

## Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis

Amy Y. Chan,<sup>†</sup> Ian B. Perry,<sup>†</sup> Noah B. Bissonnette, Benito F. Buksh, Grant A. Edwards, Lucas I. Frye, Olivia L. Garry, Marissa N. Lavagnino, Beryl X. Li, Yufan Liang, Edna Mao, Agustin Millet, James V. Oakley, Nicholas L. Reed, Holt A. Sakai, Ciaran P. Seath, and David W. C. MacMillan\*

Cite This: <https://doi.org/10.1021/acs.chemrev.1c00383>

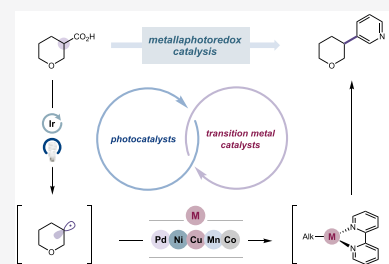
Read Online

ACCESS |

Metrics & More

Article Recommendations

**ABSTRACT:** The merger of photoredox catalysis with transition metal catalysis, termed metallaphotoredox catalysis, has become a mainstay in synthetic methodology over the past decade. Metallaphotoredox catalysis has combined the unparalleled capacity of transition metal catalysis for bond formation with the broad utility of photoinduced electron- and energy-transfer processes. Photocatalytic substrate activation has allowed the engagement of simple starting materials in metal-mediated bond-forming processes. Moreover, electron or energy transfer directly with key organometallic intermediates has provided novel activation modes entirely complementary to traditional catalytic platforms. This Review details and contextualizes the advancements in molecule construction brought forth by metallaphotocatalysis.



### CONTENTS

1. Introduction	B	5.2. Alkyne Functionalization	AF
1.1. Transition Metal Catalysis	B	5.3. Biaryl Coupling	AH
1.2. Photoredox Catalysis	B	5.4. Miscellaneous Transformations	AI
2. Nickel Metallaphotocatalysis	B	5.5. Direct Excitation	AJ
2.1. Carbon–Carbon Bond Formation	B	6. Cobalt Metallaphotocatalysis	AJ
2.1.1. Carboxylic Acids as Nucleophiles	C	6.1. Cross-Dehydrogenative Coupling	AJ
2.1.2. Alkylboron Derivatives as Nucleophiles	D	6.2. Dehydrogenation and Hydrogenation	AL
2.1.3. Other Carbon Nucleophiles	E	6.3. Hydrofunctionalization of Olefins	AM
2.1.4. C–H Bonds as Nucleophiles	F	6.4. Miscellaneous Transformations	AN
2.1.5. Cross-Electrophile Couplings	I	7. Other Metallaphotocatalysis	AN
2.2. Carbon–Heteroatom Bond Formation	K	7.1. Titanium Metallaphotocatalysis	AN
2.2.1. C–O Bond Formation	K	7.2. Chromium Metallaphotocatalysis	AN
2.2.2. C–N Bond Formation	L	7.3. Rhodium Metallaphotocatalysis	AO
2.2.3. Other Heteroatomic Nucleophiles	N	7.4. Ruthenium Metallaphotocatalysis	AP
2.2.4. Multicomponent Reactions and 1,2-Difunctionalization	O	7.5. Iron Metallaphotocatalysis	AP
3. Copper Metallaphotocatalysis	P	7.6. Manganese Metallaphotocatalysis	AQ
3.1. C–C Bond Formation: Fluoroalkylation	P	8. Conclusions and Outlook	AQ
3.2. C(sp)–C Bond Formation	Q	Author Information	AQ
3.3. 1,2-Difunctionalization of $\pi$ -Unsaturation	T	Corresponding Author	AQ
3.4. Copper as a Lewis Acid	V	Authors	AR
3.5. Other Nucleophiles	V	Author Contributions	AR
4. Palladium Metallaphotocatalysis	AA	Notes	AR
4.1. Early Work	AA	Biographies	AR
4.2. C–H Activation	AA		
4.3. Allylation	AC		
4.4. Carbonylation and Carboxylation	AE		
5. Gold Metallaphotocatalysis	AE		
5.1. Alkene Functionalization	AE		

**Special Issue:** Photochemical Catalytic Processes

**Received:** May 3, 2021

Acknowledgments

AS

References

AS

## 1. INTRODUCTION

### 1.1. Transition Metal Catalysis

Transition metal catalysis has long been recognized as a reliable and modular way to construct complex molecules from simple, readily accessible starting materials.<sup>1</sup> Since the turn of the century, three Nobel Prizes have been awarded in the diverse arena of transition metal catalysis, with developments in stereoselective catalysis,<sup>2–4</sup> olefin metathesis,<sup>5–7</sup> and palladium-catalyzed cross-coupling<sup>8–10</sup> all garnering the prestigious prize. Of the myriad reasons transition metal catalysis has been so broadly adopted, perhaps most compelling is the capacity for novel activation modes of abundant, often feedstock chemicals. Metal-mediated bond-breaking and forming mechanisms have allowed for the incorporation of simple chemical fragments into synthesis, broadening the pool of available precursors to chemical complexity, thereby dramatically shortening synthetic sequences.

Although the field of transition metal catalysis encompasses an extensive swath of chemical reactivity, the strategies employed to manipulate the reactivity of a given metal have remained somewhat constant since the inception of the field two centuries ago. Specifically, modulation of either the metal's ligand field or oxidation state have represented a majority of the strategies employed to enable a desired transformation (Scheme 1a). In the context of ligand design, perhaps no example of this strategy has proven more fruitful than the Buchwald-Hartwig amination. Nearly 30 years of ligand development for Pd-catalyzed C–N couplings has resulted in a spectrum of robust Buchwald-Hartwig amination reactions, capable of constructing pharmaceutically relevant anilines of nearly any type, substitution pattern, or pendant functionality.<sup>11</sup>

However, while the oxidation state of metal catalysts has likewise represented an important design element in the development of novel catalytic platforms, the adjustment of this property has not been as operationally straightforward. Whereas coordinating ligands can be highly selective in the binding of metal centers, modification of oxidation state by either addition of stoichiometric oxidants or reductants will inherently affect the overall reaction mixture. Nevertheless, pioneering work first by Kochi<sup>12</sup> and later by Hillhouse<sup>13–15</sup> conclusively illustrated the effect that metal center oxidation has in forging challenging bonds by inducing reductive elimination. Copper-catalyzed C–N couplings reported by Chan, Evans, and Lam demonstrated the propensity for high-valent Cu(III), generated via nucleophile coordination followed by aerobic oxidation, to provide valuable C–N linkages, likewise via oxidant-promoted reductive elimination step.<sup>16–18</sup> Yu and Sanford went on to demonstrate this principle similarly applies to palladium catalysis, with a number of Pd(IV)-mediated transformations forging previously catalytically inaccessible bonds, once again via the assistance of a strong chemical oxidant.<sup>19–21</sup> In the wake of these remarkable advancements in oxidant-mediated transition metal catalysis, the potential value of a catalytic electron shuttle, capable of precisely modifying the electronic structure of transition metal centers for catalytic applications, is clear.

### 1.2. Photoredox Catalysis

Despite the countless transformations enabled by photochemistry over the past century, until recently, light-mediated chemistries have not seen the same broad adoption across all fields of the science. The use of high-energy light, coupled with the disparate set of absorption properties of organic molecules as a whole, has hampered the development of general photochemical reactions. Nevertheless, from the earliest reports detailing the [2+2] cycloaddition of natural products by exposure to sunlight,<sup>22</sup> the conversion of photonic energy into chemical energy has captivated the synthetic community. More recent discoveries of absorptive organometallic complexes and organic dyes (with early applications in materials and inorganic chemistry)<sup>23–25</sup> have enabled photochemistry on an extensive range of organic and organometallic substrates, without regard to substrate photophysical properties. This field—termed photoredox catalysis—has enabled a renaissance of photochemical reactions enabled by single-electron-transfer (SET) and energy-transfer (ET) processes.<sup>26–28</sup>

