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Mechanisms of Nickel-Catalyzed Coupling Reactions and Applications in Alkene Functionalization

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CONSPECTUS:

Nickel complexes exhibit distinct properties from other group 10 metals, including a small nuclear radius, high paring energy, low electronegativity, and low redox potentials. These properties enable Ni catalysts to accommodate and stabilize paramagnetic intermediates, access radical pathways, and undergo slow β-H elimination. Our research program investigates how each of these fundamental attributes impact the catalytic properties of Ni, in particular in the context of alkene functionalization.

Alkenes are versatile functional groups, but stereoselective carbofunctionalization reactions of alkenes have been under-developed. This challenge may derive from the difficulty of controlling selectivity via traditional two-electron migratory insertion pathways. Ni catalysts could lead to different stereo-determining steps via radical mechanisms, allowing access to molecular scaffolds that are otherwise difficult to prepare. For example, an asymmetric alkene diarylation reaction developed by our group relies upon the radical properties of Ni(III) intermediates to control the enantioselectivity and give access to a library of chiral α,α,β-triarylethane molecules with biological activity.

Mechanistic studies on a two-component reductive 1,2-difunctionalization reaction have shed light on the origin of the cross-electrophile selectivity, as C sp^2 and C sp^3 electrophiles are independently activated at Ni(I) via two-electron and radical pathways, respectively. Catalyst reduction has been identified to be the turnover-limiting step in this system. A closer investigation of the radical formation step using a (Xantphos)Ni(I)Ar model complex reveals that Ni(I) initiates radical formation via a concerted halogen-abstraction pathway.

The low redox potentials of Ni have allowed us to develop a reductive, *trans*-selective diene cyclization, wherein a classic two-electron mechanism operates on a Ni(I)/Ni(III) platform, accounting for the chemo- and stereoselectivity. This reaction has found applications in the efficient synthesis of pharmaceutically relevant molecules, such as 3,4-dimethylgababutin.

The tendency of Ni to undergo one-electron redox processes prompted us to explore dinuclear Ni-mediated bond formations. These studies provide insight into Ni–Ni bonding and how two metal centers react cooperatively to promote C–C, C–X, and N–N bond forming reductive elimination.

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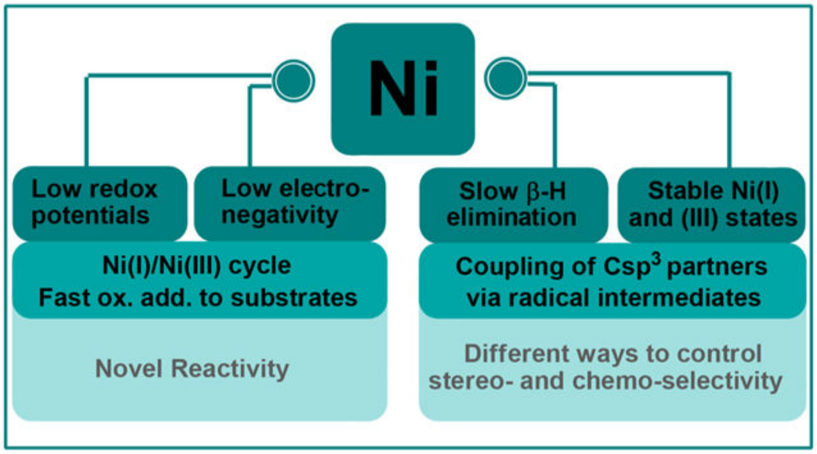
Finally, isolation of β-agostic Ni and Pd complexes has allowed for X-ray and neutron diffraction characterization of these highly reactive molecules. The bonding parameters serve as unambiguous evidence for β-agostic interactions and help rationalize the slower β-H elimination at Ni relative to Pd. Overall, our research has elucidated the fundamental properties of Ni complexes in several contexts. Greater mechanistic understanding facilitates catalyst design and helps rationalize the reactivity and selectivity in Ni-catalyzed alkene functionalization reactions.

Graphical Abstract



INTRODUCTION

Nickel (Ni) catalysts are an inexpensive and earth-abundant alternative to precious metal catalysts, such as Pd, for cross-coupling reactions. In addition, Ni exhibits unique reactivity, leading to different mechanisms.[1] First, Ni complexes can adopt both high- and low-spin configurations and are stable in a variety of oxidation states ranging from Ni(0) to Ni(IV).[2] In comparison, Pd compounds are primarily low-spin and are most commonly encountered as diamagnetic Pd(0), Pd(II), and Pd(IV) compounds (Scheme 1A).[3] The propensity of Ni to adopt open-shell electronic configurations, such as Ni(I) and Ni(III), is likely a result of the higher pairing energy of Ni compared to Pd. The nucleus radius of Ni is smaller than Pd, hence the electron distribution of the valence orbitals is smaller. When two electrons occupy the same orbital, they experience higher repulsion (Scheme 1C).[4] Moreover, the geometry of high-spin Ni species could lead to a lower barrier for single electron transfer. For example, one electron reduction of a tetrahedral Ni(II) complex is easier than that of a square planar Pd(II) complex by introducing the electron to a lower SOMO (Scheme 1C). As a consequence of the stable open-shell electronic configuration, activation of electrophiles by Ni can proceed either by two-electron oxidative addition to give organonickel intermediates or by single-electron pathways to afford radicals (Scheme 1B).[5]

The reduction potential,[6] atomic radius,[7] and electronegativity[8] of Ni are lower than those of Pd (Scheme 1D,E). This leads to facile oxidative addition of Ni(0) to bonds that traditionally do not undergo oxidative addition with Pd(0), such as ether C–O[9] and amide C–N bonds.[10] Finally, Ni–alkyl compounds undergo β-hydride (β-H) elimination more slowly than Pd compounds, when compared in the same ligand framework (Scheme 1F).[11] As a result, alkyl coupling partners that decompose via β-H elimination with Pd are compatible with Ni.

The different reactivity and selectivity of Ni in alkene functionalization, compared to Pd, highlights the distinct properties outlined above. Alkenes are versatile functional groups. The Pd-catalyzed Heck reaction proceeds through migratory insertion of Pd–carbyl intermediates to alkenes (Scheme 2A, step ii), followed by β-H elimination to restore unsaturation (Scheme 2 A, step iii).[12] In contrast, Ni catalysts have been shown to perform olefin insertions without subsequent β-H elimination. In addition, Ni can induce radical formation from electrophiles, which then add to alkenes. This reactivity has been leveraged to develop hydroarylation,[13] hydroalkylation,[14] and dicarbofunctionalization[15] reactions. Ni typically activates C sp^2 electrophiles through a classic two-electron oxidative addition pathway to afford organonickel intermediates, which then undergo migratory insertion to alkenes (Scheme 2B, step iv).[16] In contrast, activation of C sp^3 electrophiles by Ni can proceed by halide abstraction to form radicals, which then add to alkenes (step v).[14,17] Organic radical intermediates can be trapped by Ni to afford Ni–alkyl **1** (step iv). Due to a slow β-H elimination, relative to Pd compounds, **1** can undergo further transformations to form new C–C bonds and afford difunctionalization or hydrofunctionalization product **2** (step vii). These reactions enable the rapid construction of complex motifs starting from simple and readily available coupling partners (Scheme 2C).[15] The necessity of stoichiometric and often air-sensitive, organometallic reagents can be avoided through the use of reductive strategies for olefin functionalization.[18]

In addition to diversifying the methods of alkene functionalization, Ni catalysts could provide new ways to control stereochemistry. The Pd-catalyzed asymmetric Heck reaction has been limited to electronically biased or engineered substrates.[19] The constraints may derive from the difficulty of controlling selectivity via traditional alkene coordination and migratory insertion (Scheme 2A, step i or ii) or the reversible β-H elimination.[12] Ni-catalyzed asymmetric alkene functionalizations with C sp^2 coupling partners mostly proceed through two-electron migratory insertion (Scheme 2B, step iv). Intramolecular examples include the difunctionalization of allyl ethers with aryl boronates[20] and the reductive difunctionalization of acrylamides with aryl halides.[21] Ni-catalyzed intermolecular asymmetric diarylation reactions are rare,[22] and asymmetric difunctionalizations with C sp^3 coupling partners have yet to be discovered. Both intramolecular and intermolecular asymmetric hydrofunctionalization reactions have been developed with Ni catalysts. Intramolecular hydroarylation reactions provide access to indoline derivatives.[23] The intermolecular hydroarylation of styrenes with boronic acids has led to enantioselective formation of α,α-diarylethanes.[13] In contrast to two-electron pathways in hydroarylation, Ni-catalyzed hydroalkylation reactions of olefins with α-bromoamides may proceed through radical pathways with different enantio-determining steps.[24]

This Account summarizes our efforts to probe the mechanistic details of Ni-mediated bond activation and formation processes, including radical formation, reduction of Ni intermediates, reductive elimination, and β-H elimination (Scheme 3). The stoichiometric studies have been performed on isolated complexes, which represent different conditions compared to the catalytic reactions. Nevertheless, modest catalytic reactivity of the isolated model molecules demonstrates their catalytic relevance. The stoichiometric studies are complemented by kinetic and spectroscopic characterizations of catalytic alkene functionalization reactions. The combined organometallic and catalytic studies allowed us to draw conclusions on the mechanisms and helped us develop stereoselective alkene functionalization reactions for synthesizing biologically active molecules.

REDUCTIVE ASYMMETRIC ALKENE DIARYLATION

The α,α,β-triarylated ethane motif is present in a number of important pharmaceutical compounds and biologically active molecules. Accessing enantioenriched compounds would facilitate the assessment of their efficacy in biological studies. Previous methods to prepare these structures, including asymmetric hydrogenation[25] and stereospecific and stereoconvergent cross-coupling,[26] require multistep synthesis of the substrates. We developed an asymmetric 1,2-diarylation of vinylarenes to assemble chiral α,α,β-triarylated ethane structures with simple vinylarene and bromoarene building blocks (Scheme 4).[27] The use of reductive conditions, in combination with aryl bromide electrophiles, avoids stoichiometric air-sensitive organometallic reagents.

During catalyst optimization, we noticed that changing the substituents on the biOx (bioxazoline) ligands had a relatively small effect on the ee of the products. The use of vinylarene that was purified by distillation reduced the ee compared to substrate used directly from the commercial bottle, in which radical inhibitors are present to prevent polymerization. This observation prompted us to systematically evaluate radical inhibitors, which did not drastically improve the ee. Given that radical inhibitors form stabilized radicals after H-atom abstraction, we reasoned that stabilized radicals may be important to the enantioselectivity. Indeed, the addition of TEMPO in catalytic amounts allowed us to obtain consistent enantioselectivities. Screening stabilized radicals revealed that the ee of the reaction exhibits a correlation with the steric bulk of the *N*-oxyl radicals (Scheme 4). The least hindered *N*-oxyl radicals, ABNO and AZADO, gave the highest ee. Although further mechanistic investigation is underway, the different reaction colors in the presence and absence of *N*-oxyl radicals suggest that they may serve as a ligand to Ni.[28]

Preliminary mechanistic observations reveal the formation of benzylic radicals as intermediates (Scheme 5). A plausible mechanism begins with a Ni(I)–Ph-mediated migratory insertion (step iii), followed by oxidative addition to activate another molecule of PhBr (step iv). The resulting Ni(III) intermediate undergoes reversible radical ejection that scrambles the benzylic stereocenter (step v). This process has been proposed by Kozlowski, Molander, and co-workers based on computational studies[29] and accounts for the observed *trans*-diphenylation of indene. The formation of dimers at the benzylic position of the monoarylation intermediate, the lack of a Hammett correlation between *para*-substituents on vinylarenes, and er implies formation of organic radicals rather than polar intermediates. The subsequent reductive elimination (step vi) may serve as the enantio-determining step. We are carrying out a more detailed study to precisely identify the enantio-determining step, build the stereochemical model for predicting the enantioselectivity, resolve the sequence of reagent activation, and elucidate the role of *N*-oxyl radical additives.

REDUCTIVE TWO-COMPONENT ALKENE DICARBOFUNCTIONALIZATION

Inspired by previous reports on radical cyclizations and followed by reductive cross-coupling reactions,[30] we developed a two-component alkene difunctionalization reaction in which the C sp^3-electrophile is tethered to the alkene (Scheme 6).[31] The use of reductive conditions with electrophiles bypasses the need for pregeneration of organometallic reagents, which broadens the substrate scope to aryl, heteroaryl, and alkyl bromide electrophiles, while improving tolerance to functional groups such as chlorides, ketones, aldehydes, pyridines, and indoles. This combinatorial approach gives access to a variety of cyclopentane, pyrrolidine, piperidine, and tetrahydrofuran derivatives that are of pharmaceutical interest. We envision that this methodology can be used to rapidly build a library of structurally diverse molecules for medicinal chemistry screening.

