* **2018**, *4*, 153–165.
44. Rahim, A.; Feng, J.; Gu, Z. 1,4-Migration of Transition Metals in Organic Synthesis. *Chin. J. Chem.* **2019**, *37*, 929–945.
45. Wang, Y.; He, Y.; Zhu, S. Nickel-Catalyzed Migratory Cross-Coupling Reactions: New Opportunities for Selective C–H Functionalization. *Acc. Chem. Res.* **2023**, *56*, 3475–3491.
46. Chen, J.; Wu, L.; Song, Z.; Wang, Y.; Li, Z.; Wang, Y.; Zhu, S. Cobalt-Catalyzed Asymmetric Migratory Nozaki–Hiyama–Kishi Coupling. *J. Am. Chem. Soc.* **2024**, *146*, 26223–26232.
47. Yang, Y.; Yu, B. Recent Advances in the Chemical Synthesis of *C*-Glycosides. *Chem. Rev.* **2017**, *117*, 12281–12356.
48. Wei, Y.; Lin, L. Q. H.; Lee, B. C.; Koh, M. J. Recent Advances in First-Row Transition Metal-Catalyzed Reductive Coupling Reactions for π-Bond Functionalization and *C*-Glycosylation. *Acc. Chem. Res.* **2023**, *56*, 3292–3312.
49. Cao, X.; Du, X.; Jiao, H.; An, Q.; Chen, R.; Fang, P.; Wang, J.; Yu, B. Carbohydrate-Based Drugs Launched During 2000–2021. *Acta Pharm. Sin. B* **2022**, *12*, 3783–3821.
50. Zhao, S.; Yu, Y.; Xie, X.; Cheng, G.; Nian, Y.; Xie, L.-G.; Han, Y.; Yang, B.; Li, Y.; Zhu, F. Photoinduced Cobalt-Catalyzed Reductive Addition of Glycosyl *C*-Aldehydes: Stereoselective Synthesis of *C*-Hydroxymethine Glycosides. *CCS Chem.* **2025**. DOI: https://doi.org/10.31635/ccschem.025.202505656
51. Lin, C.; Zhang, J.; Sun, Z.; Guo, Y.; Chong, Q.; Zhang, Z.; Meng, F. Cobalt-Catalyzed Enantioselective Alkenylation of Aldehydes. *Angew. Chem. Int. Ed.* **2024**, *63*, e202405290.
52. Gu, P.; Ding, L.; Fang, X.; Zhu, J.; Kang, S.; Wu, B.; Zhang, J.; Zhao, Y.; Shi, Z. Chromium- and Metal-Reductant-Free Asymmetric Nozaki–Hiyama–Kishi (NHK) Reaction Enabled by Metallaphotoredox Catalysis. *Angew. Chem. Int. Ed.* **2024**, *63*, e202408195.
53. Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: on the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230–13319.
54. Malapit, C. A.; Prater, M. B.; Cabrera-Pardo, J. R.; Li, M.; Pham, T. D.; McFadden, T. P.; Blank, S.; Minteer, S. D. Advances on the Merger of Electrochemistry and Transition Metal Catalysis for Organic Synthesis. *Chem. Rev.* **2022**, *122*, 3180–3218.

Citation: *CCS Chem.* **2025**, Just Published. DOI: 10.31635/ccschem.025.202506433
Link to VoR: https://doi.org/10.31635/ccschem.025.202506433

55. Wang, Y.; Dana, S.; Long, H.; Xu, Y.; Li, Y.; Kaplaneris, N.; Ackermann, L. Electrochemical Late-Stage Functionalization. *Chem. Rev.* **2023**, *123*, 11269–11335.
56. Gao, Y.; Hill, D. E.; Hao, W.; McNicholas, B. J.; Vantourout, J. C.; Hadt, R. G.; Reisman, S. E.; Blackmond, D.; Baran, P. S. Electrochemical Nozaki–Hiyama–Kishi Coupling: Scope, Applications, and Mechanism. *J. Am. Chem. Soc.* **2021**, *143*, 9478–9488.
57. Wan, Z.-K.; Choi, H.-W.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. Asymmetric Ni(II)/Cr(II)-Mediated Coupling Reaction: Stoichiometric Process. *Org. Lett.* **2002**, *4*, 4431–4434.
58. Choi, H.-W.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. Asymmetric Ni(II)/Cr(II)-Mediated Coupling Reaction: Catalytic Process. *Org. Lett.* **2002**, *4*, 4435–4438.
59. Kurosu, M.; Lin, M.-H.; Kishi, Y. Fe/Cr- and Co/Cr-Mediated Catalytic Asymmetric 2-Haloallylations of Aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 12248–12249.
