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Authors: Rui Sun, Yangzong Qin, and Daniel G. Nocera

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General Paradigm in Photoredox Ni-Catalyzed Cross-Coupling Allows for Light-Free Access to Reactivity

Rui Sun, Yangzhong Qin and Daniel G. Nocera*

Abstract: We establish self-sustained Ni(I/III) cycles as a potentially general paradigm in photoredox Ni-catalyzed carbon-heteroatom cross-coupling reactions by presenting a strategy that allows us to recapitulate photoredox-like reactivity in the absence of light across a wide range of substrates in the amination, etherification, and esterification of aryl bromides, the latter of which has remained, hitherto, elusive under thermal Ni catalysis. Moreover, the accessibility of esterification in the absence of light is especially notable since previous mechanistic studies on this transformation under photoredox conditions have unanimously invoked energy transfer-mediated pathways.

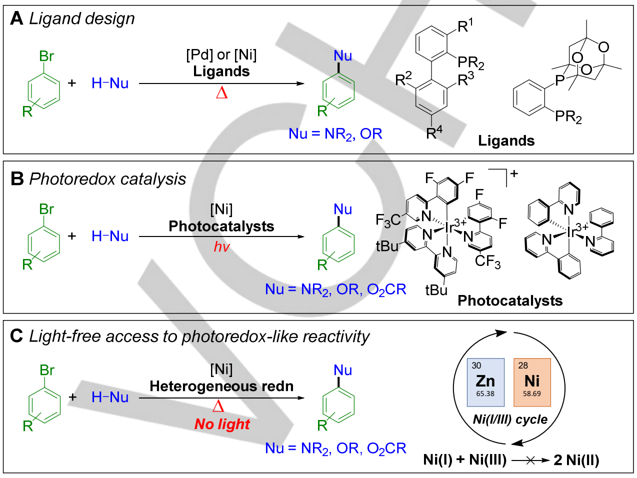

Figure 1. Strategies for carbon-heteroatom cross-coupling: **A** traditional thermal catalysis, ligand-controlled reactivity; **B** redox catalysis, oxidation state-controlled reactivity; **C** this work, light-free access to photoredox-like oxidation state-controlled reactivity.

Introduction

Transition metal catalyzed cross-coupling of aryl halides with nucleophiles is a powerful strategy employed in the construction of the *sp*^{2} carbon-heteroatom bonds that are ubiquitous in pharmaceutical and natural products.[1] Although Pd-catalyzed cross-coupling reactions constitute an established field, there has been interest in developing Ni-catalyzed systems due to the broader range of accessible electrophiles and innately more sustainable qualities of Ni as an earth-abundant metal.[2] Traditionally, the development of these methodologies emphasizes the design of elaborate and specialized ligands (Figure 1A) to make the stereoelectronic properties of the metal center amenable towards the elementary steps that constitute a cross-coupling cycle.[3] However, recent developments in photoredox catalysis (Figure 1B) have demonstrated that these transformations can be effected using simple commercially available ligands under exceptionally mild conditions through the synergistic action of a photocycle and a transition metal cross-coupling cycle.[4] Several seminal studies in this field have demonstrated that the amination, etherification, and esterification of aryl bromides can be realized under Ni photoredox catalysis using either no exogenous ligand (amination) or simple bipyridyl ligands (etherification and esterification), whereby an Ir(III) photocatalyst has been proposed to generate Ni(II) excited state or Ni(III) intermediates that are necessary for the kinetically challenging reductive elimination of carbon-heteroatom bonds.[5] The interest ignited by these discoveries has led to an immense and ever-growing body of photochemical literature that report the recapitulation of this Ni-catalyzed carbon-heteroatom cross-coupling reactivity across a myriad of different photocatalyst combinations.[6]

