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Leveraging the redox promiscuity of Nickel to catalyze C–N coupling reactions

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ABSTRACT: This perspective details advances made in the field of Ni-catalyzed C–N bond formation. The use of this Earth abundant metal to decorate amines, amides, lactams, and heterocycles enables direct access to a variety of biologically active and industrially relevant compounds in a sustainable manner. Herein, different strategies that leverage the propensity of Ni to facilitate both one- and two-electron processes will be surveyed. The first part of this perspective focuses on strategies that facilitate C–N couplings at room temperature by accessing oxidized Ni(III) intermediates. In this context, the advances in photochemical, electrochemical, and chemically-mediated processes will be analyzed. A special emphasis has been put on providing a comprehensive explanation of the different mechanistic avenues that have been proposed to facilitate these chemistries; either Ni(I/III) self-sustained cycles or Ni(0/II/III) photochemically-mediated pathways. The second part of this perspective details the ligand designs that also enable access to this reactivity via a two-electron Ni(0/II) mechanism. Finally, we discuss our thoughts on possible future directions of the field.

Nitrogen-containing molecules are ever-present in biologically active compounds and materials.[1] A convenient and frequently used approach to access these functional groups is through direct C–N coupling, which can be achieved via: nucleophilic substitutions,[2] condensations,[3] rearrangements,[4] and transition metal-catalyzed reactions.[5] This perspective will focus on the use of Ni catalysis to afford this bond connection, and how the diversity of oxidation states and mechanistic manifolds accessible to this Earth abundant metal have been leveraged to facilitate these reactions.

When utilizing organometallic complexes to mediate C–N bond formation, two major strategies have been devised: (i) reactions that proceed via amino-metalation of unsaturated systems (either via migratory insertion or an outer-sphere attack to a metal-coordinated π-system); and (ii) reactions that afford the new C–N bond through a reductive elimination step. The amino-metalation of π-systems is often energetically more favorable than reductive elimination of C–N bonds. This is because reactions that proceed via migratory insertion cleave a π-bond and a metal–N bond, and generate two new sigma bonds (C–N and metal–C). In contrast, when forming C–N bonds via reductive elimination, a metal–C and a metal–N bond are broken, and only the new C–N bond is formed. An additional challenge to the development of metal-catalyzed C–N couplings is the ability of nitrogenated groups to tightly bind to metals, further hampering reductive elimination steps. As a result, high reaction temperatures are often required to enable the C–N reductive elimination.

In spite of these challenges, reports describing the reductive elimination of C–N bonds date back to 1903, when Ullmann reported the coupling of aniline and 2-chlorobenzoic acid in the presence of stoichiometric Cu metal.[6] Following this pioneering work, advances in ligand design for Cu- and Pd-mediated transformations have enabled the use of these metals in catalytic amounts, turning these reactions into workhorses of modern synthetic organic chemistry.[1c, 7]

While Cu and Pd have driven most of the past research efforts, Ni-mediated approaches have also been recognized as promising alternatives.[8] In 1950 the use of Ni salts for C–N couplings was reported by The Standard Oil Company.[9] However, it wasn't until 1997 when the first in-depth study of a Ni-catalyzed amine arylation protocol was published by Wolfe and Buchwald.[10] These, and other early studies, highlighted the ability of Ni catalysis to enable C–N reductive eliminations through 2-electron pathways analogous to those described for Pd.[8] More recently, the MacMillan and Buchwald groups reported the use of a Ni-photoredox tandem system to facilitate an alternative pathway for amine arylation.[11] This approach exploits the ability of Ni to access multiple oxidation states to furnish the new C–N bonds at ambient temperatures.

From a general perspective, the publication of this report together with other Ni-photoredox pioneering examples, has caused a shift in the perception of the synthetic utility of the redox promiscuity of Ni.[11-12] Traditionally, the tendency of Ni to adopt multiple oxidation states was regarded as a drawback due to our inability to control and understand its reactivity. However, our understanding has improved and now we recognize the redox properties of Ni complexes as an advantage that can be leveraged towards C–heteroatom couplings (the focus of this perspective), $C(sp^3)$–$C(sp^3)$ couplings, and C–H activation protocols.[11-13]

In the context of C–N coupling reactions, three different general mechanisms have been observed, depending on the nitrogen nucleophile and the ligand utilized (Figure 1). Ni(I/III) cycles where a Ni(III) aryl amido readily undergoes reductive elimination at room temperature is the most commonly exploited strategy. The main limitation of this approach is the instability of the Ni(I) and Ni(III) intermediates, which can lead to formation of inactive Ni species that require external stimuli to reengage in catalysis. The necessity of a constant stimulus, together with the difficulties related to the scale-up of light- or electrochemically-mediated processes, has reduced the widespread application of these methodologies.[14] For the implementation of these systems on industrial scales, specialized set ups like flow reactors, which increase light penetration in reaction vessels, are often required.[15]

Ni(0/II/III) manifolds have also been proposed for C–N couplings. In these mechanisms, the oxidation and reduction of different Ni intermediates is needed for every turnover. Finally, Ni(0/II) catalytic cycles can also be leveraged to access C–N couplings. This is the only strategy that does not rely on the use of external redox processes. Early reports leveraging this manifold showcased the use of commercially available phosphine ligands (like 1,1′-Ferrocenediyl-bis(diphenylphosphine), DPPF) and required high reaction temperatures.[8, 10, 16] Subsequent development of specialized ligands purposefully designed for Ni catalysis has allowed substantial reduction of the reaction temperatures.[8, 17]

Figure 1. Ni catalytic cycles for C–N bond-forming reactions.
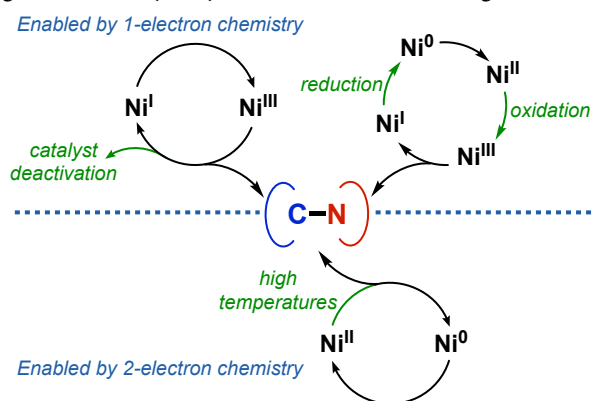
For each of these three general mechanistic manifolds, we will discuss how different reaction conditions can favor alternative reaction pathways, the key experiments that have shown which mechanism predominates, and the gaps in our knowledge that still need to be addressed to overcome the current limitations. A deeper emphasis will be placed on the 1-electron approaches. For a more comprehensive review of the Ni(0/II) systems please refer to other reviews.[8]

## ACCESSING NI(III) ACCELERATES C–N REDUCTIVE ELIMINATION

Stoichiometric studies from Hillhouse and coworkers demonstrated that C–N reductive elimination could be facilitated by oxidation of Ni(II) alkyl amido complexes (**1**, Scheme 1a).[18] A series of Ni(II) alkyl amido complexes bearing bipyridine ligands (bpy) were isolated and subjected to elevated temperatures and no reductive elimination product was observed. However, the same complexes yielded the cross-coupled product upon addition of chemical oxidants.[18] An intermolecular example of this behavior was later showcased by Nakamura.[19] It is not unexpected that oxidation will facilitate the reductive elimination process. However, the lack of reactivity of upon heating contrasts with the other group 10 elements that readily undergo reductive elimination of C–N bonds under thermal conditions. This divergent behavior has been studied by using density-functional theory (DFT) calculations, which showed that, unlike for Pd analogs, reductive elimination of C–heteroatom bonds from Ni(II) is usually an endothermic process.[12a, 20]

A systematic study of Ni-catalyzed C–heteroatom reductive elimination reactions by the Zargarian group also supports the hypothesis that generating Ni(III) is an effective way to promote the new bond formation.[21] Their work shows that C–N, C–O, and C–halogen bonds can be forged via reductive elimination from Ni(III) pincer complexes at room temperature.

