

Switching on elusive organometallic mechanisms with photoredox catalysis

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Transition-metal-catalysed cross-coupling reactions have become one of the most used carbon–carbon and carbon–heteroatom bond-forming reactions in chemical synthesis. Recently, nickel catalysis has been shown to participate in a wide variety of C–C bond-forming reactions, most notably Negishi, Suzuki–Miyaura, Stille, Kumada and Hiyama couplings^{1,2}. Despite the tremendous advances in C–C fragment couplings, the ability to forge C–O bonds in a general fashion via nickel catalysis has been largely unsuccessful. The challenge for nickel-mediated alcohol couplings has been the mechanistic requirement for the critical C–O bond-forming step (formally known as the reductive elimination step) to occur via a Ni(III) alkoxide intermediate. Here we demonstrate that visible-light-excited photoredox catalysts can modulate the preferred oxidation states of nickel alkoxides in an operative catalytic cycle, thereby providing transient access to Ni(III) species that readily participate in reductive elimination. Using this synergistic merger of photoredox and nickel catalysis, we have developed a highly efficient and general carbon–oxygen coupling reaction using abundant alcohols and aryl bromides. More notably, we have developed a general strategy to ‘switch on’ important yet elusive organometallic mechanisms via oxidation state modulations using only weak light and single-electron-transfer catalysts.

Visible-light-mediated photoredox catalysis has gained momentum over the past decade as a platform for the development of novel synthetic transformations via the implementation of non-traditional open-shell mechanisms. This catalysis field employs transition metal polypyridyl complexes or organic dyes that, upon excitation by visible light, readily engage in an array of single-electron transfer (SET) processes^{3–5} that often include oxidation, reduction or redox pathways that have previously been elusive^{6–9}. Indeed, several research groups have demonstrated that photoredox catalysis can be combined with transition metal catalysis to achieve a series of unique bond-forming reactions that take advantage of the known reactivity of each individual mode of catalysis^{10–16}. We recently questioned whether the combination of photoredox catalysis and transition metal catalysis might be capable of delivering fundamentally new organometallic reactivity by providing access to currently unknown or inaccessible mechanistic pathways.

In a series of seminal studies, Hillhouse and colleagues demonstrated that Ni(II) alkoxide complexes do not readily undergo reductive elimination at ambient or elevated temperature and that stoichiometric conversion to a less stable Ni(III) system is required for productive C–O bond formation^{17–19}. Similarly, C–heteroatom reductive elimination has been demonstrated when stoichiometrically accessing Ni(IV) intermediates^{20,21}. In fact, computational studies have revealed that Ni(II) alkoxide reductive elimination is endothermic, in contrast to Pd, Pt or alkyl Ni(II) variants, which are exothermic (Fig. 1)²². Indeed, the use of palladium and copper catalysis to generate aryl ethers from alcohols is well preceded and broadly employed^{23–25}. The utilization of nickel catalysis in C–O bond construction would be an important complementary method, considering the diversity of electrophiles amenable to nickel cross-couplings, such as alkyl halides

and aryl pseudohalides^{1,2}. Hartwig and colleagues have reported a Ni(COD)₂-catalysed aryl etherification at elevated temperature using three preformed oxides, namely sodium methoxide, ethoxide and *tert*-butyldimethylsiloxide with electron-deficient aryl bromides²⁶. However, a general nickel-catalysed C–O coupling strategy under mild conditions has thus far been elusive and no examples with alcohols have been documented. We recently questioned whether photoredox catalysis might be used to modulate the range of nickel alkoxide oxidation states that can be accessed during a conventional catalytic cycle. More specifically, we recognized that it should be possible to utilize the photonic energy of weak visible light to expand thermodynamically the number of nickel-catalyst oxidation states via two discrete photocatalyst SET events: first, oxidation of Ni(II) to the elusive Ni(III)–alkoxide complex (which we assumed would facilitate the critical C–O bond-forming step); and second, reduction of Ni(III) to Ni(II), to enable the subsequent aryl bromide oxidative addition steps. If successful, we recognized that this new synergistic catalysis pathway might provide (1) the first general example of a nickel-catalysed C–O coupling reaction employing simple alcohols and aryl halides, and

