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Photoredox Catalysis Unlocks Single-Electron Elementary Steps in Transition Metal Catalyzed Cross-Coupling

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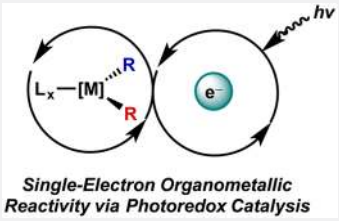
ABSTRACT: Since initial reports, cross-coupling technologies employing photoredox catalysts to access novel reactivity have developed with increasing pace. In this Outlook, prominent examples from the recent literature are organized on the basis of the elementary transformation enabled by photoredox catalysis and are discussed in the context of relevant historical precedent in stoichiometric organometallic chemistry. This treatment allows mechanistic similarities inherent to odd-electron transition metal reactivity to be generalized to a set of lessons for future reaction development.



INTRODUCTION

The ability for transition metal catalysts to forge bonds between ligated fragments has become a cornerstone of modern synthetic chemistry. Cross-coupling methodologies allow access to a variety of carbon−carbon and carbon−heteroatom coupled products via straightforward retrosynthetic disconnections, and the systematic exploration of this paradigm has expanded the canon of accessible reactivity to cover a wide swath of chemical space.[1]

The vast majority of these methodologies rely on the same three two-electron elementary steps as a means to accomplish their target transformation: oxidative addition, transmetalation, and reductive elimination (Figure 1). The centrality of these reactions is underscored by the numerous mechanistic studies conducted that outline the influence of the metal catalyst and its ligand environment. Despite the attention given to these polar mechanisms, many worthwhile challenges remain in this field.[2]

The key development in recent reports has been the implementation of visible-light photocatalysts as a means to induce the desired redox processes in a mild and selective manner.

Meanwhile, it has long been known that the chemistry of 17- and 19-electron transition metal complexes is marked by dramatically faster rates compared to their even-electron congeners for virtually all elementary transformations.[3] Despite the wealth of stoichiometric precedent in this area, translation of odd-electron organometallic reactivity into mild catalytic reactions remained, until recently, far rarer than the two-electron analogues.

The key development in recent reports has been the implementation of visible-light photocatalysts as a means to induce the desired redox processes in a mild and selective manner. Examination of a generalized photoabsorption scheme reveals that such an activation mode is a natural means of accessing odd-electron intermediates (Figure 2). As noted by early studies on these photoredox catalysts, excited states become both stronger single-electron oxidants and stronger single-electron reductants.[4−6] By employing catalysts with absorption bands in the visible region of the spectrum (rather than in the ultraviolet), the source of open shell intermediates can be effectively controlled.[7,8]

The rapid pace of recent developments combining photocatalysis with transition metal catalysis has prompted a survey of the field.[9] We have endeavored here, for instructive purposes, to organize these landmark examples by virtue of the elementary step in which the photocatalyst is engaged, as the guiding principles and mechanistic homologies of this new field are clearer when the catalyzed elementary steps are delineated. In each case, we aim to tie these novel catalytic methodologies back to their prior stoichiometric analogues as a means to both rationalize the observed reactivity and inspire the next generation of technologies.

It is prudent to note that, in many cases, the photocatalysts may serve as chain initiators, with chain lengths measured for many photoredox processes exceeding one.[10] As such, we have chosen to abstract the involvement of these catalysts to the level of a photoinduced electron transfer (signified by an electron), rather than imply the specific species involved in any given reduction or oxidation event.[11] This Outlook is not meant as a comprehensive review[12−15] but rather as a tutorial, and the lessons involved do not hinge on the presence or absence of chain processes.[16]

PHOTOCATALYSIS OF OXIDATIVE ADDITION

Oxidative addition involves the formation of bonds between a metal and an electrophilic substrate concomitant with the formal two-electron oxidation of the metal center.[2] In cross-coupling this step typically involves concerted oxidative