Notwithstanding the high chemical efficiency achievable under photoredox cross-coupling, the sustainability of these methodologies has been comparatively underemphasized. In particular, the energy cost of the photons employed (typically blue, violet, or near-UV) in photoredox chemistry has often been overlooked, despite the importance of Energy Intensity, defined as energy consumption per unit mass of product, as a metric in quantifying the sustainability of chemical processes.[7] Furthermore, the majority of photocatalysts used are based on precious metals such as iridium and ruthenium, and the reaction mechanisms, an understanding of which is critical for rational optimization towards more energy efficient and sustainable methodologies, remain largely undefined. Previous work by our group demonstrated that, in contrast to the closed photocycles commonly proposed for photoredox cross-coupling reactions (Scheme 1, **A** and **B**),[5, 6b-d, 8] a Ni(I/III) cycle (Scheme 1, **C**) may be operative in the reaction between aryl bromides and alcohols to form *O*-aryl ethers, where the photon serves to resuscitate the cycle once the catalytically active Ni(I) or Ni(III) species are depleted to form inactive Ni(II) complexes *via* a highly exergonic comproportionation reaction, akin to what had been proposed for the related electrochemical amination of aryl bromides.[9] Given the various mechanistic possibilities proposed for photoredox Ni cross-coupling,[8] it was unclear if similar dark cycles were operative in other reactions. A productive dark cycle has important ramifications for methodology development and optimization, as it implies that the necessity of both continuous energy input and precious metal photocatalysts can be entirely obviated while preserving all the advantages of photoredox cross-coupling systems (i.e. exceptionally mild conditions using inexpensive and readily accessible ligands under Ni catalysis). Despite numerous examples of Ni(I/III) cross-coupling cycles,[10] the propensity of Ni to undergo one-electron redox processes has made elucidation of reaction mechanisms challenging in many cases,[11] and the factors that dictate whether a reaction occurs through a Ni(0/II) or a Ni(I/III) cycle are not fully

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R. Sun, Dr. Y. Qin, and Prof. Dr. D. G. Nocera
Department of Chemistry and Chemical Biology
Harvard University
12 Oxford St., Cambridge MA 02138, United States of America
E-mail: dnocera@fas.harvard.edu

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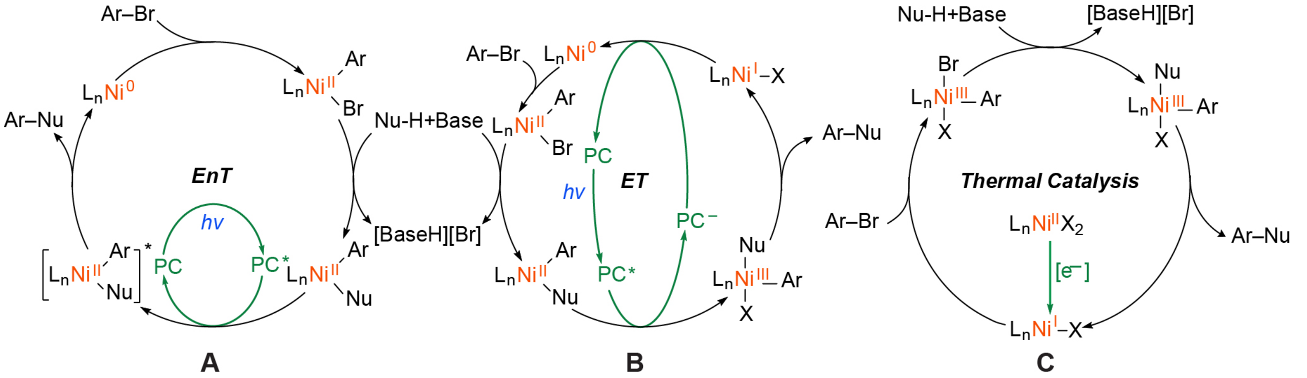


Scheme 1. Mechanisms invoked in photoredox Ni-catalyzed cross-coupling: **A** energy transfer-mediated catalysis; **B** oxidation state modulation; **C** thermally-sustained Ni(I/III) cycle.

understood. Hence, a general strategy for selectively engaging the Ni(I/III) redox couple under thermal catalysis has remained largely elusive.