60. Namba, K.; Kishi, Y. New Catalytic Cycle for Couplings of Aldehydes with Organochromium Reagents. *Org. Lett.* **2004**, *6*, 5031–5033.
61. Guo, H.; Dong, C. G.; Kim, D. S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. Toolbox Approach to the Search for Effective Ligands for Catalytic Asymmetric Cr-Mediated Coupling Reactions. *J. Am. Chem. Soc.* **2009**, *131*, 15387–15393.
62. Ding, L.; Wang, M.; Liu, Y.; Lu, H.; Zhao, Y.; Shi, Z. Stereoselective Vinylic C–H Addition via Metallaphotoredox Migration. *Angew. Chem. Int. Ed.* **2025**, *64*, e202413557.
63. Li, Y.-L.; Zhang, S.-Q.; Chen, J.; Xia, J.-B. Highly Regio- and Enantioselective Reductive Coupling of Alkynes and Aldehydes via Photoredox Cobalt Dual Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 7306–7313.
64. Wang, Y.; Mi, R.; Yu, S.; Li, X. Expedient Synthesis of Axially and Centrally Chiral Diaryl Ethers via Cobalt-Catalyzed Photoreductive Desymmetrization. *ACS Catal.* **2024**, *14*, 4638–4647.
65. Fürstner, A.; Shi, N. A Multicomponent Redox System Accounts for the First Nozaki–Hiyama–Kishi Reactions Catalytic in Chromium. *J. Am. Chem. Soc.* **1996**, *118*, 2533–2534.
66. Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. The First Catalytic Enantioselective Nozaki–Hiyama Reaction. *Angew. Chem. Int. Ed.* **1999**, *38*, 3357–3359.
67. Inoue, M.; Suzuki, T.; Nakada, M. Asymmetric Catalysis of Nozaki–Hiyama Allylation and Methallylation with a New Tridentate Bis(oxazolinyl)carbazole Ligand. *J. Am. Chem. Soc.* **2003**, *125*, 1140–1141.
68. Berkessel, A.; Menche, D.; Sklorz, C. A.; Schröder, M.; Paterson, I. A Highly Enantioselective Catalyst for the Asymmetric Nozaki–Hiyama–Kishi Reaction of Allylic and Vinylic Halides. *Angew. Chem. Int. Ed.* **2003**, *42*, 1032–1035.
69. Lee, J.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S. Stereochemical Diversity in Chiral Ligand Design: Discovery and Optimization of Catalysts for the Enantioselective Addition of Allylic Halides to Aldehydes. *Org. Lett.* **2005**, *7*, 1837–1839.
70. Xia, G.; Yamamoto, H. Catalytic Enantioselective Nozaki–Hiyama Allylation Reaction with Tethered Bis(8-quinolinolato) (TBOx) Chromium Complex. *J. Am. Chem. Soc.* **2006**, *128*, 2554–2555.
71. McManus, H. A.; Cozzi, P. G.; Guiry, P. J. Application of Tridentate Bis(oxazoline) Ligands in Catalytic Asymmetric Nozaki–Hiyama Allylation and Crotylation: An Example of High Enantioselection with a Non-Symmetric Bis(oxazoline) Ligand. *Adv. Synth. Catal.* **2006**, *348*, 551–558.
72. Hargaden, G. C.; McManus, H. A.; Cozzi, P. G.; Guiry, P. J. The Application of Bis(oxazoline) Ligands in the Catalytic Enantioselective Methallylation of Aldehydes. *Org. Biomol. Chem.* **2007**, *5*, 763–766.
73. Hargaden, G. C.; Müller-Bunz, H.; Guiry, P. J. New Proline-Oxazoline Ligands and Their Application in the Asymmetric Nozaki–Hiyama–Kishi Reaction. *Eur. J. Org. Chem.* **2007**, *2007*, 4235–4243.
74. Inoue, M.; Suzuki, T.; Kinoshita, A.; Nakada, M. Catalytic Asymmetric Nozaki–Hiyama Reactions with a Tridentate Bis (oxazolinyl)carbazole Ligand. *Chem. Rec.* **2008**, *8*, 169–181.
75. Miller, J. J.; Sigman, M. S. Quantitatively Correlating the Effect of Ligand-Substituent Size in Asymmetric Catalysis Using Linear Free Energy Relationships. *Angew. Chem. Int. Ed.* **2008**, *47*, 771–774.
76. Liu, X.; Henderson, J. A.; Sasaki, T.; Kishi, Y. Dramatic Improvement in Catalyst Loadings and Molar Ratios of Coupling Partners for Ni/Cr-Mediated Coupling Reactions: Heterobimetallic Catalysts. *J. Am. Chem. Soc.* **2009**, *131*, 16678–16680.
77. Sigman, M. S.; Miller, J. J. Examination of the Role of Taft-Type Steric Parameters in Asymmetric Catalysis. *J. Org. Chem.* **2009**, *74*, 7633–7643.