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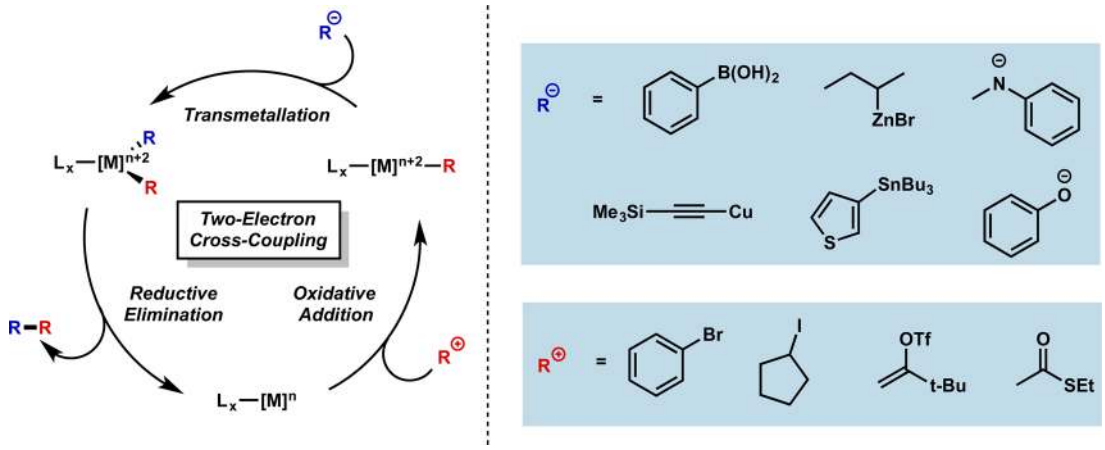

Figure 1. Generalized mechanism for cross-coupling and representative nucleophiles and electrophiles. Tf = trifluoromethanesulfonyl.

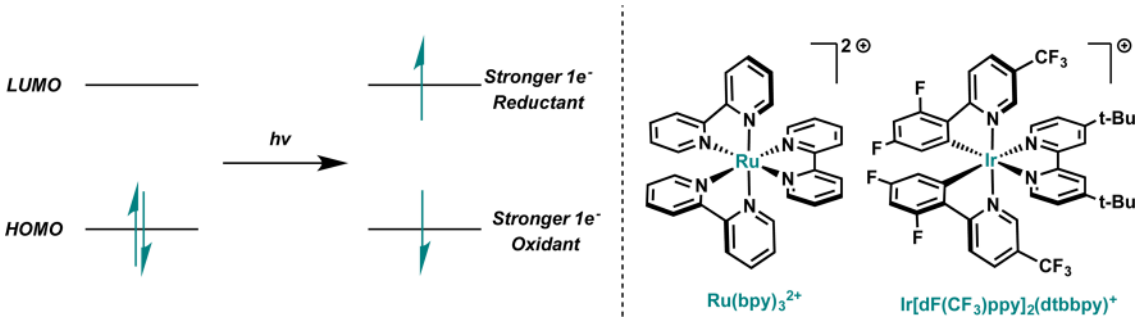

Figure 2. Simplified photoabsorption scheme and commonly employed photoredox catalysts.

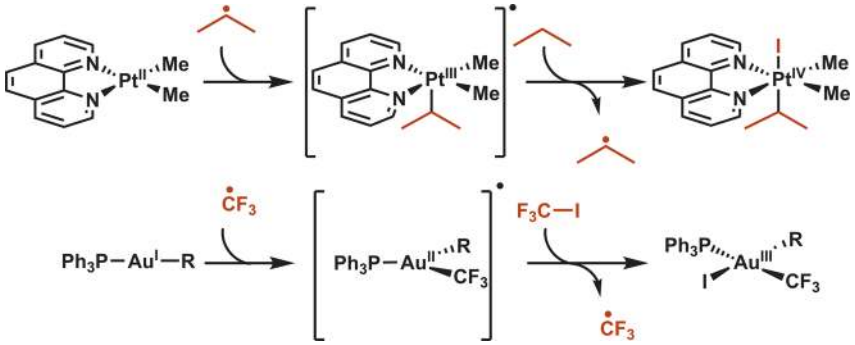

Figure 3. Stoichiometric precedent: radical chain oxidative addition to Pt(II) and Au(I).

addition of a carbon−halogen or carbon−pseudohalogen bond to generate the oxidized organometallic species. However, many metals and electrophiles undergo prohibitively slow reactions by this mechanism.