MECHANISM OF Ni-CATALYZED REDUCTIVE ALKENE DICARBOFUNCTIONALIZATION

The aforementioned reductive 1,2-dicarbofunctionalization provides us with a platform to investigate the mechanism of Ni-catalyzed cross-electrophile coupling reactions. In general, two types of mechanisms have been proposed for cross-electrophile coupling reactions, “radical chain”[32] and “sequential reduction” pathways[33] (Scheme 7). The main distinguishing feature of these pathways is the sequence of electrophile activation. In the radical chain mechanism, C sp^3 electrophiles are activated by Ni(I)–X (X = halide) to form radicals prior to the oxidative addition of C sp^2 electrophiles to Ni(0) (pathways A and B). The radical can either combine with Ni(0) (step iii, pathway A) or Ni(II) (step vii, pathway B). This pathway is kinetically feasible when the Ni species that combines with the radical is the catalyst resting state. In the sequential reduction pathway, oxidative addition of the C sp^2 electrophile precedes reduction to afford a Ni(I)–aryl intermediate, which then activates the C sp^3 electrophile and immediately combines with the radical (pathway C). The sequence and mechanism of the activation of C sp^2 and C sp^3 electrophiles are critical to achieving chemoselectivity in cross-electrophile coupling.

We carried out kinetic, spectroscopic, and organometallic studies on the 1,2-dicarbofunctionalization of alkenes (Scheme 6).[31] The sequential reduction pathway is most consistent with the data (Scheme 8).[34] The lack of rate dependence on olefin and PhBr concentrations, in combination with the coexistence of (phen)NiBr$_2$ **3** and (phen)Ni(Ar)(Br) **4** as the catalyst resting state, suggests that the reduction of Ni by Zn is the turnover-limiting step, which is consistent with previous observations.[35] This result highlights the importance of catalyst reduction, suggesting that it is critical to ensure efficient mixing of the heterogeneous reductants in order to maintain the reaction rate for large scale production. The preference of (phen)Ni(I)Br to activate ArBr relative to alkyl-Br (step i, Scheme 7) suggested that the radical chain mechanism was not operative, since step i in Scheme 7 would be outcompeted by the reaction of (phen)Ni(I)Br with ArBr. A closer investigation of the catalyst reduction step by cyclic voltammetry, NMR, and EPR spectroscopy, as well as stoichiometric studies, reveals that Zn is only sufficient to reduce (phen)Ni(II) to (phen)Ni(I) rather than (phen)Ni(0).

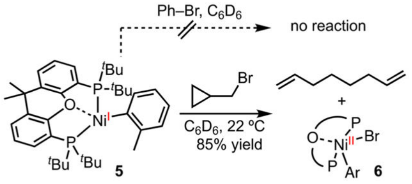
Our data shed light on the selectivity of cross-electrophile coupling reactions and can be explained on the basis of steric and electronic properties of the Ni intermediates (Table 1). Oxidative addition of the C sp^2–Br most likely proceeds through a two-electron oxidative addition pathway, due to the instability of C sp^2 radicals and the high C sp^2–Br bond strength. Stoichiometric studies reveal that two molecules of (phen)Ni(I) Br react with one molecule of Ar–Br to afford (phen)$NiBr_2$ and (phen)Ni(Ar)Br in a 1:1 ratio. While the precise mechanism of this step is still under investigation, it is conceivable that a two-electron oxidative addition on (phen)Ni(I)Br affords (phen)-Ni(III)(Ar)Br_2, which undergoes rapid comproportionation with an equivalent of (phen)Ni(I)Br. The two-electron activation of the C sp^2–Br by different Ni species is therefore primarily influenced by steric effects. (Phen)Ni(I)Br is sterically more accessible than (phen)Ni(I)Ar; thus it preferentially reacts with the C sp^2–Br. The activation of the C sp^3–Br proceeds through a one-electron pathway to generate radicals and is largely influenced by electronic effects. The more electron-rich, yet sterically hindered, (phen)Ni(I)Ar therefore reacts with the C sp^3–Br faster than the C sp^2–Br.

MECHANISM OF Ni(I)-MEDIATED RADICAL FORMATION FROM ALKYL BROMIDES

Formation of radicals from the single-electron oxidative activation of alkyl halides by Ni(I) has been extensively proposed in Ni-catalyzed cross-coupling reactions (Scheme 8, step iv).[36] Radical intermediates erase the stereochemical information of racemic electrophiles in stereoconvergent cross-coupling,[37] enable selectivity in reductive cross-electrophile coupling,[18] and accommodate new reactivity via Ni–photoredox dual catalysis.[38] Four pathways are possible for Ni(I)-mediated radical formation from alkyl halides (Scheme 9). Two-electron oxidative addition at a Ni(I) center gives a Ni(III) intermediate, which can eject a radical and form a Ni(II) species (Scheme 9A). An outer-sphere single-electron transfer (SET) from Ni(I) to alkyl halides can form a radical anion, which fragments to generate a C-centered radical and a halide anion (Scheme 9B). Alternatively, SET could take place through an inner-sphere pathway via an encounter complex (Scheme 9C). Finally, the concerted halogen atom abstraction has been proposed on the basis of recent DFT calculations (Scheme 9D).[39] Prior to our work, there was no experimental study to distinguish these pathways, which was, in part, due to the fact that Ni(I) complexes, with a d^9 configuration, are difficult to synthesize and isolate.[2a]

Bulky bidentate phosphine ligands, such as di-*t*Bu-phosphinoethane (dtbpe) and 1,1′-bis(diphenylphosphino)ferrocene (dppf), have been employed to stabilize Ni(I)–halide complexes,[40] but Ni(I)–carbyl molecules are more challenging to isolate. We discovered that *t*-Bu-Xantphos enabled the isolation of a series of Ni(I)–Ar compounds, which can be stored as solids in the glovebox at room temperature for weeks.[5] The large bite angle and the secondary interaction of the O-atom on Xantphos to Ni may contribute to this stabilization. Typically, Ni(I) complexes are prepared by reduction of Ni(II),[36d] comproportionation of Ni(0) and Ni(II),[36e] or oxidation of Ni(0).[41] In our experience, the former method gives the cleanest Ni(I)-halides with mild reductants, such as Zn and cobaltocene, being optimal. Ni(I)–aryl **5** was inert toward PhBr, but reacted with alkyl bromides to give radicals and

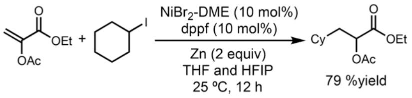
Ni(II) **6**, as verified by radical clocks and trapping experiments (eq 1). The selective activation of alkyl halides over aryl halides is consistent with our observations in the mechanistic study of a reductive 1,2-dicarbofunctionalization (Scheme 8).



(1)

Kinetic studies, in combination with DFT calculations, allowed us to differentiate the four pathways (Table 2). Using in situ NMR measurements, we found that secondary R–Br reacts faster than primary R–Br, which is inconsistent with the oxidative addition pathway (Scheme 9A). Bulky aryl groups on the Ni(I) compound reduce the rate of halide abstraction, which is inconsistent with the outer-sphere electron transfer pathway (Scheme 9B). The faster rates with electron-rich Ni–Ar complexes are consistent with all four pathways, but the slope of $\Delta G^{\ddagger}$ vs ΔG deviates from the prediction by Marcus theory. The difference between the inner-sphere electron transfer (Scheme 9C) and the concerted mechanism (Scheme 9D) is the formation of an ionic intermediate. An ionic intermediate formed from inner-sphere electron transfer should be stabilized by polar solvents, and the lack of kinetic correlation to solvent polarity rules out this pathway. DFT calculations identified concerted halogen-atom abstraction (Scheme 9D) as the pathway with the lowest activation barrier. In transition state **7**, the Ar group, Ni, Br, and the R group organize in a nearly linear geometry, where the unpaired electron is donated to the σ^* orbital of the C–Br bond.

Based on this mechanism, we developed a reductive coupling of α-oxyacrylates with alkyl halides to access lactic acid derivatives (eq 2).[42] 1,1′-Bis(diphenylphosphino)ferrocene exhibits the best reactivity in combination with Ni and Zn to generate a radical, which adds to α-oxyacrylates, an excellent radical acceptor due to the captodative effect. This method represents a concise and efficient way to access α-oxyacrylates, as building blocks for pharmaceutically relevant molecules.



(2)

Bidentate and tridentate N-ligands, such as bipyridine (bpy), bioxazoline (biOx), terpyridine (terpy), and pyridine-bioxazo-line (pybox), are more frequently utilized than phosphine ligands in Ni-catalyzed cross-coupling reactions. These stronger donors, relative to phosphine ligands,[43] lead to higher field splitting. The redox activity of these chelating ligands may stabilize the open-shell Ni intermediates. The fundamental advantages of N-ligands over phosphine ligands are worth more in-depth investigation. Our ongoing studies focus on exploring the mechanism of Ni-mediated electrophile activation with N-ligands, as well as understanding the effect of their redox activity on catalysis.

Ni(I)-MEDIATED CO_2 INSERTION

Ni-catalyzed functionalization of carbon dioxide (CO_2) has become an efficient and sustainable approach to synthesize carboxylate molecules.[44] These reactions are proposed to proceed through a pathway consisting of substrate activation by Ni, reduction of Ni(II) to Ni(I) species, and carboxylation of the Ni(I)–alkyl intermediates to form carboxylates (Scheme 10A).[45] Previous experimental[46] and computational studies[39b] show that Ni(II) species are not nucleophilic enough to insert into CO_2, but once reduced to Ni(I), CO_2 insertion is facile. In order to provide experimental evidence for the reduction of Ni(II) to Ni(I) and the insertion of CO_2 at a Ni(I)–alkyl center, we prepared (*t*-Bu-Xantphos)Ni(II)Br_2 **8**, which is reduced by excess Zn to afford (*t*-Bu-Xantphos)Ni(I)Br **9**.[47] NMR and XRD experiments show that $ZnBr_2$ is coordinated to the bromide of Ni(I) **9**. (*t*-Bu-Xantphos)NiMe **10** and (*t*-Bu-Xantphos)NiEt **11** were obtained by transmetalation of Ni(I)Br **9** with lithium reagents (Scheme 10B). These (*t*-Bu-Xantphos)-Ni(I)–alkyl complexes are much more sensitive than their aryl counterparts, decomposing at room temperature within 30 min and requiring handling at low temperature in the glovebox.

Rapid insertion of CO_2 at **10** and **11** afforded the corresponding carboxylates **12** and **13** at room temperature in seconds. In contrast, (*t*-Bu-Xantphos)NiPh and (*t*-Bu-Xantphos)Ni-acetylide are unreactive toward CO_2. This contrasting reactivity between sp, sp^2, and sp^3 Ni(I) complexes sheds light on the mechanism of CO_2 insertion. Ni(I)–C sp^3 complexes could undergo insertion via nucleophilic attack of the alkyl groups to CO_2 (intermediate **14**), where sp and sp^2 nucleophiles can only undergo migratory insertion (TS **15**), but the approach of CO_2 to these (*t*Bu-Xantphos)Ni(I) complexes is inhibited by the bulky substituents on the ligand.

REDUCTIVE INTRAMOLECULAR ALKENE COUPLING VIA TWO-ELECTRON PATHWAYS MEDIATED BY Ni(I)/Ni(III)

The low oxidation potentials of Ni complexes (Scheme 1E) motivated us to pursue reactions going through two-electron redox pathways mediated by Ni(I)/Ni(III) intermediates. The redox potentials of Ni(I)/Ni(III) couples may resemble those of Pd(0)/Pd(II), but the radical properties of Ni(I) and Ni(III) intermediates can lead to different selectivity. Cycloisomerization reactions of 1,5-dienes typically give unsaturated products (Scheme 11).[48] Employing d^8 transition metal catalysts, these reactions commence with hydride insertion to one alkene, followed by insertion to the other alkene, and β-H elimination, which restores the unsaturation. In light of the prevalence of *trans*-vicinal disubstituents in carbocycles[49] and heterocycles[50] of biological relevance, we developed a reductive diene coupling reaction where formation of the C–C bond is accompanied by the installation of *trans*-stereocenters (Scheme 11).[51] This reaction is accomplished by simply changing the electronic structure of the catalyst from d^8 to d^9 **18** and using Et_2SiH_2 as the reductant. The utility of this method was demonstrated in the preparation of 3,4-dimethyl pyrrolidine **17** and cyclopentane derivative **19** that are of pharmaceutical interest. The (*R*, *R*) enantiomer of 3,4-dimethylgababutin derivative **19** exhibits excellent efficacy toward neuropathic pain and anxiety. In contrast to the previous synthesis,[49] which requires 13 steps for a 14% overall yield, the route going through the reductive diene coupling requires 6 steps with an overall yield of 42%.