Expanding on Hillhouse's discovery that accessing Ni(III) allows for C–N couplings at room temperature, the Buchwald and MacMillan labs devised a strategy to make these reactions catalytic in Ni (Scheme 1b).[11] Key to the development of this chemistry was the use of an Ir-based photocatalyst which facilitates the redox processes leading to the formation of Ni(III) intermediates that render the new C–N bond. The optimized conditions did not require the addition of an exogenous ligand and facilitated the coupling of primary and secondary amines, anilines, allylamines, and sulfonamides with aryl and heteroaryl bromides (Scheme 1b).

Scheme 1. Seminal stoichiometric and catalytic examples of accelerating C–N reductive elimination from Ni(III) complexes
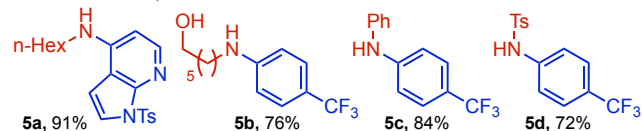

a) Oxidation of Ni(II) complexes triggers C–N reductive elimination
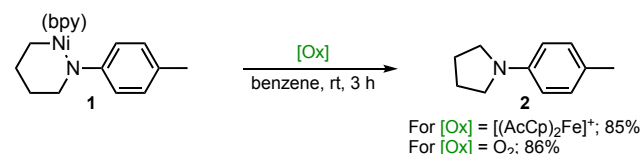
*b) Seminal report of Ni-photoredox C–N coupling*
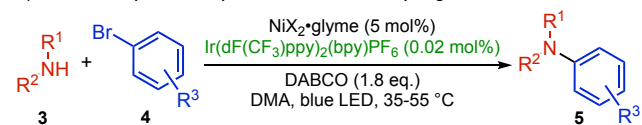
Selected examples:

Following their initial report, the MacMillan group published an in-depth study of the reaction mechanism.[22] Quantum yield measurements highlighted the presence of a self-sustained cycle that did not involve an excited photocatalyst in every turnover.[23] Photophysical, electrochemical, stoichiometric, and kinetic experiments were used to investigate the system, which collectively support that a Ni(I/III) cycle predominates in this reaction (Figure 2). The conclusions drawn in this paper parallel those reported by the Nocera lab for an analogous system, where a Ni-photoredox C–O coupling mechanism was investigated.[24]

The Ni catalytic cycle starts with the oxidative addition of Ni(I) complex **6** into the aryl bromide (**4**). Subsequent ligand exchange renders Ni(III) aryl amido **8** which is poised for a fast reductive elimination that yields the functionalized amine product **5**. Despite the presence of a self-sustained "dark cycle", the reaction requires continuous photoirradiation, as seen by the plateau in product formation when the lamp is switched off. The reduced efficiency of the Ni(I/III) cycle has been attributed to the limited stability of the Ni(I) and Ni(III) bipyridine complexes, which results in the formation of off-cycle Ni complexes (**9**, **10**).[22]

The photocatalyst is thought to serve as reductant for Ni(II) species (**10**), which is both used as the precatalyst and re-formed via an undesired side reaction. The photocatalyst catalytic cycle, depicted in the green box, is initiated by light absorption (**11** → **12**). Subsequent oxidation of the redox-active base, 1,4-diazabicyclo[2.2.2]octane (DABCO), yields Ir(II) complex **13**. This Ir(II) complex is then proposed to reduce the Ni(II) complexes (**10**), allowing both catalytic cycles to resume.

Figure 2. Proposed Ni(I/III) cycle for photochemical amine arylation
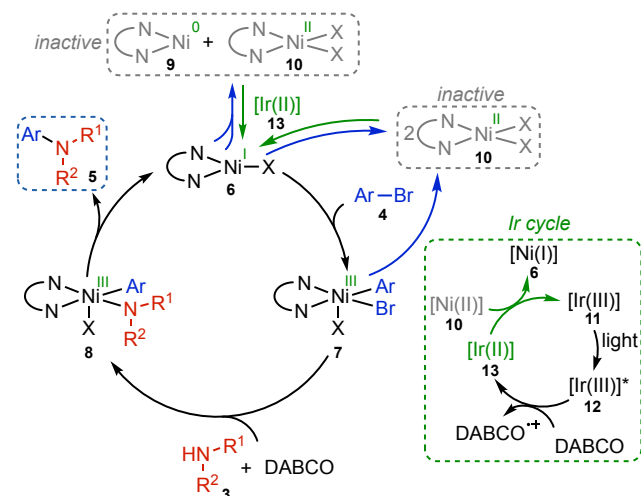
The discovery of DABCO's unexpected dual role in the reaction mechanism was a pivotal finding in this study.[22] This organic base is required to both quench the HBr generated during the reaction and to reduce the excited Ir photocatalyst (**12** → **13**). Stern-Volmer quenching experiments were used to reveal this electron transfer event. It was also observed that the initial rates and reaction yield are diminished by decreasing the DABCO concentration, further validating this proposed mechanism.

The mechanistic insights gathered in this study showed that the Ni(II) reduction, required to initiate and sustain the catalysis (shown by the green arrows in Figure 2), was the reaction rate determining step (RDS). With this information in hand, the MacMillan lab was able to identify a more reducing photocatalyst that increased the reaction rate by more than 10-fold.[22]

This seminal publication on the use of Ni-photoredox for amine functionalization,[11] together with other early reports on C–O coupling,[25] have served as inspiration for a number of groups that extended this methodology to facilitate other C–heteroatom couplings.[12a, 12l, 15] Most methodologies are proposed to undergo similar mechanisms to that depicted in Figure 2, and require the use of a redox-active base to facilitate the Ir photocatalyst reduction (**12** → **13**). Given the key nature of this step in enabling this mechanism, the Miyake group recently published a detailed study exploring alternative oxidants that can facilitate this step.[26] This work highlighted that, when using Ir(ppy)₃ as the photocatalyst, halides can also facilitate this step and an acceleration of the reaction rate can be observed upon addition of ammonium halides. Additionally, studies on the speciation of the off-cycle Ni(II) complexes were presented.[27]