On the other hand, the facile addition of alkyl radicals to transition metals in both chain and nonchain processes has been studied in detail for a variety of complexes (Figure 3).[17] For example, photochemical initiation to generate isopropyl radical was shown to accelerate the oxidative addition of isopropyl iodide to Pt(II) via a radical chain process.[18] Fluoroalkyl iodides similarly undergo radical chain oxidative additions to Au(I).[19,20] These precedents highlight the ability of otherwise sluggish oxidative addition processes to be facilitated by injection into a radical manifold.

With a photoredox catalyst, the involvement of a photochemical process allows for the generation of the intermediate radical species in milder fashion and with transition metal catalysts kinetically incompetent for such an initiation on their own. In the most general scheme, an electrophilic reagent is reduced by a photoexcited species, leading to its radical congener. Subsequent addition to the metal species followed by oxidation yields the net oxidative addition product. In this way, the photocatalyst catalyzes the oxidative addition (Figure 4).

One of the earliest examples of this activation mode in the context of catalysis is in Pd-catalyzed directed C−H functionalization (Figure 5).[21] Sanford and co-workers showed that, in contrast to much harsher methods for accessing Pd(IV), which require elevated temperature, the use of aryldiazonium cations in combination with a photoredox catalyst allowed for the generation of the high-valent intermediate at room temperature. This was found to be broadly applicable with respect to the directing group employed and to the diazonium structure. Subsequent studies expanded this manifold to diaryliodonium electrophiles.[22]

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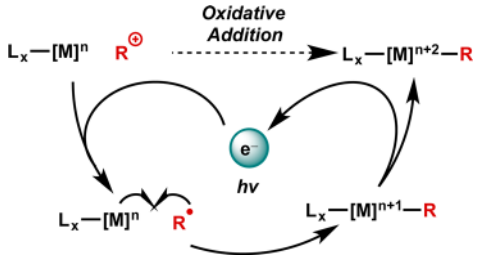

Figure 4. Generalized scheme for photoredox catalysis of oxidative addition.

> Beyond the mechanistic novelty in these processes, a striking feature of all systems developed to date is that the nucleophiles employed are all air-stable, easily prepared, and yet still capable of effectively delivering sp^3 nucleophiles to transition metal centers.

This same strategy employing diazonium electrophiles was subsequently applied in the context of gold catalysis by the Glorius and Toste groups, providing access to highly reactive Au(III) intermediates in a straightforward fashion.[23,24] Initial studies focused on the activation of alkenes to provide oxy- and aminoarylated as well as ring expanded products (Figure 6).[25] Mechanistic investigations including time-resolved FT-IR, labeling studies, and DFT support a mechanism in which photocatalysis generates the Au(III)−aryl intermediate prior to intervention of the unsaturated substrate.[23,26] Subsequent studies have expanded the scope to a wide variety of Au-catalyzed reactions of alkynes,[27−30] allenes,[31] and heteroatom nucleophiles[32] allowing arylation to terminate catalytic cycles typically closed via protodeauration.