The widespread adoption and growth of the field can, in part, be owed to the well-established photophysical properties of photoredox catalysts. These complexes, often polypyridyl complexes of ruthenium or iridium, can be excited by low-energy visible light, with this photonic energy selectively targeting the catalyst over any number of organic and organometallic substrates in solution. Thereafter, a metal-to-ligand charge-transfer event (MLCT) followed by intersystem crossing provides a long-lived triplet excited state (Scheme 1b). This reactive species possesses both a metal-centered vacancy, capable of oxidizing a suitable electron donor, and a  $\pi^*$ -centered unpaired spin, capable of reducing an adequate acceptor. After this initial photoinduced SET, the corresponding redox-modified ground state can perform the opposite downstream SET event, rendering the complex a catalyst in both the oxidation and reduction of substrates.<sup>29</sup> This well-defined relationship between catalyst structure and reactivity has enabled rapid developments in the rational design of novel catalysts.<sup>30</sup>

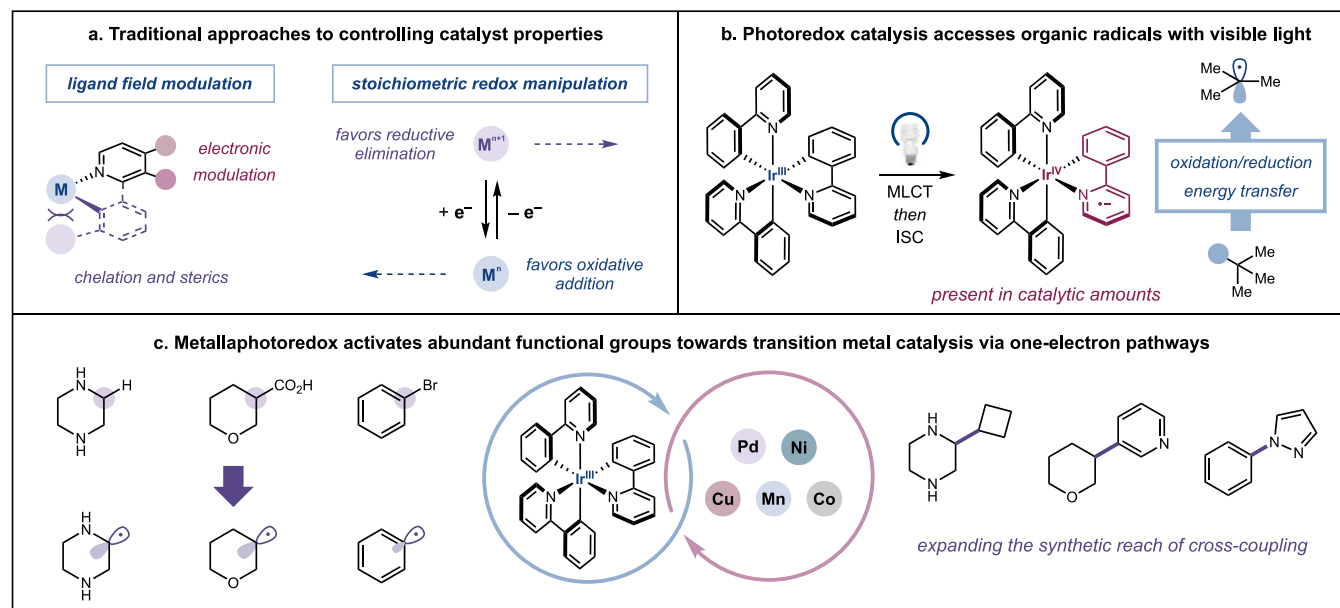
While photoredox catalysis has seen broad adoption for the activation and transformation of organic substrates, the platform has more recently garnered attention in the context of dual catalysis with transition metals.<sup>31–34</sup> The productive interfacing of transition metal-mediated substrate activation with the excited-state chemistry of photoredox catalysis represents a unique opportunity to merge two powerful platforms in pursuit of novel disconnections and unprecedented reactivity. Moreover, the application of photoinduced SET and ET in the modification of metal catalyst electronic structure expands opportunities for high-valent and excited-state catalysis, notably in the absence of stoichiometric strong oxidants or high-energy light irradiation (Scheme 1c). This Review will detail the merger of transition metal catalysis with photoredox catalysis—termed metallaphotoredox catalysis—from seminal studies to the most recent applications in synthetic contexts.

## 2. NICKEL METALLAPHOTOCATALYSIS

### 2.1. Carbon–Carbon Bond Formation

Over the last half century, the advent and development of palladium-catalyzed cross-coupling has revolutionized the means by which chemists synthesize new molecules. Groundbreaking work from Heck, Negishi, and Suzuki,<sup>35</sup>

## Scheme 1. Merger of Photoredox and Transition Metal Catalysis



among many others,<sup>36</sup> has allowed for the construction of unprecedented molecular complexity from simple, abundant starting materials. However, despite the widespread success of palladium-catalyzed cross-couplings in the forging of bonds to  $sp^2$ -hybridized carbon centers, significant limitations remain with respect to the coupling of  $sp^3$ -hybridized fragments. Substantial progress toward this challenging objective has been made in the area of nickel catalysis, which, when compared to palladium, undergoes a more rapid oxidative addition into alkyl electrophiles and suffers less from deleterious  $\beta$ -hydride elimination with aliphatic ligands.<sup>37</sup> While these developments have broadened the spectrum of strategies at the disposal of the modern chemist, the desire to expand the scope of coupling partners to simpler, cheaper, and more abundant starting materials has pushed the frontiers of catalysis. In this context, photoredox catalysis has played an integral role incorporating native functional groups in novel bond disconnections.

**2.1.1. Carboxylic Acids as Nucleophiles.** Given our laboratory's experience in the use of carboxylic acids as radical precursors,<sup>38–40</sup> and the well-established role of radical intermediates in nickel-mediated cross-couplings,<sup>37</sup> we hypothesized that abundant carboxylic acids could function as latent nucleophiles in cooperative photoredox and nickel catalytic cycles. In collaboration with the Doyle group, we successfully realized this merger of catalytic manifolds in an  $C(sp^2)$ – $C(sp^3)$  decarboxylative cross-coupling of carboxylic acids with aryl halide electrophiles.<sup>41</sup> A mechanistic picture of this transformation is shown in Scheme 2. Upon excitation and intersystem crossing of photocatalyst **1**, the highly oxidizing and long-lived triplet excited state **2** can interface with carboxylate nucleophile **3** in an SET event. Subsequent decarboxylation affords alkyl-centered radical **4**. Concurrently, nickel(0) species **5**, presumably generated via two sequential electron-transfer events from a nickel(II) precatalyst, can undergo oxidative addition with the aryl halide electrophile (**6**) to afford nickel-aryl species **7**. Oxidative radical capture by this intermediate affords Ni(III)-aryl-alkyl complex **8**, which undergoes rapid reductive elimination to afford the desired

$C(sp^2)$ – $C(sp^3)$  coupled product (**9**). Finally, the resultant nickel(I) species **10** and the reduced photocatalyst **11** can undergo SET to regenerate both active catalysts simultaneously.

