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Review

Mechanisms of Nickel-Catalyzed Cross-Coupling Reactions

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Advances in nickel-catalyzed cross-coupling reactions have expanded the chemical space of accessible structures and enabled new synthetic disconnections. The unique properties of Ni catalysts facilitate the activation of traditionally inert substrates, tolerate alkyl coupling partners that undergo decomposition via β-hydride (β-H) elimination with Pd, and enable stereoconvergent cross-couplings. The radical pathways accessed by Ni catalysts have been merged with photoredox and electrochemical catalysis to achieve new reactivity. The growing utility of Ni catalysis is, in no small part, due to advances in our fundamental understanding of the properties of Ni catalysts and the mechanisms by which the reactions occur. This review highlights recent important contributions to the field with an emphasis on studies that have afforded mechanistic insight.

Highlights

The stability of open-shell Ni(I) and Ni(III) intermediates, in combination with the use of N-containing ligands, gives rise to Ni-mediated radical pathways that are prevalent in the cross-coupling of alkyl electrophiles. These pathways create opportunities in stereoconvergent synthesis, cross-electrophile coupling, and photoredox-Ni dual catalysis.

The activation of traditionally inert substrates, such as ethers and amides, can be accomplished by electron-rich Ni(0)-mediated oxidative addition.

Slow β-H elimination with Ni expands the scope of cross-coupling reactions to alkyl electrophiles and nucleophiles, which form metal-alkyl intermediates that would decompose via β-H elimination with Pd catalysts.

What Sets Nickel Apart?

Palladium-catalyzed cross-coupling reactions account for more than 40% of C–C bond-forming reactions in pharmaceutical synthesis [1], owing to their predictable and controllable reactivity and selectivity [2]. The reactivity of nickel in catalyzing cross-coupling reactions was discovered in the early 1900s, long before that of Pd in the 1950s [2], but only recently has its potential been exploited [3]. In addition to serving as a cheaper, Earth-abundant alternative to Pd, Ni can access various reaction mechanisms, leading to distinct reactivity [4]. This review summarizes the characteristic properties of Ni catalysts and their inherent reactivity in catalyzing cross-coupling reactions that have been discovered in the past two decades, with a focus on the underlying reaction mechanisms.

Ni exhibits several unique properties compared with Pd (Figure 1A). First, various oxidation states ranging from Ni(0) to Ni(IV) [5–7] are readily accessible, whereas Pd most commonly adopts Pd(0) and Pd(II) states (Figure 1Ai). The open-shell electronic configurations of Ni [e.g., Ni(I), Ni(III)] are more stable than its second and third row counterparts [8], which is likely a result of the higher pairing energy of Ni due to a more condensed electron cloud [9]. Consequently, the activation of an electrophile by Ni can involve either the classic two-electron **oxidative addition** (see Glossary) or a single-electron process to afford radicals (Figure 1Aii) [10]. Radical pathways are commonplace for enzymatic reactions occurring on cofactor F430 of methylcoenzyme M reductase (MCR) that contains a Ni hydrocorphinate in its active site [11] and NiFe-hydrogenase [12]. The reduction potential [13] and electronegativity of Ni [14] are significantly lower than Pd and the atomic radius of Ni is smaller than that of Pd [15] (Figure 1Aiii,iv). **β-H elimination** occurs via an intermediate with a β-**agostic interaction**. The lower electronegativity of Ni results in a weaker agostic interaction relative to Pd and the smaller radius of Ni leads to a more strained geometry in the transition state. Both factors contribute to slower (β-H) elimination of Ni-alkyl compounds (Figure 1Av) [16–18]. Taken together, these properties lead to diverse mechanisms of Ni-catalyzed cross-coupling reactions, including two-electron and single-electron pathways mediated by Ni(0), Ni(I), Ni(II), and Ni(III) intermediates, and provide opportunities for achieving new products that are inaccessible with Pd (Figure 1B).

Two-Electron Redox Mechanism via Ni(0)/Ni(II)

Typical cross-coupling reactions with Csp^2 electrophiles are expected to occur by the two-electron mechanism via Ni(0)/Ni(II) intermediates (Figure 2A) [19], although early reports evidenced aryl radicals and Ni(I) intermediates in a $(PPh_3)_4$Ni-catalyzed cross-coupling of aryl iodides [20]. For reactions proceeding via Ni(0)/Ni(II)-mediated two-electron pathways, Ni(I) may hinder reactivity, serving as an off-cycle species [21,22]. Concerted oxidative addition of Ni(0) to aryl halides is followed by **transmetalation** with a nucleophile and subsequent reductive elimination (Figure 1Bi). Transmetalation of Zn

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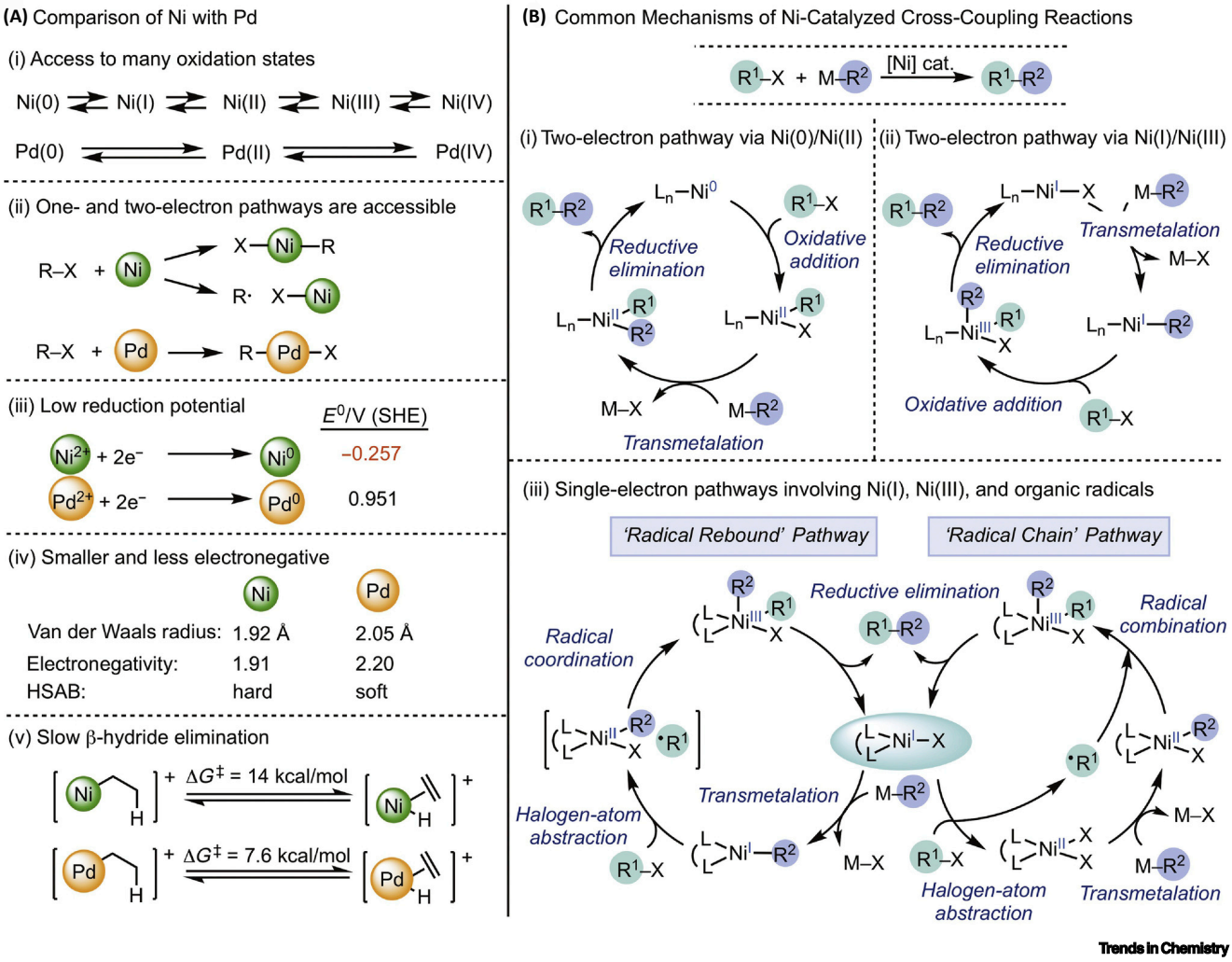