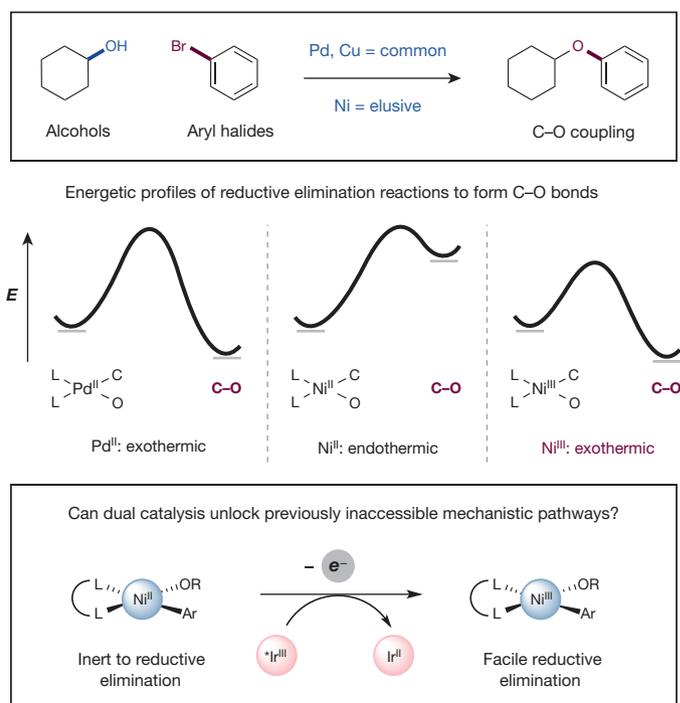


Figure 1 | Modulating oxidation states of nickel enables challenging carbon–heteroatom coupling. Pd(II)-catalysed C–O reductive elimination is an exothermic process and well preceded. Ni(II) C–O reductive elimination is thermodynamically disfavoured—we postulated that accessing Ni(III) by photoredox-mediated oxidation state manipulation could switch on C–O coupling in a general fashion, circumventing this thermodynamic restriction.

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(2) a demonstration of a new strategy by which elusive organometallic couplings can be ‘switched on’ via oxidation state modulation.

A detailed description of our proposed mechanistic cycle for the photoredox/nickel-catalysed C–O coupling is outlined in Fig. 2a. Oxidative addition of Ni(0) (species **1**) into an aryl bromide would deliver a Ni(II) aryl complex **2** (ref. 27). At this stage, ligand exchange (displacement of the bromide ion with the substrate alcohol) would produce the Ni(II) aryl alkoxide (**3**)—an organometallic species that traditionally represents a catalytic ‘dead end’. At the same time, visible light irradiation of heteroleptic iridium(III) photocatalyst Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ [dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine] (**4**) would produce the long-lived photoexcited *Ir^{III} state **5** (excited-state lifetime $\tau = 2.3 \mu\text{s}$) (ref. 28). At this juncture, we hypothesized that the nickel and photoredox cycles would merge via SET between the

Ni(II) complex **3** and the highly oxidizing photoexcited *Ir(III) **5** to generate the critical Ni(III) aryl alkoxide **6** and the reduced Ir(II) photocatalyst **7**. On the basis of the established redox potentials of these catalytic intermediates, we envisioned this key electron transfer step to be kinetically and thermodynamically favourable under standard reaction conditions (half-reaction reduction potential $E_{1/2}^{\text{red}}[*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.21 \text{ V}$ versus the saturated calomel electrode (SCE) in CH₃CN, $E_{1/2}^{\text{red}}[\text{Ni}^{\text{III}}/\text{Ni}^{\text{II}}] = +0.71 \text{ V}$ versus Ag/AgCl in CH₂Cl₂ for (bpy)Ni^{II}(Mes)OMe)^{28,29}. Once formed, we assumed the transient Ni(III) complex **6** would rapidly undergo reductive elimination to forge the desired C–O bond, while delivering the aryl ether product and Ni(I) complex **8**. At this stage, we envisioned both catalytic cycles merging for a second time, enabling the single-electron reduction of Ni(I) to Ni(0) by Ir(II) species **7** ($E_{1/2}^{\text{red}}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37 \text{ V}$ versus SCE in CH₃CN), thereby completing the nickel and photoredox catalytic cycles at the same moment²⁸.