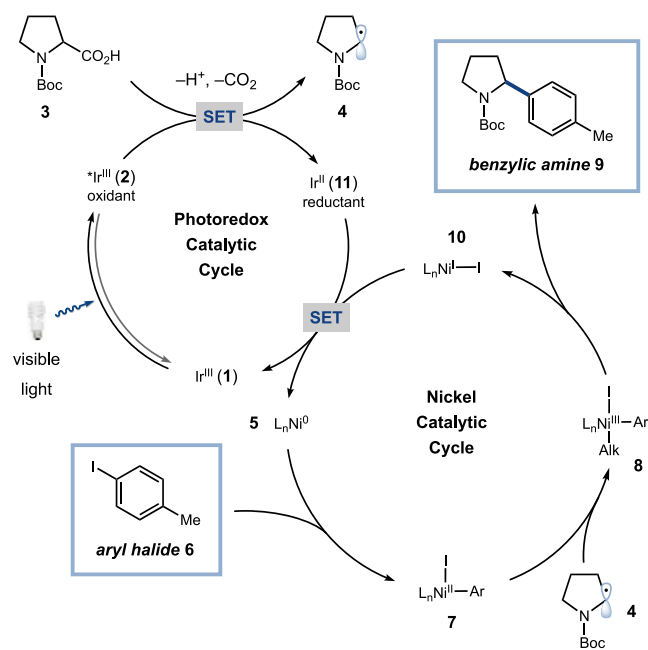
While this initial report provided an efficient method for the decarboxylative arylation of simple and abundant  $\alpha$ -heteroatom carboxylic acids with (hetero)aryl halides, it has since been expanded to a number of mechanistically related transformations (Scheme 3). In collaboration with the Fu group, the decarboxylative arylation was rendered asymmetric through optimization of the bis(oxazoline) ligand, with the joint venture affording an efficient protocol for the enantioselective arylation of amino acids.<sup>42</sup> Furthermore, Flanagan and co-workers employed electron-deficient pyridyl carboxamide ligands to develop a water-compatible platform for the arylation of  $\alpha$ -amino acids with DNA-tagged aryl halides.<sup>43</sup> Mild and DNA-compatible reaction conditions underscore potential bio-relevant applications, particularly toward the construction of DNA-encoded libraries. The decarboxylative coupling protocol was later expanded to include new classes of nucleophiles, with  $\alpha$ -ketoacids functioning effectively as  $sp^2$ -hybridized nucleophilic radical precursors to ketones in the dual-catalytic platform.<sup>44</sup> Exploration of the electrophile scope revealed that vinyl halides could also serve as productive coupling partners, affording the corresponding alkenes in good yields through an analogous mechanism.<sup>45</sup> A second decarboxylative vinylation, disclosed thereafter, made use of simple alkynes as coupling partners, and was proposed to operate via a migratory-insertion–protodemetalation mechanism.<sup>46</sup> Mixed carboxylic acid anhydrides (formed *in situ* from the corresponding acid chlorides and free carboxylates) were demonstrated to provide access to aryl and alkyl ketones via a  $CO_2$ -extrusion–recombination mechanism,<sup>47</sup> expanding the scope  $CO_2$ -extrusion methods for the synthesis of ketones beyond traditional palladium-catalyzed methods limited to activated benzylic and allylic ester starting materials.<sup>48,49</sup>

While many early advancements in metallaphotoredox-catalyzed C–C bond formation involved an  $sp^2$ -hybridized

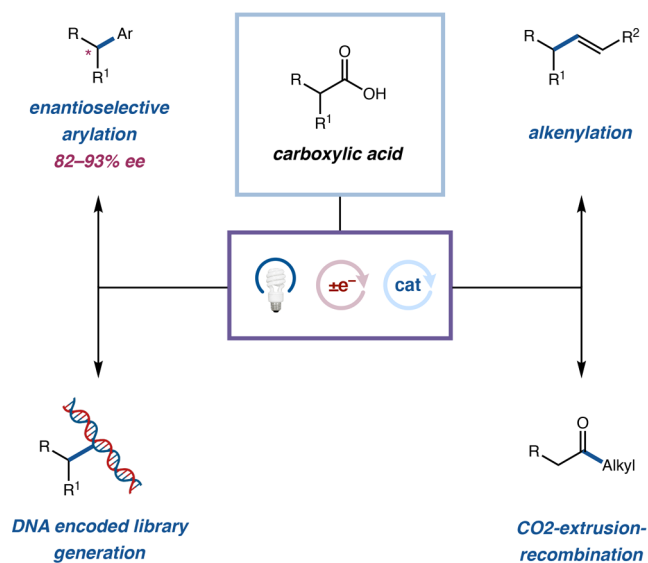
electrophile, metal-catalyzed  $C(sp^3)-C(sp^3)$  bond formations remain one of the most attractive strategies for complex molecule synthesis, and thus have remained a longstanding goal. On the basis of the well-established activation of alkyl electrophiles by nickel catalysts,<sup>37,50,51</sup> we brought forth a decarboxylative arylation protocol, wherein primary and secondary alkyl bromide electrophiles were coupled in good efficiencies to a number of carboxylic acid pronucleophiles.<sup>52</sup> This complementary photocatalyzed protocol obviated the need for organometallic nucleophiles, which are traditionally used in challenging alkyl-alkyl cross-couplings.<sup>53</sup>

**2.1.2. Alkylboron Derivatives as Nucleophiles.** Concurrently with the initial collaboration between our lab and the Doyle lab,<sup>41</sup> a nickel- and photoredox-catalyzed cross-coupling using alkylboron nucleophiles was described by Molander and co-workers.<sup>54</sup> This report detailed the use of benzyltrifluoroborate salts as benzylic radical precursors, likewise in a  $C(sp^2)-C(sp^3)$  cross-coupling with aryl bromides. Analogous to the oxidative radical generation from alkyl carboxylates described by our lab and others, Molander and co-workers found that alkyltrifluoroborates can be expediently converted to carbon-centered radicals upon SET with an excited photocatalyst. The proposed single-electron pathway by which the alkyl-nickel species is formed circumvents a traditionally sluggish transmetalation by alkylboron reagents,<sup>54</sup> a key insight which has enabled numerous challenging bond formations via reductive elimination from a high-valent Ni(III) intermediate. In the same report, the authors found that by employing a chiral ligand on nickel, racemic alkylborate nucleophiles could give moderately enantioenriched arene-containing products. In a collaborative effort between the labs of Molander and Kozlowski, DFT calculations provided evidence supporting the proposed mechanism of the  $C(sp^2)-C(sp^3)$  cross-coupling, while suggesting the origin of stereoselection in the asymmetric protocol lies in the reversible capture of the stabilized, prochiral radical by the nickel complex prior to reductive elimination.<sup>55</sup> The original and revised mechanisms are detailed in Scheme 4. Photo-

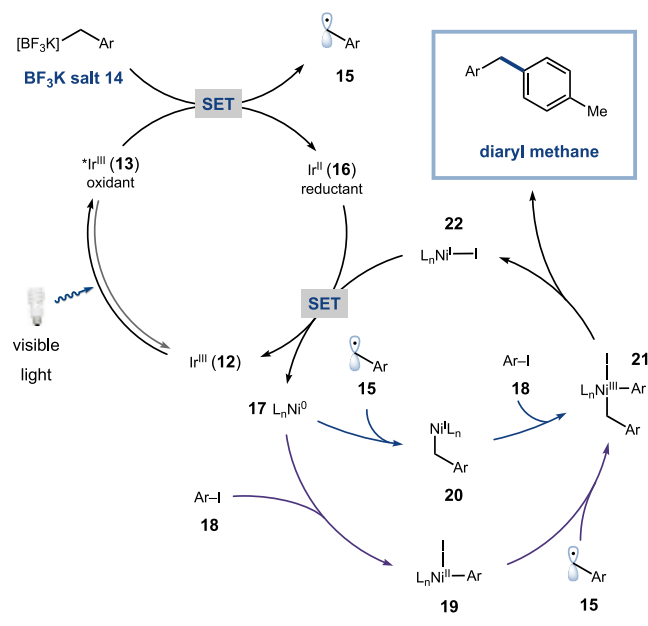
Scheme 2. Nickel-Catalyzed Decarboxylative Arylation



Scheme 3. Decarboxylative Transformations



Scheme 4. Photoredox Organoboron Cross-Coupling

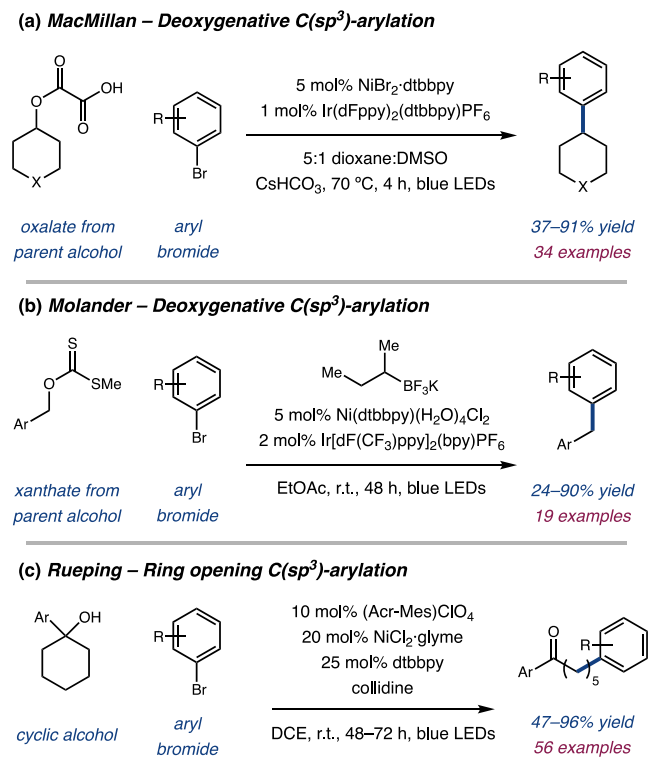


excitation of iridium photocatalyst **12** affords excited-state species **13**, which can readily undergo SET with benzylic trifluoroborate salt **14** to furnish the corresponding benzylic radical **15** and reduced photocatalyst **16**. Here, the original and revised mechanisms diverge. Molander and co-workers' original report postulated that Ni(0) precatalyst **17** would undergo oxidative addition into aryl electrophile **18**, and the subsequent nickel oxidative addition complex (**19**) could capture carbon-centered radical **15**. The revised mechanism proposes a lower energy pathway by which nickel species **17** first captures the benzylic radical to afford nickel(I)-alkyl species **20**. Oxidative addition then affords key Ni(III) intermediate **21**, from which radical **15** can reversibly dissociate. Both proposed mechanisms then converge, where reductive elimination from intermediate **21** yields the desired product and Ni(I) species **22**. A final electron-transfer between the metal catalyst and reduced photocatalyst **16** closes both catalytic cycles. This general strategy for bond formation has