Recently, the Hadt group published a thorough study showing that bipyridine Ni(II) aryl halide complexes can undergo photolysis to generate aryl radicals when irradiated at 390 nm.[28] Because of decreased absorption at longer wavelengths, it was observed that aryl radical formation gradually diminished when longer wavelengths were employed. Inspired by these findings, and aiming to avoid side reactions associated with the photolysis of Ni intermediates, Rovis and coworkers developed a complementary method for amine arylation that uses longer wavelength light (Scheme 2).[15] Deep red and near-infrared wavelengths are more selective than the higher energy blue wavelengths required for the use of Ir photocatalysts, as the latter can also be absorbed by Ni complexes. This approach improves

the functional group tolerance and reduces the likelihood of side-reactivity. Additionally, higher wavelengths penetrate further into the reaction vessels, allowing more uniform irradiation of the mixture, thus simplifying reaction scale-up. This Ni/Os-mediated reaction is proposed to undergo a Ni(I/III) cycle analogous to the Ni/Ir systems detailed previously (Figure 2). The reaction scope includes primary (**16c**) and secondary (**16a**) amines, anilines (**16b**), and tolerates unprotected alcohols, olefins, heterocycles (**16a**) and stereocenters (**16c**).

Scheme 2. Alternative photocatalysts allow the use of lower energy light
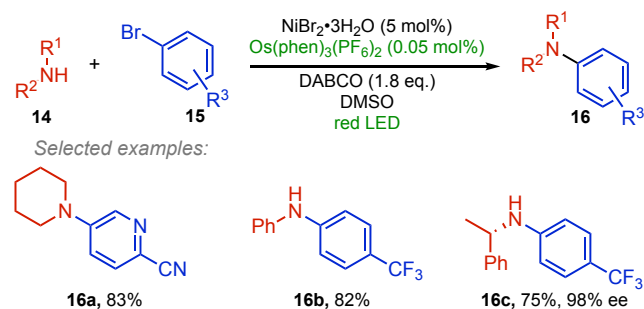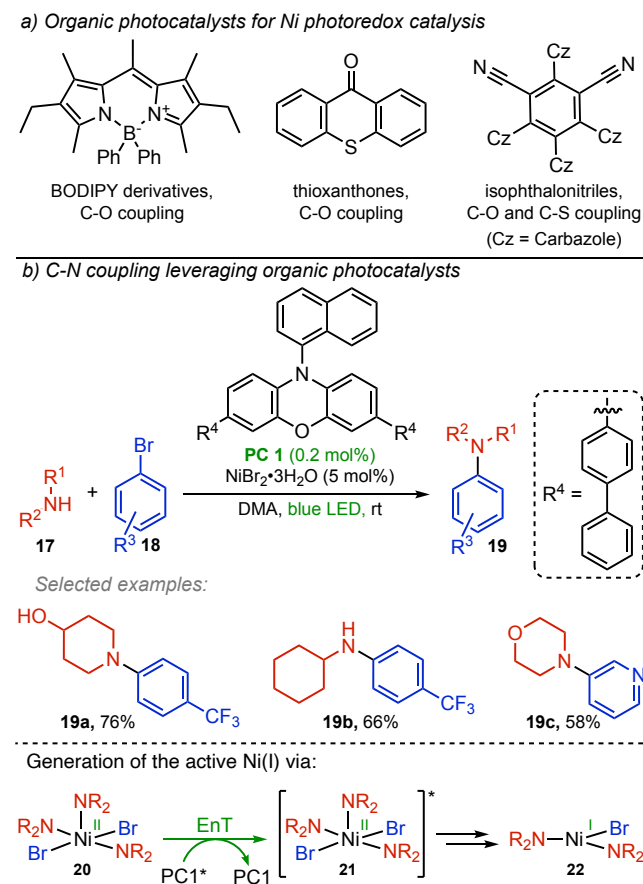

The use of tandem systems that combine Ni and precious metal-based (Ir, Ru, Os) photocatalysts to promote C–heteroatom coupling has been shown to be a versatile technique, providing access to a wide range of products.[12a, 12l] However, the dependence on these photocatalysts presents a challenge due to the high cost of precious metals. Three main strategies have been devised to avoid the use of expensive photocatalysts: (1) the development of organic-based photocatalysts that allow for more sustainable photochemical reactions;[29] (2) while less selective, the use of shorter wavelengths has been shown to enable these couplings in the absence of added photocatalysts;[30] and (3) other efforts have focused on the design of ligands that enable Ni intermediates to facilitate catalysis and directly undergo the photochemical steps under visible light irradiation.[31]

A major research focus within photoredox catalysis is the identification and design of organic photocatalysts that can be utilized instead of those based upon precious metals like Ir and Ru.[29] Metal-free photocatalysts have been known for quite some time, with reports dating back to 2011 showing that the use of organic dyes like Methylene Blue, Eosin Y, or Rose Bengal, in conjunction with other catalysts, can promote light-mediated reactions.[32] In the context of Ni-photoredox catalysis, several dyes have been identified as suitable photocatalysts that can facilitate the oxidation and reduction of Ni intermediates (Figure 3a).[33] Most of the reported examples describe the use of organic photocatalysts for other types of Ni-photoredox reactions or for facilitating C–O couplings.

The use of an organic photocatalyst to promote Ni-catalyzed C–N bond formation has been reported by Miyake.[34] As depicted in Figure 3b, phenoxazine and phenazine derivatives were shown to facilitate the coupling of alkyl amines with aryl bromides. It should be noted that, in this transformation, **PC1** was shown to outperform commonly used Ru- and Ir-based photocatalysts. Additionally, in this paper, Miyake and coworkers uncovered an alternative mechanism for Ni-mediated C–N coupling. Extensive spectroscopic evidence is presented that supports an energy transfer (EnT) photochemical step. As shown Figure 3b, an EnT from the excited **PC1** to Ni(II) complex **20** leads to the formation of Ni(I) complex **22**
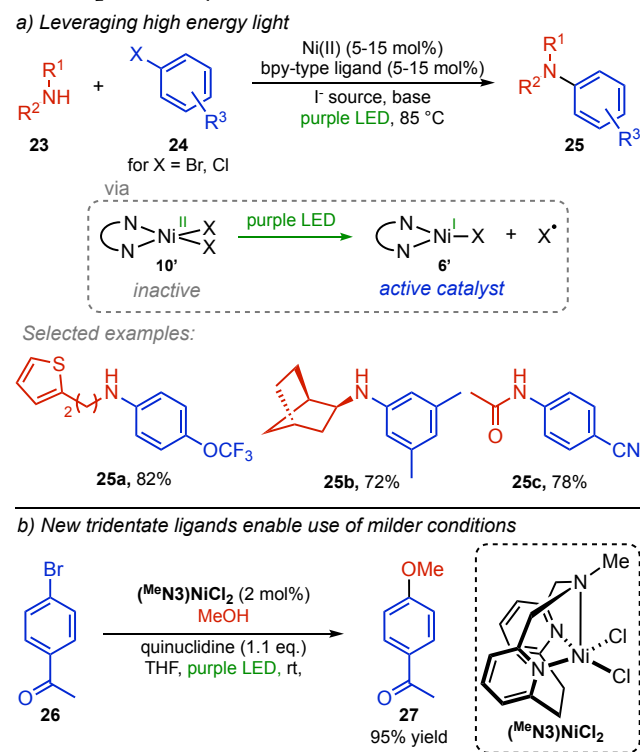
responsible for the C–N coupling. It should be noted that energy transfer-mediated Ni-catalyzed C–N couplings are rare and prior to this report it had only been previously demonstrated by the MacMillan lab in the context of sulfonamide arylations.[35] The reaction conditions are compatible with substrates bearing unprotected alcohols (**19a**) or heterocycles (**19c**).