Figure 1. Fundamental Properties of Nickel Catalysts and Consequences in Catalysis.

(A) Comparison of the properties of Ni and Pd. (B) Common mechanisms of Ni-catalyzed cross-coupling reactions. (i) Two-electron redox pathway mediated by Ni(0) and Ni(II) intermediates. (ii) Two-electron redox pathway mediated by Ni(I) and Ni(III) intermediates. (iii) One-electron redox pathways.

reagents was determined to be the **turnover-limiting step** for an oxidative diarylation [23] and a Suzuki–Miyaura coupling reaction [24]. In the Suzuki–Miyaura coupling, catalyst deactivation occurs when Ni(II) intermediate **1** aggregates to form dimer **2** in the presence of OH^- (Figure 2A) [24]. The OH^- is necessary to activate the boronate for transmetalation. The deactivation of Ni can be avoided by applying bulky, electron-rich phosphine ligands (e.g., PCy_3) at the expense of slower transmetalation. Comparatively, Pd catalysts exhibit better compatibility with aqueous conditions than do Ni catalysts due to the less exergonic dimerization of Pd catalysts. While basic conditions are usually required to activate boronic acid nucleophiles, a base-free decarboxylative Suzuki–Miyaura coupling was recently achieved with Ni catalysts [25].

The low reduction potentials and electronegativity of Ni suggest that Ni(0) is highly reducing and can facilitate oxidative addition. This effect is enhanced by strong σ-donor ligands [e.g., alkyl phosphines, ***N*-heterocyclic carbenes (NHCs)**] (see Box 1). Bulky, electron-rich NHC ligands enforce a coordinatively unsaturated 14-electron $(NHC)_2Ni(0)$ complex that further increases the oxidative-addition reactivity [26]. As a result, $Ni(0)(PR_3)_n$ or $Ni(0)(NHC)_n$ complexes can activate typically inert

Box 1. Ligands in Nickel Catalysis

Reactions proceeding through two-electron redox pathways (see Figure 1Bi,ii in main text) utilize strong σ-donor ligands, such as bidentate and monodentate phosphine and NHC ligands (Figure I). A large portion of Ni-catalyzed cross-coupling reactions proceeding through radical pathways employ bidentate and tridentate *N*-ligands, including bipyridine (bpy), bioxazoline (biOx), terpyridine (terpy), and pyridine-bioxazoline (pybox) (see Figure 1Biii in main text). These weak-field ligands relative to phosphines lead to lower ligand field-splitting energy that promotes the formation of paramagnetic species. The redox activity of these chelating ligands may stabilize the open-shell Ni intermediates, and a variety of chiral pybox, box, and biOX ligands are readily available for asymmetric catalysis.

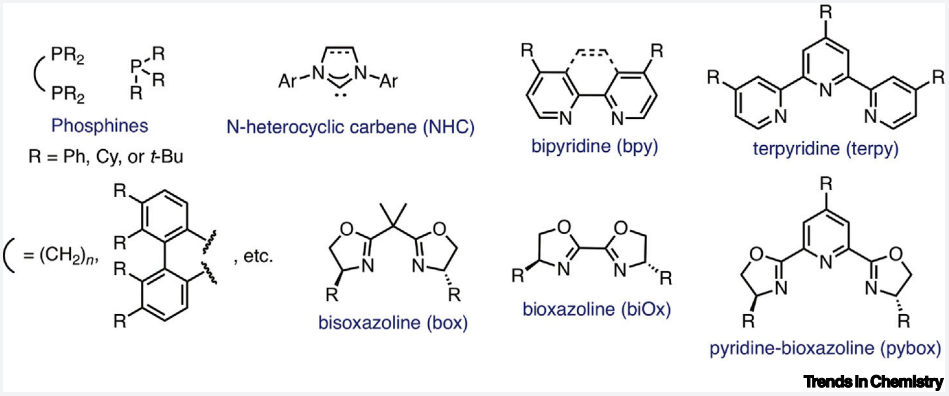


Figure I. Common Ligands for Nickel-Catalyzed Cross-Coupling Reactions.

electrophiles, including aryl chlorides [27], aryl ethers [28], sulfamates [29], alkyl and aryl fluorides [30], epoxides [31], aziridines [32], amides [33], nitriles [34], and esters via both decarbonylation [35] and C–O bond cleavage [36] (Figure 2B). Oxidative addition is the turnover-limiting step of most cross-coupling reactions of challenging electrophiles [21,37]. The oxidative addition of a (dcpe)Ni(0) (dcpe = dicyclohexylphosphinoethane) **4** to pivalate **5** has been directly observed and characterized to afford Ni(II) **6** [38].

The slow β-H elimination of Ni-alkyl complexes (Figure 1Av) has expanded the scope of cross-coupling to Csp^3 electrophiles [39] that typically suffer from side-reactions associated with β-H elimination when Pd catalysts are employed. The **stereospecific** couplings of benzylic and allylic ethers and esters [40,41] give access to allylic diarylmethanes and arylmethanes with biological activity, such as analogs to the antibreast-cancer drug tamoxifen [42]. With NHC or bisphosphine ligands, oxidative addition occurs via an S_N2 pathway, where nucleophilic attack of Ni to the benzyl ether results in inversion at the benzylic position (Figure 2C) [43]. The following sequence of transmetalation and concerted reductive elimination leads to overall inversion of the stereochemistry at the benzylic position. Conversely, when PCy_3 is used as a ligand in conjunction with a benzyl ester, concerted oxidative addition is facilitated by a more flexible ligand-Ni-substrate angle and results in retention of stereochemistry, leading to retention of stereochemistry in the cross-coupling product [44]. Finally, in a **cross-electrophile coupling**, Pd and Ni catalysts separately activate aryl triflates **7** and aryl bromides **8**, respectively [45], giving rise to biaryls **9** that are ubiquitous in pharmaceuticals (Figure 2D).