78. Deng, Q. H.; Wadepohl, H.; Gade, L. H. The Synthesis of a New Class of Chiral Pincer Ligands and Their Applications in Enantioselective Catalytic Fluorinations and the Nozaki–Hiyama–Kishi Reaction. *Chem. Eur. J.* **2011**, *17*, 14922–14928.
79. Chen, W.; Yang, Q.; Zhou, T.; Tian, Q.; Zhang, G. Enantioselective Synthesis of *a-exo*-Methylene *g*-Butyrolactones via Chromium Catalysis. *Org. Lett.* **2015**, *17*, 5236–5239.
80. Tian, Q.; Bai, J.; Chen, B.; Zhang, G. Chromium-Catalyzed Asymmetric Dearomatization Addition Reactions of Halomethyl Heteroarenes. *Org. Lett.* **2016**, *18*, 1828–1831.
81. Xiong, Y.; Zhang, G. Enantioselective Synthesis of Quaternary Stereocenters via Chromium Catalysis. *Org. Lett.* **2016**, *18*, 5094–5097.
82. Ji, H.-T.; Tian, Q.-S.; Xiang, J.-N.; Zhang, G.-Z. Chromium-Catalyzed Asymmetric Synthesis of 1, 3-Diols. *Chin. Chem. Lett.* **2017**, *28*, 1182–1184.
83. Chen, W.; Bai, J.; Zhang, G. Chromium-Catalysed Asymmetric Dearomatization Addition Reactions of Bromomethylnaphthalenes. *Adv. Synth. Catal.* **2017**, *359*, 1227–1231.
84. Xiong, Y.; Zhang, G. Enantioselective 1,2-Difunctionalization of 1,3-Butadiene by Sequential Alkylation and Carbonyl Allylation. *J. Am. Chem. Soc.* **2018**, *140*, 2735–2738.
85. Wang, L.; Wang, L.; Li, M.; Chong, Q.; Meng, F. Cobalt-Catalyzed Diastereo- and Enantioselective Reductive Allyl Additions to Aldehydes with Allylic Alcohol Derivatives via

Citation: *CCS Chem.* **2025**, Just Published. DOI: 10.31635/ccschem.025.202506433
Link to VoR: https://doi.org/10.31635/ccschem.025.202506433

Allyl Radical Intermediates. *J. Am. Chem. Soc.* **2021**, *143*, 12755–12765.
86. Shi, C.-Z.; Li, F.-S.; Chen, Y.-Q.; Lin, S.-J.; Hao, E.-J.; Guo, Z.-W.; Wosqa, U. T.; Zhang, D.-D.; Shi, L. Photocatalytic Umpolung Synthesis of Nucleophilic π-Allylcobalt Complexes for Allylation of Aldehydes. *ACS Catal.* **2021**, *11*, 2992–2998.
87. Cristòfol, À.; Limburg, B.; Kleij, A. W. Expedient Dual Co/Organophotoredox Catalyzed Stereoselective Synthesis of All-Carbon Quaternary Centers. *Angew. Chem. Int. Ed.* **2021**, *60*, 15266–15270.
88. Limburg, B.; Cristòfol, À.; Kleij, A. W. Decoding Key Transient Inter-Catalyst Interactions in a Reductive Metallaphotoredox-Catalyzed Allylation Reaction. *J. Am. Chem. Soc.* **2022**, *144*, 10912–10920.
89. Calogero, F.; Pinosa, E.; Gualandi, A.; Sensoli, L.; Dutta, S.; Maity, B.; Cavallo, L.; Fermi, A.; Ceroni, P.; Cozzi, P. G. Photoredox/Nickel-Catalyzed Diastereoselective Allylation of Aldehydes with Morita–Baylis–Hillman Adducts. *ACS Catal.* **2025**, *15*, 8303–8316.
90. Calogero, F.; Potenti, S.; Bassan, E.; Fermi, A.; Gualandi, A.; Monaldi, J.; Dereli, B.; Maity, B.; Cavallo, L.; Ceroni, P. Nickel Mediated Enantioselective Photoredox Allylation of Aldehydes with Visible Light. *Angew. Chem. Int. Ed.* **2022**, *61*, e202114981.
91. Xue, J.; Zou, J.; Gao, S.; Zheng, Q.; Fang, W.; Liu, J. Photoexcited Hantzsch Ester and Cobalt Catalysis Enable Diastereo and Enantioselective Allylation of Aldehydes. *ACS Catal.* **2025**, *15*, 6165–6172.
92. Wang, L.; Lin, C.; Chong, Q.; Zhang, Z.; Meng, F. Photoredox Cobalt-Catalyzed Regio-, Diastereo- and Enantioselective Propargylation of Aldehydes via Propargyl Radicals. *Nat. Commun.* **2023**, *14*, 4825–4839.