Figure 3. Organic photocatalysts enable C-N couplings via energy transfer mechanisms

a) Organic photocatalysts for Ni photoredox catalysis

BODIPY derivatives, C-O coupling

thioxanthones, C-O coupling

isophthalonitriles, C-O and C-S coupling (Cz = Carbazole)

b) C-N coupling leveraging organic photocatalysts

Selected examples:

19a, 76%　　**19b**, 66%　　**19c**, 58%

Generation of the active Ni(I) via:

The Xue group has contributed extensively to the second approach, leveraging the higher energy of purple light to facilitate these processes in the absence of added photocatalysts.[30] The arylations of primary amines, secondary amines, ammonium salts, and amides have been achieved utilizing this approach (Scheme 3a). These transformations are believed to undergo similar mechanisms to those mediated by Ir photocatalysts, where a Ni(I/III) cycle renders the new functionalized nitrogenated groups. However, in the absence of photocatalysts, an alternative mechanism must facilitate the conversion of Ni(II) intermediates into the active Ni(I) complexes (**10** → **6**, Figure 2). Higher reaction temperatures and the more energetic, lower wavelength irradiation are proposed to enable the direct excitation of the Ni(II) intermediates (**10'**) and trigger the homolytic cleavage of one of the anionic ligands to render the active Ni(I) catalyst **6'** (Scheme 3a). The continuous irradiation of these reactions is also required to access the product in high yields. Additionally, and contrasting with the seminal reports that used an Ir photocatalyst to enable the arylation of amines (Scheme 3b),[11] control experiments revealed that bipyridine ligands are required to access this reactivity.

Scheme 3. Photochemical C–N and C–O couplings in the absence of photocatalysts

a) Leveraging high energy light

Selected examples:

25a, 82%　　**25b**, 72%　　**25c**, 78%

*b) New tridentate ligands enable use of milder conditions*

Albeit only investigated in the context of C–O coupling, the Mirica group has designed a new ligand scaffold capable of stabilizing both high and low valent Ni species (Scheme 3b).[31] Their design aimed to balance both the steric and electronic advantages and disadvantages that come with typical bidentate and tetradentate ligands by introducing a new tridentate pyridinophane ligand scaffold. Bidentate bipyridine ligands are commonly used for Ni catalysis but are not very effective for stabilizing high valent Ni(III) species. Conversely, tetradentate pyridinophane ligands yield stable Ni(III) complexes, but the steric crowding of the Ni center renders the formation of Ni(I) species unfavorable. By designing tridentate ligands that could accommodate both oxidation states of Ni, they were able to study otherwise fleeting Ni species involved in the reaction.

This approach allowed the Mirica lab to successfully couple methanol to aryl bromide **26** at room temperature.[31] the reaction mechanism is believed to be analogous to that described by Xue, where the direct excitation of Ni(II) complexes facilitates the photolysis of an X-type ligand and generates the active Ni(I) catalyst. Quantum yield measurements ($\varphi < 0.26$) were not able to definitively show the prevalence of the proposed a self-sustained Ni(I/III) cycle. However, in-situ infrared measurements revealed prolonged consumption of starting material when the lamp was periodically switched off. Accordingly, it was proposed that a Ni(I/III) cycle is operative but inefficient due to competitive reactions leading to off-cycle Ni species. Indeed, NMR and EPR spectroscopic data supports the presence of an unproductive Ni(I)/Ni(III) comproportionation that hampers the catalytic cycle. Thus, once again, a constant supply of photons is needed to reactivate the off-cycle Ni(II) complexes and allow the reaction to reach higher yields.

An advantage of using photochemical systems for these transformations is that both high- and low-valent Ni can be generated in solution concurrently. The Baran lab showed an alternative method for

achieving this same goal by utilizing electrochemical means.[36] The initial report was followed by a collaboration with the Neurock and Minteer groups, where DFT calculations and spectroscopic and electrochemical methods were used to investigate the reaction mechanism and further optimize the system (Figure 4).[37] Similarly to the approaches described before, their data suggested that the reductive elimination step yielding the new C–N bond was achieved from a highly reactive Ni(III) intermediate (35). Additionally, an oxidative addition from Ni(I) complex 31 was proposed to yield intermediate 32. Cyclic voltammetry studies showed that the Ni(II/I) redox couple by was rendered irreversible in the presence of aryl bromide. This suggested that the oxidative addition into Ni(I) is fast compared to the CV timescale and unlikely to be the rate determining step.

Figure 4. Electrochemically mediated Ni(I/III) cycle


a) Electrochemically-mediated
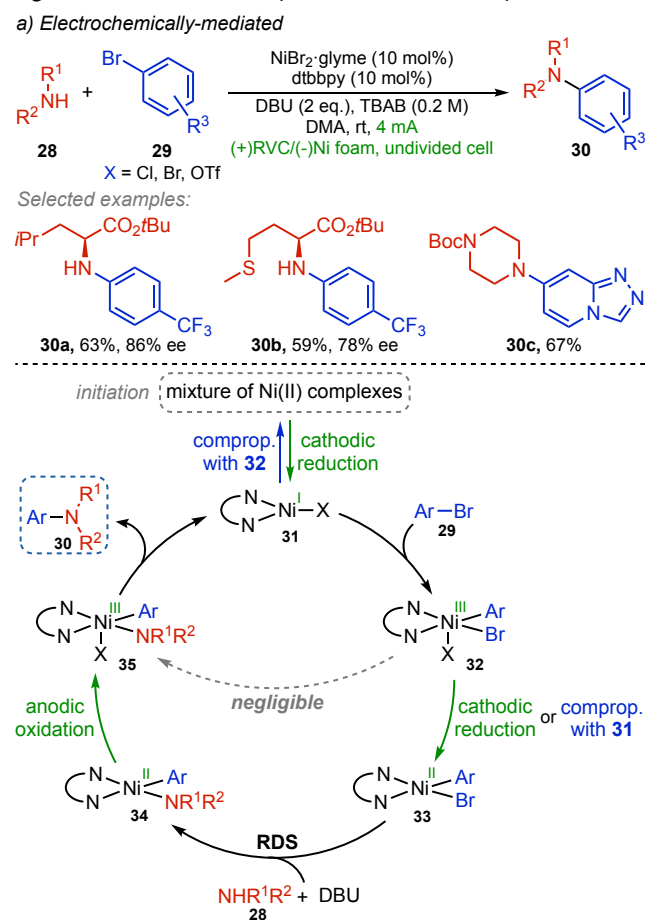
Similar to the previously described methods, comproportionation of Ni(I) and Ni(III) species to form catalytically inactive Ni(II) species poses a significant challenge. Continuous current input is required to funnel these off-cycle species back into the catalytic cycle. Low efficiency of experiments performed under catalytic amount of electricity suggest that, unlike the photochemical-mediated processes, the direct formation of 35 via ligand exchange is unlikely at this stage (32 → 35). Further studies indicate that 32 is quickly reduced at the cathode, or by comproportionation with 31, to yield stable Ni(II) complex 33. A rate-limiting ligand exchange yields aryl amido 34. This Ni(II) complex is subsequently oxidized at the anode to form a fleeting Ni(III) intermediate 35, which rapidly

undergoes reductive elimination, generating the product and restarting the catalytic cycle.