Two-Electron Redox Mechanism via Ni(I)/Ni(III) Intermediates

A number of two-electron redox pathways are mediated by Ni(I)/Ni(III) intermediates (Figure 1Bii), such as the Suzuki coupling catalyzed by $(NHC)_2$Ni(I)-Br (Figure 2E) [46], due to the more reducing properties of Ni complexes relative to Pd and the stability of Ni(I) and Ni(III) species. Characterization of the key oxidative-addition step of (IPr)Ni(I)(NPh_2) **10** to aryl halides [47] to form Ni(III) species **11**, as

Glossary

β-Hydride (β-H) elimination: the process by which an alkyl group that is bonded to a metal center and has a hydrogen atom attached to the carbon β to the metal center can be converted into an alkene and a metal hydride.

Agostic interaction: the donation of electron density from the β-C–H to the metal d orbital in a metal-alkyl complex.

Cross-electrophile coupling: a C–C bond-forming reaction between two different electrophiles (often organic halides) under reductive conditions.

***N*-Heterocyclic carbenes (NHCs)**: a persistent six-electron carbon center that is stabilized by adjacent nitrogen atoms in a ring system.

Oxidative addition: a process that increases the oxidation state and coordination number of the metal center by the insertion of a metal into a covalent bond of a substrate.

Single-electron transfer: a process involving the movement of an electron from one atom or molecule (donor) to another (acceptor), which changes the oxidation state of the atoms or molecules.

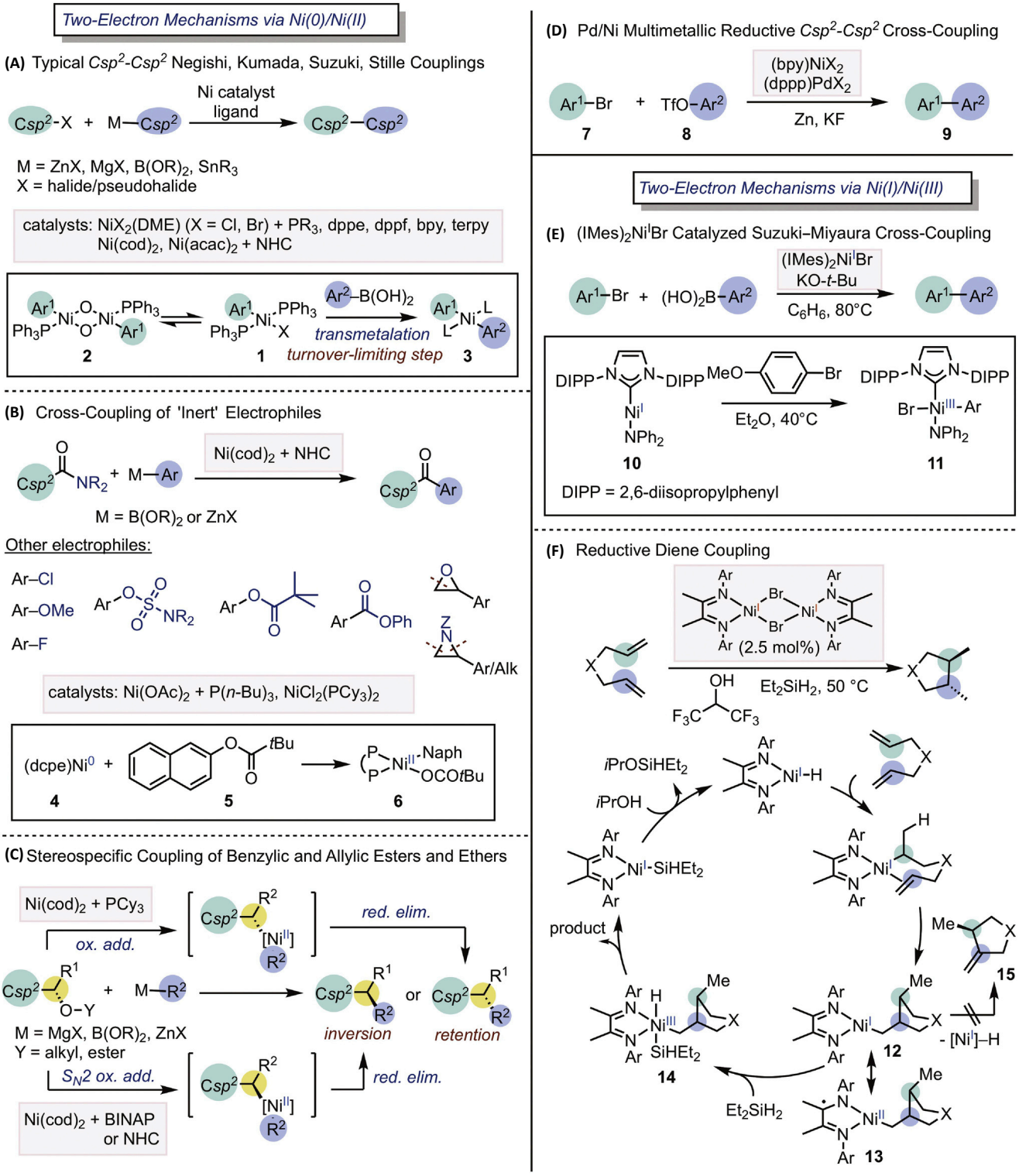
Stereoconvergent: describes a transformation that converts any mixture of two stereoisomers of starting material into one stereoisomer of product.

Stereospecific: describes a transformation that retains or inverses the stereocenter of the substrate by certain mechanism (e.g., the S_N2 reaction).

Transmetalation: transfer of ligands from one metal center to another.

Turnover-limiting step: the reaction with the slowest rate constant in a catalytic cycle, which limits the frequency of the entire catalytic cycle, or 'turns over'.

Valence tautomers: isomeric compounds in which electrons occupy different orbitals without migration of atoms or groups.



Trends in Chemistry

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well as a study on the oxidative addition of a Ni(I)-amino complex with alkyl halides [48], reveals that Ni(I)-mediated oxidative addition can be facile. The reductive elimination from Ni(III) complexes has been characterized in the context of C–C [6] and C–halogen bond formations [49].

A two-electron process on the paramagnetic Ni(I)/Ni(III) platform has been observed in a *trans*-selective reductive cycloisomerization of dienes (Figure 2F) [50]. The redox-active α-diimine ligand stabilizes Ni(I) intermediates (e.g., **12**) by delocalizing the unpaired electron to the ligand π* orbitals to form Ni(II) **valence tautomer 13**. The electron-rich, formally Ni(I) intermediate **12** can undergo oxidative addition with Et_2SiH_2 to give Ni(III) **14**. Oxidative addition outcompetes β-H elimination that occurs with Ni(II) to form the unsaturated cycloisomerization product **15** [51]. The electron-paramagnetic-resonance (EPR) spectrum of a frozen reaction mixture displays a Ni(III) species, consistent with Ni(III) **14** as the catalyst resting state.

Radical Mechanisms

Slow β-H elimination of Ni-alkyl intermediates and the application of bidentate and tridentate ligands has greatly expanded the scope of cross-coupling reactions to primary, secondary, and tertiary alkyl halides [3,39], pseudohalides [52], and carboxylates [53] as well as redox-active esters [54] and sulfones [55] (Figure 3A). These reactions often adopt *N*-containing chelating ligands (Box 1). The vast majority of Ni-catalyzed cross-coupling reactions with Csp^3 electrophiles involve **single-electron transfer** pathways and organic radical intermediates (Figure 1Biii). The sequence of electrophile and nucleophile activation may be system dependent, leading to two possible pathways. All cases commence with a Ni(I)–halide intermediate (highlighted in the center of Figure 1Biii). In the 'radical rebound cycle', the Ni(I)–halide first undergoes transmetalation with the nucleophile to form a Ni(I)–carbyl intermediate that interacts with the alkyl electrophile to generate a radical. Combination of the radical with Ni(II) forms a Ni(III) intermediate that undergoes subsequent reductive elimination. In the 'radical chain pathway', the Ni(I)–halide intermediate initiates the formation of a radical from the alkyl electrophile prior to transmetalation with the nucleophile.