93. Zhang, F.-H.; Guo, X.; Zeng, X.; Wang, Z. Catalytic Enantioconvergent Allenylation of Aldehydes with Propargyl Halides. *Angew. Chem. Int. Ed.* **2022**, *61*, e202117114.
94. Zeng, X.; Zhang, F.-H.; Wang, Z. Cr-Catalyzed Chiral Allenone Synthesis via Sequential Radical-Polar Crossover and Oppenauer Oxidation. *Org. Chem. Front.* **2023**, *10*, 310–316.
95. Zhang, F.-H.; Guo, X.; Zeng, X.; Wang, Z. Asymmetric 1,4-Functionalization of 1,3-Enynes via Dual Photoredox and Chromium Catalysis. *Nat. Commun.* **2022**, *13*, 5036–5046.
96. Choppin, S.; Ferreiro-Medeiros, L.; Barbarotto, M.; Colobert, F. Recent Advances in the Diastereoselective Reformatsky-Type Reaction. *Chem. Soc. Rev.* **2013**, *42*, 937–949.
97. Fernández-Ibáñez, M. Á.; Maciá, B.; Alonso, D. A.; Pastor, I. M. Recent Advances in the Catalytic Enantioselective Reformatsky Reaction. *Eur. J. Org. Chem.* **2013**, *2013*, 7028–7034.
98. Pellissier, H. Recent Developments in the Asymmetric Reformatsky-Type Reaction. *Beilstein J. Org. Chem.* **2018**, *14*, 325–344.
99. Jiang, M.; Yu, Z.; Yang, L.; Wang, F.; Cao, W.; Liu, X.; Feng, X. Reductant-Free Enantioselective *Aza*-Reformatsky Reaction Enabled by Synergistic Visible Light Photocatalysis and Lewis Acid Catalysis. *Angew. Chem. Int. Ed.* **2025**, *64*, e202500756.
100. Lv, Y.-F.; Liu, G.; Shi, Z.; Wang, Z. Chromium Catalyzed Asymmetric Reformatsky Reaction. *Angew. Chem. Int. Ed.* **2024**, *63*, e202406109.
101. Gao, K.; Wang, Z. A Radical Approach to Chiral β-Hydroxyboronate Esters via Synergistic Co/Cr Catalysis. *ACS Catal.* **2025**, *15*, 8454–8461.
102. Hu, H.; Wang, Z. Cr-Catalyzed Asymmetric Cross Aza-Pinacol Couplings for β-Amino Alcohol Synthesis. *J. Am. Chem. Soc.* **2023**, *145*, 20775–20781.
103. Zeng, X.; Zhang, F.H.; Lai, R.; Lin, R.; Wang, Z. Cr-Catalyzed Allylic C(sp^3)–H Addition to Aldehydes Enabled by Photoinduced Ligand-to-Metal Charge Transfer. *Sci. China Chem.* **2024**, *67*, 1589–1595.
104. Shen, H.; Zhang, Z.; Shi, Z.; Gao, K.; Wang, Z. A Modular Approach to Stereoselective Homoaldol Reaction via Photoredox/Cr/Co Triple Catalysis. *Chem* **2024**, *10*, 998–1014.
105. Hu, H.; Shi, Z.; Guo, X.; Zhang, F.-H.; Wang, Z. A Radical Approach for Asymmetric α-C–H Addition of *N*-Sulfonyl Benzylamines to Aldehydes. *J. Am. Chem. Soc.* **2024**, *146*, 5316–5323.
106. Gao, Y.; Jiang, B.; Friede, N. C.; Hunter, A. C.; Boucher, D. G.; Minteer, S. D.; Sigman, M. S.; Reisman, S. E.; Baran, P. S. Electrocatalytic Asymmetric Nozaki–Hiyama–Kishi Decarboxylative Coupling: Scope, Applications, and Mechanism. *J. Am. Chem. Soc.* **2024**, *146*, 4872–4882.
107. Wang, G.; Sun, S.; Mao, Y.; Xie, Z.; Liu, L. Chromium(II)-Catalyzed Enantioselective Arylation of Ketones. *Beilstein J. Org. Chem.* **2016**, *12*, 2771–2775.
108. Zhou, P.; Xu, T. Nickel-Catalyzed Intramolecular Desymmetrization Addition of Aryl Halides to 1,3-Diketones. *Chem. Commun.* **2020**, *56*, 8194–8197.
109. Li, Y.; Li, W.; Tian, J.; Huang, G.; Lv, H. Nickel-Catalyzed Asymmetric Addition of Aromatic Halides to Ketones: Highly Enantioselective Synthesis of Chiral 2,3-Dihydrobenzofurans Containing a Tertiary Alcohol. *Org. Lett.* **2020**, *22*, 5353–5357.