This reductive diene coupling reaction differs from several recent olefin functionalization reactions in its scope and mechanism. Fe- and Co-catalyzed diene coupling reactions developed by Baran and Shenvi are selective for activated or substituted alkenes,[52] going through a H-atom transfer (HAT) pathway to form radical intermediates. Our Ni-catalyzed intramolecular reductive diene coupling is effective with unactivated alkenes, but the reaction is drastically inhibited by substituents on the olefin. When a radical clock was built into the diene substrate, no ring opening was observed, suggesting that HAT is not occurring in this system. We characterized its mechanism by kinetic and spectroscopic studies, which support a classic two-electron pathway mediated by paramagnetic Ni(I) and Ni(III) intermediates (Scheme 12). This pathway accounts for the chemoselectivity for reductive coupling relative to redox-neutral cycloisomerization. Ni(I) **22** is stabilized by the redox-active diimine ligand and is capable of undergoing oxidative addition with silanes to form Ni(III) **24**, whereas the previous Ni(II) catalyst affords unsaturated products via *β*-H elimination (**22** → **26**). The *trans*-diastereoselectivity is determined by the second olefin insertion step, **21** → **22**. This cyclization step is responsible for the limited scope in cycloisomerization reactions, as substituents on the olefin inhibit the cyclization.[48]

DINUCLEAR Ni(III)···Ni(III)-MEDIATED C–C BOND FORMING REDUCTIVE ELIMINATION

The formation and activation of a chemical bond usually involves two-electron transformations. For example, oxidative addition of Rh(I) to C–H bonds affords Rh(III) hydride compounds.[53] An illustrative example reveals that the C–H activation can be facilitated by engaging two Rh(II)-porphyrin molecules with each Rh(II) center offering one electron.[54] The one-electron redox process at each Rh center is expected to lower the kinetic barrier relative to two-electron redox chemistry. Since Ni has the tendency to undergo one-electron redox chemistry, we sought to facilitate bond formation processes by utilizing dinuclear Ni-centers.

Our investigations began with preparation of (py-^{Me}pyrr)-NiMe(2,4-lutidine) complex **27** (py-^{Me}pyrr = 3,5-dimethyl-2-(2-pyridyl)pyrrole) from transmetalation of (py-^{Me}pyrr)NiMe-(acac) (acac = acetylacetonate) with MeMgBr (Scheme 13).[55] Alternatively, addition of py-^{Me}pyrr to (TMEDA)$NiMe_2$ in the presence of 3,5-lutidine can cleanly afford **28** in high yield. 2,4-Lutidine has the right amount of steric protection for stabilizing the complex. Bulkier lutidines dissociate from Ni and less bulky pyridine derivatives are insufficient at stabilizing the Ni compounds. Oxidation of **27** by I_2 or O_2 liberates ethane. A combination of ^{1}H NMR and EPR studies revealed a rapid conversion of **27** to Ni(III) **28** upon oxidation, followed by dimerization to generate **29**. The subsequent dinuclear reductive elimination is slow and exhibits a first-order dependence on **29**. This result establishes the first dinuclear Ni-mediated C–C bond formation, where each Ni center reacts cooperatively to accept one electron.

DINUCLEAR Ni(III)···Ni(III)-MEDIATED CARBON–HALOGEN BOND FORMING REDUCTIVE ELIMINATION

Dinuclear transition metal compounds and metal–metal interactions are ubiquitous in biological and catalytic systems.[56] Multimetallic cofactors are commonly involved in redox reactions. Hydrogenase enzymes featuring a [NiFe] core catalyze the oxidation of H_2, as well as the reduction of protons to H_2, and represent well-characterized examples of metal–metal bonding in biology.[56] Synthetically, bimetallic intermediates have been observed in Ni-catalyzed vinylidene transfer reactions[57] as well as many others.[58] First-row transition metals are expected to form weaker metal–metal bonds than second-and third-row metals, which contributes to the lack of examples of isolated high-valent Ni complexes with metal–metal bonding.

Ritter and co-workers have shown that a Pd(III)–Pd(III) dimer, **30**, is stabilized by a metal–metal bond and can undergo synergistic reductive elimination to afford bromobenzo[*h*]quinoline in 95% yield (theoretical yield is 200%) and Pd(II) (Scheme 14A).[59] We prepared an analogous Ni(II)···Ni(II) dimer, **31**.[60] Oxidation of **31** with Umemoto's reagent, 5-(trifluoromethyl)dibenzothiophenium triflate (TDTT), afforded the mixed-valent Ni(2.5)–Ni(2.5), **32**. Fractional oxidation states are common in multimetallic Ni complexes[61] but are rare with Pd.[62] This one-electron oxidation, however, is insufficient to induce reductive elimination. Further oxidation is required to form carbon–halogen bonds. The use of $PhNMe_3Br_3$ led to a Ni(III)···Ni(III) dimer **34**, a geometric isomer of **33**, which underwent rapid reductive elimination at −80 °C to form bromo-benzo[*h*]quinoline in 190% yield and Ni(I).

These results suggest that the Ni(III)···Ni(III) dimer **33**, if ever formed, has a weak metal–metal bond and prefers to rearrange to **34**. This contrasts with Pd and is consistent with weaker metal–metal bonding for first-row transition metals. It is speculated that the more constrained electron-density of first-row transition metals restricts sufficient orbital overlap for metal–metal bonding interactions. The facile reductive elimination of Ni(III) **34** to form Ni(I) occurs independently at each metal center. This reactivity differs from that of Pd(III)–Pd(III) dimer **30**, which undergoes cooperative reductive elimination to eject half of the benzo[*h*]quinoline ligand as bromo-benzo[*h*]quinoline and forms Pd(II). The different reactivity likely results from a stable Ni(I) oxidation state.

DINUCLEAR Ni(III)···Ni(II)-MEDIATED N–N BOND FORMING REDUCTIVE ELIMINATION

Our investigation of Ni–Ni bonds was extended to a "paddle-wheel" system.[63] $(TBD)_4Pd_2$ **35** (TBD = triazabicyclodecene) can be oxidized to Pd(III)–Pd(III) **36**, which does not undergo reductive elimination (Scheme 15A).[64] Compared to **35**, the shorter Pd···Pd distance of **36** indicates a Pd–Pd bond order of 1. A $Ni_2(TBD)_4$ dimer has been electrocatalytically oxidized to form $[Ni_2(TBD)_4]^+$, but the structure was not characterized.[65] In order to compare Ni–Ni bonding with Pd and probe the intrinsic reactivity of the high-valent Ni system, we oxidized $Ni_2(TBD)_4$ **37** with 0.5 equiv of $PhICl_2$ to afford the mixed-valent complex **38** (Scheme 15B). The reduction of **38** is facile and can be accomplished with Tl(I) compounds. Further oxidation of **38** with excess $PhICl_2$ promotes N–N bond forming reductive elimination to give Ni(II) **39**, which represents the first example of such reactivity. Treating Ni(II) **39** with $Ni(cod)_2$ and Li(TBD) causes N–N bond cleavage, reforming the paddle-wheel Ni(II)–Ni(II) complex **37**.

Assignment of Ni–Ni bonds in this system requires careful consideration. The σ and σ^* orbitals along the metal–metal axis of the Ni(II) dimer **37** are filled; however, mixing of the 4s, 4p, and 3d orbitals reduces the energy of the σ^* orbital, resulting in partial bonding character.[66] Complex **38** forms a 3c/3e bond. The EPR spectrum of **38** shows a Ni-centered radical. DFT calculations suggest that the unpaired electron has the highest density on Ni(III). The electronic structure of **38** is best described as discrete Ni(II) and Ni(III) centers with weak bonding interactions between the two Ni atoms. This assignment is corroborated by the similar bond lengths between **37** and **38**. Although bond lengths may be constrained by the paddle-wheel geometry and may not accurately reflect the bonding interactions, contractions of bond lengths have been observed and serve as indications of increases in bond orders in previous Ni_2 paddle-wheel complexes.[66]

STRUCTURES OF (α-DIIMINE)Ni AND Pd AGOSTIC COMPLEXES AND IMPLICATIONS IN β-H ELIMINATION

Agostic interactions are three-center, two-electron bonds formed from the donation of electron density from the C–H bond of an alkyl ligand to the empty d-orbital of a transition metal.[67] Ni and Pd agostic complexes are commonly proposed intermediates in catalytic reactions going through C–H activation and β-H elimination steps. Cationic (α-diimine)Ni and Pd complexes display intriguing reactivity and properties in olefin polymerization (Scheme 16).[68] The rate of β-H elimination (step i) relative to olefin coordination (step iii) determines the polymer structure and thus its morphology and properties. Structural characterization of Ni and Pd agostic complexes, however, remains difficult, owing to their instability. Warren reported the isolation of a neutral Ni-agostic molecule,[69] but its reactivity is drastically lower than the cationic catalysts.

We discovered that a cyclohexane backbone on the α-diimine ligand can increase the catalyst stability, while maintaining its catalytic reactivity. This modification allowed us to obtain single crystals of β-agostic $[(^{iPr}\alpha\text{-diimine})Ni\text{-}Et]^+[BAr^F_4]^-$ **40** and $[(^{iPr}\alpha\text{-diimine})Pd\text{-}Et]^+[BAr^F]^-$ **41** that are suitable for characterization by X-ray diffraction and neutron diffraction (Figure 1).[70] The structures feature short M–H distances (M = Ni and Pd), short C_α–C_β distances, and acute M–C_α–C_β bond angles (Table 3). The bond lengths of C_α–C_β (C31–C32) for **40** and **41** are 1.468(7) and 1.469(6) Å, which are shorter than that of a nonagostic Pd–Et complex (1.528(3) Å), suggesting greater sp^2 character of the C_α and C_β

atoms as a C=C bond partially forms in the agostic structure. The M–C_α–C_β bond angles are substantially smaller than the ideal angle of 109° for a sp^3 hybridized carbon, consistent with the attraction between Pd and C_β. These properties combined serve as unambiguous evidence for the β-agostic interaction.

Complexes **40** and **41** with the cyclohexyl backbone are as competent as the parent catalysts in olefin polymerization. We measured kinetic barriers for β-H elimination (Scheme 17). The slower β-H elimination from Ni, relative to Pd, is reminiscent of previous studies by Brookhart.[11] Multiple factors influence this rate. The nature of the agostic bond is the donation of electron density from the C–H σ orbital to the metal d orbital. The lower electronegativity of Ni results in a weaker agostic interaction relative to Pd. Second, in the metal hydrides, **42** and **43**, the alkene resides in a conformation that is perpendicular to the square-planar complex, representing a twisted geometry in the late transition state. Ni has a smaller atom radius and thus a shorter Ni–C bond length and a more acute Ni–C–C bond angle. As a result, the transition state for Ni has a more strained geometry, which should contribute to a higher transition state energy.

CONCLUSION

We investigated the fundamental properties and the consequent reactivity of nickel catalysts in various aspects. The single-electron redox pathways led us to develop an asymmetric 1,2-diarylation reaction of alkenes via a radical pathway. Mechanistic studies of the reductive 1,2-difunctionalization reaction of alkenes shed light on the mechanistic origin for selectivity in cross-electrophile coupling reactions. C sp^2 electrophiles are activated by Ni(I)–Br via two-electron pathways, whereas C sp^3 electrophiles are activated by Ni(I)–Ar via radical processes. Activation of the C sp^3 electrophile by (Xantphos)Ni(I) has been characterized to proceed through a concerted halogen atom abstraction pathway. The low redox potentials of Ni catalysts allowed us to develop a *trans*-selective reductive diene coupling, going through a two-electron pathway mediated by a Ni(I)/Ni(III) cycle. The tendency of Ni to undergo single-electron pathways prompted us to explore dinuclear Ni-mediated C–C, C–halogen, and N–N bond formation processes. These stoichiometric studies contribute to fundamental understanding of metal–metal bonding. Finally, we obtained the X-ray crystal structures of the long-sought-after Ni and Pd β-agostic complexes, which help rationalize slower β-H elimination for Ni complexes.