The 'radical rebound mechanism' is supported by the isolation of (terpy)Ni(I)–Me (terpy = 2,2′:6′,2″-terpyridine) **17** as an intermediate derived from transmetalation of a Ni(I)-halide **16** [56] and is verified by computational studies [57]. The reaction of **17** with alkyl iodide **18** forms a radical **19** that combines with Ni(II) to generate Ni(III) **20** (Figure 3A). Closer investigation of the alkyl halide activation by a (*t*Bu-Xantphos)Ni(I)–Ar complex **21** distinguishes a concerted halogen-atom abstraction mechanism from other possible pathways, such as oxidative addition, outer-sphere electron transfer, and inner-sphere electron transfer mechanisms [10]. A separate study of a Kumada coupling reaction catalyzed by (pincer)Ni catalyst **24** points to an analogous mechanistic variant where transmetalation of the nucleophile occurs prior to electrophile activation via bimolecular oxidative addition [58]. First, transmetalation of Ni(II) **25** with RMgCl gives a Ni(II)–alkyl species **26**. Halogen-atom abstraction of alkyl bromide by **26** generates Ni(III) **28** and a radial that combines with another molecule of **26** to give Ni(III) species **29**. Reductive elimination delivers the product and Ni(I) complex **30**. Comproportionation of **30** with Ni(III) **28** regenerates Ni(II) **25**. Measurement of the distribution of cyclized to linear products as a function of catalyst loading (when a radical clock substrate is employed) reveals that the radical escapes the solvent cage and recombines with Ni.

The radical mechanism is operative in **stereoconvergent** reactions, where the stereocenters of racemic secondary alkyl electrophiles can be erased and reset on binding to a chiral Ni catalyst (Figure 3B). This concept has been extended to propargyl carbonates, α-haloketones, boronate nucleophiles in the synthesis of chiral alcohols and carbamates [3], and α-silyl bromides in the synthesis of

Figure 2. Ni-Catalyzed Cross-Coupling Reactions via Two-electron Pathways Mediated by Ni(0)/Ni(II) and Ni(I)/Ni(III) Redox Pairs.
(A) Cross-coupling of Csp^2 nucleophiles and electrophiles. Transmetalation is identified as the turnover-limiting step. (B) Activation of conventionally 'inert' bonds by Ni(0). (C) Stereospecific coupling reactions of esters and ethers. (D) Dual Ni/Pd-catalyzed cross-electrophile coupling of Csp^2 electrophiles. (E) Biaryl cross-coupling via Ni(I)/Ni(III) intermediates. (F) Reductive diene cyclization catalyzed by Ni(I)/Ni(III) redox pairs that account for the chemo- and stereoselectivity.

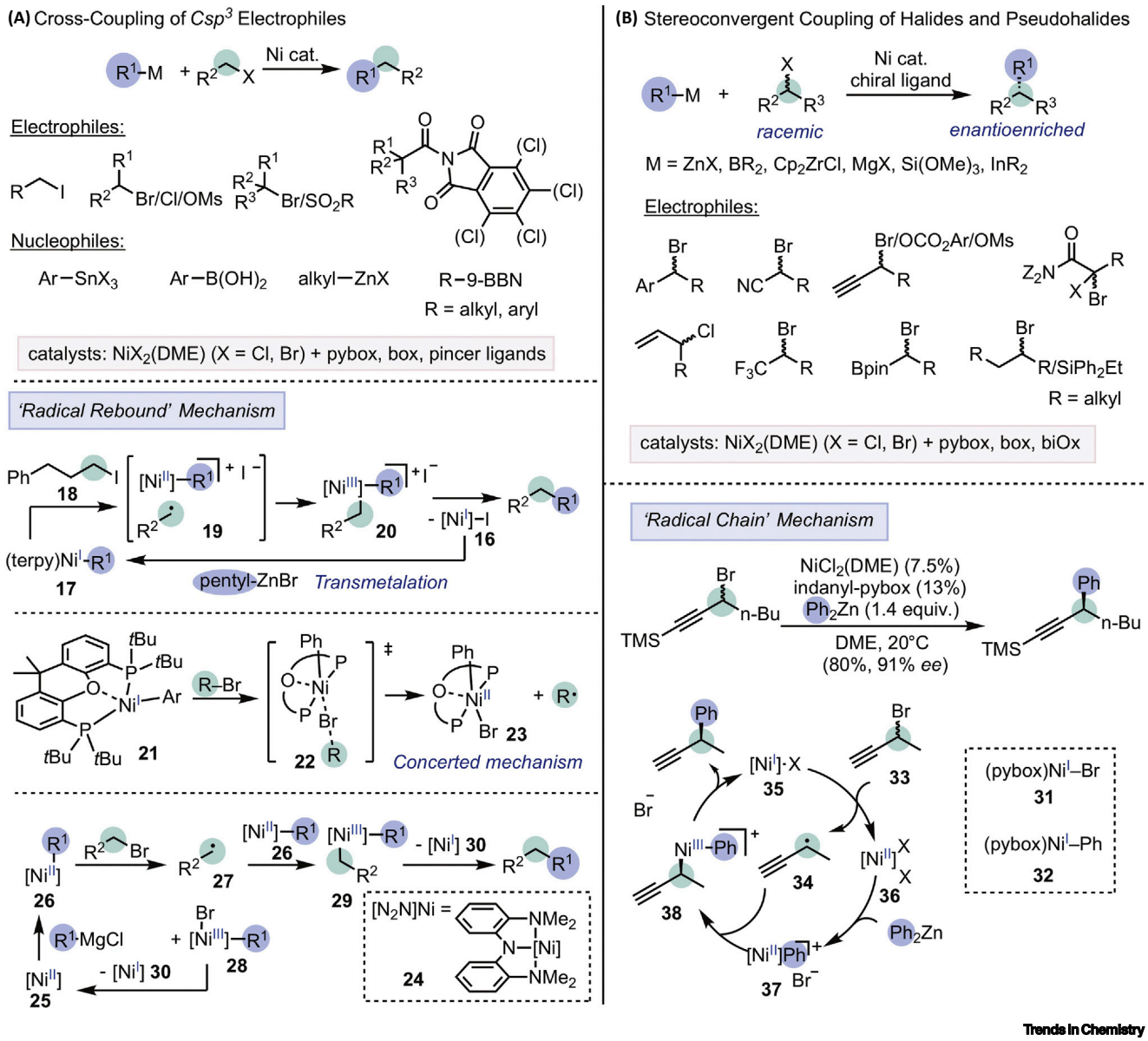


Figure 3. Ni-Catalyzed Cross-Coupling Reactions Proceeding by Radical Pathways.

