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 couplings1,2. 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 that often include oxidation, reduction or redox pathways that have previously been elusive3–5. 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 catalysis3–5. 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 formation6–8. Similarly, C–heteroatom reductive elimination has been demonstrated when stoichiometrically accessing Ni(IV) intermediates9–11. 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)9. Indeed, the use of palladium and copper catalysts to generate aryl ethers from alcohols is well preceded and broadly employed12–15. 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 pseudohalides16,17. 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-butylmethyloxide with electron-deficient aryl bromides18. 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 thermodynamically increase 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 formation of the critical C–O bond-forming step); and second, reduction of Ni(II) to Ni(0), 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) (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[CF(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 $\tau = 2.3 \mu s$) (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 stan-
donard reaction conditions (half-reaction reduction potential $E_{1/2}^{\text{red}}$
\[\text{Ir(III)/Ir(II)} = +1.21 \text{ V versus the saturated calomel electrode (SCE)}
\]
in CH3CN, $E_{1/2}^{\text{red}}[\text{Ni(III)/Ni(II)}] = +0.71 \text{ V versus Ag/AgCl in CH2Cl2}
for (bpy)Ni(III)Mes(OMe)2$). Once formed, we assumed the transient
Ni(iii) complex 6 would rapidly undergo reductive elimination to
forsure 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(ii) to Ni(0) by Ir(II) species 7 ($E_{1/2}^{\text{red}}[\text{Ir(III)/Ir(II)}] = -1.37 \text{ V versus}
SCE in CH3CN), thereby completing the nickel and photoredox
catalytic cycles at the same moment.

On the basis of this synergistic catalysis design plan, we began our
investigations into the proposed nickel-catalysed aryl–alcohol ether-
fication 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[CF(CF3)ppy]2(dtbbpy)PF6 in the presence of
(NiCOD)2, dtbbpy, quinuclidine, KC7O3 and blue light-emitting
diodes (LEDs) as the visible light source. Given the inherent advan-
tages 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 ($E_{1/2}^{\text{red}}$ [Ir(III)/Ir(II)] = -1.37 V versus SCE in
CH3CN, $E_{1/2}^{\text{red}}[\text{Ni(III)/Ni(II)}] = -1.2 V versus SCE in N,N-dimethylfor-
mandamide (DMF)). 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 trans-
formation, demonstrating the diversity of substituents that can be
tolerated (26, 80% yield). Notably, Gyclic 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 sub-
stitution at the 2 and 3 positions (nitro, 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 im-
portantly, 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 nucleophlicity (32, 77% yield). Both

![Figure 2](image-url)
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 C–O coupling reaction.

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.

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 equally effective in this etherification protocol—alkyl, benzyl and primary and secondary alcohols, the less hindered site is arylated predominantly, as demonstrated by product (71% yield, 6:1 regiomeric 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.

methanol and d₆-methanol are effective substrates, providing a valuable strategy for installing H₃CO– and D₆CO– groups on arenes. 

Relatively complex substrates are also tolerated in this transformation, as demonstrated by the etherification of a protected pyranose in excellent yield (35, 74% yield). Notably, secondary alcohols are equally effective in this etherification protocol—alkyl, benzyl and protected ether product was formed in 59% yield. We attribute this result to the formation of a transient Ni(III) complex via the single-electron reduction of *IrIII, 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 CH₂CN (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 *IrIII photocatalyst 5 (E½(red[*IrIII/ Ir²⁺] = +1.21 V versus SCE)). Finally, Stern–Volmer fluorescence quenching experiments have demonstrated that the emission intensity of *IrIII 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).
A further series of experiments were performed using Ni(COD)$_2$ as the nickel catalyst in lieu of NiC$_2$L$_2$ (see Supplementary Fig. 1). In the presence of this Ni(0) catalyst, the reaction proceeds with yields that are comparable to the Ni(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 Ni(II) oxidation state as a single-electron oxidation to Ni(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 Ni(II) and oxidation of Ni(III); however, mechanistic studies are currently ongoing to elucidate the role of quinuclidine in more detail.

We have developed a catalytic strategy for accessing transient Ni(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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1. Tasker, S. Z., Standley, E. A. & Jamison, T. F. Recent advances in homogeneous nickel catalysis. Nature 509, 299–309 (2014).

2. Netherton, M. R. & Fu, G. C. Nickel-catalyzed cross-couplings of unactivated alkyl halides and pseudohalides with organometallic compounds. Adv. Synth. Catal. 346, 1525–1532 (2004).

3. Narayanam, J. M. R. & Stephenson, C. R. J. Visible light photoredox catalysis: applications in organic synthesis. Chem. Soc. Rev. 40, 102–113 (2011).

4. Prier, C. K., Rankic, D. A. & MacMillan, D. W. C. Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. Chem. Rev. 113, 5322–5363 (2013).

5. Schultz, D. M. & Yoon, T. P. Solar synthesis; prospects in visible light photocatalysis. Science 343, 1239176 (2014).

6. Nicewicz, D. A. & MacMillan, D. W. C. Merging photoredox catalysis with organocatalysis: the direct asymmetric alkylation of aldehydes. Science 322, 77–80 (2008).

7. Ischay, M. A., Anzovino, M. E., Du, J. & Yoon, T. P. Efficient visible light photocatalysis of [2+2] enone cycloadditions. J. Am. Chem. Soc. 130, 12886–12887 (2008).

8. Narayanam, J. M. R., Tucker, J. W. & Stephenson, C. R. J. Electron-transfer photoredox catalysis: development of a tin-free reductive dehalogenation reaction. J. Am. Chem. Soc. 131, 8756–8757 (2009).