110. Sun, B.; Wang, Z.-H.; Wang, Y.-Z.; Gu, Y.-C.; Ma, C.; Mei, T.-S. Parallel Paired Electrolysis-Enabled Asymmetric Catalysis: Simultaneous Synthesis of Aldehydes/Aryl Bromides and Chiral Alcohols. *Sci. Bull.* **2023**, *68*, 2033–2041.
111. Huang, S.; Zhou, J. S. Nickel-Catalyzed Enantioselective Reductive Arylation of Common Ketones. *J. Am. Chem. Soc.* **2024**, *146*, 12895–12900.
112. Xiao, J.; Zheng, Y.; Zhao, Y.; Shi, Z.; Wang, M. Asymmetric Nozaki–Hiyama–Kishi (NHK) Reaction of Isatins with Aromatic Iodides by Cobalt Catalysis. *Chin. Chem. Lett.* **2025**, *36*, 110243–110251.
113. Zhang, L.; Zhao, M.; Pu, M.; Ma, Z.; Zhou, J.; Chen, C.; Wu, Y.-D.; Chi, Y. R.; Zhou, J. S. Nickel-Catalyzed Enantioselective Reductive Conjugate Arylation and Heteroarylation via an Elementary Mechanism of 1,4-Addition. *J. Am. Chem. Soc.* **2022**, *144*, 20249–20257.
114. Zhao, M.; Zhang, L.; Zhou, J. S. Enantioselective Reductive Conjugate Alkenylation of α,β-Unsaturated Ketones and Amides via Nickel Catalysis. *ACS Catal.* **2024**, *14*, 6228–6235.

Citation: *CCS Chem.* **2025**, Just Published. DOI: 10.31635/ccschem.025.202506433
Link to VoR: https://doi.org/10.31635/ccschem.025.202506433

115. Su, Z.-M.; Deng, R.; Stahl, S. S. Zinc and Manganese Redox Potentials in Organic Solvents and Their Influence on Nickel-Catalysed Cross-Electrophile Coupling. *Nat. Chem.* **2024**, *16*, 2036–2043.
116. Turro, R. F.; Wahlman, J. L. H.; Tong, Z. J.; Chen, X.; Yang, M.; Chen, E. P.; Hong, X.; Hadt, R. G.; Houk, K. N.; Yang, Y.-F.; Reisman, S. E. Mechanistic Investigation of Ni-Catalyzed Reductive Cross-Coupling of Alkenyl and Benzyl Electrophiles. *J. Am. Chem. Soc.* **2023**, *145*, 14705–14715.
117. Lin, Q.; Diao, T. Mechanism of Ni-Catalyzed Reductive 1,2-Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 17937–17948.
118. Zhao, M.; Xu, W.; Wu, Y.-D.; Yang, X.; Wang, J.; Zhou, J. S. Cobalt-Catalyzed Enantioselective Reductive Arylation, Heteroarylation, and Alkenylation of Michael Acceptors via an Elementary Mechanism of 1,4-Addition. *J. Am. Chem. Soc.* **2024**, *146*, 20477–20493.
119. Xiong, W.; Jiang, X.; Wang, W.-C.; Cheng, Y.; Lu, L.-Q.; Gao, K.; Xiao, W.-J. Dynamic Kinetic Reductive Conjugate Addition for Construction of Axial Chirality Enabled by Synergistic Photoredox/Cobalt Catalysis. *J. Am. Chem. Soc.* **2023**, *145*, 7983–7991.
120. Ye, Z.; Ma, W.; Zhang, X.; Liu, H.; Zhang, F. Electrochemically Driven Nickel-Catalyzed Enantioselective Hydro-Arylation/Alkenylation of Enones. *Adv. Sci.* **2024**, *11*, 2405926–2405935.
121. Somprasong, S.; Wan, B.; Harutyunyan, S. R. Enantioselective Nickel-Catalyzed Electrochemical Reductive Conjugate Alkenylation of α,β-Unsaturated Ketones. *Chem. Sci.* **2025**, *16*, 802–808.
122. Pang, X.; Su, P.-F.; Shu, X.-Z. Reductive Cross-Coupling of Unreactive Electrophiles. *Acc. Chem. Res.* **2022**, *55*, 2491–2509.
123. Pan, X.; Shu, X.-Z. Reductive Deoxygenative Functionalization of Alcohols by First-Row Transition Metal Catalysis. *Chin. J. Chem.* **2023**, *41*, 1637–1652.