(A) Cross-coupling of alkyl electrophiles with alkyl or aryl nucleophiles. The 'radical rebound' mechanism has been characterized in three systems: a (terpy)Ni(I)-Me mediated electrophile activation, a (*t*-BuXantphos)Ni(I)Ar-mediated electrophile activation via a concerted pathway, and a (*N*,*N*,*N*)Ni-catalyzed Kumada coupling. (B) Stereoconvergent cross-coupling reactions with alkyl electrophiles. The 'radical chain' mechanism has been characterized in a (pybox)Ni-catalyzed stereoconvergent coupling.

chiral alkyl silanes containing heterocycles and polar functional groups [59]. Kinetic studies, in combination with stoichiometric investigations of isolated organometallic intermediates **31** and **32**, reveal that racemic propargyl bromide **33** is activated by Ni(I) **35** to generate a radical [60]. Transmetalation of **36** gives **37**, which combines with radical **34**. The facial selectivity of this radical coordination to Ni is controlled by chiral ligands and serves as the enantiodetermining step. In this 'radical chain mechanism' (Figure 1Biii) where electrophiles are activated prior to nucleophiles, it appears to be important to stabilize the free radical intermediate, such as **34**, with α-substituents.

Reductive Cross-Electrophile Coupling

Cross-electrophile coupling reactions under reducing conditions can bypass the need for the pre-generation of air-sensitive organometallic coupling reagents (Figure 4A) [61]. The greater availability of electrophiles relative to nucleophiles indicates that a broader scope of structures is accessible. Typical reductants are zero-valent metals such as Zn and Mn. Organic reductants [e.g., tetrakis(dimethylamino)ethylene (TDAE)] can provide strong reducing power but are more expensive [62]. Electrochemical reduction has also been demonstrated with tertiary amines as the sacrificial reductants [63]. The major challenge of reductive couplings is achieving selectivity for cross-coupling of different electrophiles over homocoupling [64]. Ni catalysts can undergo both two-electron and single-electron activation pathways for electrophiles, allowing sequential activation of different electrophiles via different mechanisms and imparting selectivity (Figure 1Aii). Csp^2 electrophiles are expected to undergo oxidative addition with Ni(0), whereas the activation of Csp^3 electrophiles proceeds via

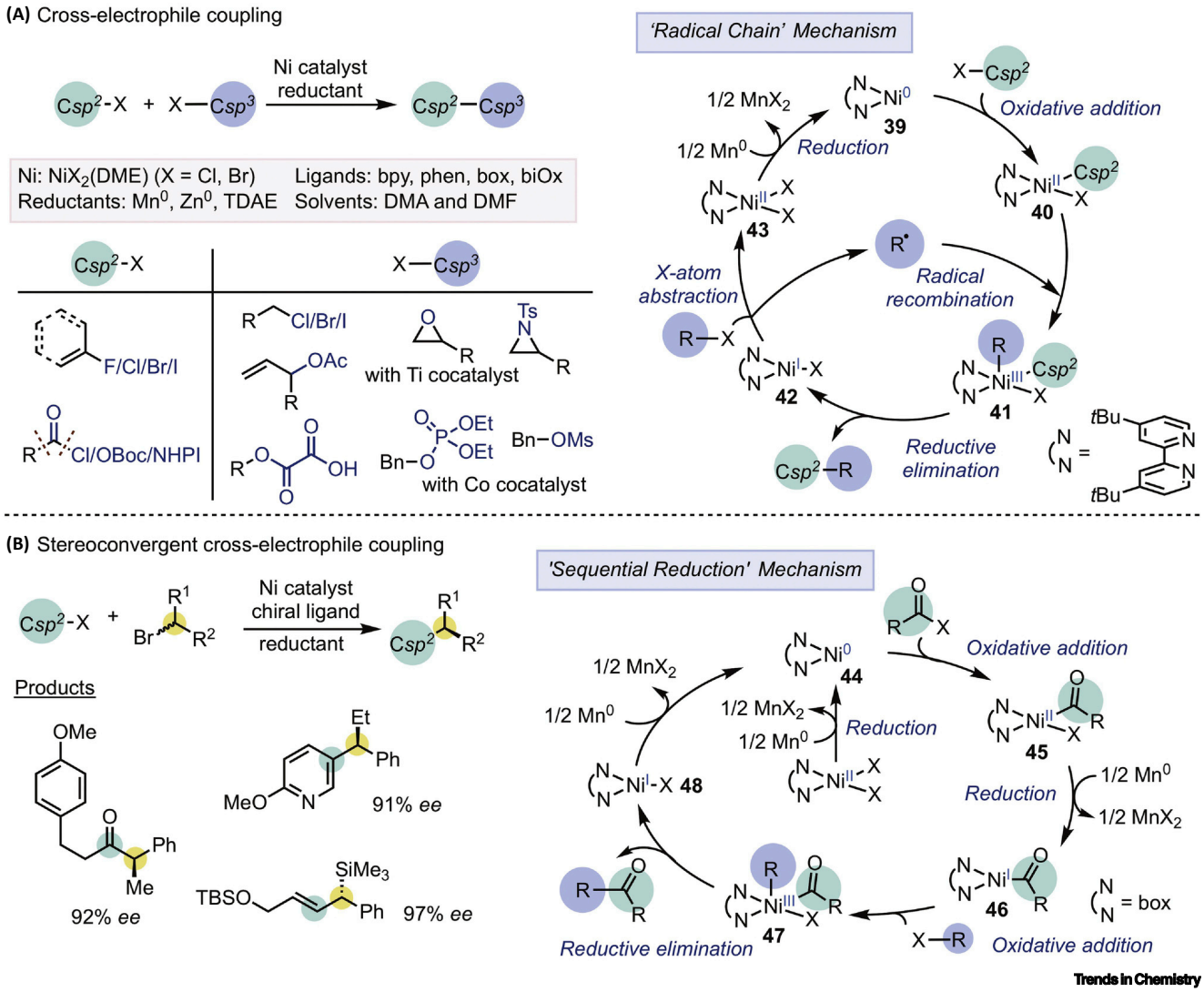


Figure 4. Reductive Cross-Electrophile Coupling Reactions.
(A) The general scope of cross-electrophile coupling and the 'radical chain' mechanism for a (bpy)Ni catalyst in combination with Mn. (B) Stereoconvergent cross-coupling going through a 'sequential reduction' mechanism.

radical formation [10]. The scope of Csp^2 electrophiles includes aromatic halides, acyl halides, acids, and esters [65]. The scope of Csp^3 electrophiles extends to radical precursors beyond alkyl halides and pseudohalides [61], including epoxides [66], aziridines [67], phosphates [68], *N*-hydroxyphthalimide (NHPI) esters [69], and oxalates [70]. Additionally, cocatalysts (e.g., Co, Ti) have been utilized to facilitate radical formation [68]. Chiral titanocenes in combination with (bpy)Ni have facilitated the enantioselective coupling of epoxides with Csp^2 electrophiles [66].