Finally, a variant on this activation mode was demonstrated by Fu and Peters in which a copper catalyst serves as both the photocatalyst and ultimate bond-forming agent, albeit with UV rather than visible light in most cases. These processes vary in their nucleophiles and electrophiles, encompassing both aryl and alkyl halide substrates in C−S,[33] C−N,[34−37] C−C,[38,39] and C−O[40] forming reactions. Recent mechanistic studies have shown that the copper-mediated pathway involves photo-induced electron transfer from the nucleophile−cuprate complex followed by in-cage radical recombination to afford the coupled product, though oxidative addition and outer-sphere recombination could not be distinguished (Figure 7).[41] As such, it remains unclear the extent to which these precedents are analogous to other photoredox-catalyzed oxidative additions. Nonetheless, a recent study demonstrated an enantioselective variant of this process for C−N bond formation.[42]

In addition to these illustrative examples, several other reports have emerged utilizing photoredox catalysis to enable oxidative addition. Notably, the combination of photoredox catalysts with copper has enabled mild C-fluoroalkyl and C−N coupling reactions to occur.[43,44]

■ PHOTOCATALYSIS OF REDUCTIVE ELIMINATION

Reductive elimination involves the formation of a new bond between ligands bound to a metal with concomitant 2-electron reduction of the metal center.[2] As the key bond-forming step in cross-coupling reactions, this process has been widely explored for diverse combinations of metals and ligands, and virtually all classes of reductive elimination are precedented in the literature. Nonetheless, there remain examples for which bond formation is prohibitively slow.

Again, the literature surrounding single-electron processes provides a potential solution;[45,46] seminal studies by Kochi and Hillhouse showed that complexes that are inert to reductive elimination or undergo unselective decomposition can be coaxed to perform the desired bond-forming process by single-electron oxidation with a diverse array of oxidants (Figure 8).[47,48]

On the basis of these precedents, it is conceivable that a photoredox catalyst can be applied to accomplish such a transformation in a dual catalytic process. "Temporary" oxidation of the metal catalyst allows photocatalysis of the desired reductive elimination, which is followed by rereduction of the catalyst, as outlined in Figure 9.

A powerful realization of this activation strategy was employed by the Macmillan group in a nickel-catalyzed C−O coupling aided by an iridium photocatalyst (Figure 10).[49] In addition to demonstrating the scope of this process for a range of coupling partners, stoichiometric experiments on an isolated

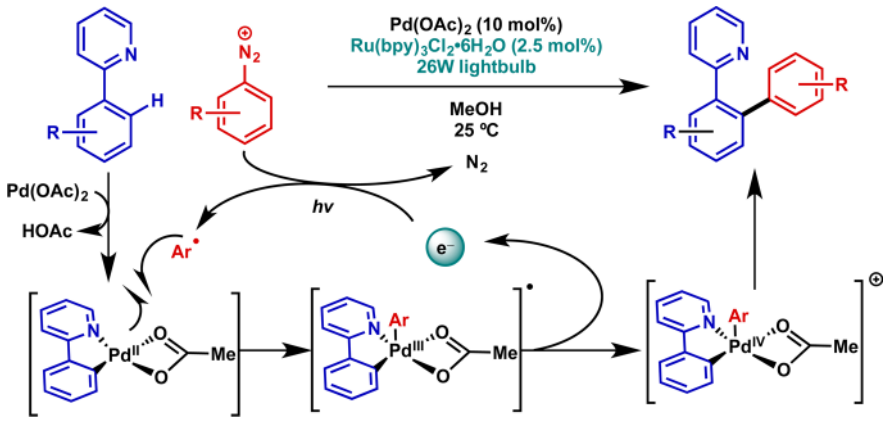

Figure 5. Catalytic application: palladium-catalyzed C−H functionalization at room temperature via Pd(IV) intermediates generated by photoredox catalysis.