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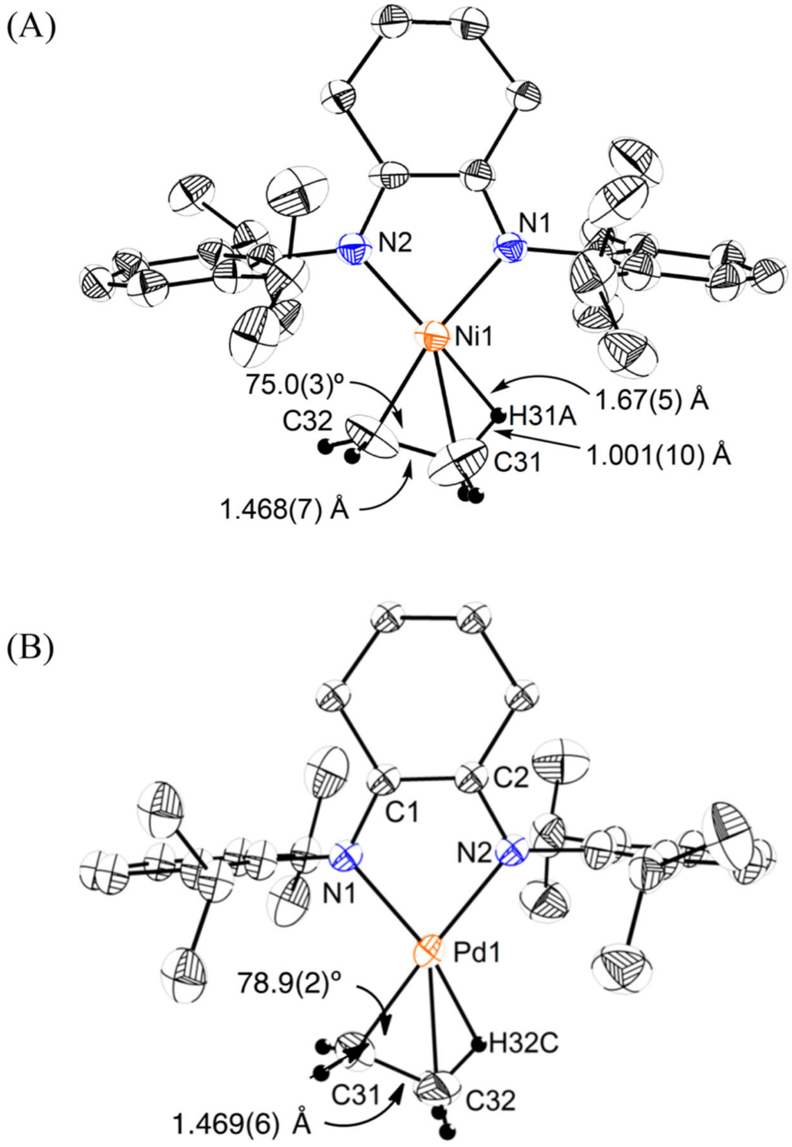
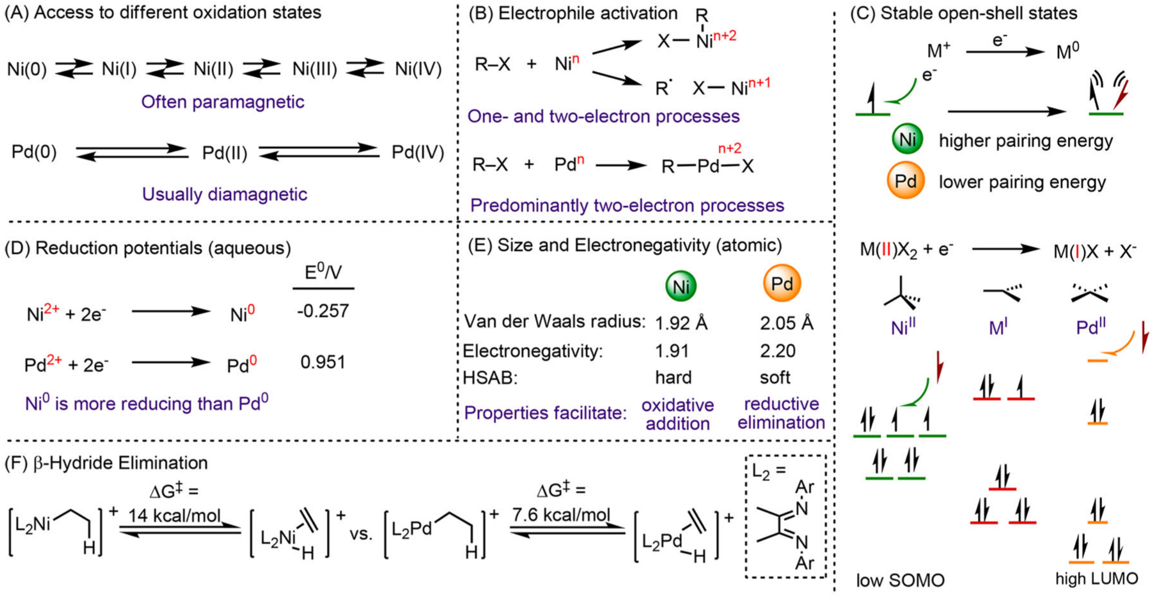


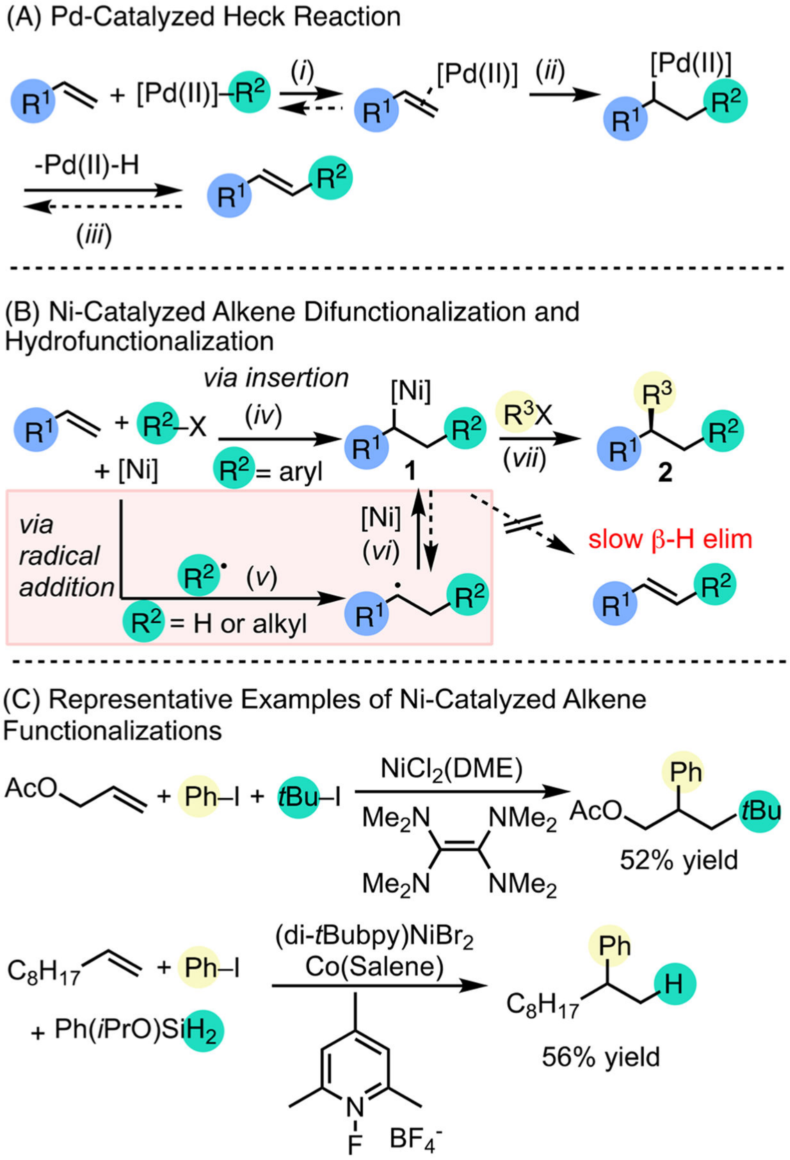
Figure 1.

X-ray structure of [($^{iPr}\alpha$-diimine)Ni-Et]$^+$[BAr$^F{}_4$]$^-$ (**40**) and [($^{iPr}\alpha$-diimine)Pd-Et]$^+$[BAr^F]$^-$ (**41**). Atom thermal ellipsoids are shown at the 50% probability level. The hydrogen atoms on the α-diimine ligands and [BAr$^F{}_4$]$^-$ are omitted for clarity.



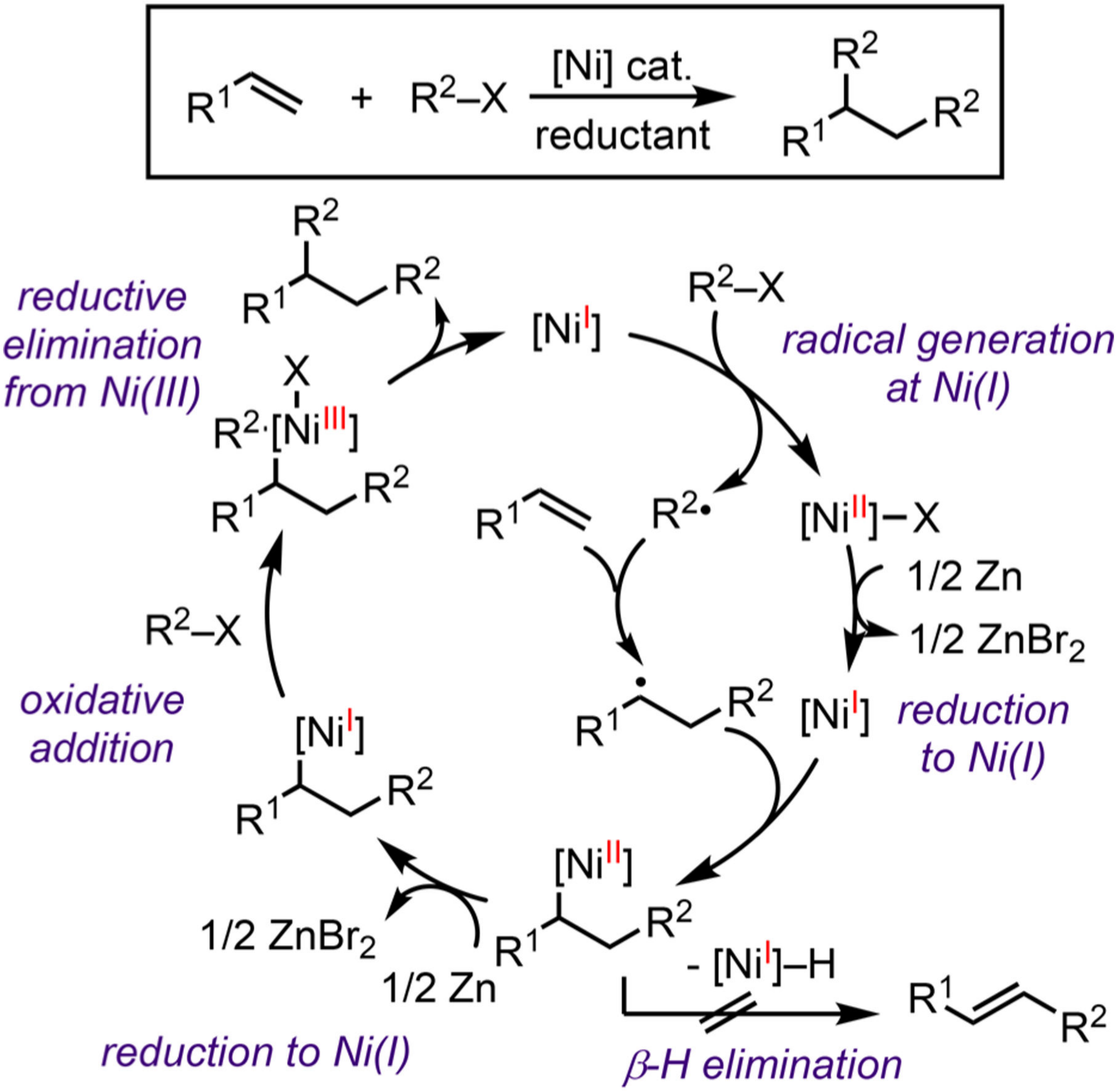
Scheme 1.