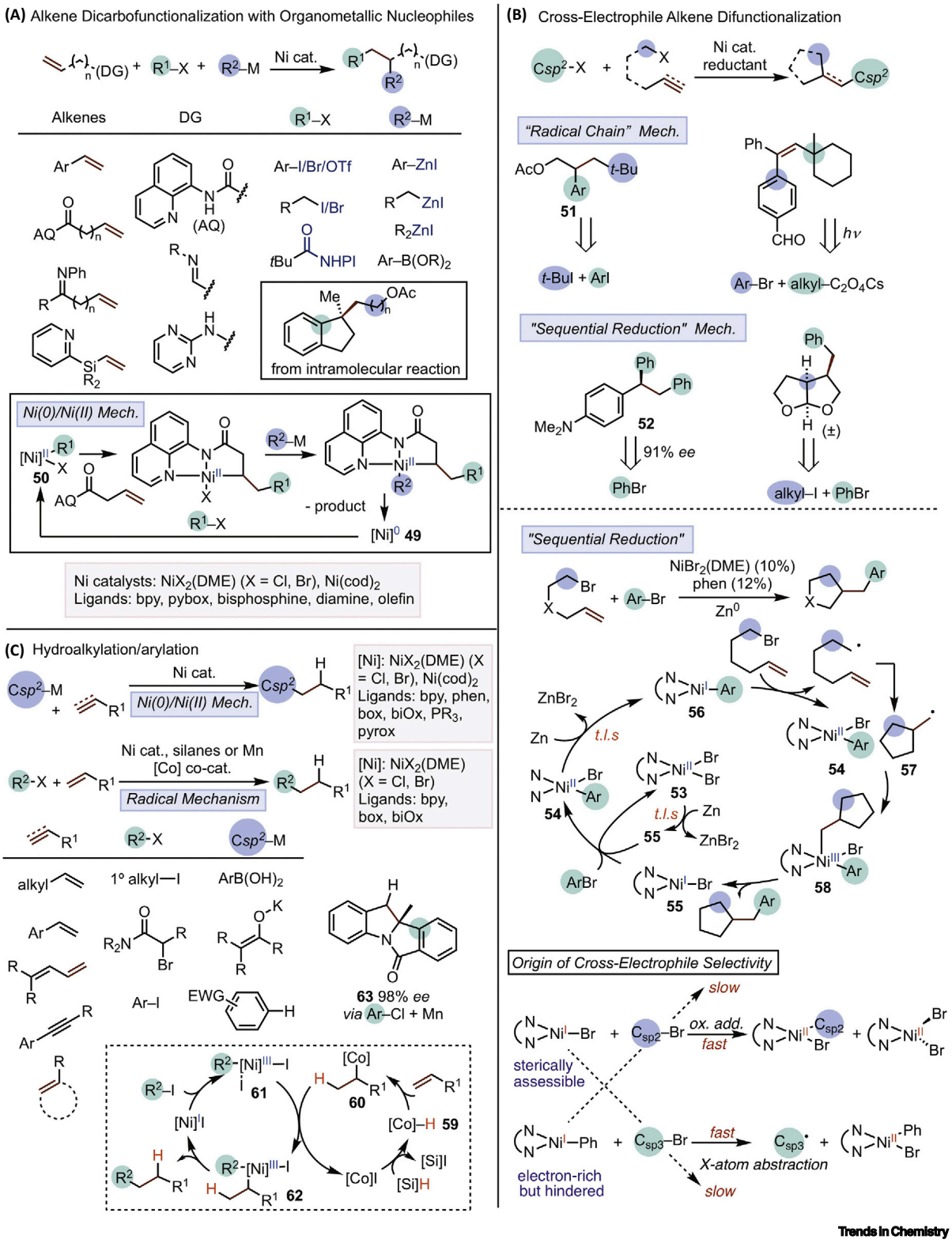
Mechanistic investigations (i.e., radical clock tests, kinetics, organometallic studies) on Csp^3-Csp^2 cross-electrophile coupling reactions with (bpy)$NiBr_2$ as the catalyst and Mn as the reductant are consistent with a radical chain mechanism (Figure 4A) [71]. In this mechanism, the Csp^3 electrophile is activated prior to the Csp^2 electrophile. Ni(I) **42** initiates radical formation from the Csp^3 electrophile to form Ni(II) **43**. On reduction, Ni(0) **39** undergoes oxidative addition to the Csp^2 electrophile to form Ni(II) **40**, which combines with the organic radical to form Ni(III) **43**, followed by reductive elimination to give the product and Ni(I) **42**. Key data supporting this cycle include: the faster oxidative addition of Ni(0) to aryl halides than alkyl halides; stoichiometric activation of aryl and alkyl halides by Ni(II) species; and the increase of the ratio of cyclized to uncyclized products from cyclizable radical probes with higher catalyst loadings, implying unbound free radicals.

The formation of radicals from Csp^3 electrophiles provides opportunities for stereoconvergent reductive coupling reactions (Figure 4B). This concept has been demonstrated by the coupling of aryl bromides and acyl chlorides with various benzylic chlorides [72]. The asymmetric coupling of aziridines with iodoarenes invokes a 'sequential reduction' pathway, where oxidative addition of the Csp^2 electrophile by Ni(0) **44** occurs prior to the reduction of Ni(II) **45** to Ni(I) **46**. Activation of the Csp^3 electrophile forms a radical that scrambles the stereocenter [67]. On binding of the radical to Ni, Ni(III) **47** forms and proceeds to undergo reductive elimination. The resulting Ni(I) **48** is further reduced to Ni(0) **44**. Recent computational studies reveal close barriers for the radical chain mechanism and 'sequential reduction mechanism' and do not allow differentiation between them [73].

Alkene Carbofunctionalization

While Pd-catalyzed Heck reactions restore the olefin functionality via β-H elimination, the slow β-H elimination of Ni-alkyl intermediates has allowed the development of 1,2-dicarbofunctionalization, hydroarylation, and hydroalkylation reactions of alkenes. 1,2-Dicarbofunctionalizations of alkenes typically use alkyl halides as the electrophile and organozinc reagents as the nucleophile (Figure 5A) [54]. Other nucleophiles include Mg reagents [74] and boron reagents [75]. The olefin scope has been primarily limited to vinylarenes [76] and Michael acceptors [54] until the recent development of directing-group (DG) strategies, which have expanded the scope to include terminal aliphatic alkenes [77]. Computational analysis reveals that the reaction goes through a two-electron redox pathway mediated by Ni(0) **49** and Ni(II) **50** intermediates [77]. A remaining challenge is to expand the scope of olefins to internal alkenes. Such reactivity has been achieved by tethering an electrophile to the olefin to give cyclized products via intramolecular 1,2-dicarbofunctionalization, but intermolecular examples are lacking.

1,2-Dicarbofunctionalization reactions of alkenes have been pursued with two electrophiles under reductive conditions. Cross-electrophile selectivity has been achieved in the reductive 1,2-aryl-alkylation of allylic acetates and amines to afford products such as **51** (Figure 5B) [62], with the Csp^3 electrophile scope limited to tertiary iodides [62]. Chiral box ligands have been used to accomplish an asymmetric intramolecular olefin difunctionalization to afford 5- and 6-membered carbocycles and heterocycles [78]. The enantioselective intermolecular diarylation of vinylarenes with aryl bromides affords a library of α,α,β-triarylethanes, including **52** [79]. A comprehensive mechanistic study on the two-component reductive alkyl-arylation of alkenes reveals a sequential reduction pathway [80]. Kinetic data suggest that the reductions of Ni(II) species **53** and **54** by Zn are the turnover-limiting steps under optimized conditions. Organometallic studies, in combination with electrochemical investigations, reveal that Zn is insufficient for reducing Ni(II) to Ni(0), but instead affords Ni(I)–Br **55** and Ni(I)–Ar **56**. Csp^2 and Csp^3 electrophiles are independently activated by different Ni(I) species



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via distinct mechanisms. (phen)Ni(I)–Br **55** selectively activates ArBr via oxidative addition, facilitated by the sterically accessible Ni(I)–Br center. By contrast, the increased steric bulk of (phen)Ni(I)–Ph **56** hinders oxidative addition, but the electron-rich Ni center can promote halogen-atom abstraction of the alkyl bromide to give radicals. This sequence of electrophile activation accounts for the selectivity observed in cross-electrophile coupling reactions.