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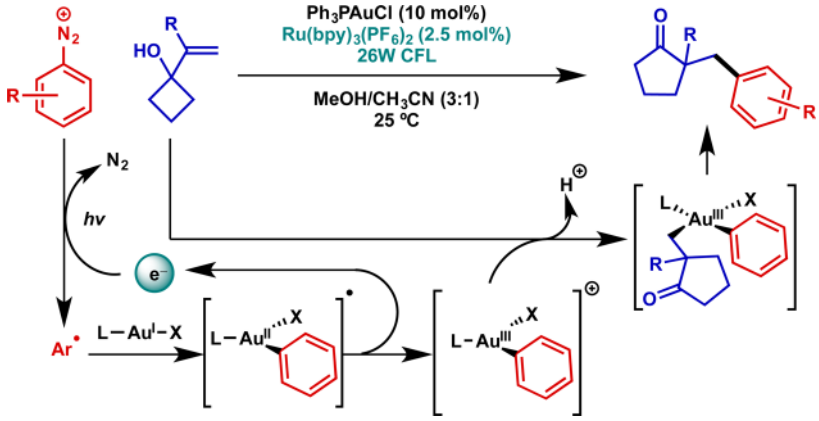

Figure 6. Catalytic application: gold-catalyzed arylative ring expansion of vinylcyclobutanols via aryl−Au(III) intermediates generated by photoredox catalysis.

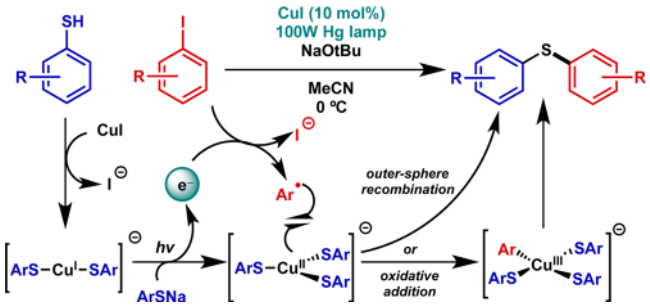

Figure 7. Catalytic application: copper-catalyzed C−S bond formation via photoinduced electron transfer. Mechanistic experiments have not distinguished the two potential pathways.

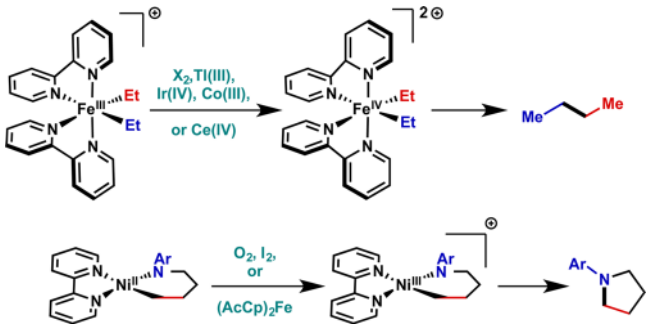

Figure 8. Stoichiometric precedent: oxidatively induced reductive elimination from Fe(IV) and Ni(III). Cp = cyclopentadienyl.

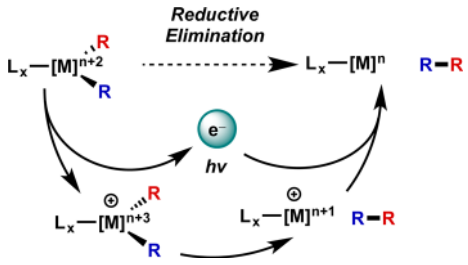

Figure 9. Generalized scheme for photoredox catalysis of reductive elimination.

Ni(II)−aryl alkoxide complex clearly demonstrate the crucial influence of the photoredox catalyst on the desired reductive elimination process.

> These challenges should be taken as a call to action, as the power demonstrated in the reports thus far suggests a wealth of untapped reactivity. Most tantalizingly, the involvement of a photoprocess suggests that endergonic transformations may be possible in these catalytic reactions.

A second example from Jamison and co-workers concerns the synthesis of indolines via the coupling of ortho-iodoaniline derivatives with alkenes (Figure 11).[50] Having observed that small amounts of the desired indoline product were formed upon exposure of the reaction mixture to air, they employed a photoredox catalyst to serve as a reversible means to access the requisite Ni(III) intermediate. The proposed mechanism bears many similarities to the example in Figure 10.