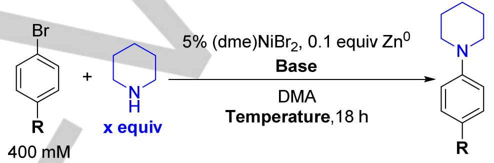
Herein, we demonstrate that photoinitiated, thermally sustained reactivity may constitute a general paradigm in photoredox nickel cross-coupling by showing that the amination, etherification, and esterification of aryl bromides are all accessible under strictly thermal conditions. To this end, we show that photoredox-like reactivity can be recapitulated in the complete absence of a photon source by replacing the Ir photocatalyst and light with a substoichiometric amount of an earth-abundant heterogeneous reductant. Although the combination of a mild heterogeneous reductant and NiX_2 precatalysts has been previously utilized in reductive coupling reactions and as a convenient substitute for sensitive Ni(0) catalysts,[12] we demonstrate that the biphasic nature of the reduction process can allow for selective access to a Ni(I/III) cycle by ensuring that the active Ni(I) and Ni(III) intermediates are maintained at sufficiently low concentrations to mitigate comproportionation. Using this approach, a variety of heteroatomic nucleophiles (amines, alcohols, and carboxylic acids) can be successfully cross-coupled with aryl bromides in the absence of light or precious metal photocatalysts under conditions which otherwise bear resemblance to the parent photoredox systems.

Results and Discussion

We began our investigation by studying the photoredox-mediated ligand-free amination of aryl bromides, for which we measured a quantum yield of $\Phi = 2.7 \pm 0.1$ (see Supporting Information). This confirms the presence of a dark cycle, in contrast to the closed Ni(0/II/III/I) cycle previously proposed for this reaction.[5a] Thus, we hypothesized that Zn(0), a commonly employed reductant in Ni cross-coupling catalysis, could replace the combination of photocatalyst and light due to the heterogeneity of the reduction process leading to the slow formation of Ni(I) equivalents, thereby disfavoring comproportionation.

As shown in Table 1, a substoichiometric amount of Zn(0) metal in combination with $(dme)NiBr_2$ (dme = 1,2-dimethoxyethane) furnished the expected aniline product in the cross-coupling between 4-bromobenzotrifluoride and piperidine in the presence of triethylamine at room temperature without exogenous ligand (Entry 1), thereby recapitulating the reactivity observed under photoredox conditions. Upon further optimization, 1,4-diazabicyclo[2.2.2]octane (DABCO) was found to be a more effective base (Entry 2) and elevated temperatures were deleterious (Entries 3-5). For more electron rich arenes (e.g. 4-bromotoluene), quinuclidine was found to be superior to DABCO in furnishing cross-coupled product (Entries 6 and 7), consistent with its higher basicity facilitating the requisite deprotonation of amine.[13] It is noteworthy that the superior performance of DABCO and quinuclidine under this light-free protocol parallels their status as the most effective bases in previously reported photoredox-mediated ligand-free amination reactions, consistent with the existence of a common productive dark cycle as we propose.

Table 1. Optimization of light-free amination.



Entry	R group	Piperidine equiv	Base (equiv)	T (°C)	Ar-NR_2 Yield (%)
1	CF_3	1.5	NEt_3 (1.5)	RT	73[a]
2	CF_3	1.5	DABCO (1.5)	RT	91[a]
3	CF_3	1.5	DABCO (0.1) + NEt_3 (1.5)	RT	88[a]
4	CF_3	1.5	DABCO (0.1) + NEt_3 (1.5)	40	72[a]
5	CF_3	1.5	DABCO (0.1) + NEt_3 (1.5)	60	53[a]
6	CH_3	2.0	DABCO (1.8)	RT	27[b]
7	CH_3	2.0	Quin. (1.8)	RT	56[b]

[a] Yields determined by ^{19}F NMR. [b] Yields determined by ^1H NMR. DMA = *N*,*N*-dimethylacetamide. DABCO = 1,4-diazabicyclo[2.2.2]octane. Quin. = quinuclidine.