Hydroarylations of alkenes with Csp^2 nucleophiles mostly proceed through two-electron pathways mediated by Ni(0)/Ni(II) or Ni(I)/Ni(III) intermediates (Figure 5C). Since the early observation of hydroarylation of activated alkenes, the olefin scope has been expanded to α,β-unsaturated ketones, aldehydes [81], and dienes [82]. Hydroarylation reactions proceeding through two-electron pathways via Ni(I)/Ni(III) intermediates disregard the position of the olefin in the substrate but form C–C bonds from the most stable benzylic organonickel intermediate via reversible chain walking [83]. Asymmetric variants have been achieved by intramolecular hydroarylation of indoles to form indoline products **63** [84], the coupling of vinylarenes with aryl boron reagents [85], and the coupling of 1,3-dienes with enolates [86]. Most hydroalkylation reactions are conducted with electrophiles under reductive conditions and proceed through radical pathways. Hydroalkylations of unactivated olefins are facilitated by metal hydride cocatalysts, such as (Salen)Co–H [87] and (dpm)Mn–H (dpm = dipivaloylmethane) [88]. A detailed mechanistic study reveals that [Co]–H **59** inserts into the olefin to form an alkyl-[Co] **60**, which transmetalates to Ni(III) **61** to afford **62**, followed by reductive elimination [89]. Asymmetric hydroalkylation is rare but has been accomplished through the stereoconvergent coupling of olefins with α-bromoamides mediated by Ni–H and radical intermediates [90].

The Merger of Ni with Photoredox Catalysis and Electrocatalysis

The stability of Ni-centered radicals and the ability of Ni to bind to organic radicals have inspired the development of coupling reactions that use a wide range of radical precursors. Traditionally, radicals are formed from peroxides, azobisisobutyronitrile (AIBN), and tin hydrides. Modern studies have discovered transition-metal, electrocatalytic, and photocatalytic means to initiate radical formation (Figure 6A). Oxidative and reductive quenching of light-excited photoredox catalysts by electrophiles and nucleophiles, respectively, have broadened the scope of radical precursors to trifluoroborate salts, carboxylates, silicates, and dihydropyridines [91]. Alkyl halides [92] and phthalimides [63] are versatile radical precursors that can be activated electrocatalytically, photocatalytically, and by transition metals. Oxalates have found utility in both transition-metal and photocatalytic reactions [93]. Dual photoredox-Ni catalysis is particularly useful in light of the large library of available alcohols and carboxylates. Reductive coupling reactions can also be driven with photocatalysis and allow the use of amines [94] and silanes [95] as reductants in place of more commonly encountered heterogeneous reductants (e.g., Zn, Mn).

Despite the recent, prolific success of photoredox-Ni dual catalysis, detailed mechanistic understanding remains elusive. Comparing the redox potentials of (dtbpy)Ni complexes **65** and **66** (dtbpy = 4,4′-di-*t*Bu-bpy) [96,97]with those of $(bpy)_3Ir(III)$ **67** [98], a common photosensitizer employed in dual catalysis, reveals multiple possible redox processes between Ni at various oxidation states and **67** in different states (Figure 6B). Typically proposed pathways comprise a photoredox cycle, mediated by the photosensitizer, and the bond-formation cycle, mediated by Ni catalysts (Figure 6C,D). The photocatalytic cycle is relatively well understood from previous photophysical studies [98], but the substrate cycle mediated by Ni remains elusive. Computational studies on the cross-coupling of benzyl boronates with aryl bromides suggest that the photoredox cycle and the Ni catalysis cycle meet when

Figure 5. Ni-Catalyzed Alkene Functionalization Reactions.

(A) Redox-neutral alkene dicarbofunctionalization with organometallic nucleophiles. Directing groups are applied to facilitate a difunctionalization mediated by Ni(0)/Ni(II) intermediates. (B) Reductive cross-electrophile alkene difunctionalization reactions. These reactions typically proceed through 'radical chain' and 'sequential reduction' mechanisms. A two-component coupling has been characterized to proceed through a sequential reduction mechanism. Csp^2 and Csp^3 electrophiles are separately activated by Ni(I)–Br and Ni(I)–Ar species, respectively, via different mechanisms, accounting for the cross-selectivity. (C) Hydroarylation and hydroalkylation reactions. Redox-neutral hydroarylation usually proceeds through two-electron pathways via Ni(0)/Ni(II) intermediates, whereas reductive hydroalkylation undertakes radical pathways.