Overview of Fundamental Properties of Ni and Comparison with Pd



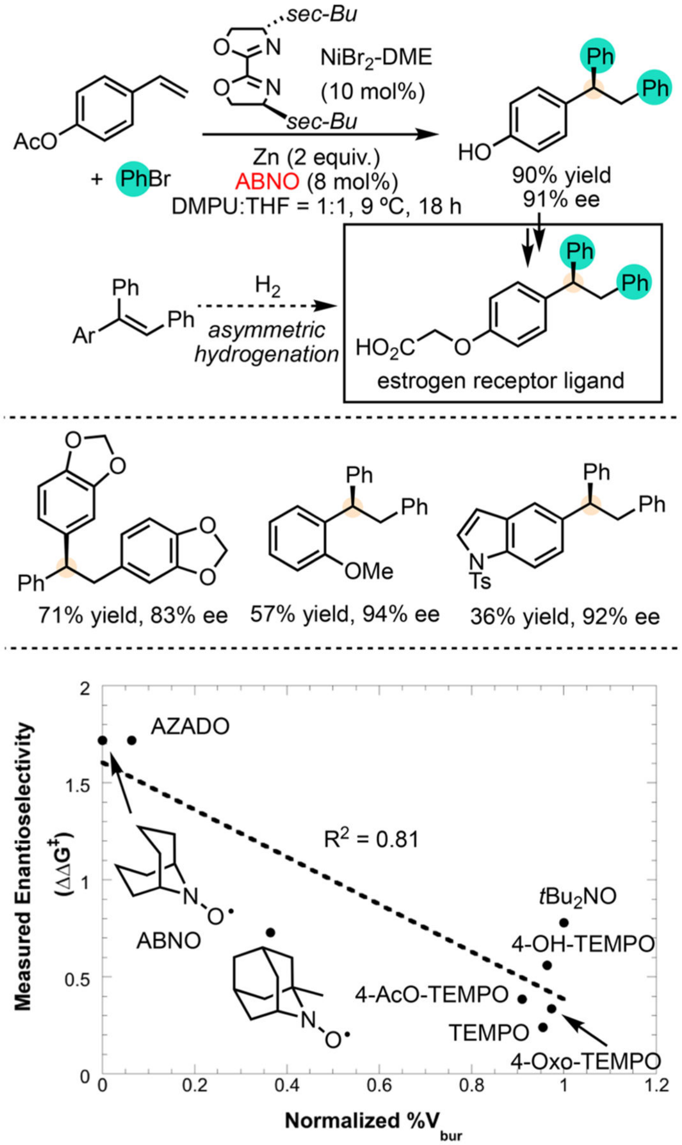
Scheme 2.

Ni-Catalyzed Difunctionalization and Hydrofunctionalization, in Comparison to the Pd-Catalyzed Heck Reaction



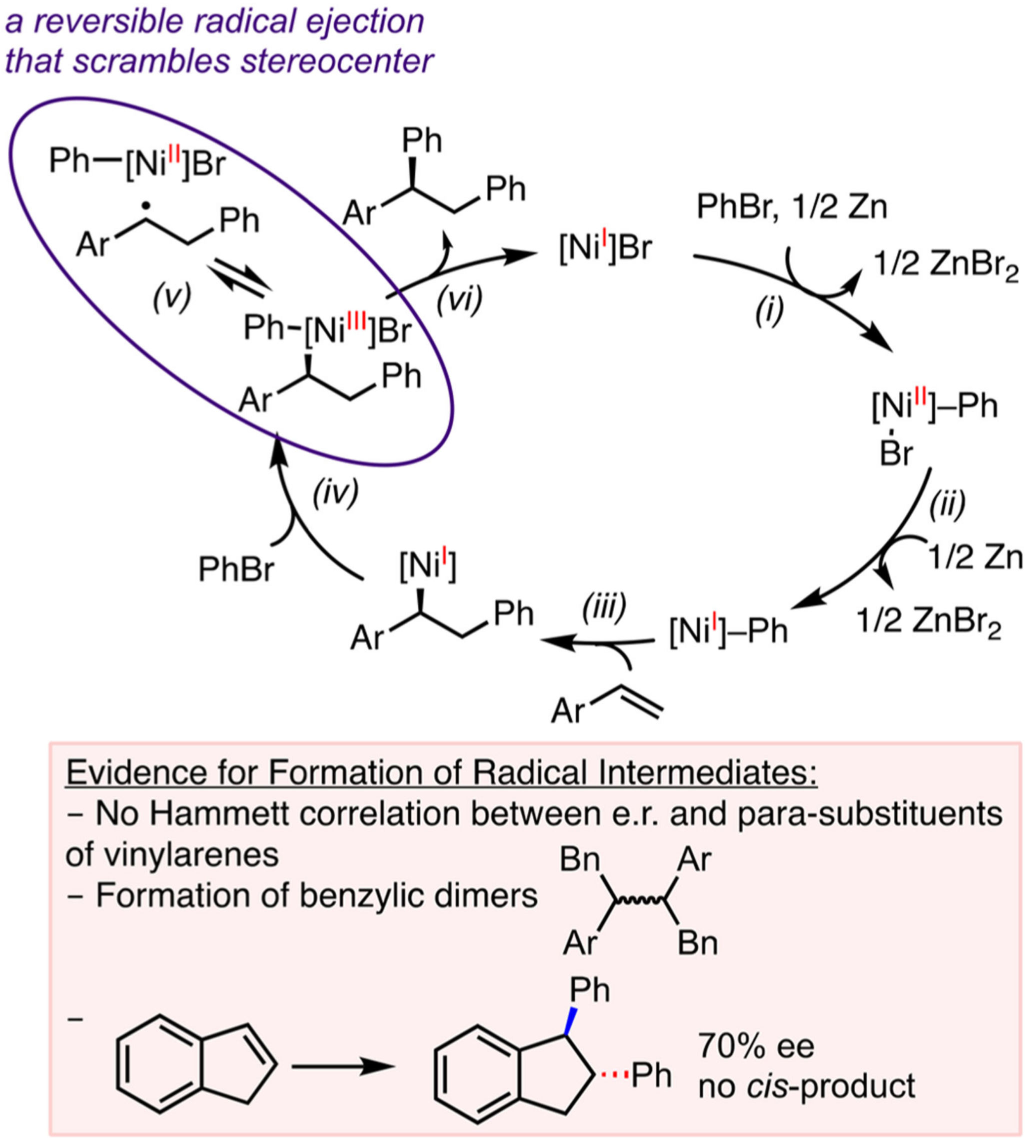
Scheme 3.

Plausible Fundamental Steps in Alkene Difunctionalization



Scheme 4.

Ni-Catalyzed Asymmetric Diarylation of Vinylarenes

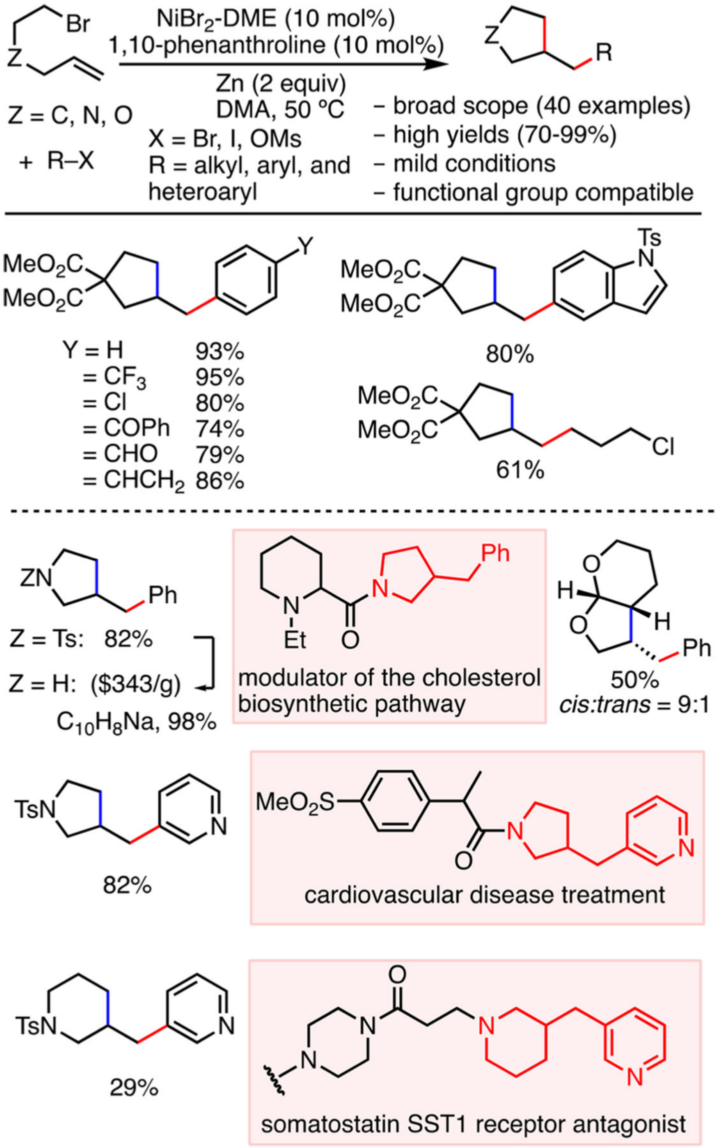


Evidence for Formation of Radical Intermediates:

- No Hammett correlation between e.r. and para-substituents of vinylarenes
- Formation of benzylic dimers
-

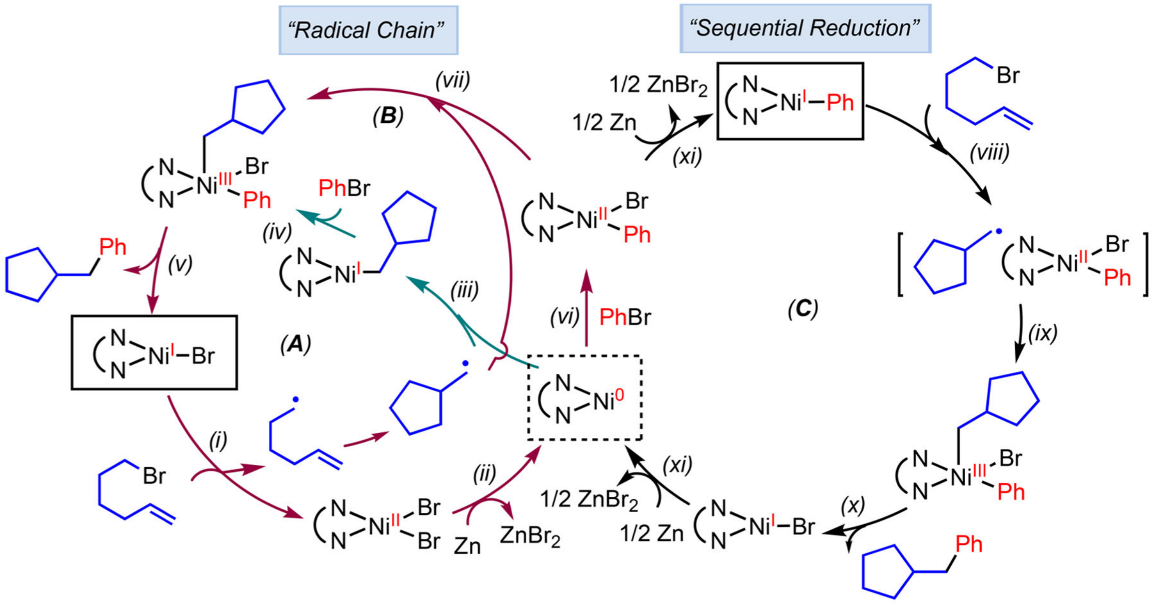
Scheme 5.

Proposed Mechanism for Ni-Catalyzed Asymmetric Diarylation of Vinylarenes



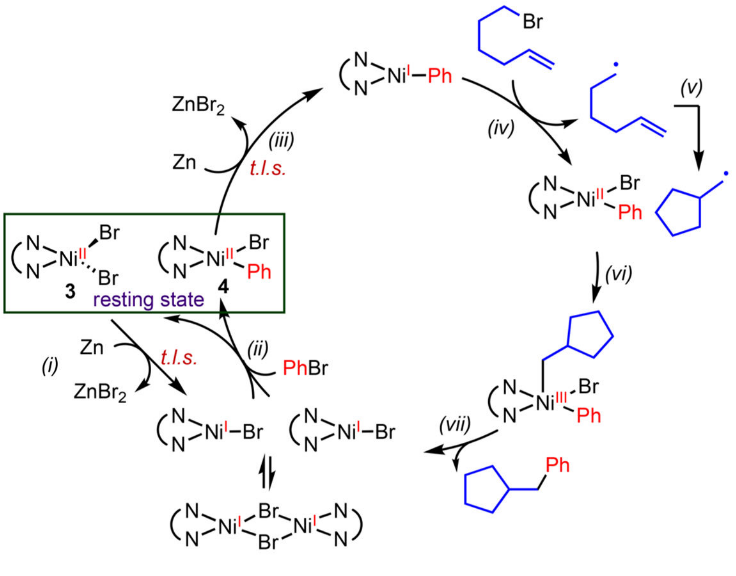
Scheme 6.