■ PHOTOCATALYSIS OF TRANSMETALATION

Transmetalation involves the formation of a bond between a nucleophilic substrate and a metal, with no change in formal oxidation state of the metal.[2] These reactions typically involve displacement of a metal halide, and are mechanistically the most complex of the steps discussed herein. Despite several in-depth studies into the underlying elementary steps, many transmetalation processes remain poorly understood.[51−53] Worse yet, transmetalation of sp^3 alkyl fragments is typically challenging, requiring the use of sensitive reagents or harsh conditions.

In this arena, limited stoichiometric precedent employing open-shell intermediates has been reported; as such, the simultaneous discovery by the Macmillan, Doyle, and Molander groups that photoredox catalysis can be used to enable mild transmetalation from otherwise weakly nucleophilic coupling partners is perhaps even more impressive.[54,55]

Though many mechanisms have been proposed, the general scheme for such a photocatalyzed transmetalation can be conceived as follows: single-electron oxidation of a nucleophile and subsequent reduction of a transition metal complex generates complementary odd-electron species that can then efficiently undergo recombination (Figure 12). The order of

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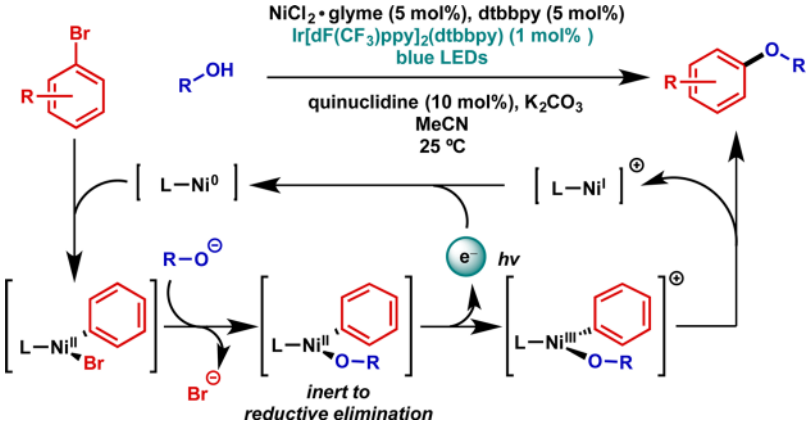

Figure 10. Catalytic application: nickel-catalyzed etherification with C−O reductive elimination enabled via photoredox catalysis.

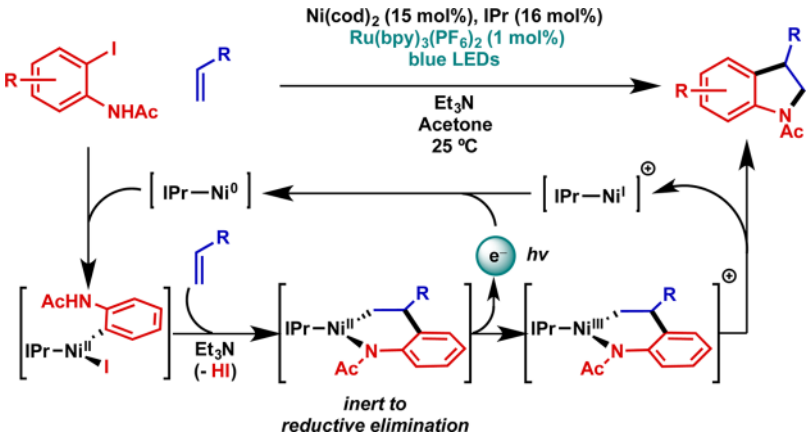

Figure 11. Catalytic application: nickel-catalyzed Larock-type indoline synthesis with C−N reductive elimination enabled via photoredox catalysis. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

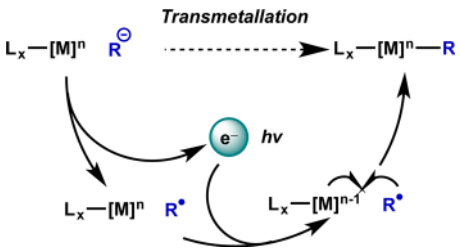

Figure 12. Generalized scheme for photoredox catalysis of transmetalation.

these two steps can likely be inverted, and other elementary steps can intervene, but the sense of redox is likely maintained regardless of the conditions employed.