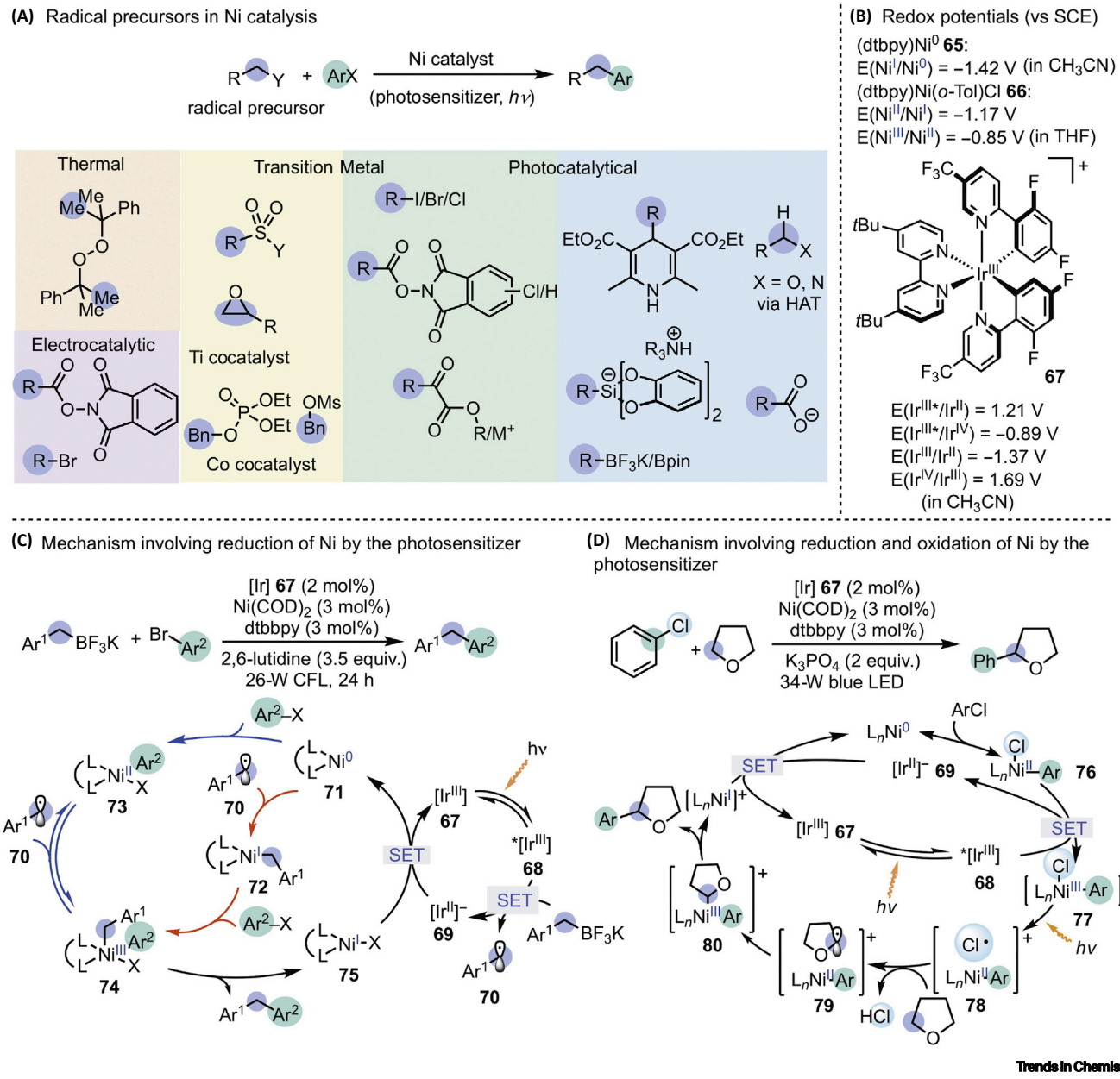

Figure 6. Radical Precursors for Ni Catalysis and Ni-Photoredox Dual Catalysis.

(A) Radical precursors used in Ni-catalysis sorted by method of activation. (B) Redox potentials for Ni intermediates and a common Ir photoredox catalyst in Ni-photoredox dual catalysis. (C) A computational study on Ni-photoredox dual catalysis, in which [Ir] acts as a reductant for Ni. (D) An experimental study on Ni-photoredox dual catalysis, in which [Ir] acts as both a reductant and an oxidant for Ni.

Ni(I) **75** is reduced by **69** to form Ni(0) **71** (Figure 6C) [99]. The Ni catalysis cycle comprises two plausible pathways: the benzylic radical **70**, formed on activation of the benzyl boronate by excited [Ir] **68**, can combine with either Ni(0) **71** (red pathway) or Ni(II) **73** (blue pathway) (Figure 6C). An important finding is that the Ni(III)-benzyl intermediate **74** undergoes reversible radical ejection to form **73** and radical **70**. In addition, this reversible radical ejection can scramble the stereocenter, and has profound implications in identifying the enantiodetermining step of stereoselective reactions.

In addition to reducing Ni(I) to Ni(0), Ir photosensitizers can oxidize Ni intermediates. In the α-arylation of tetrahydrofuran, the excited Ir **68** is proposed to oxidize Ni(II) **76** to form Ni(III) **77** [100] (Figure 6D). Moreover, Ni itself can act as a photosensitizer [96,101]. Irradiation of **77** can induce homolytic bond cleavage to generate halide radicals that can abstract weak hydrogen atoms from ether [100] or alkane [102] substrates. Computational and ultrafast spectroscopic data reveal a long-lived triplet excited state of the photoexcited Ni(II) **76**, opening opportunities for Ni to catalyze photoredox cross-coupling reactions alone [96].

Nickel-catalyzed electroreductive coupling reactions have been pursued as an alternative to methods using heterogeneous metal powders [103]. The electrocatalytic coupling of α-chloroesters with aryl halides produces chiral α-arylamides using chiral auxiliaries [104] and an asymmetric reductive coupling of vinyl bromides and secondary alkyl chlorides affords excellent enantioselectivity [105]. Besides an early study on the electrocatalytic homocoupling of acyl and benzyl halides [106], the mechanisms of Ni-catalyzed electroreductive coupling reactions have not been closely investigated. It is reasonable to presume a mechanism similar to the corresponding variants using chemical reductants, but the electron transfer rate may change the turnover-limiting steps. The rate of electron transfer can be determined by cyclic voltammetry (CV).

Concluding Remarks

Ni is relatively stable in open-shell oxidation states, can readily access single-electron pathways, and is electron rich in its low-valent states. These properties have been exploited in the growing field of Ni-catalyzed cross-coupling reactions. Recent efforts have begun to unfurl the diverse and complex mechanisms by which Ni-catalyzed reactions occur. Future mechanistic studies will provide insight to address synthetic limitations, design new catalysts, and troubleshoot large-scale process applications.

An important outstanding question to address is why nitrogen-containing ligands (e.g., redox active ligands) are successful with Ni catalysts (see Outstanding Questions). Recent work has just started to tackle this issue [107]. Characterization of critical intermediates would illuminate their electronic structures, but isolation of open-shell d^9 Ni(I) and d^7 Ni(III) intermediates remains challenging. *In situ* EPR and NMR, can be used to identify intermediates when isolation is not possible [107]. The redox potentials of possible intermediates can be better compared with systematic CV measurements. Mechanistic understanding of the Ni-photoredox dual catalysis is insufficient, and reaction design would benefit from an understanding of how transition metal cycle is merged with the photocatalytic cycle.

The greatest advances in Ni catalysis are likely to be in the fields of stereoselective coupling, reductive coupling, Ni-photoredox dual catalysis, and electrocatalysis. There is a large chemical space to explore with respect to stereoconvergent coupling. Radical pathways are yet to be applied to asymmetric functionalization of alkenes. Reductive coupling reactions obviate the need for stoichiometric organometallic reagents but face issues of selectivity when the hybridization of the electrophiles is the same. A challenge is to achieve biaryl and alkyl–alkyl cross-electrophile coupling in a way that does not use a large excess of one reactant and suppresses homocoupling byproducts. Photoredox chemistry has been dominated by expensive, precious-metal-based photocatalysts, but as new radical precursors are discovered, opportunities arise to use less expensive organic photocatalysts or even to use Ni compounds as photocatalysts [101]. Few Ni-mediated electrochemical reactions have been reported and only one enantioselective example exists [95], so there is significant potential for innovation and discovery in this field. The ability to exclude stoichiometric organometallic reagents and the intermediacy of nonpolar radical intermediates engender greater air and water compatibility, possibly enabling the use of 'greener' solvents like alcohols or mixtures with water. Aqueous phase coupling reactions could enable biological applications, such as modifications of proteins and DNA [108]. These reactions rely on the ability of Ni catalysts to generate or accept radical species, so an advanced knowledge of these processes will be imperative for driving the field forward.

Outstanding Questions

What is the precise role of nitrogen-based ligands in promoting radical processes at the Ni center?

What is the enantiodetermining step for Ni-catalyzed asymmetric alkene functionalization reactions and can the scope be expanded?

Can cross-electrophile selectivity be achieved to prepare biaryl and dialkyl products?

What makes different reductants effective in reductive coupling reactions?

Can high enantioselectivity be achieved in photoredox-Ni dual catalysis?

Can electrochemical-Ni dual catalysis access new reactivity and selectivity that is beyond known methods with chemical reductants?

How amenable are Ni-catalyzed cross-coupling conditions for chemical biology applications?

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