These mechanistic insights revealed that the ligand exchange was the slow step of the reaction (33 → 34). Aiming to accelerate this step, the authors utilized a polar aprotic media and added a base to their previous conditions. The new reaction conditions were shown to tolerates a broad scope of amine nucleophiles bearing protected amines (30c), ethers, thioethers (30b), and a large variety of heterocycles (30c). Notably, the reported scope includes a series of amino acids which were shown to be competent partners, albeit a moderate racemization was observed in most cases (30a, 30b). Furthermore, the scalability of the reaction was showcased in a 0.1 mol scale example.

Another approach that accesses Ni(I/III) cycles in the absence of light irradiation was developed by the Nocera group. As detailed earlier, they demonstrated that a Ni(I/III) cycle is operative in Ni-photoredox aryl etherification reactions.[24] Central to this manifold is that the photochemical steps are only necessary to recover off-cycle species generated because of deleterious side reactions (see green and blue arrows in Figure 2). To further challenge this theory, the substitution of the photocatalyst and light by a chemical reductant was tested (Figure 5).[38] The use of catalytic amounts of Zn was shown to effectively achieve C–N coupling to form aniline derivatives in good yields. Notably, this methodology was also successfully adapted to facilitate the cross coupling of aryl bromides with oxygen nucleophiles to form phenols, ethers, and esters. All of these reactions are believed to undergo a Ni(I/III) pathway, where Zn serves as a reductant to funnel inactive Ni(II) complexes (39) back into the catalytic cycle. While the rapid comproportionation of Ni(I) and Ni(III) species remains a pervasive issue with Ni(I/III) cycles, it is hypothesized that the heterogeneous nature of this reaction mitigates this unproductive pathway by ensuring low concentrations of these complexes. High yields are obtained when coupling electron-poor aryl bromides with primary and secondary amines and anilines (38a-38c), but a lower reactivity was observed when using electron-rich aryl bromides (38d).

Figure 5. Accessing Ni(I/III) cycles with stoichiometric reductants

Selected examples:
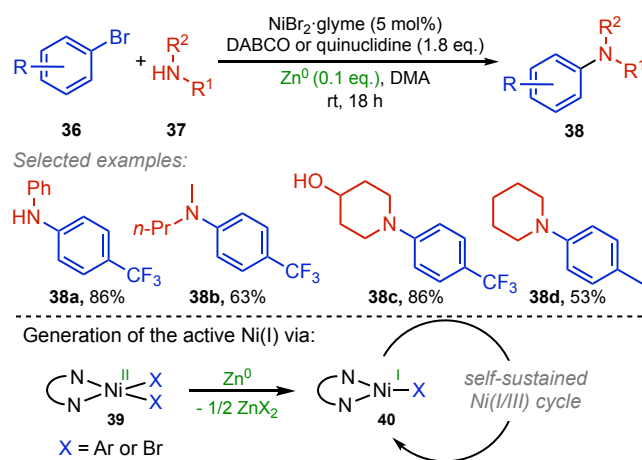
The previously discussed reactions and the vast majority of Ni-photoredox C–heteroatom couplings have employed redox-active bases like DABCO, quinuclidine, tetramethylguanidine (TMG), or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). This is not particularly
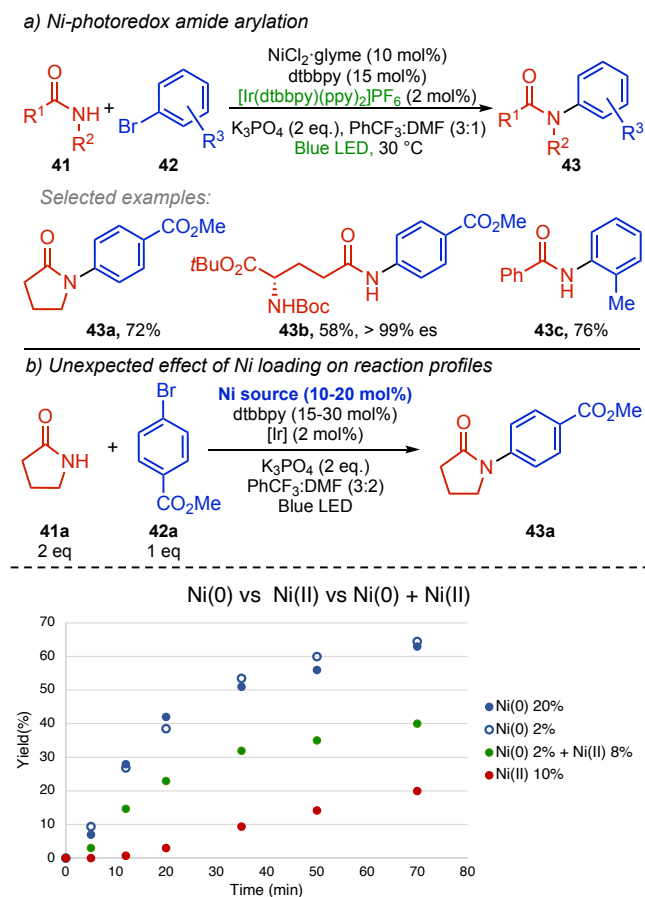
surprising given the proposed dual role of these species, which are thought to quench the acid by-products and serve as sacrificial reductants for the excited Ir photocatalyst ($12 \rightarrow 13$). While the formation of the oxidized bases did not lead to significant side reactions for the arylation of amines, these open-shell species have been shown to enable hydrogen-atom transfer (HAT) processes.[39] Indeed, our group observed that side-products derived from HAT processes become more prevalent when trying to extend this chemistry to include less nucleophilic nitrogenated substrates.[40]

In this context, our lab became interested in studying whether alternative bases that cannot undergo electron transfer are suitable for Ni-photoredox C–N couplings. We selected the arylation of amides as a case study as due to the relevance of amides in organic synthesis.[41] During the optimization campaign, the formation of side products due to competing HAT processes was observed when using conditions analogous to those commonly employed in other heteroatom functionalizations. The use of a more weakly oxidizing Ir photocatalyst, $[Ir(dtbbpy)(ppy)_2]PF_6$ instead of $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$, was found to be key to avoiding these side reactions. Additionally, inorganic redox-inactive bases like K_2CO_3 or K_3PO_4 were found to outperform the more commonly used organic redox-active bases. The optimized conditions depicted in Figure 6a enable access to a wide scope of amides and aryl bromides, which included epimerizable stereocenters and heterocycles (43b). However, this initial report did not tolerate the use of aryl chlorides as coupling partners or non-cyclic secondary amides.[40]