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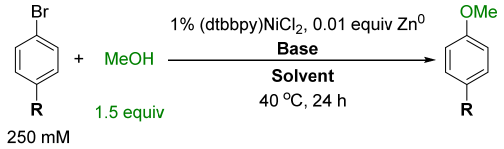
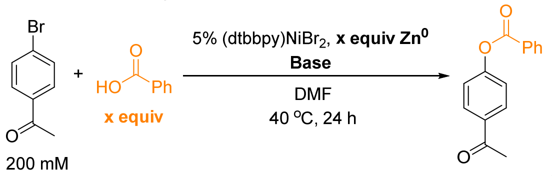
Table 2. Optimization of light-free etherification.



Entry	R group	Base (equiv)	Solvent	Ar-OR Yield (%)[a]
1	Ac	NEt_3 (3.0)	MeCN	87
2	Ac	DBU (1.1)	THF	95
3	Ac	Quin. (0.1) + K_3PO_4 (3.0)	THF	N.D.
4	CH_3	DBU (1.1)	THF	14
5	CH_3	MTBD (1.1)	THF	37
6	CH_3	MTBD (2.0)	THF	5

[a] Yields determined by ^{1}H NMR. Ac = acetyl. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene.

Table 3. Optimization of light-free esterification.



Entry	BzOH equiv	Base (equiv)	Zn^0 equiv	Ar-O_2CR Yield (%)[a]
1	2.0	Quin. (2.0)	0.1	46
2	2.0	NEt_3 (2.0)	0.1	54
3	2.0	HN(^{t}Bu)(^{i}Pr) (2.0)	0.1	64
4	2.0	HN(^{t}Bu)(^{i}Pr) (2.0)	0.5	82
5	3.0	HN(^{t}Bu)(^{i}Pr) (3.0)	0.5	61
6	2.0 as [TBA][OBz]	None	0.5	75

[a] Yields determined by ^{1}H NMR. TBA = tetrabutylammonium. OBz = benzoate

Given the similarity of conditions employed across Ni photoredox cross-coupling methodologies,[5, 14] we hypothesized that this strategy of using a heterogeneous reducing agent to thermally access and sustain a Ni(I/III) cycle may be generalized to other nucleophiles. As shown in Entry 1 of Table 2, we obtained the expected cross-coupled product in the reaction between methanol and 4´-bromoacetophenone using only 0.01 equivalents of Zn(0) and 1 mol% (dtbbpy)$NiCl_2$ (dtbbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl) prepared *in situ* from (dme)$NiCl_2$ and dtbbpy. This result further lends credence to the productive Ni(I/III) cycle invoked in our previous mechanistic study.[9a]

Upon further optimization, we discovered that switching to THF in combination with the stronger amidine base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), led to a higher yield (Entry 2). Inorganic bases such as K_3PO_4 were ineffective (Entry 3), possibly due to slow proton transfer kinetics or the precipitation of halides required to stabilize *in situ* generated Ni(I) species. For less active aryl bromides, the use of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) in place of DBU resulted in superior yields (Entries 4 and 5), whereas increasing the base concentration had a deleterious effect (Entry 6), consistent with the coordinative inhibition of catalytic intermediates by amine bases previously observed for related Pd-catalyzed systems.[15] We next targeted cross-coupling carboxylic acids with aryl bromides to generate the respective *O*-aryl esters. As shown in Entry 1 of Table 3, we observed the formation of the desired ester in the reaction between 4´-bromoacetophenone and benzoic acid in the presence of (dtbbpy)$NiBr_2$ and Zn(0) metal. Reaction optimization revealed HN(^{t}Bu)(^{i}Pr) to be the most effective base (Entries 2 and 3) and, in contrast to amination and etherification, a higher Zn(0) loading was found to be necessary for efficient cross-coupling (Entry 4). Increasing the amount of acid and base beyond two equivalents did not increase the yield (Entry 5). The use of tetrabutylammonium benzoate in place of benzoic acid and base gave a comparable yield (Entry 6), suggesting that the active nucleophile engaging with the nickel catalyst may be carboxylate rather than carboxylic acid.