On the basis of this synergistic catalysis design plan, we began our investigations into the proposed nickel-catalysed aryl–alcohol etherification using 1-hexanol and 4-bromoacetophenone. As expected, the use of traditional nickel cross-coupling conditions (that is, without photoredox), led to no observable product despite the implementation of a range of Ni(II) and Ni(0) complexes (Fig. 2b, equation (1)). By contrast, we found that the desired C–O bond could be forged in excellent yield (86%) at room temperature via the introduction of the photocatalyst Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ in the presence of Ni(COD)₂, dtbbpy, quinuclidine, K₂CO₃ and blue light-emitting diodes (LEDs) as the visible light source. Given the inherent advantages of employing a bench-stable Ni(II) catalyst in lieu of Ni(COD)₂, we hypothesized that a catalytically active Ni(0) species **1** might be accessible *in situ* via two SET reductions of (dtbbpy)Ni(II)Cl₂ using the iridium photocatalyst ($E_{1/2}^{\text{red}}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37 \text{ V}$ versus SCE in CH₃CN, $E_{1/2}^{\text{red}}[\text{Ni}^{\text{II}}/\text{Ni}^{\text{0}}] = -1.2 \text{ V}$ versus SCE in *N,N*-dimethylformamide (DMF))^{28,30}. In this vein, we hypothesized that quinuclidine may also serve as a sacrificial reductant and were pleased to observe that with NiCl₂(dtbbpy) the desired fragment etherification was accomplished in 91% yield (Fig. 2b, equation (2)).

With the optimal conditions in hand, we next sought to explore the scope of the aryl bromide component in this new nickel-catalysed C–O coupling reaction. As shown in Fig. 3, a diverse array of electron-deficient bromoarenes with a variety of functional groups (ketones, trifluoromethyls, nitriles, sulfones, esters) perform well using this synergistic protocol (compounds **9–14**, 88–96% yield). Moreover, 3-bromoanisole was found to be a competent substrate in this transformation, demonstrating the diversity of substituents that can be tolerated (**26**, 80% yield). Notably, bicyclic aromatics such as phthalimides and phthalides couple with high levels of efficiency (**15** and **16**, 92% and 80% yield, respectively). With respect to heteroaromatic coupling partners, we have found that a range of pyridines with substitution at the 2 and 3 positions (nitrile, trifluoromethyl, methyl) are effective electrophiles in this protocol (**17–20**, 67–91% yield). Furthermore, quinolines, azaindoles and pyrimidines can be employed without loss in efficiency (**21–23**, 60–88% yield). Perhaps most importantly, this transformation is not limited to electron-deficient aryl bromides. For example, phenyl and *tert*-butylphenyl can be readily incorporated in this nickel etherification (**24** and **25**, 68% and 77% yield, respectively). It should be noted that comparable yields of aryl ether product **13** were achieved when either coupling partner was employed in excess (1.5 equiv.) (see Supplementary Information).

We next turned our attention to the alcohol reaction component. As shown in Fig. 3, we discovered that a host of primary alcohols were effective coupling partners, including substrates that incorporate benzyl, *tert*-butyl, cyclopropyl and alkene functionalities (**27–30**, 77–89% yield). Moreover, carbamates and ester groups are tolerated, as exemplified by the etherification of a serine derivative in 78% yield (**31**). Interestingly, trifluoroethanol couples proficiently in this reaction despite its diminished nucleophilicity (**32**, 77% yield). Both