Intrigued by the unexpected finding of reactivity in the absence of a redox-active base, which played a central role in the previously discussed approaches, we decided to embark on an in-depth study of the reaction mechanism.[42] When using the optimized conditions, which employed a Ni(II) salt as the Ni source, the studies of the reaction profiles revealed a 10-20 minute induction period (see red points in Figure 6b). Furthermore, the induction periods were found to be longer when higher Ni(II) loadings were used. In sharp contrast, for reactions carried out with Ni(0) or Ni(I) precursors, no induction period was observed (see blue points in Figure 6b). This would be consistent with either Ni(I/III) or Ni(0/II/III) pathways, as the initial Ni(II) complex needs to be reduced to start the reaction in either case. However, the similar profiles obtained when Ni(0) and Ni(I) precursors were used was unexpected. To further study the origins of the induction period, a series of kinetics experiments were performed. These revealed that the addition of increasing amounts of Ni(II) salts to reactions carried out with either Ni(I) or Ni(0) precatalysts leads to slower rates and observable induction periods (see green points in Figure 6b). Thus, although Ni(II) precatalysts facilitated catalysis in our original report, their addition to reactions containing other Ni precatalysts was impeding product formation.

It was hypothesized that the negative impact of increasing the concentration of Ni(II) complexes on the reaction rate was related to undesired comproportionation events, and that Ni(0) was the active catalyst. If Ni(I) was the active species, one would have expected that mixtures of Ni(0) and Ni(II), which was confirmed to generate Ni(I) via comproportionation in control experiments, would outperform reactions carried out solely with Ni(0) precatalysts. Additionally, the formation of unreactive Ni(I) aggregates to explain the observed behavior was inconsistent with the saturation kinetics observed when utilizing both Ni(0) and Ni(I) precatalysts.

Figure 6. Ni-photoredox amide arylations scope and Ni(II) loading effects

a) Ni-photoredox amide arylation

Selected examples:

43a, 72%   43b, 58%, > 99% es   43c, 76%

*b) Unexpected effect of Ni loading on reaction profiles*

In light of these experiments, the catalytic cycle shown in Figure 7a was proposed. When using Ni(II) precatalysts, the reaction is proposed to begin with the reduction of these complexes into the active Ni(0) catalysts ($44 \rightarrow 45 \rightarrow 46$). The induction period and overall reaction rate were found to be dependent on the light intensity, consistent with the initial photochemically-mediated reduction events proposed. Upon the formation of active catalyst 46, there is a competition between oxidative addition into the aryl bromide (42) that would lead to 47 en route to product formation, and comproportionation with Ni(II) species 44 to give an inactive Ni(I) complex (45). This side reactivity accounts for the negative effects that higher loading of Ni(II) precatalysts have on the reaction rate. When the ratio of Ni(0) to Ni(II) is sufficiently high for oxidative addition to outcompete comproportionation, the desired reactivity begins. After oxidative addition into the aryl bromide (42), a ligand exchange leads to the formation of aryl amido complex 48. The formation of this intermediate during the reaction was confirmed by ^{19}F NMR spectroscopy.

At this stage it was proposed that a photoinduced oxidation of 48 takes place to facilitate reductive elimination and product formation. This hypothesis was tested by subjecting independently prepared Ni aryl amido complexes to both the reaction conditions and chemical oxidants. Product formation was observed in both cases. In contrast, when heating or irradiating the Ni aryl amido complexes, no product formation was observed. Resultingly, an oxidatively-induced reductive elimination to render product was proposed. Subsequent reduction of Ni(I) complex 50 was proposed to allow both catalytic cycles

to resume. Finally, kinetic measurements showed that the reaction presented saturation kinetics with respect to every reaction component but light, suggesting that a photochemical step was rate limiting ($48 \rightarrow 49$).

Figure 7. A Ni(0/II/III) cycle facilitates Ni-photoredox amide arylations

a) Ni-photoredox amide arylation via a Ni(0/II/III) cycle
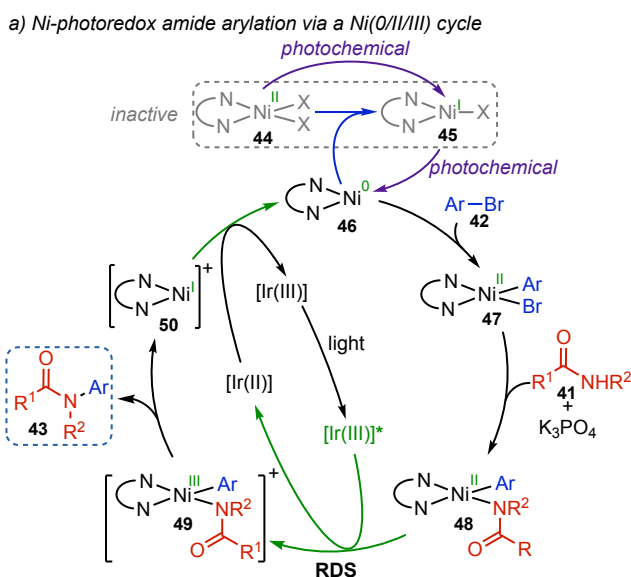
b) Further reaction optimization based on mechanistic insights
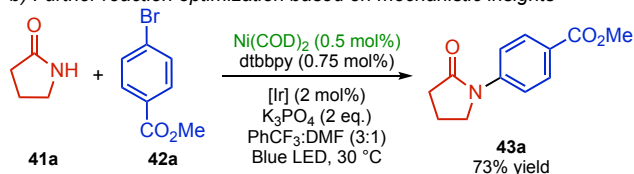
With this information in hand, a new round of optimization studies was conducted. Aiming to avoid the induction periods and reduce the side reactivity related to comproportionation events, the use of Ni(COD)$_2$ as the precatalyst was tested. The use of this alternative Ni catalyst precursor allowed us to greatly reduce the catalyst loading from 10% to 0.5% (Figure 7b) and enabled the use of aryl chlorides with a small loss in the product yield (from 72% to 58% yield).[42]

LIGAND DESIGN TO ENABLE C–N COUPLINGS VIA A NI(0/II) MECHANISM

The previously discussed approaches were all designed around the formation of Ni(III) aryl amido intermediates that are known to quickly undergo reductive elimination at room temperature. However, due to the instability of this high-valent Ni species, and its most common precursor Ni(I) complex, all of these transformations present Ni(II) resting states which are often off-cycle. Resultingly, a continuous external stimulus that activates these stable Ni(II) complexes is required. As shown before, such a stimulus can be an oxidation or reduction event that may be triggered by a photochemical, electrochemical, or chemical process.