124. Zhao, Z.-Z.; Guo, P.; Pang, X.; Shu, X.-Z. Nickel-Catalyzed Reductive Alkenylation of Enol Derivatives: A Versatile Tool for Alkene Construction. *Acc. Chem. Res.* **2024**, *57*, 3356–3374
125. Wu, Y.-X.; Chang, M.-R.; Guan, Z.-P.; Chi, R.; Yu, J.-X.; Wu, X.; Dong, Z.-B. Deoxygenative Radical Reactions of Alcohols: A Review. *Sci. China Chem.* **2025**, *68*, 4595–4641.
126. He, R.-D.; Luo, Y.-L.; Pan, Q.-Q.; Yao, Q.-W.; Shu, X.-Z. Enantioselective Reductive Conjugate Alkenylation of α,β-Enones with Keto Alkenyl Acetates by Nickel Catalysis. *Sci. China Chem.* **2025**, *68*, 157–162.
127. Xie, H.; Wang, S.; Shu, X.-Z. C–OH Bond Activation for Stereoselective Radical *C*-Glycosylation of Native Saccharides. *J. Am. Chem. Soc.* **2024**, *146*, 32269–32275.
128. Li, W.; Zheng, Y.; Gu, Y.; Cheng, S.; Xie, J.; Lu, Y.; Chen, S.; Song, Q. Bis(pinacolato)Diboron-Enabled Nickel-Catalyzed Regio- and Enantioselective Reductive [3 + 2] Annulation of β-Bromoenones with Alkynes. *Angew. Chem. Int. Ed.* **2025**, *64*, e202506873.
129. Miller, J. J.; Sigman, M. S. Design and Synthesis of Modular Oxazoline Ligands for the Enantioselective Chromium-Catalyzed Addition of Allyl Bromide to Ketones. *J. Am. Chem. Soc.* **2007**, *129*, 2752–2753.
130. Harper, K. C.; Sigman, M. S. Three-Dimensional Correlation of Steric and Electronic Free Energy Relationships Guides Asymmetric Propargylation. *Science* **2011**, *333*, 1875–1878.
131. Huang, X.-R.; Chen, C.; Lee, G.-H.; Peng, S.-M. A Spirocyclic Chiral Borate for Catalytic Enantioselective Nozaki–Hiyama Allylation of Ketones. *Adv. Synth. Catal.* **2009**, *351*, 3089–3095.
132. Chen, R.-Y.; Dhondge, A. P.; Lee, G.-H.; Chen, C. A Chiral Bipyridyl Alcohol for Catalytic Enantioselective Nozaki–Hiyama–Kishi Allylation of Aldehydes and Ketones. *Adv. Synth. Catal.* **2015**, *357*, 961–966.
133. Guo, X.; Shi, Z.; Zhang, F.-H.; Wang, Z. Cr-Catalyzed Regio-, Diastereo-, and Enantioselective Reductive Couplings of Ketones and Propargyl Halides. *ACS Catal.* **2023**, *13*, 3170–3178.
134. Xia, H.; Jiang, X.; Lin, D.; Zhang, S.; Yu, Z.; Wu, W.; Qu, J.; Chen, Y. Catalytic Asymmetric Barbier Reaction of Ketones with Unactivated Alkyl Electrophiles. *J. Am. Chem. Soc.* **2024**, *146*, 28468–28481.
135. Chi, Z.; Liao, J.-B.; Cheng, X.; Ye, Z.; Yuan, W.; Lin, Y.-M.; Gong, L. Asymmetric Cross-Coupling of Aldehydes with Diverse Carbonyl or Iminyl Compounds by Photoredox-Mediated Cobalt Catalysis. *J. Am. Chem. Soc.* **2024**, *146*, 10857–10867.
136. Friestad, G. K.; Mathies, A. K. Recent Developments in Asymmetric Catalytic Addition to C=N Bonds. *Tetrahedron* **2007**, *63*, 2541–2569.
137. Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. Transition Metal-Catalyzed Enantioselective Hydrogenation of Enamines and Imines. *Chem. Rev.* **2011**, *111*, 1713–1760.
138. Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. Catalytic Enantioselective Formation of C–C Bonds by Addition to Imines and Hydrazones: A Ten-Year Update. *Chem. Rev.* **2011**, *111*, 2626–2704.
139. Eftekhari-Sis, B.; Zirak, M. α-Imino Esters in Organic Synthesis: Recent Advances. *Chem. Rev.* **2017**, *117*, 8326–8419.
140. Morisaki, K.; Morimoto, H.; Ohshima, T. Recent Progress on Catalytic Addition Reactions to *N*-Unsubstituted Imines. *ACS Catal.* **2020**, *10*, 6924–6951.
141. Foubelo, F.; Yus, M. Chiral *N*-*tert*-Butylsulfinyl Imines: New Discoveries. *Chem. Rec.* **2021**, *21*, 1300–1341.