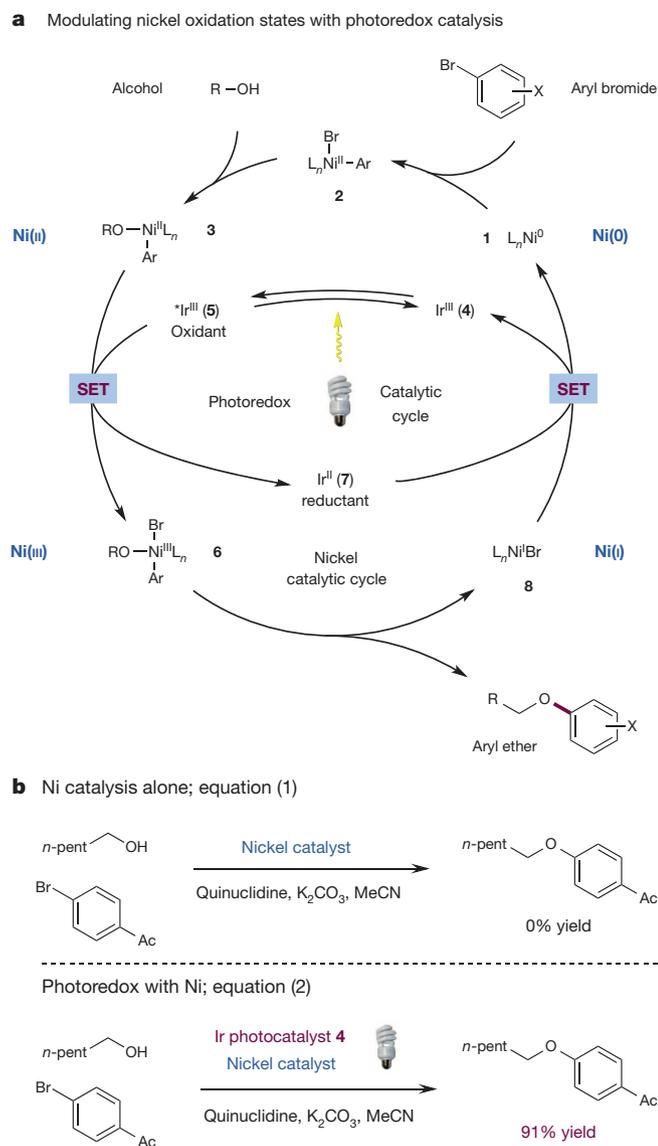


Figure 2 | Proposed mechanism by which photoredox catalysis switches on challenging nickel-catalysed C–O coupling. **a**, The catalytic cycle begins with oxidative addition of Ni(0) (species **1**) into an aryl bromide to give Ni(II) aryl **2**. Ligand exchange with an alcohol under basic conditions produces Ni(II) aryl alkoxide **3**. Excitation of photocatalyst **4** gives the excited state **5**, which can then oxidize **3** to the key Ni(III) intermediate **6** and generate Ir(II) **7**. Ni(III) **6** readily reductively eliminates to form the aryl ether product and Ni(I) **8**. A second SET event closes the two catalytic cycles, regenerating Ni(0) **1** and Ir(III) **4**. **b**, Nickel-catalysed C–O reductive elimination can be turned on by addition of a photoredox catalyst and visible light.