Beyond the mechanistic novelty in these processes, a striking feature of all systems developed to date is that the nucleophiles employed are all air-stable, easily prepared, and yet still capable of effectively delivering sp^3 nucleophiles to transition metal centers. Four main classes of photoredox-activated alkyl nucleophiles have been developed: carboxylates,[54,56−59] alkyl trifluoroborates,[55,60−65] alkyl silicates,[66−70] and α-heteroatom C−H bonds.[54,71,72] In each, oxidation generates an alkyl radical via a subsequent fragmentation process, generating CO_2, BF_3, bis(catecholato)silane, or acid, respectively.

The most comprehensive mechanistic experiments and DFT calculations have been carried out for the nickel-catalyzed variants of these processes, and the studies support a process in which a Ni(0) intermediate combines with the nascent radical species to generate the corresponding Ni(I) alkyl.[73,74] The overall cycle is then closed via oxidative addition of the sp^2 halide coupling partner, reductive elimination from Ni(III), and single-electron reduction to regenerate the Ni(0) complex. Two representative examples are shown in Figure 13, including a recently reported enantioselective method leveraging this protocol to generated enantioenriched benzylic amines in a stereoconvergent fashion.[75]

An interesting application of the carboxylate nucleophiles has been reported in which the carboxylate moiety is generated by oxidative addition to palladium forming a π-allyl intermediate.[76,77] Other photoredox-facilitated transmetalations in cross-coupling have also been reported.[78−80]

■ CONCLUSIONS AND OUTLOOK

The leveraging of single-electron chemistry via the enabling technology of photoredox catalysis has clearly opened new doors in the realm of transition metal catalyzed cross-coupling. The motifs outlined herein are only some of the powerful new strategies accessed by this fruitful marriage of catalytic modes.[81−85] For example, several reports have employed photoredox catalysts to access oxidative cross-couplings with a variety of transition metals.[86−93]

Moreover, there still exist stoichiometric precedents in single-electron acceleration of reactivity that have yet to be realized in a catalytic sense. One potentially instructive example of an accelerated migratory insertion is the documented

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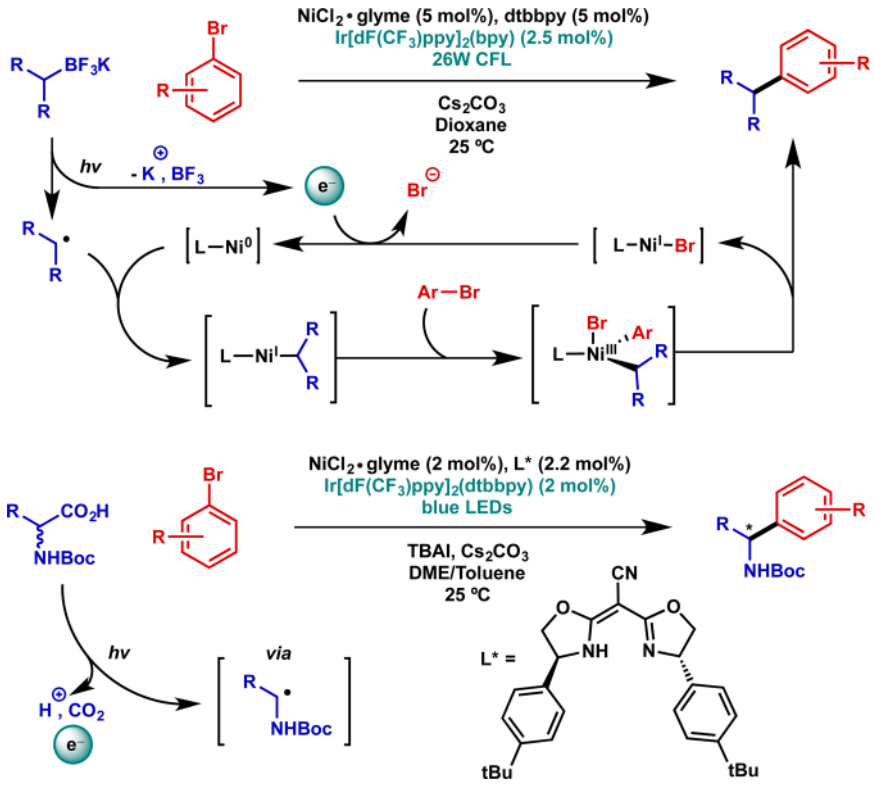