A common limitation of these protocols is the high Ni catalyst loadings required, likely related to the undesired competing processes of comproportionation and disproportionation. Furthermore, the widespread adoption of photochemical approaches is also hampered by the difficulties related to their scale up. The percentage of irradiating light that is able to penetrate the solution in a reaction vessel is

small, especially when utilizing blue or purple light.[15] Consequently, the surface to volume ratio of the vessels used greatly influences the reaction efficiency. This does not present a problem for academic scale reactions, but when increasing the reaction scale to industrially relevant quantities the surface to volume ratio is greatly diminished, which leads to extended reaction times and/or lower yields. To overcome these problems, specialized flow reactors are often required for industrial scales.[14]

Approaches that invoke Ni(0/II) cycles largely overcome the challenges associated with the side reactions of comproportionation and disproportionation by avoiding the required formation of Ni(I) or Ni(III) intermediates, and often allow for lower Ni loadings. This section will include key mechanistic findings and highlight breakthroughs in this area, but for a more comprehensive review of Ni(0/II) strategies to forge C–N please refer to Nicasio's review.[8]

Scheme 4. Aniline arylation reactions via Ni(0/II) cycles

a) Seminal report of Ni-catalyzed C-N coupling

Selected examples:
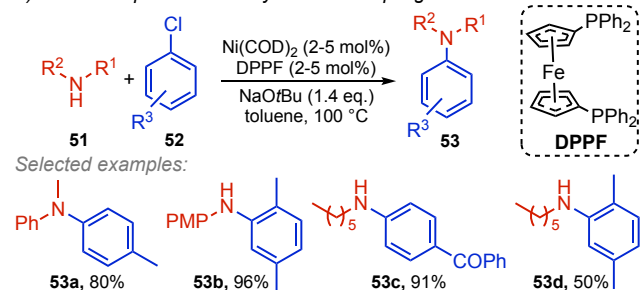
b) Wider functional group compatibility


Selected examples:
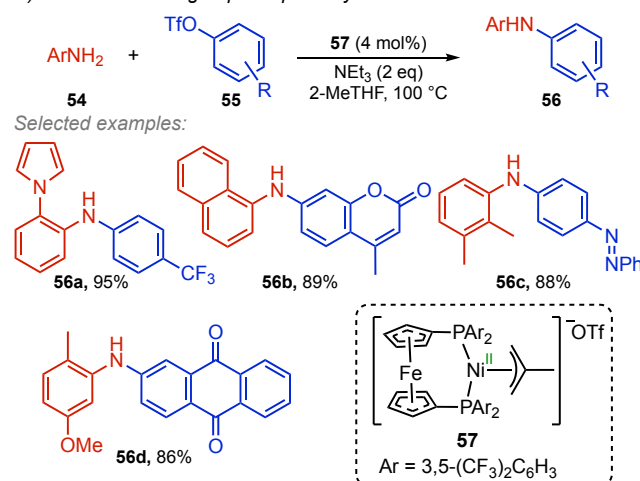
The first detailed study of the use of Ni-catalysis to afford C–N coupling dates back to 1997, when the Buchwald group demonstrated the coupling of aryl chlorides and a series of anilines (**53a**, **53b**) and alkyl amines (**53c**, **53d** in Scheme 4a).[10] Early reports employed bisphosphine, *N*-heterocyclic carbene, and bipyridine ligands, and required high temperatures.[8, 10, 16] In contrast to most Ni(I/III) approaches, which are limited to the use of aryl bromides, aryl chlorides a pseudohalides are suitable coupling partners for the Ni(0/II) approach. Furthermore, the Buchwald lab recently demonstrated that, in spite of the high temperatures required for most of these reactions, a large reaction scope can be **The main limitation associated with these methodologies is the difficult scale-up of light- or electrochemically-mediated processes which often require specialized** achieved when using the electron poor Ni complex **57** as precatalyst

and triethyl amine as a base (Scheme 4b).[43] The scope reported by the Buchwald lab included a pyrrole (**56a**), an α,β-unsaturated ester (**56b**), a diazo compound (**56c**), and a quinone(**56d**) with most products obtained with excellent yields. While the reaction scope includes a large variety of functional groups that are not tolerated under most reaction conditions, it should be noted that this paper is limited to the use of anilines.

The most pervasive limitation of the initial publications was observed when coupling primary alkyl amines, which required the use of activated aryl chlorides (**53c**, **53d**). The use of unactivated aryl chlorides often rendered undesired biaryl species.[44] Independently, the Hartwig[44-45] and Stradiotto[17] labs devised different strategies to overcome these limitations and enable the couplings at lower temperatures.

**Figure 8. Use of unactivated amines and lower temperatures**
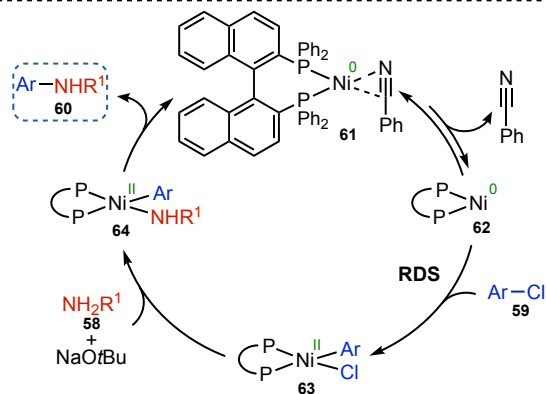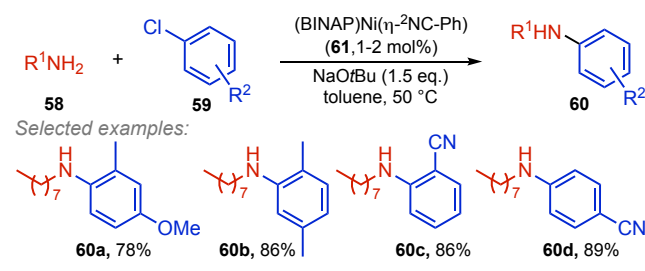
The Hartwig group demonstrated that the use of a Ni(BINAP) complex bearing a benzonitrile group avoided the formation of the undesired biaryl products and afforded the coupling of a range of primary amines (Figure 8).[44] The in-depth mechanistic studies detailed in this paper first demonstrated the presence of a Ni(0/II) cycle and identified a series of catalyst decomposition pathways. Notably, the formation of a Ni(I) species was detected, but the control experiments were able to discard any Ni(I)-mediated active cycle. As shown in Figure 8, the reaction is initiated by the dissociation of the nitrile from Ni(0) complex **61**. Subsequently, oxidative addition into the aryl chloride (**59**) takes place (**62 →63**). This step was shown to be turnover-limiting for this reaction, and **61** is the catalyst resting state. This is not universal for Ni(0/II)-mediated C–N couplings, as the reductive elimination has been shown to be rate-limiting in other cases.[8] A follow-up study, also by the Hartwig lab, of an analogous Ni-bisphosphine catalyzed C–N coupling reaction utilizing a radical clock demonstrated that the oxidative addition does not involve the formation of radical intermediates.[45] Subsequently, a base-mediated ligand exchange renders Ni(II) aryl amido **64**, which undergoes reductive elimination to yield product. It is hypothesized that in these cases, the oxidation of Ni(II) complex **64** to trigger the

reductive elimination can be avoided due to the synergistic effect of the different ligand environment and the higher temperatures.