since been extended to the coupling of both  $\alpha$ -amino<sup>56</sup> and  $\alpha$ -oxy alkyltrifluoroborates,<sup>57</sup> as well as unstabilized secondary alkylboron nucleophiles.<sup>58</sup> Additionally, Ley and co-workers were able to translate this reaction platform to a homogeneous high-throughput continuous-flow process by modifying the radical precursor from alkyltrifluoroborate salts to more soluble Lewis-base-activated boronic esters.<sup>59</sup> Methods for the synthesis of  $\alpha$ -branched alcohols, both protected<sup>60</sup> and unprotected,<sup>61</sup> have been disclosed by Molander and co-workers, and variation of the electrophilic coupling partner to acyl chlorides<sup>62</sup> or imides<sup>63</sup> has given rise to valuable methods for the construction of carbonyl-containing compounds. With an analogous goal, Doyle and Rovis reported the use of a chiral nickel catalyst in combination with a photoredox catalyst in the desymmetrization of *meso*-anhydride electrophiles with alkyltrifluoroborates in the synthesis of chiral ketones.<sup>64</sup> The chiral catalyst performed an enantioselective oxidative addition, followed by capture of a trifluoroborate-derived radical, and reductive elimination to forge the enantioenriched ketone in good yields and moderate selectivities. Compellingly, Molander and co-workers achieved expedient assembly of challenging quaternary carbon centers utilizing tertiary alkyltrifluoroborate salts.<sup>65</sup> Recent quantum mechanical calculations attributed the reaction's success to the critical role of the anionic diketonate ligand in the conventionally challenging coupling, suggesting an outer-sphere reductive elimination was operative in the bond-forming step.<sup>66</sup>

**2.1.3. Other Carbon Nucleophiles.** Photoredox-catalysis-triggered adoption of carboxylic acids and alkyltrifluoroborates in metal-catalyzed couplings represents a large body of foundational work in the area of metallaphotoredox catalysis. Still, interest in extending this powerful mode of activation toward the incorporation of ever-simpler starting materials in metal-mediated cross-couplings has driven innovation toward novel strategies for radical generation. In 2015, a collaboration with the Overman group established that oxalate esters, formed from the corresponding alcohol in a single step without purification, were able to undergo the sequential loss of two molecules of CO<sub>2</sub> upon oxidation to afford carbon-centered radicals in a novel means of C(sp<sup>3</sup>)-O bond activation.<sup>67</sup> We speculated that this strategy could be incorporated into a metallaphotoredox dual-catalytic platform, bringing alcohols, one of the most abundant functional groups in synthetic chemistry, into the fold of nucleophiles available for cross-coupling. This transformation was realized under a familiar mechanistic picture, with the doubly decarboxylative strategy affording novel C(sp<sup>3</sup>)-aryl linkages in good yield from a broad range of alcohol starting materials and (hetero)aryl halides (Scheme 5a).<sup>68</sup> In a complementary report, Molander and co-workers successfully employed benzylic alcohols, prefunctionalized as well-established xanthate ester radical precursors<sup>69</sup> via C-O bond fragmentation upon reaction of an alkyl radical activator derived from an alkyltrifluoroborate additive with the thiocarbonyl of a xanthate pronucleophile, in a deoxygenative C(sp<sup>3</sup>)-arylation protocol (Scheme 5b).<sup>70</sup> In a mechanistically distinct effort to engage alcohols in selective distal functionalization of pendant carbon chains, Rueping and co-workers developed a metallaphotocatalytic ring-opening arylation to afford linear ketones from cyclic benzylic alcohols (Scheme 5c),<sup>71</sup> a radical generation strategy akin to the work of Knowles and co-workers.<sup>72</sup> Martin and co-workers recognized the utility of engaging unactivated aliphatic alcohols as sp<sup>3</sup> synthons and developed a dual nickel/photoredox

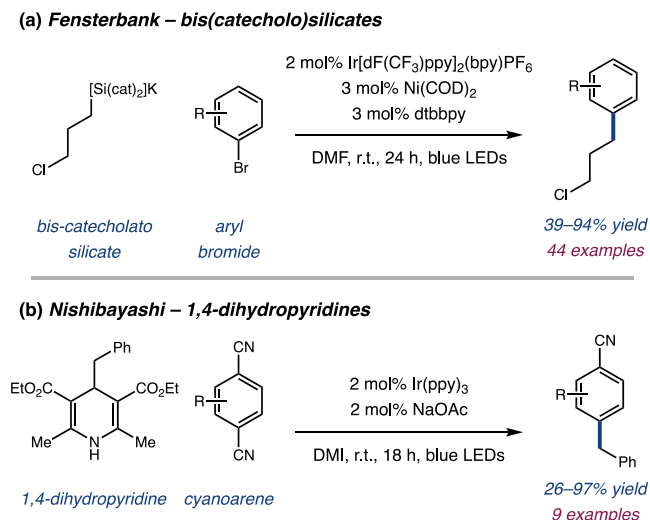
## Scheme 5. Deoxygenative Cross-Couplings



catalytic method to forge sp<sup>2</sup>-sp<sup>3</sup> and sp<sup>3</sup>-sp<sup>3</sup> carbon bonds with aryl and alkyl halides via  $\beta$ -scission of *N*-phthalimide ethers derived from aliphatic alcohol.<sup>73</sup> Soon after, Zuo and co-workers disclosed the cerium ligand-to-metal charge transfer (LMCT) activation of easily accessible free alcohols toward a photocatalytic dehydroxymethylative arylation protocol with aryl halides to furnish sp<sup>2</sup>-sp<sup>3</sup> carbon bonds.<sup>74</sup>

Alkylsilicates have emerged as reliable sources of unstabilized carbon-centered radicals, and the relatively mild oxidation potential of these silicate salts has provided opportunities for the exploration of less oxidizing photocatalysts in metallaphotocatalytic manifolds. Based on foundational work by Nishigaichi and co-workers,<sup>75</sup> Fensterbank et al. successfully engaged alkylbis(catecholato)silicates as coupling partners in a dual-catalytic strategy for the cross-coupling of aryl bromides with transiently generated primary alkyl radicals (Scheme 6a).<sup>76,77</sup> In a related study, Molander and co-workers developed a base-free arylation reaction from these silicate radical precursors and aryl halides, utilizing Ru(bpy)<sub>3</sub>Cl<sub>2</sub> in lieu of a more expensive iridium photocatalyst.<sup>78</sup> Notably, the absence of base enabled C(sp<sup>2</sup>)-C(sp<sup>3</sup>) bond formation in the presence of unprotected amines (as zwitterionic ammonium silicate salts) and successfully engaged a number of traditionally challenging *N*-heterocyclic aryl halide electrophiles. This platform was extended to alkenyl halides<sup>79</sup> and thereafter to bifunctional bromoarenes bearing orthogonal boronic ester functional handles.<sup>80</sup> Ollivier and Fensterbank later incorporated sp<sup>3</sup>-hybridized electrophiles in a contribution to the challenging area of C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond formation.<sup>81</sup> In a separate report, alkyl sulfonates also proved to be competent coupling partners with a comparably low oxidation potential.<sup>82</sup> Sulfonates were engaged as radical precursors in a cross-coupling with a variety of druglike aryl and heteroaryl