Figure 13. Catalytic applications: nickel-catalyzed Csp^3–Csp^2 coupling reactions of alkyltrifluoroborates (racemic) and amino acids (enantioselective). TBAI = tetrabutylammonium iodide, DME = 1,2-dimethoxyethane, Boc = tertbutoxycarbamoyl.

catalysis of alkyl carbonylation at iron via single-electron oxidation (Figure 14); a dual catalytic coupling reaction making use of this behavior is likely possible by some combination of photoredox and transition metal catalysts.[94]

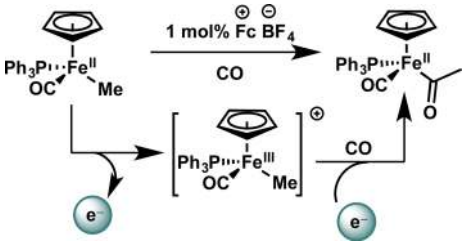

Figure 14. Redox catalysis of migratory insertion. Fc^+ = ferrocenium.

Though the power of open-shell intermediates to provide rapid turnover has evidently been demonstrated, there are a number of challenges that lie ahead. For one, while the stereoconvergent nature of radical addition to transition metals has allowed the development of enantioselective processes,[75] it also imposes limitations in the diastereoselectivity for radical transmetalation,[62] making the synthesis of mismatched stereoisomers a more complex problem (Figure 15).[95]

These challenges should be taken as a call to action, as the power demonstrated in the reports thus far suggests a wealth of untapped reactivity. Most tantalizingly, the involvement of a photoprocess suggests that endergonic transformations may be possible in these catalytic reactions.[96]

Additionally, there are a wide variety of photoredox catalysts and metals yet to be engaged in dual catalytic reactions. Recent reports of photoinduced electron transfer from supramolecular host complexes[97] are particularly intriguing given the synergy

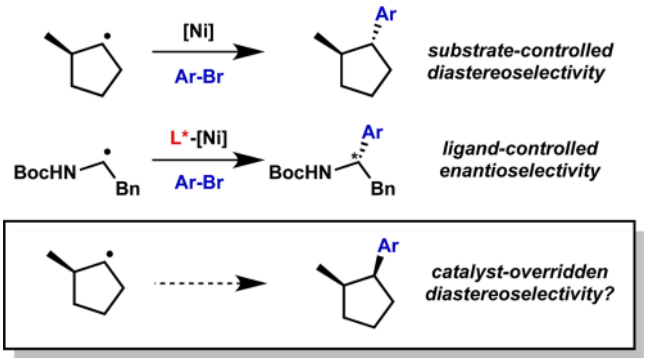

Figure 15. Stereoconvergence and diastereoselectivity in nickel-catalyzed radical cross-coupling.

displayed between transition metal catalysts and supramolecular catalysts.[98]

Furthermore, the combination of more than one of the activation modes presented herein, though challenging, promises to enable progressively more complex transformations to be developed. To date, no sp^3–sp^3 C–C coupling protocols have taken advantage of the newly discovered photoredox manifolds, but such an advance, not to mention many others, is undoubtedly on the horizon.

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Notes

The authors declare no competing financial interest.

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