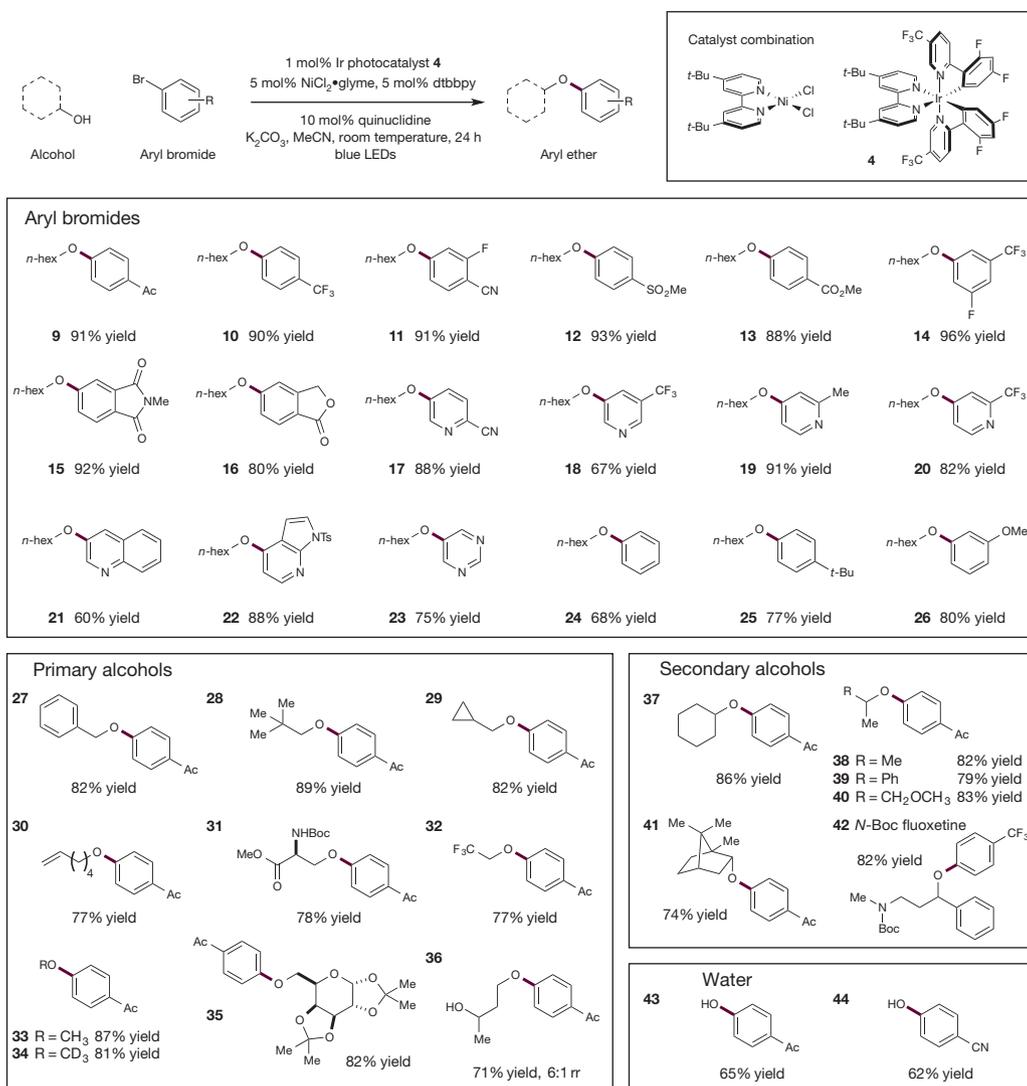


Figure 3 | Alcohol and aryl halide scope in the photoredox-nickel-catalysed C–O coupling reaction. A broad range of aryl bromides and alcohols are efficiently coupled to produce aryl ethers under the standard reaction conditions (top, generalized reaction). The aryl bromide scope includes electron-deficient and electron-neutral arenes and heteroarenes with diverse

functionalities. Both primary and secondary alcohols are proficient coupling partners under the standard conditions. Water can be employed as the nucleophile to generate phenol derivatives in a single step. Isolated yields are indicated below each entry. See Supplementary Information for experimental details.

methanol and *d*₄-methanol are effective substrates, providing a valuable strategy for installing H₃CO– and D₃CO– groups on arenes (**33** and **34**, 87% and 81% yield, respectively).

Relatively complex substrates are also tolerated in this transformation, as demonstrated by the etherification of a protected pyranose in excellent yield (**35**, 82% yield). Notably, secondary alcohols are equally effective in this etherification protocol—alkyl, benzyl and protected ether functionalities all being amenable to this technology (**37–40**, 79–86% yield). Moreover, secondary alcohols possessing β-quaternary carbons could be employed with good levels of efficiency (**41**, 74% yield). In the case of a substrate possessing both a primary and secondary alcohol, the less hindered site is arylated predominantly, as demonstrated by product **36** (71% yield, 6:1 regiomer ratio (rr)). This nickel-catalysed process can be applied to the expedient synthesis of medicinally relevant molecules, such as the antidepressant fluoxetine (Prozac), in three chemical steps (**42**, 82% yield for coupling step). It is important to note that using H₂O as the nucleophile delivers the corresponding phenol product in a single step from commercially available materials (**43** and **44**, 65% and 62% yield, respectively).

On the basis of our proposed design plan (Fig. 2a), we initiated mechanistic studies to determine if the critical Ni(III) oxidation state

was indeed operative in this new photoredox protocol. As shown in Fig. 4a, we preformed the stable Ni(II)(aryl)(alkoxide) complex **45** to examine whether C–O reductive elimination might be achieved under various photoredox or non-photoredox conditions. Importantly, in the absence of either light or photocatalyst, none of the desired aryl ether product **46** was observed. However, when complex **45** was exposed to Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (**4**) and a visible light source, the desired ether product **46** was formed in 59% yield. We attribute this result to the formation of a transient Ni(III) complex **47** via the single-electron reduction of *Ir^{III}, thereby enabling the favourable Ni(III) C–O reductive elimination, a result that is consistent with the seminal studies of Hillhouse. Furthermore, cyclic voltammetry of complex **45** showed an irreversible oxidation at +0.83 V versus SCE in CH₃CN (Fig. 4b), which we attribute to the oxidation of Ni(II) to Ni(III) (**45** to **47**). As such, we expect the oxidation of Ni(II) aryl alkoxides such as **3** to be readily accomplished by *Ir^{III} photocatalyst **5** (*E*_{1/2}^{red} [*Ir^{III}/Ir^I] = +1.21 V versus SCE)²⁸. Finally, Stern–Volmer fluorescence quenching experiments have demonstrated that the emission intensity of *Ir^{III} **5** is diminished in the presence of Ni(II) complex **45**, presumably signifying an oxidation event to form Ni(III) **47** (see Supplementary Fig. 7).