## Scheme 6. Other Radical Precursors



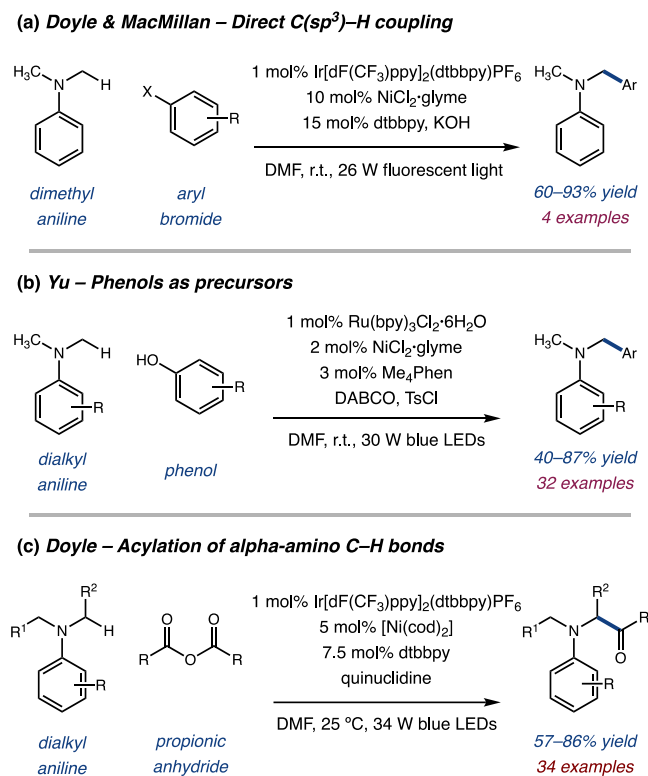
bromides, notably with a substantially less-oxidizing ruthenium catalyst.

Nishibayashi and co-workers hypothesized that 4-substituted 1,4-dihydropyridines (DHPs) could serve as latent alkyl radical sources, reasoning that after SET, the formation of the aromatic pyridine derivative could provide sufficient driving force for the generation of a high-energy carbon-centered radical. These unconventional reagents, derivatives of which have historically served as reductants in hydrogenation reactions,<sup>83</sup> successfully provided access to stabilized alkyl radicals under photoredox conditions (Scheme 6b).<sup>84</sup> In a follow-up report, the group demonstrated the use of these reagents in a dual nickel- and photoredox-catalyzed coupling of benzylic nucleophiles with (hetero)aryl iodides.<sup>85</sup> Meanwhile, the Melchiorre group reports direct photoexcitation of 4-alkyl DHPs, generating a highly reducing excited state that generates C(*sp*<sup>3</sup>)-centered radicals upon oxidation and homolytic cleavage. The dual-reactivity of DHPs was leveraged in nickel-catalyzed arylation<sup>86</sup> and asymmetric acylation using chiral box ligands<sup>87</sup> of the alkyl radicals. Concurrently, Molander and co-workers recognized that these dearomatized pyridines could be synthesized in a single high-yielding step from aldehydes and questioned whether these reagents could further expand the scope of available coupling partners to feedstock aldehyde starting materials for metallaphotoredox reactions. These efforts were once again met with success, and a range of aldehydes were converted to DHP congeners and ultimately coupled to a range of (hetero)arenes.<sup>88</sup> Thereafter, Molander and co-workers disclosed a novel strategy for C–C bond formation in a metallaphotoredox-catalyzed Tsuji–Trost allylation. DHP derivatives, as well as the more-familiar alkyl trifluoroborate salts, were employed in a dual-catalyzed reaction with allylic electrophiles.<sup>89</sup> While the authors did employ traditional allylic halides as electrophiles, a majority of the electrophilic coupling partners were vinyl epoxide derivatives. Quantum mechanical calculations suggested a nickel(0)-mediated coordination and subsequent S<sub>N</sub>2-like ring opening of the vinyl epoxide, followed by radical capture and inner-sphere reductive elimination. Notably, this Ni(0)–Ni(II)–Ni(III) mechanistic picture represents a departure from previous work suggesting radical capture precedes oxidative addition,<sup>55</sup> which serves to highlight the sensitivity of metallaphotocatalysis mechanisms to the specific identities

of both coupling partners present in the reaction mixture. Additionally, Melchiorre and co-workers extended the use of DHPs toward the generation of carbamoyl radicals for the synthesis of benzamides from (hetero)aryl halides, likewise in a nickel- and photoredox-catalyzed cross-coupling.<sup>90</sup>

**2.1.4. C–H Bonds as Nucleophiles.** Yet another longstanding challenge in the area of transition metal catalysis is the direct functionalization of C–H bonds in cross-coupling. Engaging the simplest organic moiety, the C–H bond, in fragment coupling reactions remains among the most sought-after transformations in synthetic chemistry. Photoredox catalysis, given its many robust methods for SET-mediated radical generation, has moved to the forefront of C–H functionalization strategies in recent years.<sup>91</sup> By merging light-enabled strategies for homolytic C–H cleavage with nickel catalysis, innumerable feedstock chemicals have become viable reagents for cross-coupling, without necessitating a stoichiometric prefunctionalization step. The first example of this powerful strategy stemmed from the serendipitous discovery of an oxidation–deprotonation mechanism of  $\alpha$ -amino radical generation. It was discovered that upon exposure of an aniline substrate bearing  $\alpha$ -amino C–H bonds to photoredox conditions, an SET event would afford an amine radical cation. Subsequent deprotonation of the now acidic adjacent C–H bond by a suitable base would then furnish a stabilized  $\alpha$ -amino radical.<sup>92</sup> Our lab, in collaboration with the Doyle lab, hypothesized that this species, when generated under metal-laphotoredox conditions, should act as a competent open-shell nucleophile in a dual-catalytic cross-coupling. As predicted, *N,N*-dimethylaniline served as a suitable precursor to benzylic amines derived from (hetero)aryl bromides and iodides (Scheme 7a).<sup>41</sup> This strategy was developed further by Doyle and co-workers to include a range of biorelevant cyclic

## Scheme 7. Oxidation Deprotonation C–H Cross-Coupling

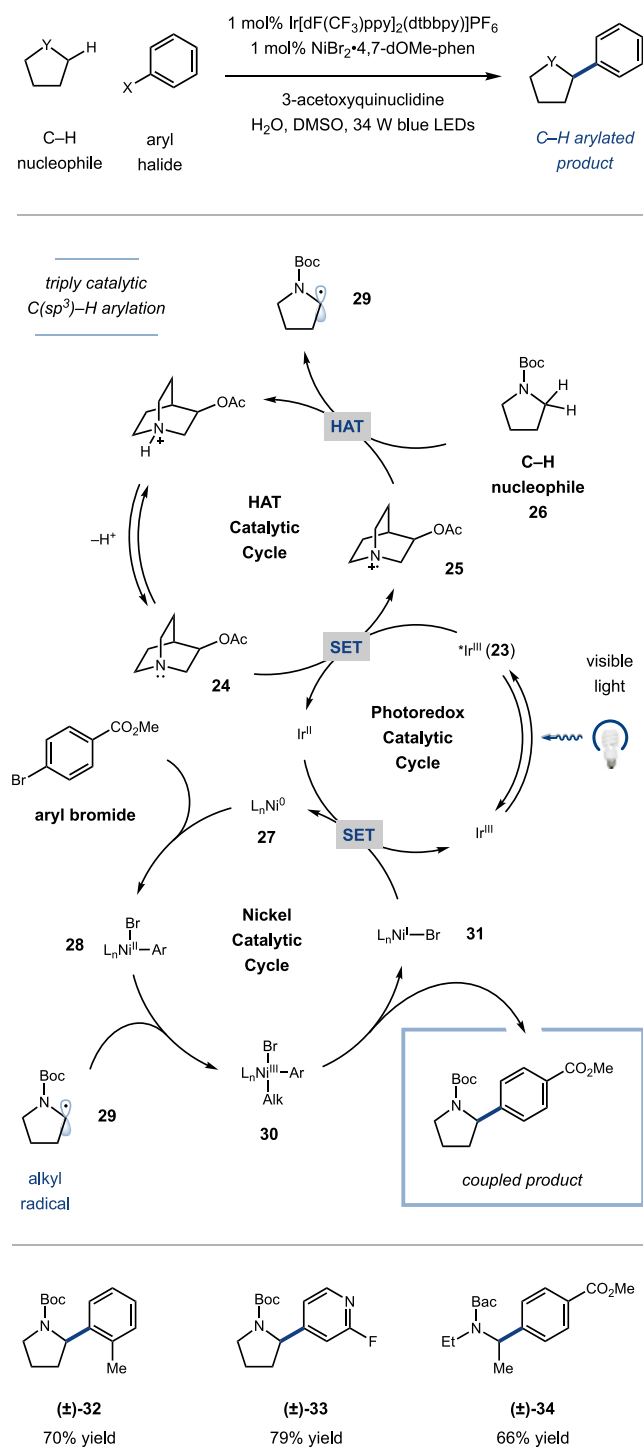


and acyclic amines, and a number of complex, pharmaceutically important aryl halides,<sup>93</sup> along with work by Yu and co-workers to include phenols as electrophiles, activated *in situ* as aryl tosylates (Scheme 7b).<sup>94</sup> Additionally, this open-shell C–H functionalization manifold was extended to carbonyl-based electrophiles (both anhydrides and thioesters) in the first metallaphotoredox C–H acylation (Scheme 7c).<sup>95</sup>