142. Tolstoy, P.; Lee, S. X. Y.; Sparr, C.; Ley, S. V. Synthesis of Enantiomerically Enriched 3-Amino-2-oxindoles Through a Palladium-Mediated Asymmetric Intramolecular Arylation of α-Ketimino Amides. *Org. Lett.* **2012**, *14*, 4810–4813.
143. Xiao, J.; Wang, M.; Yin, X.; Yang, S.; Gu, P.; Lv, X.; Zhao, Y.; Shi, Z. Enantioselective Reductive (Hetero)Arylation of Cyclic *N*-Sulfonyl Imines by Cobalt Catalysis. *Angew. Chem. Int. Ed.* **2023**, *62*, e202300743.
144. Zhang, L.; Wang, X.; Pu, M.; Chen, C.; Yang, P.; Wu, Y.-D.; Chi, Y. R.; Zhou, J. S. Nickel-Catalyzed Enantioselective Reductive Arylation and Heteroarylation of Aldimines via an Elementary 1,4-Addition. *J. Am. Chem. Soc.* **2023**, *145*, 8498–8509.

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Link to VoR: https://doi.org/10.31635/ccschem.025.202506433

145. Yang, P.; Wang, Q.; Cui, B.-H.; Zhang, X.-D.; Liu, H.; Zhang, Y.-Y.; Liu, J.-L.; Huang, W.-Y.; Liang, R.-X.; Jia, Y.-X. Enantioselective Dearomative [3 + 2] Umpolung Annulation of *N*-Heteroarenes with Alkynes. *J. Am. Chem. Soc.* **2022**, *144*, 1087–1093.
146. Xiong, W.; Zhao, R.-R.; Wang, H.-S.; Lu, L.-Q.; Gao, K.; Xiao, W.-J. Asymmetric [3 + 2] Annulation of *N*-Sulfonyl Ketimines and Alkynes via Synergistic Photoredox/Cobalt Catalysis. *CCS Chem.* **2025**. DOI: https://doi.org/10.31635/ccschem.025.202505699
147. Xia, T.; Wu, Y.; Hu, J.; Wu, X.; Qu, J.; Chen, Y. Cobalt-Catalyzed Asymmetric Aza-Nozaki–Hiyama–Kishi (NHK) Reaction of α-Imino Esters with Alkenyl Halides. *Angew. Chem. Int. Ed.* **2024**, *63*, e202316012.
148. Bishop, H. D.; Zhao, Q.; Uyeda, C. Catalytic Asymmetric Synthesis of Zinc Metallacycles. *J. Am. Chem. Soc.* **2023**, *145*, 20152–20157.
149. Ding, D.; Zhang, L.; Wen, H.; Wang, C. Cobalt-Catalyzed Asymmetric Reductive Dicarbofunctionalization of 1,3-Dienes with *o*-Bromoaryl Imines as a Bis-Electrophile. *ACS Catal.* **2023**, *13*, 744–748.
150. Xia, T.; Wu, W.; Wu, X.; Qu, J.; Chen, Y. Cobalt-Catalyzed Enantioselective Reductive α-Chloro-Carbonyl Addition of Ketimine to Construct the β-Tertiary Amino Acid Analogues. *Angew. Chem. Int. Ed.* **2024**, *63*, e202318991.
151. Ni, S.; Garrido-Castro, A. F.; Merchant, R. R.; de Gruyter, J. N.; Schmitt, D. C.; Mousseau, J. J.; Gallego, G. M.; Yang, S.; Collins, M. R.; Qiao, J. X.; Yeung, K.-S.; Langley, D. R.; Poss, M. A.; Scola, P. M.; Qin, T.; Baran, P. S. A General Amino Acid Synthesis Enabled by Innate Radical Cross-Coupling. *Angew. Chem. Int. Ed.* **2018**, *57*, 14560–14565.
152. Ni, S.; Padial, N. M.; Kingston, C.; Vantourout, J. C.; Schmitt, D. C.; Edwards, J. T.; Kruszyk, M. M.; Merchant, R. R.; Mykhailiuk, P. K.; Sanchez, B. B.; Yang, S.; Perry, M. A.; Gallego, G. M.; Mousseau, J. J.; Collins, M. R.; Cherney, R. J.; Lebed, P. S.; Chen, J. S.; Qin, T.; Baran, P. S. A Radical Approach to Anionic Chemistry: Synthesis of Ketones, Alcohols, and Amines. *J. Am. Chem. Soc.* **2019**, *141*, 6726–6739.
153. Turro, R. F.; Brandstätter, M.; Reisman, S. E. Nickel-Catalyzed Reductive Alkylation of Heteroaryl Imines. *Angew. Chem. Int. Ed.* **2022**, *61*, e202207597.