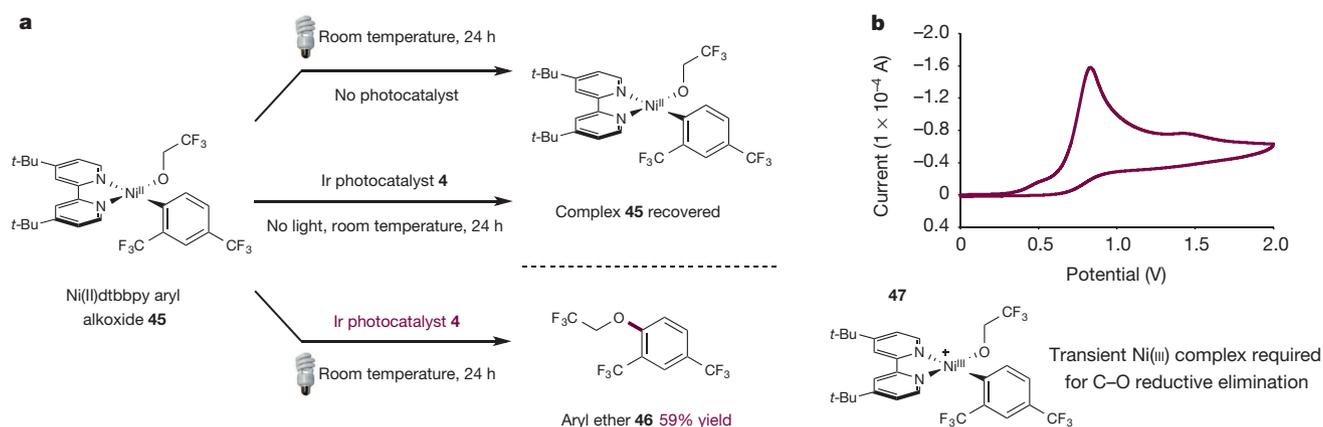


Figure 4 | Mechanistic studies support the intermediacy of transient Ni(III) complex to enable C–O reductive elimination. **a**, Reductive elimination to form C–O bond only occurs in the presence of photocatalyst and light. Reactions performed on 5.55 μmol scale with 41 mol% photocatalyst **1** and blue

LEDs. See Supplementary Information for experimental details. **b**, Cyclic voltammogram of **45** shows $\text{Ni}^{\text{III}}/\text{Ni}^{\text{II}}$ couple at +0.83 V versus SCE in CH_3CN with 0.1 M tetrabutylammonium hexafluorophosphate as the supporting electrolyte at 100 mV s^{-1} .

A further series of experiments were performed using $\text{Ni}(\text{COD})_2$ as the nickel catalyst in lieu of NiCl_2 (see Supplementary Fig. 1). In the presence of this $\text{Ni}(0)$ catalyst, the reaction proceeds with yields that are comparable to the $\text{Ni}(\text{II})$ precatalyst; however, when the iridium photocatalyst is omitted, the desired C–O coupling is not observed. This result suggests again that reductive elimination does not occur from the $\text{Ni}(\text{II})$ oxidation state as a single-electron oxidation to $\text{Ni}(\text{III})$ is required to enable product formation. Interestingly, when quinuclidine is omitted, the reaction efficiency is greatly diminished (8% yield over 24 h). This effect can possibly be attributed to the amine functioning as an electron shuttle, facilitating reduction of $\text{Ni}(\text{I})$ and oxidation of $\text{Ni}(\text{II})$; however, mechanistic studies are currently ongoing to elucidate the role of quinuclidine in more detail.

We have developed a catalytic strategy for accessing transient $\text{Ni}(\text{III})$ complexes through the use of visible-light-mediated photoredox catalysis for application in various challenging C–O cross-couplings. This method of modulating transition metal oxidation states has enabled a previously elusive transformation within the realm of nickel catalysis. We anticipate that this new mechanistic paradigm will find application in using nickel and other transition metals in a series of challenging bond constructions.

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Supplementary Information is available in the online version of the paper.

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