The success of aryl esterification is noteworthy given the diminished nucleophilicity of carboxylates relative to other heteroatomic cross-coupling substrates, as demonstrated by the requirement for super-stoichiometric amounts of silver salts in a reported Pd-catalyzed methodology for the esterification of aryl iodides,[16] and a scarcity of examples for the direct cross-coupling of carboxylic acids with aryl bromides under thermal nickel catalysis. Moreover, reports of this transformation under photochemical conditions unanimously invoke photosensitization pathways that necessitate access to a Ni(II) excited state as a precondition for reductive elimination,[5c, 6d, 6g, 6l] whereas our reactions in the absence of light preclude any possibility of excited state formation. These results suggest a Ni(I/III) pathway as an alternative, and hitherto unexplored, mechanistic strategy for achieving this transformation.

Next, we performed a series of control experiments to assess our contention that the dominant productive pathways in all three transformations involve a Ni(I/III) cycle. The necessity of both nickel and Zn(0) was demonstrated by the absence of product formation when either was excluded under the ‘A’ conditions in Figure 2 (see Supporting Information). Furthermore, the yields were greatly diminished when the combination of Ni(II) and Zn(0) was replaced with a Ni(0) source under analogous conditions (Figure 2, B), suggesting that the Ni(II) aryl species which form after oxidative addition of the aryl bromide are incapable of undergoing the requisite carbon-heteroatom reductive elimination. Control experiments wherein COD was added to the reactions under the 'A' conditions of Figure 2 showed that the difference in reactivity between the 'A' and 'B' conditions of Figure 2 is not entirely attributable to the presence of COD (see Supporting Information). This is consistent with a Ni(I/III) mechanism being the dominant productive pathway as suggested by our previous mechanistic study and literature precedent proposing the necessity of Ni(III) for reductive elimination.[6b, 8a, 8b, 9a, 10b, 17] The background reactivity observed in these control experiments with Ni(0) sources may be attributed to the generation of Ni(I) equivalents during oxidative addition of aryl bromide to Ni(0) as previously

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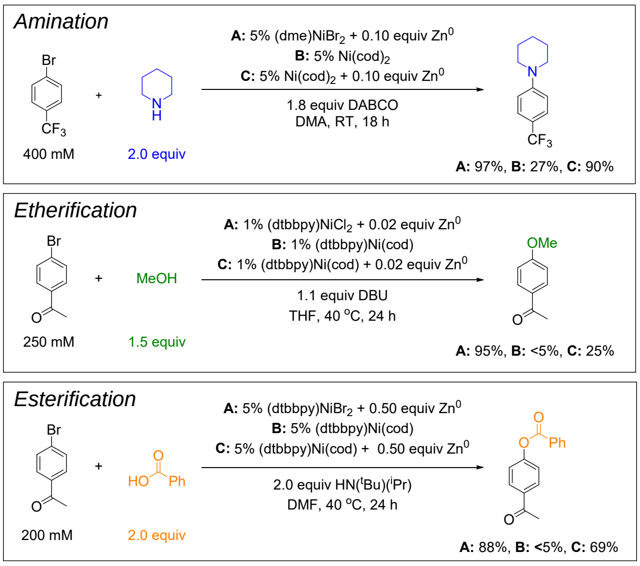