Radical generation via oxidation–deprotonation has proved a valuable method for the functionalization of redox-active amine substrates. Yet, in an effort to separate the redox properties of the substrate from the mode of activation, our lab and others have recently become interested in hydrogen atom transfer (HAT) as an approach to directly activate a broader range of C–H bonds. In this context, it was discovered that electron-deficient heteroatom-centered radicals could perform polarity-matched HAT events with suitable hydridic C–H bond-bearing substrates.<sup>96–98</sup> With these principles in mind, we developed a triple catalytic C(sp<sup>3</sup>)–H arylation reaction enabled by photoredox, nickel, and HAT catalysis.<sup>99</sup> The proposed mechanism, shown in Scheme 8, relies on a favorable SET between excited photocatalyst **23** and electron-rich bridgehead amine **24**, followed by a polarity-matched hydrogen atom abstraction by amine radical cation **25** from the anomerically activated, electron-rich  $\alpha$ -amino C–H bond of protected amine **26**. While the mechanism may be distinct from single-step, SET-mediated radical generations, the remaining components of the mechanism retain the same underlying elementary steps of earlier nickel metallaphotocatalysis publications. Namely, oxidative addition of nickel catalyst **27** into the aryl halide electrophile affords nickel(II) complex **28**, which, following oxidative radical capture of HAT-derived alkyl radical **29**, furnishes the key Ni(III)-aryl-alkyl intermediate **30**. Reductive elimination and SET between Ni(I) species **31** and the reduced photocatalyst affords the product and regenerates the active catalysts, respectively. This triply catalytic strategy provided access to a broad range of valuable benzylic amine products (**32–34**, 66%–79% yield). This quinuclidine-mediated HAT protocol has since been applied to an  $\alpha$ -amino C(sp<sup>3</sup>)–H alkylation protocol with alkyl bromide electrophiles, another significant advancement in the field of alkyl–alkyl coupling.<sup>100</sup> A computational investigation into the triple catalytic arylation and alkylation mechanisms provided support for the radical generation step, yet called into question the role of Ni(0) in the reaction mechanisms.<sup>101</sup> A lower energy pathway was proposed, wherein Ni(I) participates first in radical capture followed by SET, with the resulting electron-rich Ni(I)-alkyl complex undergoing oxidative addition to afford the penultimate Ni(III) species. Later, the synthesis of aromatic and aliphatic ketones via amine radical cation-mediated C–H abstraction from aldehydes was achieved in a mechanistically analogous fashion.<sup>102</sup> The regioselective  $\alpha$ -arylation of unprotected alcohols was achieved in a likewise manner, enabled by the introduction of a Lewis acid additive.<sup>103</sup> The formation of the Lewis acid-alkoxide complex was found to be crucial in achieving the desired  $\alpha$ -selectivity in the presence of otherwise more hydridic C–H bonds.

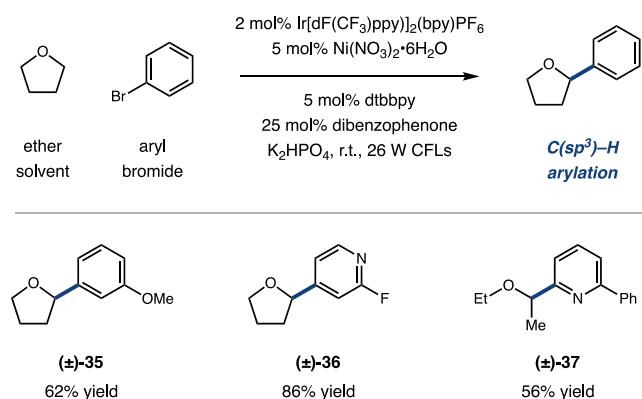
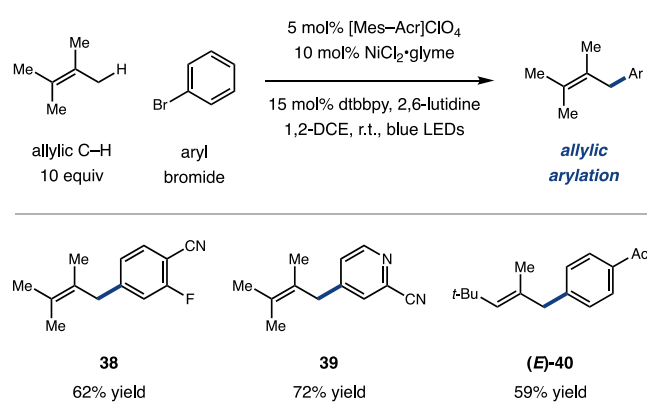
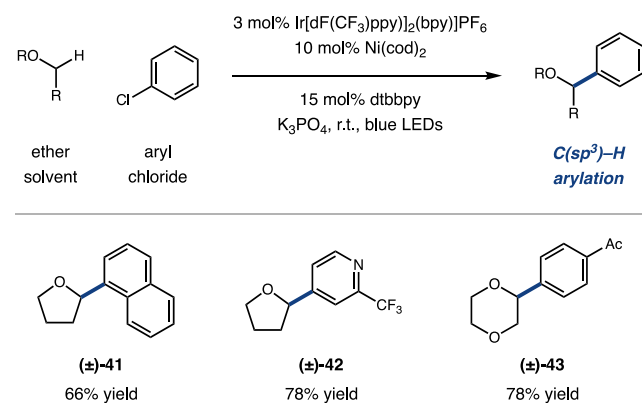
In addition to electrophilic nitrogen-centered radicals, halogen radicals have also been shown to engage productively in C–H abstraction events. In simultaneous reports, the laboratories of Molander and Doyle described the first halogen atom-mediated C–H arylations. Both reports detailed the C(sp<sup>3</sup>)–H cross-coupling of ethereal solvents via a dual-

Scheme 8. Triple Catalytic C–H Arylation



catalytic strategy. Molander and co-workers found that nickel(II) oxidative addition complexes of aryl bromides, upon triplet energy transfer from an excited iridium or benzophenone photocatalyst, could eject a bromine atom (Scheme 9a).<sup>104</sup> In the presence of the hydridic C–H bonds of ethereal solvents, this bromine radical could undergo an endothermic yet polarity-matched (and statistically favored) HAT event to generate an  $\alpha$ -oxy radical, which could rebound onto the nickel center, ultimately affording a range of  $\alpha$ -(hetero)aryl ethers (**35–37**, 56%–86% yield). Given the proposed energy-transfer mechanism, Molander and co-

## Scheme 9. Halogen Atom C–H Arylation

a) Molander – Br<sup>•</sup>-mediated  $\alpha$ -heteroatom C(sp<sup>3</sup>)-H arylationb) Rueping – Br<sup>•</sup>-mediated allylic C(sp<sup>3</sup>)-H arylation and vinylationc) Doyle – Cl<sup>•</sup>-mediated  $\alpha$ -heteroatom C(sp<sup>3</sup>)-H arylation