The reductive elimination step from Ni(II) complexes in the absence of oxidants has been studied by both the Nicasio and Sandford groups in the context of indole arylation reactions (Scheme 5a and b, respectively).[46] Independently, these groups isolated Ni aryl indole complexes bearing either an NHC (**65**) or a biphenyl ligand (**67**) and demonstrated that C–N reductive elimination could be promoted by heating.

Scheme 5. Stoichiometric experiments of C–N reductive elimination in Ni(II) complexes
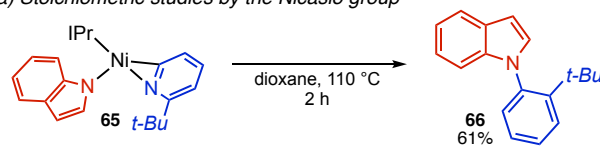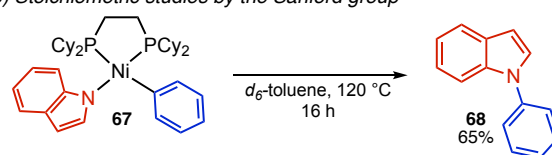
As previously mentioned, the Stradiotto group has played a key role in advancing this chemistry by designing a novel ligand scaffold that enables a wide range of C–N couplings (Scheme 6).[17] Using this catalyst system, they were able to achieve unprecedented coupling of ammonia and various primary alkyl amines with (hetero)aryl (pseudo)halides at room temperature. Also, this was the first example of ammonia mono-arylation with (hetero)aryl mesylate electrophiles (**71a**).[17a] Since their initial report describing the use of this new ligand scaffold, the Stradiotto group has been able to further expand the reaction scope to include other challenging substrates like bulky primary amines (**71b**),[17e] amides and lactams (**71c**),[17d] indoles,[17c] and protected amino acids (**71d**)[17g] thus establishing the generality of their ligand design for mediating this reactivity. From a mechanistic perspective, this ligand is also proposed to favor a Ni(0/II) catalytic cycle analogous to that depicted in Figure 8.

Scheme 6. Novel ligand scaffold affords general C-N coupling method
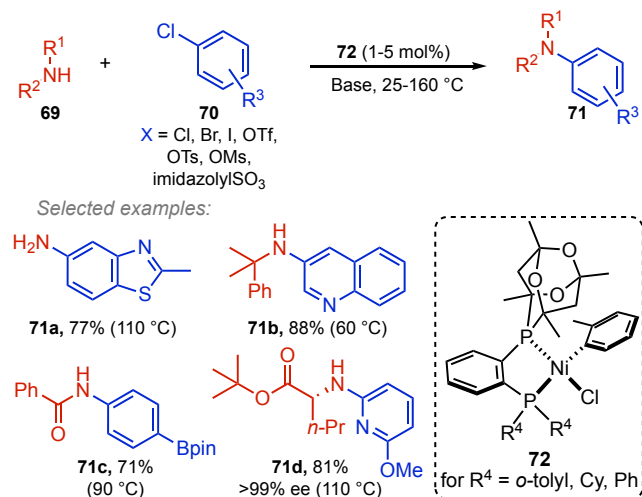
Key to the success of these protocols has been the identification of a ligand scaffold tailored for the unique characteristics of Ni; in particular, its smaller atomic radius and lower electronegativity when compared to Pd. This approach contrasts with most prior efforts that instead use ligands that were originally designed for Pd-catalyzed cross-couplings. Since oxidative addition of aryl chlorides is more facile with Ni(0) than Pd(0), the electronics of the ligand can be tuned to favor the slow reductive elimination step without compromising the oxidative addition. In line with this hypothesis, the *ortho*-phenylene bisphosphine ligand (Pad-DalPhos) developed is sterically demanding and relatively electron-poor compared to ligands traditionally used for Pd catalysis. These are both features a that are expected to accelerate reductive elimination steps while hampering the oxidative addition.[47] Additionally, the Pad-DalPhos ligand and the (PAd-DalPhos)(*o*-tolyl)NiCl complexes (**72**) are also air-stable, highlighting another advantage of this approach.

OUTLOOK

While different approaches have been devised to afford Ni-catalyzed C–N coupling reactions, each strategy still presents inherent limitations and drawbacks. The methodologies relying on two-electron manifolds to afford Ni(0/II) cycles represent a more mature field. A primary advantage of this strategy is its ability to minimize the occurrence of side reactions, which are more common when Ni(I) and Ni(III) intermediates are directly involved and when Ni loadings are higher.

The most significant contributions have been made by the Stadiotto group, which has designed a ligand system to exploit the unique characteristics of Ni. This ligand has been shown to enable the coupling of nucleophilic nitrogenated compounds at ambient temperatures. However, when more challenging substrates are employed, higher temperatures and strong bases are required to accelerate the rate-limiting C–N reductive elimination. This limitation is intrinsic to these approaches due to the challenging nature of C–N couplings involving Ni(II).

The alternative approach to those protocols has been constructed around accessing Ni(III) intermediates that are more prone to undergo fast reductive elimination. Resultingly, these reactions form product at lower temperatures and do not require the use of strong bases.

However, there are also significant limitations currently hindering further developments in this field. To enable direct access to Ni(III) species, a Ni(I/III) cycle must be established. This scenario requires Ni(I) and Ni(III) complexes to coexist in the reaction flask. However, the current ligand systems are often unable to prevent undesired comproportionation reactions among these species, leading to the formation of Ni(II) resting states that are often off-cycle. To overcome this inherent problem, continuous irradiation, electricity, or high loadings of reducing agents are required. As a result, most reactions are limited by either light or current, and the intensity of irradiation or effective current influences the overall reaction rate.

In light-mediated reactions, typical flasks present a low surface to volume ratio. Furthermore, when using larger flasks, the increase in volume and surface area are not proportional, and thus the effective light penetration is reduced.[14-15] As a result, specialized reactors are often required to increase the efficiency of the light irradiation when increasing the reaction scale. For electrochemically driven transformations, the reactivity is limited to the species in contact with the electrode surface, so similar problems are often observed.

Within this landscape, we anticipate that the next breakthrough will be driven by either a chemical engineering team that improves the current large-scale reactors or a chemistry-driven approach that introduces a new ligand class. Historically, innovative ligand designs have been the center of major advancements in transition metal catalysis. Quintessential examples of such revolutionary discoveries include the development of Noyori's catalyst[48] or Buchwald's biaryl phosphine ligands.[7d, 49] For Ni C–N couplings, this could involve the development of a new scaffold that reduces the barriers for reductive elimination from Ni(II) complexes, or the creation of a new ligand class that enables longer-lived Ni(I/III) cycles. The latter design must still promote fast reductive eliminations while removing the need for continuous stimuli and precious metal co-catalysts. Either of these breakthroughs would significantly impact the synthetic chemistry community and have the potential to make these transformations even more suitable for large-scale industrial applications. We hope that the mechanistic insights compiled and reflected upon in this perspective will help spur the development of this new generation of Ni catalysts for C–N coupling reactions.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article.

Supporting Information

The supporting information is available free of charge on…

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Author Contributions

The manuscript was written through contributions of all authors.

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