Figure 2. Effects of nickel source on yields for the three cross-coupling reactions. Yields were determined by ^{19}F NMR for amination and ^{1}H NMR for etherification and esterification. cod = 1,5-cyclooctadiene.

proposed.[18] We also discovered that Ni(0) in combination with Zn(0) gave higher yields than Ni(0) alone (Figure 2, C), suggesting that inactive Ni(II) aryl complexes may be reductively resurrected to re-enter the Ni(I/III) cycle. This may indicate that Zn(0) can further reduce Ni(II) aryl complexes to form Ni(I) aryl species that undergo subsequent oxidative addition to give on-cycle Ni(III) intermediates, in a manner analogous to what has been proposed for Ni-catalyzed reductive coupling.[11]

We were able to establish further parallels between the reactivity reported herein and that under the previously studied photochemical conditions. For example, we observed the formation of a previously characterized Ni(I)-Ni(II) dimer upon treatment of a solution containing Ni(II) precatalyst with Zn(0) (see Figure S1 in the Supporting Information),[9a] suggesting that Zn(0) serves a role analogous to the Ir photocatalyst in the related photoredox reaction by providing access to Ni(I) equivalents necessary for catalysis. Furthermore, similar to the photoredox reaction, there is evidence to suggest the existence of deleterious bimetallic pathways leading to the formation of off-cycle intermediates since we observed a decrease in reaction yield with increasing nickel loading under certain conditions (see Figure S2 in the Supporting Information for details).

In order to verify the generality of our conclusions across multiple substrates, we investigated the scope to which photoredox-like reactivity could be recapitulated without light, as shown in Figure 3. For amination, anilines (**8-10**) and cyclic secondary amines (**1-5**) such as piperidine, which is the most ubiquitous heterocyclic moiety in FDA-approved pharmaceuticals, can all be effectively cross-coupled.[19] Notably, pyrrolidine was not required as an additive for the cross-coupling of anilines, in contrast to the photoredox-mediated reaction where it serves an indispensable role.[5a] More challenging substrates such as cyclic primary amines (**6**) or acyclic secondary amines (**7**) can be successfully cross-coupled using quinuclidine as the base. Furthermore, high chemoselectivity for C-N coupling was observed in the presence of alcoholic functionality (**3**). The yield was found to be highly sensitive towards the coordinating abilities of the amine, with attempts to couple linear primary alkyl amines and heterocyclic aryl bromides being unsuccessful, consistent with their greater binding affinity resulting in the formation of coordinatively saturated Ni(I) species that are unable to dissociate a sufficient number of ligands to undergo concerted oxidative addition.[20] This supposition is supported by the observation that a sterically hindered primary amine (cyclohexylamine) could be successfully coupled (**6**). Given the evidence for mechanistic substrate dependence in Ni cross-coupling reactions,[21] the inefficiency of these recalcitrant coupling partners under our light-free conditions may imply that the extent to which photochemical resuscitation of inactive Ni(II) complexes contributes to the overall observed reactivity could be similarly substrate dependent. With respect to the aryl bromide, the highest yields were obtained with those possessing electron deficient substituents such as ketone (**11**), sulfone (**12**), nitrile (**19**), and trifluoromethyl ether (**20**) functionality. Protic moieties such as those found in amides were well-tolerated (**16** and **17**), and C–N bond formation occurred preferentially at the bromide-functionalized carbon with high fidelity when carbon-chlorine bonds were present on the arene (**13**). Arenes without electron withdrawing groups could also be cross-coupled, albeit in lower yields (**14** and **15**). For etherification, sterically unencumbered primary alcohols (**21-23**) were found to be the most active substrates, consistent with the photoredox system. Notably, weakly nucleophilic alcohols such as 2,2,2-trifluoroethanol could be coupled in moderate yield (**22**). However, secondary alcohols more sterically hindered than cyclobutanol (**24**) were ineffective under our conditions. We discovered that cross-coupling with water proceeds well under conditions analogous to those for esterification (see Supporting Information), allowing us to obtain **25** in 75% yield. Electron deficient arenes were found to be the most reactive with various polar groups being well-tolerated (**26**, **27**, and **29**). The inclusion of amide functionality significantly diminishes the yield (**30**), possibly due to coordinative inhibition of the nickel catalyst. Regarding esterification, *Boc*-protected amino acids and benzoic acid were very efficiently coupled (**31**, **33–35**), and sterically hindered pivalic acid gave product in moderate yield (**32**). Aryl bromide reactivity was consistent with that observed for etherification and amination, where electron poor arenes proved to be efficient substrates (**36–38**). However, in contrast to the two previous reactions, derivatives of heterocyclic amines were also accessible (**39** and **40**). Taken together, the breadth of products for which we could successfully recapitulate photoredox-like reactivity in the absence of light establishes the generality of a Ni(I/III) cycle as a productive pathway in photoredox-mediated Ni cross-coupling catalysis.