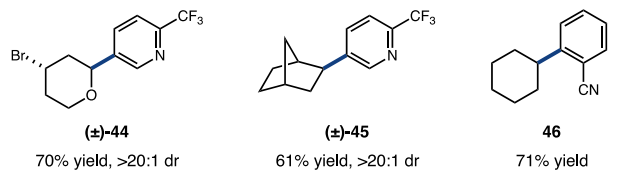
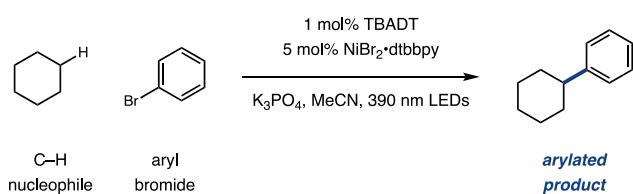
workers invoked bond-forming reductive elimination from a Ni(II) species, a deviation from the familiar Ni(III)-mediated bond formation traditionally proposed in metallaphotoredox cross-couplings. Thereafter, Rueping and co-workers applied this strategy toward a metallaphotocatalytic arylation and vinylation of allylic C–H bonds (Scheme 9b, **38–40**, 59%–72% yield).<sup>105</sup> Coinciding with the Molander lab's report, Doyle and co-workers disclosed a chlorine-radical-mediated C(sp<sup>3</sup>)-H arylation (Scheme 9c). The proposed mechanism calls upon precedent by Nocera and co-workers,<sup>106</sup> wherein a Ni(III)-Cl complex was shown to undergo visible-light excitation, followed by metal–halogen bond homolysis in the charge-transfer excited state. Doyle and co-workers suggested

an analogous step, wherein the aryl chloride Ni(II) oxidative addition complex first undergoes SET with the excited photocatalyst to afford the corresponding Ni(III) complex, followed by direct excitation to generate a highly oxidizing chlorine atom. Hydrogen atom abstraction by this species from a number of ether solvents was demonstrated, coupling an array of aryl chlorides with the C–H-bearing chemical feedstocks (**41–43**, 66%–78% yield).<sup>107</sup> Stoichiometric studies and emission-quenching experiments provided evidence for the halogen photoelimination step from the Ni(III)-aryl chloride complex. Reducing the nucleophile loading from solvent quantity to merely 10 equiv in benzene solvent was well tolerated, affording tetrahydrofuran and toluene-derived products in good yields. While the strategy did provide synthetically useful yields for arylation of the strong, unactivated C–H bonds in cyclohexane, competitive consumption of the chlorine radical by the resultant weakened tertiary benzylic C–H bond of the product was postulated to reduce reaction efficiency. To circumvent this issue, Doyle and co-workers next employed chloroformates as electrophiles in a complementary transformation.<sup>108</sup> The electron-deficient nature of the  $\alpha$ -carbonyl C–H bond disfavors abstraction by the polarity-mismatched chlorine radical, which prevents deleterious product inhibition. Under optimized conditions, a broad scope of alkanes were functionalized in good yields with predictable site-selectivity by the principle of polarity-matching.<sup>96</sup> Doyle and co-workers employed this HAT mechanism in the formylation of aryl chlorides via chlorine-radical-mediated HAT from the weak 2-substituted  $\alpha$ -oxy C–H bond of dioxolane.<sup>109</sup> In a subsequent work, the group reported the methylation of chloroarenes, a reaction of significant interest to the pharmaceutical sector.<sup>110</sup> The authors proposed that a similar chlorine-radical-mediated HAT from the weak C–H bond of the trimethyl orthoformate solvent could provide, through a  $\beta$ -scission mechanism, high-energy methyl radicals. This key insight enabled the methylation of a broad scope of biorelevant arenes and heteroarenes in a regioselective fashion.<sup>111</sup> Additionally, the Wu group invoked a chlorine radical photoelimination mechanism in the hydroalkylation of alkynes with C(sp<sup>3</sup>)-H nucleophiles.<sup>112</sup>

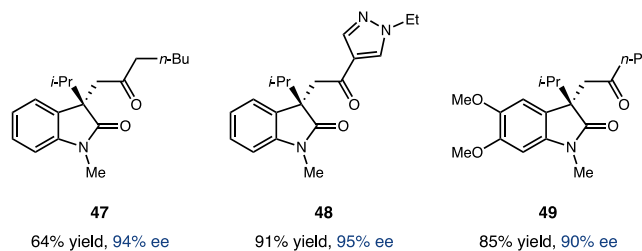
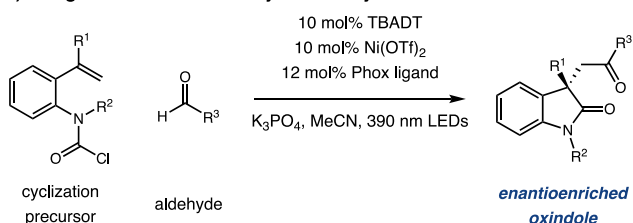
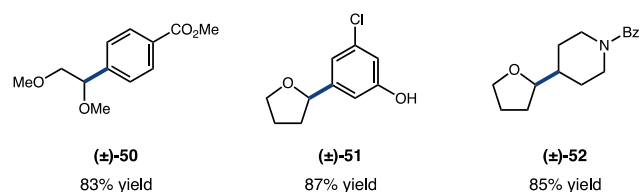
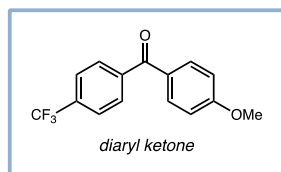
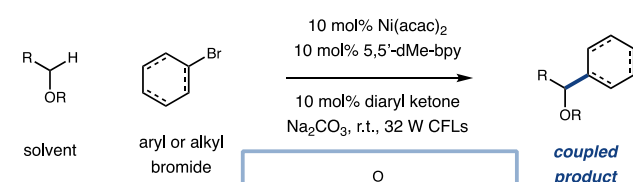
Until recently, the predominant strategy for engaging C(sp<sup>3</sup>)-H bonds in metallaphotoredox catalysis relied on the photocatalytic generation of an electrophilic, open-shell species to act as a transiently formed HAT reagent.<sup>99,104,107</sup> However, there exist a variety of well-established photocatalysts which, upon excitation, develop electrophilic heteroatom-centered radical character and can themselves be productively employed in direct C–H cleavage reactions to afford versatile radical intermediates.<sup>113</sup> Our laboratory recently questioned if a HAT catalyst could be employed in a dual-catalytic C–H cross-coupling strategy, substituting the intermediacy of a transiently generated reagent for a light-activated catalyst capable of hydrogen atom abstraction. The polyoxometalate photocatalyst tetrabutylammonium decatungstate (TBADT) was selected for its highly oxidizing excited state,<sup>114</sup> well studied selectivity parameters,<sup>115</sup> and suitable potentials for the electron-transfer steps necessary for metal catalyst turnover.<sup>114</sup> This selection proved fruitful, and the use of TBADT and nickel in a dual-catalytic C–H cross-coupling reaction productively engaged a broad array of strong C–H bond-bearing carbon frameworks as coupling partners, albeit in moderate excess (5 equiv, Scheme 10a).<sup>116</sup> A variety of aryl and heteroaryl bromides