Two-Component Reductive 1,2-Dicarbofunctionalization of Alkenes



Scheme 7.

Possible Mechanisms of Ni-Catalyzed Reductive 1,2-Dicarbofunctionalization of Alkenes



Observations

- $Rate = k_{obs}$ [olefin]^0[PhBr]^0[Ni][Zn]^x

- Rate increases with increasing **agitation rate** and **Zn loading**.

- A mixture of **(phen)NiBr$_2$** and **(phen)Ni(Ar)(Br)** were observed to be the catalyst resting state by ^{1}H NMR and EPR spectroscopy.

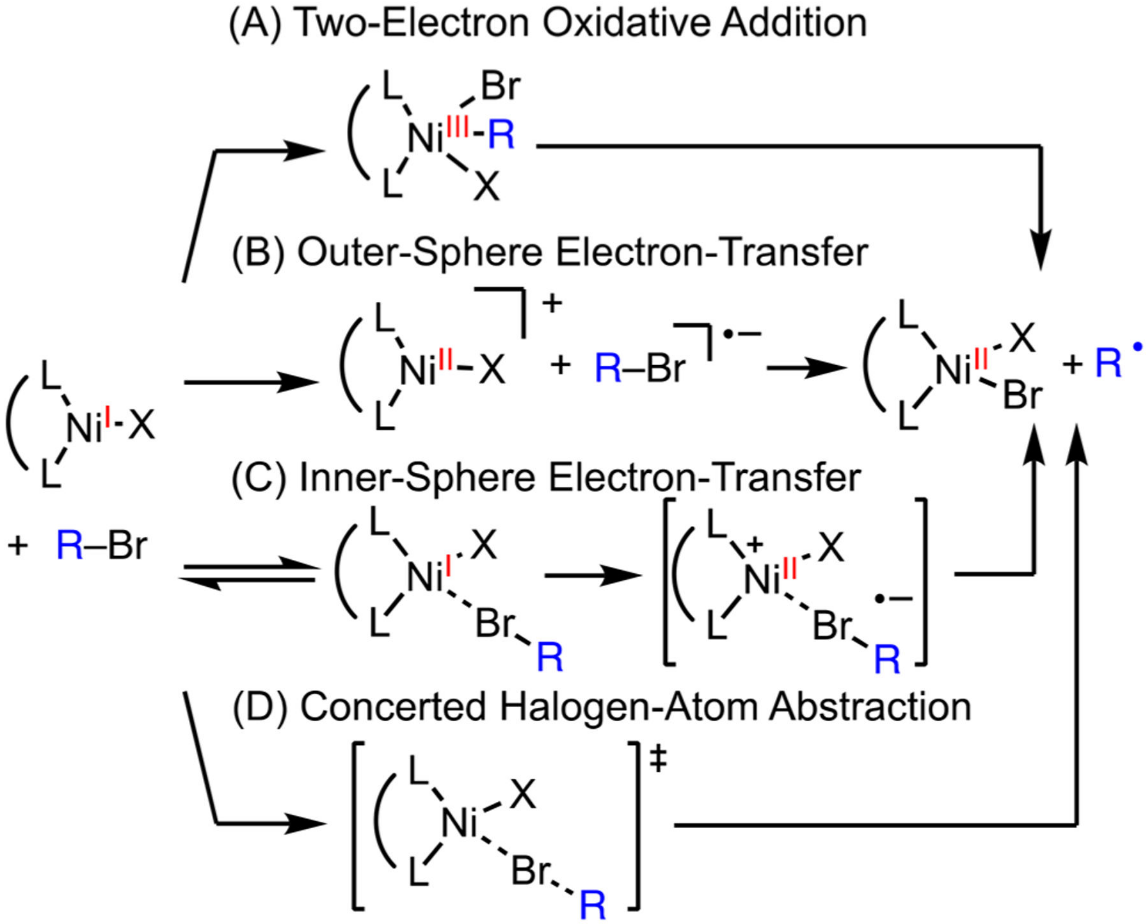
- Zn reduces (phen)Ni(II)Br$_2$ to **Ni(I)Br**, (phen)Ni(II)ArBr to (phen)Ni(I)Ar. Characterized by CV, EPR, NMR, and stoichiometric experiments.

- (phen)Ni(I)Br activates **ArBr** faster than alkyl-Br via bimolecular oxidative addition.

- (phen)Ni(I)(Ar) can activate **alkyl-Br** to form radicals.

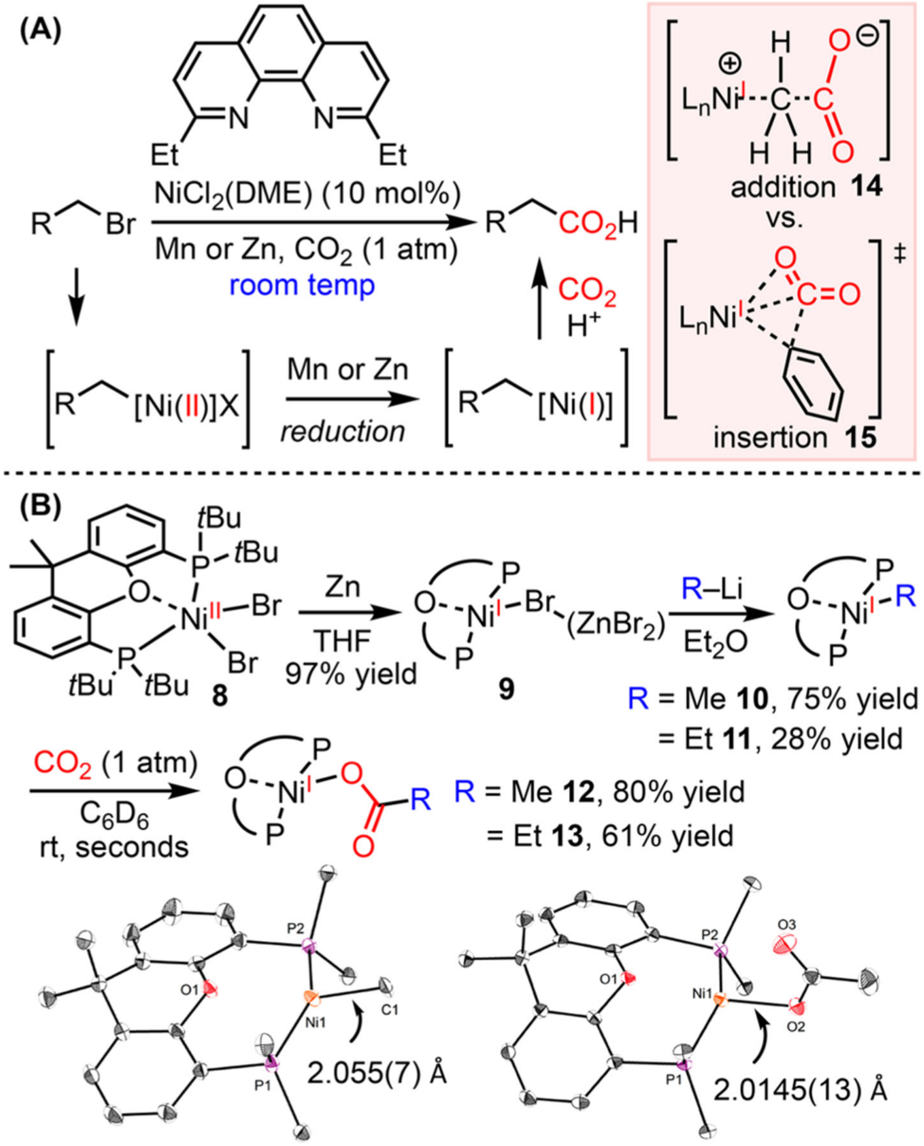
Scheme 8.

Ni-Catalyzed 1,2-Dicarbofunctionalization of Alkenes by a Proposed “Sequential Reduction” Mechanism and Experimental Evidence



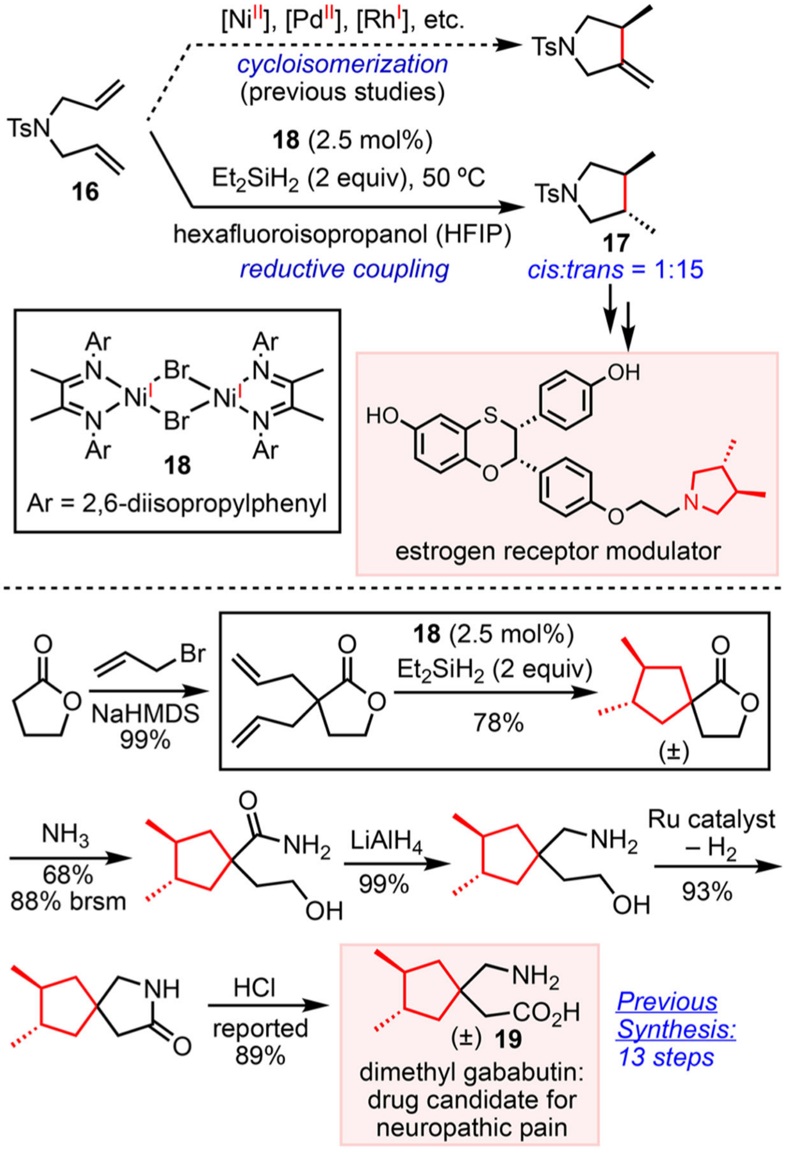
Scheme 9.