Conclusion

We demonstrate that a thermally sustained Ni(I/III) cycle may constitute a general productive mechanism in Ni-catalyzed photoredox-mediated cross-coupling. Our results show that Ni-

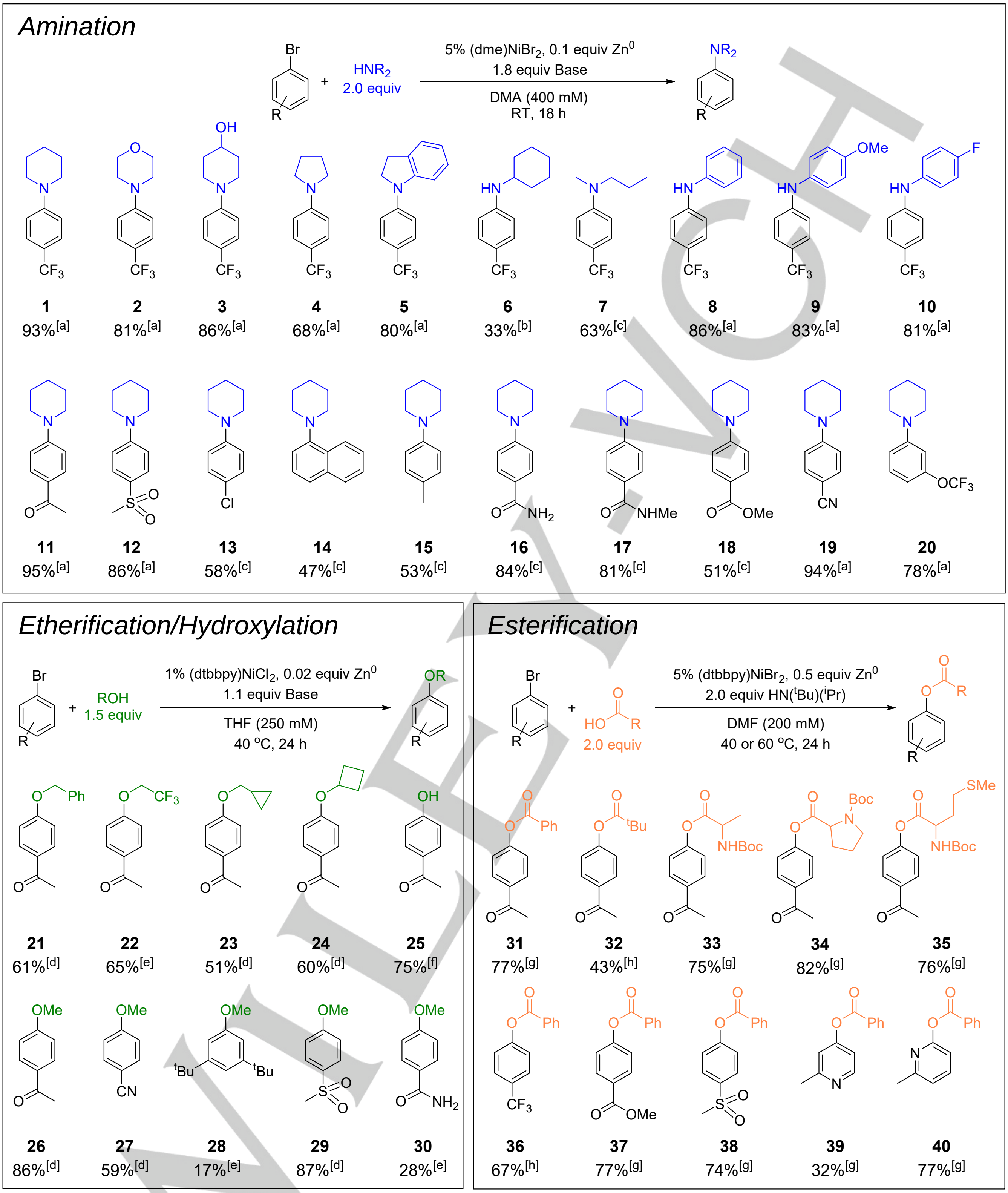

Figure 3. Demonstration of the generality of light-free reactivity. [a] DABCO used as the base. [b] Quinuclidine used as the base and DMSO used as the solvent. [c] Quinuclidine used as the base. [d] DBU used as the base. [e] MTBD used as the base. [f] See Supporting Information for details. [g] Reaction performed at 40 °C. [h] Reaction performed at 60 °C. Boc = *tert*-butyloxycarbonyl.

catalyzed amination, etherification, and esterification of aryl bromides can all be realized across a wide range of substrates *without light* under conditions which otherwise bear resemblance to the parent photochemical methodologies. To this end, one may wish to re-evaluate the growing body of literature that invokes energy transfer as the mechanism for catalysis.[5c, 6d, 6f, 6g, 6ℓ, 14, 21] As we show here, only a small amount of Ni(I) can initiate self-sustained Ni(I)/Ni(III) thermal catalysis. We suspect that in many of the cycles ascribing catalysis to energy transfer there may well be the production of small amounts of Ni(I) through photoreduction.