154. Wu, X.; Xia, H.; Gao, C.; Luan, B.; Wu, L.; Zhang, C.; Yang, D.; Hou, L.; Liu, N.; Xia, T.; Li, H.; Qu, J.; Chen, Y. Modular α-Tertiary Amino Ester Synthesis Through Cobalt-Catalysed Asymmetric Aza-Barbier Reaction. *Nat. Chem.* **2024**, *16*, 398–407.
155. Zhang, C.; Wu, X.; Qu, J.; Chen, Y. A General Enantioselective α-Alkyl Amino Acid Derivatives Synthesis Enabled by Cobalt-Catalyzed Reductive Addition. *J. Am. Chem. Soc.* **2024**, *146*, 25918–25926.
156. Hu, J.; Xia, T.; Wu, X.; Feng, H.; Qu, J.; Chen, Y. Cobalt-Catalyzed Asymmetric Reductive Addition of Ketimine with Cyclopropyl Chloride to Construct Chiral Amino Esters Bearing Cyclopropyl Fragments. *Org. Chem. Front.* **2024**, *11*, 6311–6318.
157. Bentley, R. Role of Sulfur Chirality in the Chemical Processes of Biology. *Chem. Soc. Rev.* **2005**, *34*, 609–624.
158. Li, W.; Zhang, J. Sadphos as Adaptive Ligands in Asymmetric Palladium Catalysis. *Acc. Chem. Res.* **2024**, *57*, 489–513.
159. Otocka, S.; Kwiatkowska, M.; Madalińska, L.; Kiełbasiński, P. Chiral Organosulfur Ligands/Catalysts with a Stereogenic Sulfur Atom: Applications in Asymmetric Synthesis. *Chem. Rev.* **2017**, *117*, 4147–4181.
160. Das, S.; Dhibar, A.; Sahoo, B. Strategic Synthesis of Sulfinamides as Versatile S(IV) Intermediates. *ACS Org. Inorg. Au* **2025**, *5*, 1–12.
161. Fang, X.; Xi, L.; Wang, M.; Xiao, J.; Zhao, Y.; Wills, M. C.; Shi, Z. Asymmetric Reductive Arylation and Alkenylation to Access *S*-Chirogenic Sulfinamides. *Nat. Commun.* **2025**, *16*, 2547–2556.
162. Yuan, Y.; Tian, X.; Zheng, H.; Li, Y.; Zhang, J.; Yang, J. Catalytic Enantioselective Reductive Arylation and Alkenylation of Sulfinylamines to Access Sulfinamides Enabled by Cobalt Catalysis. *Angew. Chem. Int. Ed.* **2025**, *64*, e202506243.
163. Liu, N.; Xia, H.; Shi, Y.; Xu, K.; Yu, Z.; Wu, X.; Huang, G.; Qu, J.; Chen, Y. 8-Quinox Cobalt Catalyst Enables the Reductive Alkylative Addition of Sulfinylamines with Unactivated Alkyl Halides. *J. Am. Chem. Soc.* **2025**, *147*, 26786–26796.
164. Ding, L.; Chen, J.; Lu, H.; Shi, Z. Enantio- and Diastereoselective Reductive Propargylic Sulfinamidation Enabled by Synergistic Bimetallic Catalysis. *J. Am. Chem. Soc.* **2025**, *147*, 28389–28398.
165. Serrano, E.; Martin, R. Forging Amides Through Metal-Catalyzed C–C Coupling with Isocyanates. *Eur. J. Org. Chem.* **2018**, *2018*, 3051–3064.
166. Tortajada, A.; Börjesson, M.; Martin, R. Nickel-Catalyzed Reductive Carboxylation and Amidation Reactions. *Acc. Chem. Res.* **2021**, *54*, 3941–3952.
167. Zhao, W.; Shen, Y.; Wu, X.; Xia, T.; Hu, J.; Qu, J.; Chen, Y. Cobalt-Catalyzed Asymmetric Reductive Coupling of Isocyanates with Tertiary Alkyl Halides for Sterically Bulky Chiral Amide Synthesis. *J. Am. Chem. Soc.* **2025**, *147*, 27155–27164.
168. Fu, G. C. Transition-Metal Catalysis of Nucleophilic Substitution Reactions: A Radical Alternative to S_N1 and S_N2 Processes. *ACS Cent. Sci.* **2017**, *3*, 692–700.
169. Dong, X.-Y.; Li, Z.-L.; Gu, Q.-S.; Liu, X.-Y. Ligand Development for Copper-Catalyzed Enantioconvergent Radical Cross-Coupling of Racemic Alkyl Halides. *J. Am. Chem. Soc.* **2022**, *144*, 17319–17329.
170. Yus, M.; Najera, C.; Foubelo, F.; Sansano, J. M. Metal-Catalyzed Enantioconvergent Transformations. *Chem. Rev.* **2023**, *123*, 11817–11893.

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