9. Pirot, M. T., Rankic, D. A., Martin, D. B. C. & MacMillan, D. W. C. Photoredox activation for the direct β-arylation of ketones and aldehydes. Science 339, 1593–1596 (2013).

10. Hopkinson, M. N., Sahoo, B., Li, J.-L. & Glorius, F. Dual catalysis sees the light: combining photoredox with organo-, acid, and transition-metal catalysis. Science 336, 3874–3886 (2014).

11. Osawa, M., Nagai, H. & Akita, M. Photo-activation of Pd-catalyzed Sonogashira coupling using a Ru/bipyridine complex as energy transfer agent. Dalton Trans. 827–829 (2007).

12. Kalyani, D., McMurry, K. B., Neufeldt, S. R. & Sanford, M. S. Room-temperature C–H arylation: merger of Pd-catalyzed C–H functionalization and visible-light photocatalysis. J. Am. Chem. Soc. 133, 18566–18569 (2011).

13. Ye, Y. & Sanford, M. S. Merging visible-light photocatalysis and transition-metal catalysis in the copper-catalyzed trifluoromethylation of boronic acids with CuI. J. Am. Chem. Soc. 134, 9034–9037 (2012).

14. Sahoo, B., Hopkinson, M. N. & Glorius, F. Combining gold and photoredox catalysis: visible-light-mediated oxy- and aminoorylation of alkenes. J. Am. Chem. Soc. 135, 5505–5508 (2013).

15. Telis, J. C., Primer, D. N. & Molander, G. A. Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. Science 345, 433–436 (2014).

16. Zuo, Z. et al. Merging photocatalysis with nickel catalysis: coupling of α-carboxyl sp$^2$ carbons with aryl halides. Science 345, 437–440 (2014).

17. Matsunaga, P. T., Hillhouse, G. L. & Rheingold, A. L. Oxygen-atom transfer from nitrous oxide to a nickel metallacycle. Synthesis, structure, and reactions of [cyclic](2,2′-bipyridine)Ni(OCH$_2$CH$_2$CH$_2$). J. Am. Chem. Soc. 115, 2075–2077 (1993).

18. Matsunaga, P. T., Mavropoulos, J. C. & Hillhouse, G. L. Oxygen-atom transfer from nitrous oxide (N$_2$O) to nickel alkyls. Syntheses and reactions of nickel(II) alkoxides. Polyhedron 14, 175–185 (1995).

19. Han, R. & Hillhouse, G. L. Carbon–oxygen reductive-elimination from nickel(II) oxametallacycles and factors that control formation of ether, aldehyde, alcohol, or ester products. J. Am. Chem. Soc. 119, 8135–8136 (1997).

20. Camasso, N. M. & Sanford, M. S. Design synthesis, and carbon-heteroatom coupling reactions of organonickelate(IV) complexes. Science 347, 1218–1220 (2013).

21. Zhou, W., Schultz, J. W., Rath, N. P. & Mirica, L. M. Aromatic methoxylation and hydroxylation by organonickelate(IV)-valent nickel complexes. J. Am. Chem. Soc. 137, 7604–7607 (2015).

22. Macgregor, S. A., Neave, G. W. & Smith, C. Theoretical studies on C–heteroatom bond formation via reductive elimination from group 10 M (Ph$_2$P$_2$)$_2$ (CH$_3$)$_2$X species (X = C$_2$H$_5$, NH$_2$, OH, SH) and the determination of metal–X bond strengths using density functional theory. Faraday Discuss. 124, 111–127 (2003).

23. Torracca, K. E., Huang, X., Parrish, C. A. & Buchwald, S. L. An efficient intermolecular palladium-catalyzed synthesis of aryl ethers. J. Am. Chem. Soc. 119, 10770–10771 (2001).

24. Wolter, M., Nordmann, G., Job, G. E. & Buchwald, S. L. Copper-catalyzed coupling of aryl iodides with aliphatic alcohols. Org. Lett. 4, 973–976 (2002).

25. Kataoka, N., Shelby, Q., Stambuli, J. P. & Hartwig, J. F. Air stable, sterically hindered ferrocenyl dialkylphosphines for palladium-catalyzed C–C, C–N, and C–O bond-forming cross-couplings. J. Org. Chem. 67, 5553–5566 (2002).

26. Mann, G. & Hartwig, J. F. Nickel-vs. palladium-catalyzed synthesis of protected phenols from aryl halides. J. Org. Chem. 62, 5413–5418 (1997).

27. Amatore, C. & Jutand, A. Rates and mechanism of biphenyl synthesis catalyzed by organopalladials and coordinatively unsaturated nickel complexes. Organometalics 7, 2205–2214 (1988).

28. Lowry, M. S. et al. Single-layer electroluminescent devices and photoinduced hydrogen production from an iridium(III) complex. Chem. Mater. 17, 5172–5179 (2005).
29. Klein, A. et al. Halide ligands—more than just σ-donors? A structural and spectroscopic study of homologous organonickel complexes. *Inorg. Chem.* **47**, 11324–11333 (2008).

30. Durandetti, M., Devaud, M. & Perichon, J. Investigation of the reductive coupling of aryl halides and/or ethylchloroacetate electrocatalyzed by the precursor NiX₂(bpy) with X⁻ = Cl⁻, Br⁻ or MeSO₃⁻ and bpy = 2,2'-dipyridyl. *New J. Chem.* **20**, 659–667 (1996).

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