Possible Mechanisms for Ni(I)-Mediated Halide Abstraction



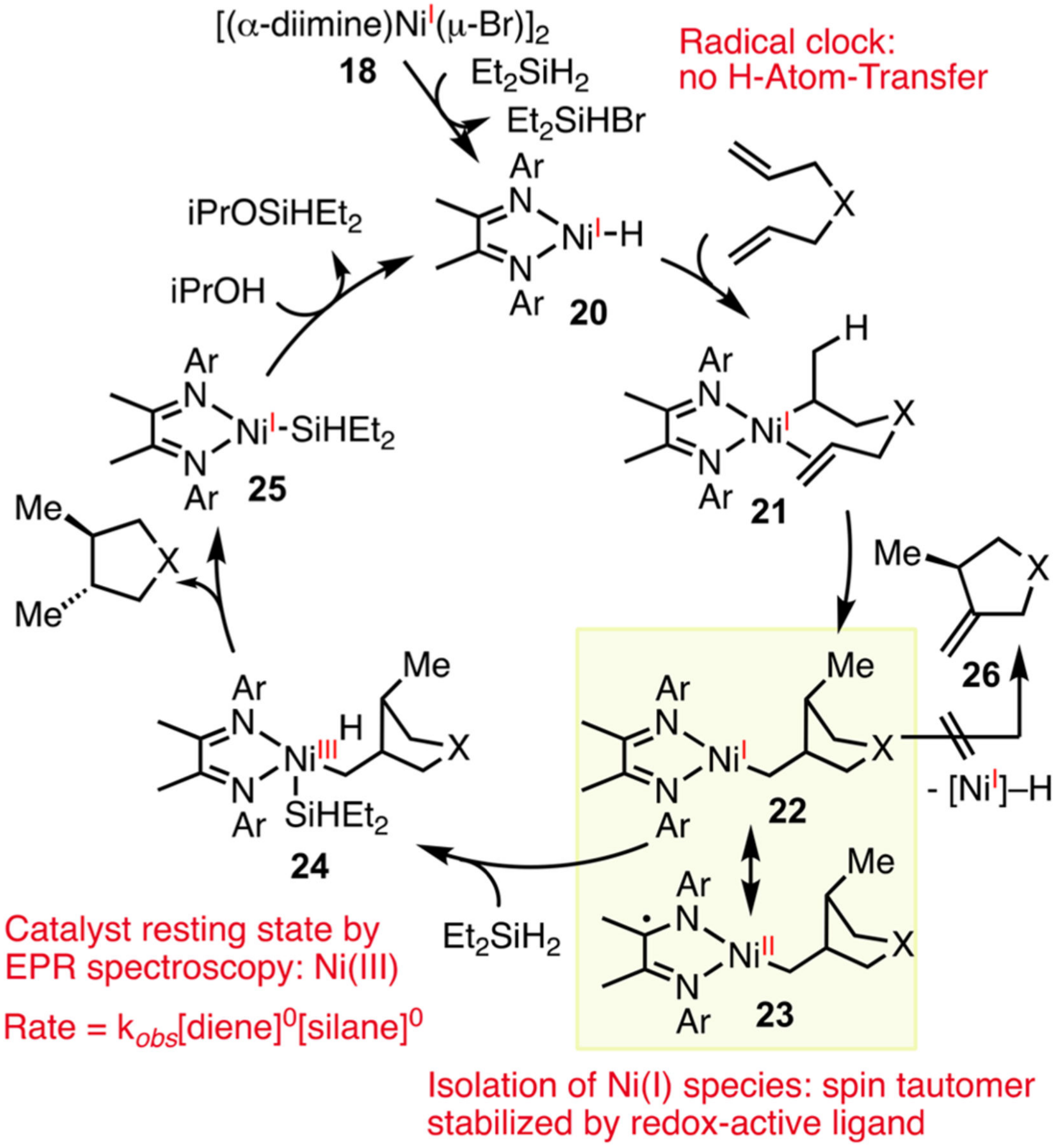
Scheme 10.

Reduction of Ni(II) to Ni(I) by Zn and Carboxylation of Ni(I)–Me



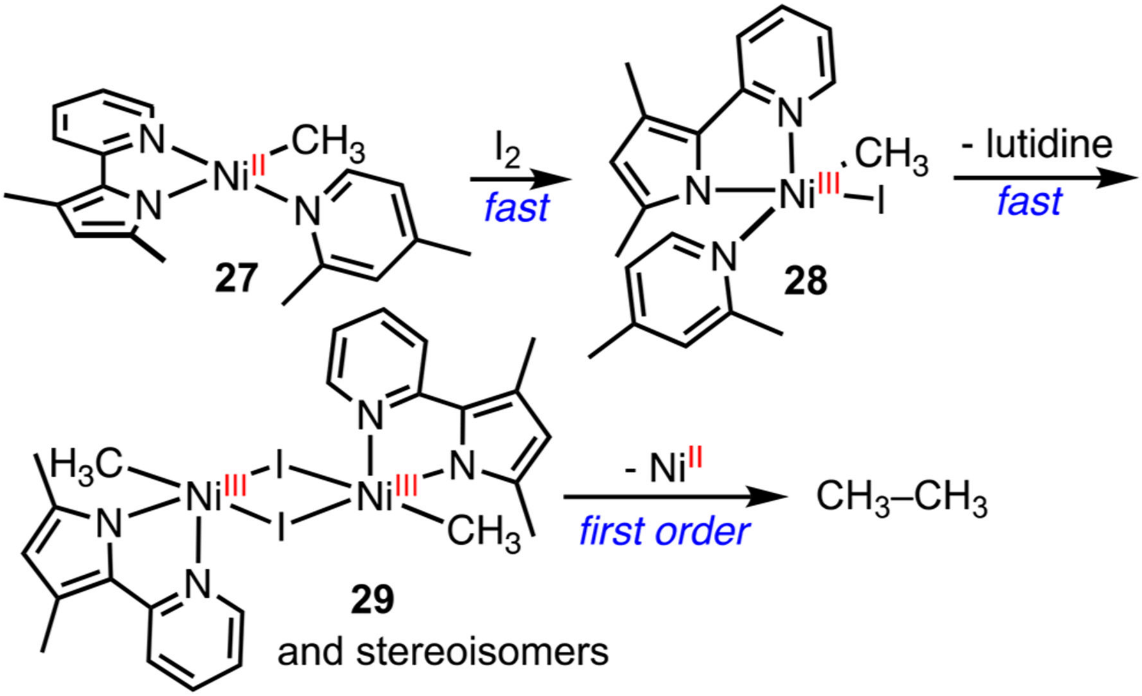
Scheme 11.

Reductive Diene Coupling and Applications



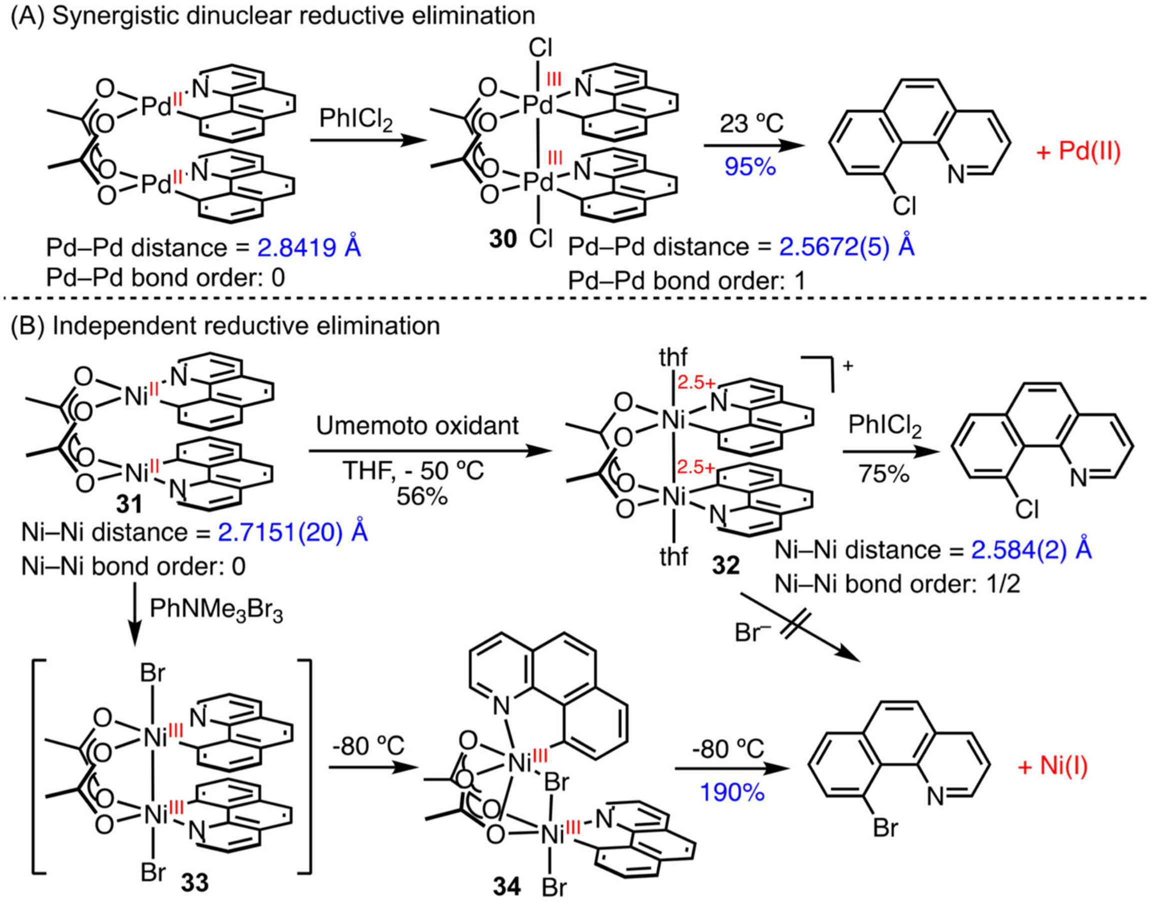
Scheme 12.

Proposed Mechanism to Account for Chemo- and Diastereoselectivity



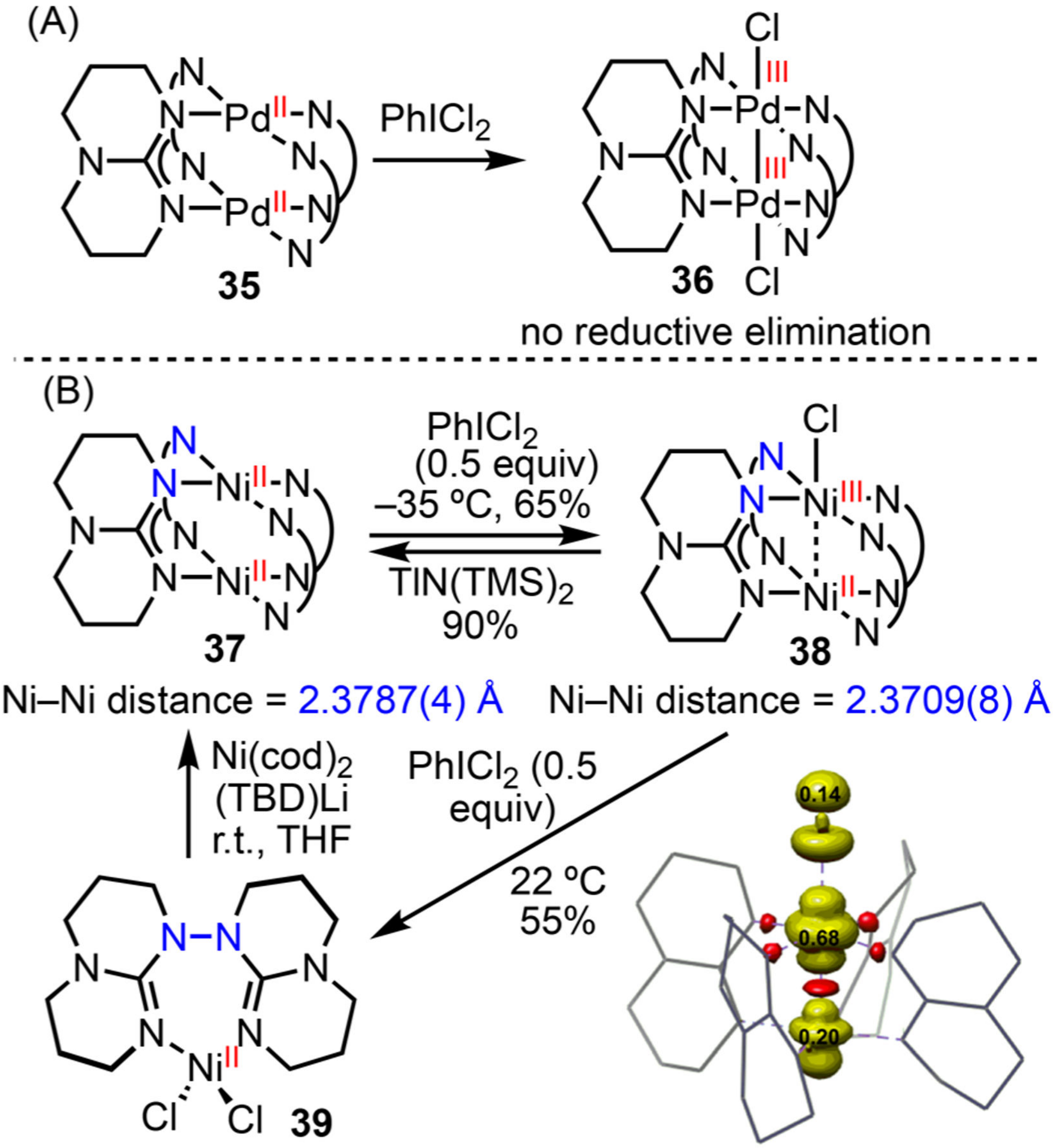
Scheme 13.