Whereas various methodologies exist for the amination and etherification of aryl bromides, our esterification protocol described herein is especially notable given the scarcity of direct Ni-catalyzed cross-coupling between carboxylic acids and aryl bromides under light-free conditions. Critical to this dark reactivity is the ability to selectively engage and sustain a Ni(I/III) catalytic cycle while attenuating deactivation of the catalyst to inactive Ni(II) complexes through bimetallic pathways. This may be achieved through the slow formation of Ni(I) equivalents from NiX_2 precursors with substoichiometric amounts of an earth-abundant heterogeneous reducing agent, thereby allowing us to access photoredox-like cross-coupling reactivity with its intrinsic advantages while obviating the need for continuous irradiation using high-energy photons or precious metal photocatalysts.

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Keywords: cross-coupling • green chemistry • photoredox catalysis • sustainable chemistry • transition metals

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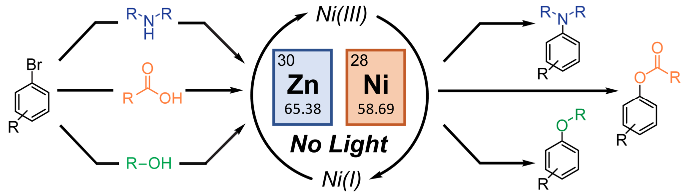

Self-sustained Ni(I/III) cycles are established as a potentially general paradigm in photoredox cross-coupling reactions. We show that photoredox-like reactivity can be recapitulated with high fidelity in the complete absence of light across multiple substrates and transformations, thus obviating the need for high-energy photons and precious metal photocatalysts.

*R. Sun, Y. Qin, D. G. Nocera**

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