Dinuclear Ni(III)-Mediated Ethane Formation



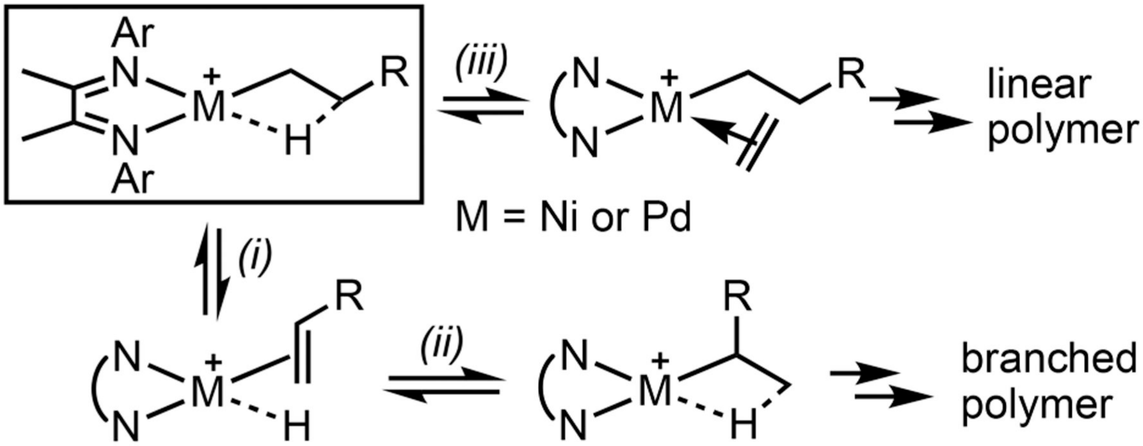
Scheme 14.

Comparison of Dinuclear Ni and Pd in Metal–Metal Bonding and Reductive Elimination

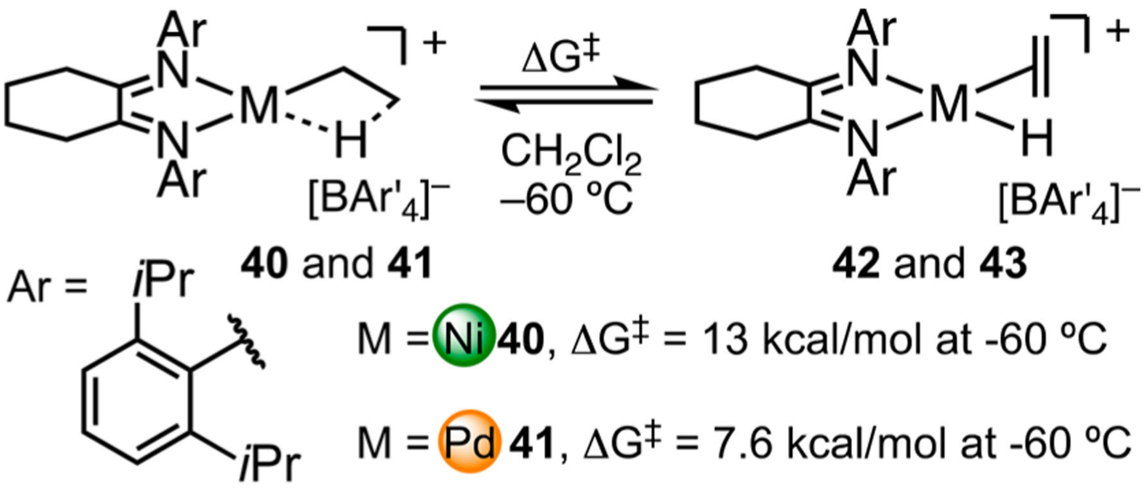


Scheme 15.

Comparison of Ni and Pd in Metal–Metal Bonding and Reductive Elimination with Paddle-wheel Complexes



Scheme 16.
(α-Diimine)Ni and Pd-Catalyzed Olefin Polymerization

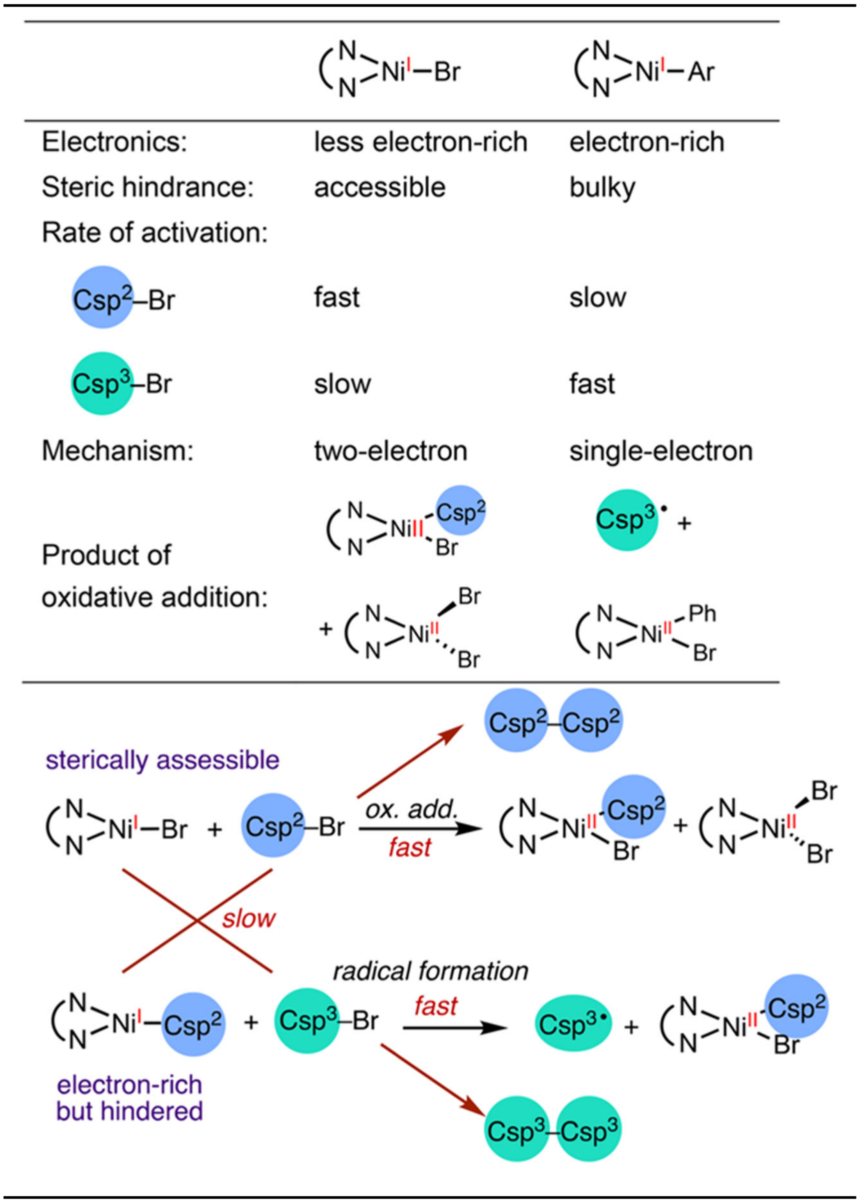


Scheme 17.

Kinetic Barriers for *β*-H Elimination

Table 1.

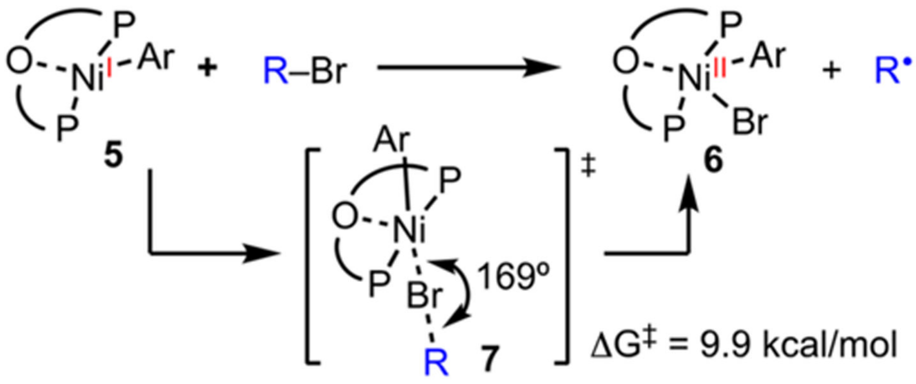
Selectivity of Different Electrophiles

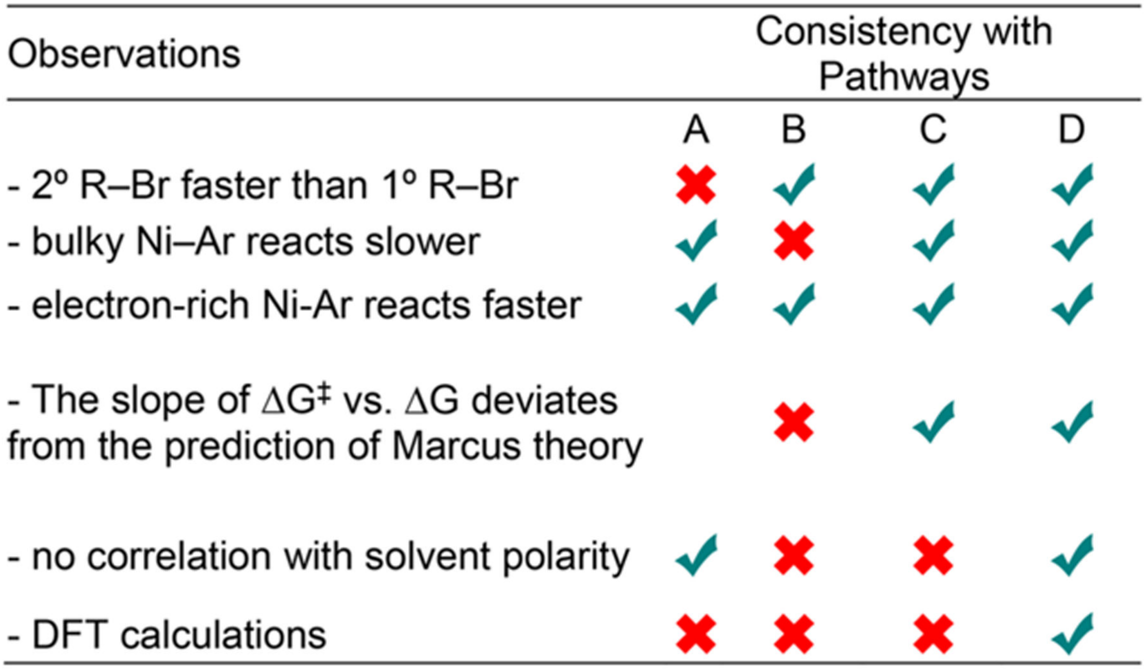


	N N Ni^{I}–Br	N N Ni^{I}–Ar
Electronics:	less electron-rich	electron-rich
Steric hindrance:	accessible	bulky
Rate of activation:		
Csp^2–Br	fast	slow
Csp^3–Br	slow	fast
Mechanism:	two-electron	single-electron
Product of oxidative addition:	N N Ni^{II} Csp^2 Br + N N Ni^{II} Br Br	Csp^3• + N N Ni^{II} Ph Br

Table 2.

Evidence for and against the Possible Pathways of Ni(I)-Mediated Alkyl Halide Activation





Observations	Consistency with Pathways			
	A	B	C	D
- 2° R–Br faster than 1° R–Br	✗	✓	✓	✓
- bulky Ni–Ar reacts slower	✓	✗	✓	✓
- electron-rich Ni-Ar reacts faster	✓	✓	✓	✓
- The slope of ΔG‡ vs. ΔG deviates from the prediction of Marcus theory		✗	✓	✓
- no correlation with solvent polarity	✓	✗	✗	✓
- DFT calculations	✗	✗	✗	✓

Table 3.

Comparison of Bond Parameters for *β*-Agostic (*α*-Diimine)Ni and Pd Complexes

	40 (Ni)	**41 (Pd)**
M–C31 (Å)	1.901(4)	2.030(4)
M–C32 (Å)	2.081(5)	2.264(4)
C31–C32 (Å)	1.468(7)	1.469(6)
M–C31–C32 (deg)	75.0(3)	78.9(2)
M–H34A (Å)	1.67(5)	1.60(4)[a]
C34–H34A (Å)	1.001(10)	1.20(5)[a]

[a] Bond lengths determined by neutron diffraction for ($^{\mathrm{iPr},\,para\text{–}\mathrm{MeO}}$*α*-diimine)Pd.