## Scheme 10. HAT Catalyst-Mediated C–H Cross-Coupling

a) MacMillan – C(sp<sup>3</sup>)–H arylation via decatungstate photocatalysis

## b) Wang – enantioselective acyl-carbamoylation of tethered alkenes

c) Martin – C(sp<sup>3</sup>)–H arylation via triplet aryl ketone activation

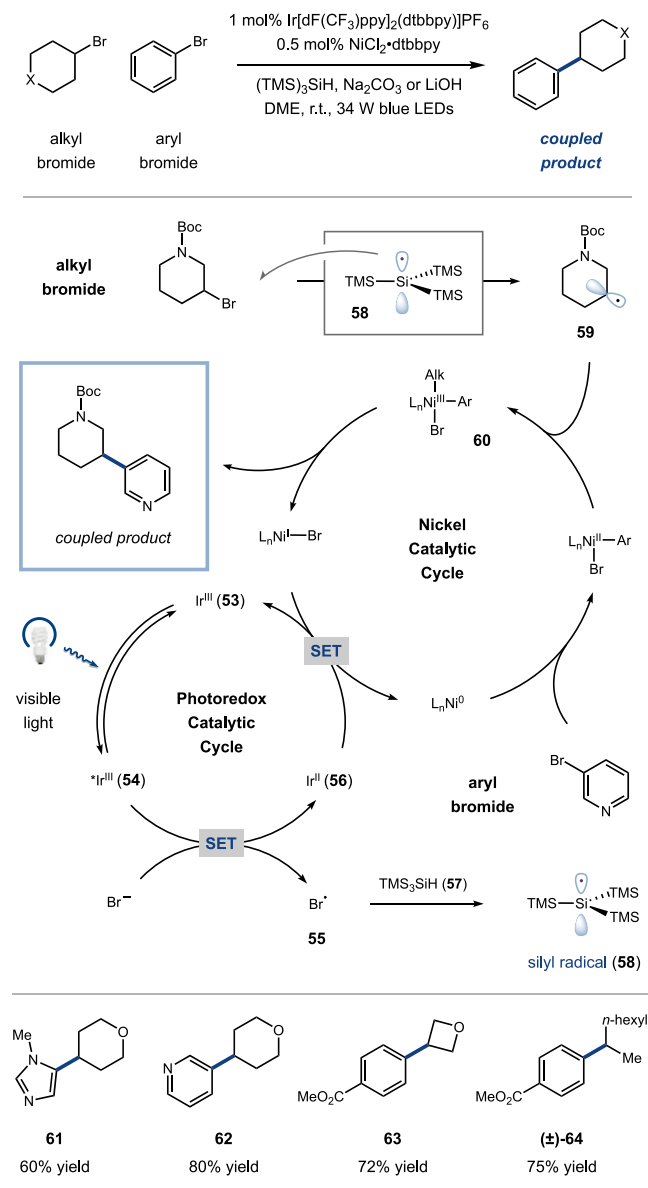
were engaged in the C(sp<sup>3</sup>)–C(sp<sup>2</sup>) bond formation, and the reaction was applied to the functionalization of several abundant feedstocks as commonly available sources of chemical complexity (44–46, 61%–71% yield). A mechanis-

tically related transformation from Wang and co-workers extended this platform to the intramolecular acyl-carbamoylation of tethered alkenes to furnish enantioenriched oxindole scaffolds (Scheme 10b, 47–49, 64%–91% yield, 90%–95% ee).<sup>117</sup> Martin and co-workers later detailed the use of triplet aryl ketones, another class of commonly employed HAT photocatalyst,<sup>113</sup> in a light-mediated nickel cross-coupling.<sup>118</sup> Importantly, both arylation and alkylation of C–H nucleophiles were reported, demonstrating a range of different bromide electrophiles for the functionalization of etheral C–H bonds (Scheme 10c, 50–52, 83%–87% yield). The value of diaryl ketones as metallaphotoredox-compatible HAT catalysts was also recognized by Rueping and co-workers in a benzylic C–H arylation, vinylation,<sup>119</sup> and acylation,<sup>120</sup> though the capacity for such ketones to undergo energy transfer with nickel complexes could not be disregarded.<sup>104,105</sup> Moreover, the Marukami group has applied this HAT platform to the carboxylation of benzylic and aliphatic C(sp<sup>3</sup>)–H bonds with CO<sub>2</sub>, providing direct access from readily available hydrocarbons to the corresponding carboxylic acids with one-carbon extensions.<sup>121</sup> Benzaldehyde has also been employed as an HAT catalyst in the presence of UVA light for metal-photocatalytic C–H arylation and alkylation.<sup>122</sup>

Targeting the regiocontrolled functionalization of C–H bonds in an aliphatic chain, independent reports from the Knowles and Rovis lab detailed C(sp<sup>3</sup>)–H functionalizations through an intramolecular 1,5-HAT event mediated by a photocatalytically generated amidyl radical.<sup>123,124</sup> Rovis and co-workers were able to apply this powerful platform for selective activation of C–H bonds toward the coupling of primary alkyl bromide electrophiles with a number of trifluoroacetamide-tethered frameworks in a dual-catalytic protocol.<sup>125</sup>

**2.1.5. Cross-Electrophile Couplings.** Halide and pseudohalide electrophiles are among the most commonly employed reagents in synthetic organic chemistry. The commercial availability of these electrophiles coupled with their bench stability and ease of synthesis has resulted in their widespread adoption throughout organic chemistry, particularly within the realm of cross-coupling. Cross-electrophile couplings, the metal-mediated forging of a bond between two electrophiles, have thus emerged as a strategy to exploit the abundance of alkyl, aryl, and vinyl halides and pseudohalides.<sup>126–128</sup> Despite the privileged role afforded to halide and pseudohalide coupling partners, limitations remain in the selective activation of one class of halide electrophiles in the presence of another, a necessity for cross-selectivity.<sup>129</sup> Our lab recently postulated that an open-shell mechanism enabled by photoredox catalysis could provide a unique solution to this longstanding challenge.<sup>130</sup> We targeted a cross-electrophile coupling between aryl bromides and alkyl bromides, wherein cross-selectivity arises from the inverse relationship between rates of oxidative addition of low-valent metal catalysts and rates of halide abstraction by main group radicals across hybridizations of bromide electrophiles.<sup>131</sup> To this end, we sought to employ a photocatalytically generated silicon-centered radical, well known to abstract halogen atoms from organic halides, as a key reactive intermediate.<sup>132</sup> Our proposed mechanism, shown in Scheme 11, begins with photoexcitation and intersystem crossing of photocatalyst 53 to afford long-lived triplet excited state 54. Upon reductive quenching with exogenous bromide anion, bromine radical (55) and reduced photocatalyst 56 are generated. We

### Scheme 11. Mechanism of Silyl-Radical-Mediated Cross-Electrophile Coupling

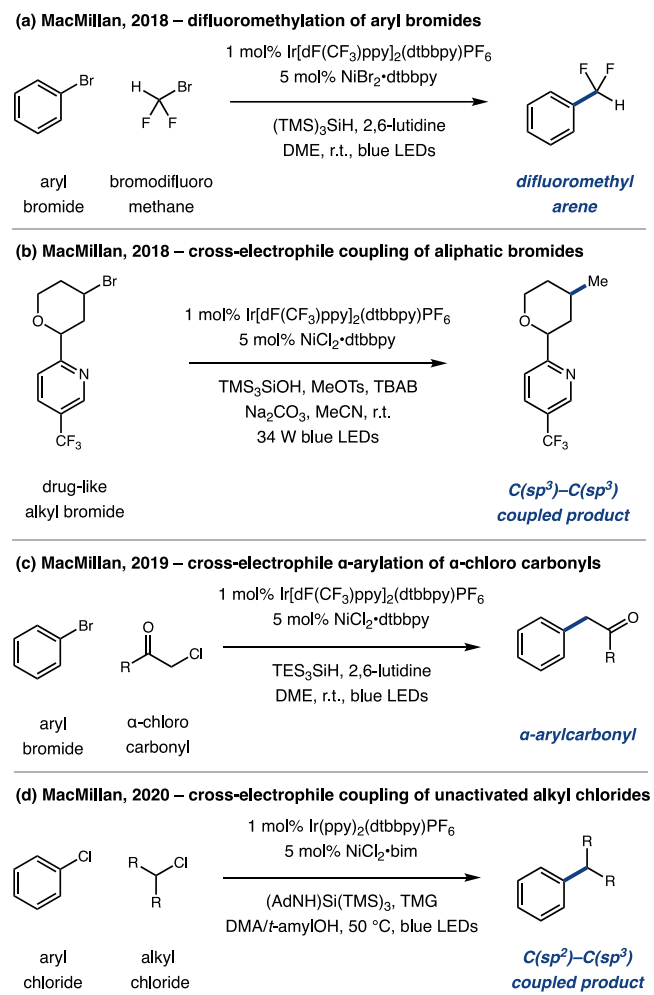


anticipated that bromine radical can activate the halogen atom abstractor, tris(trimethylsilyl)silane (**57**), via HAT. The resultant silyl radical species **58** can rapidly abstract a bromine atom from a suitable C(sp<sup>3</sup>)-Br electrophile, irreversibly generating alkyl radical **59** driven by coincident formation of the thermodynamically favored silyl halide byproduct.<sup>133</sup> The catalytic cycle continues via familiar C(sp<sup>2</sup>)-Br activation of the aryl halide coupling partner via oxidative addition, alkyl radical capture of **59**, and reductive elimination from the high-valent Ni(III)-aryl-alkyl species **60**. As previously reported, SET between the reduced photocatalyst **56** and the post-reductive elimination Ni(I) species regenerates both catalysts. Under these mild reaction conditions, a broad range of alkyl bromides were coupled to aryl bromides in good yields and excellent cross-selectivity, including several traditionally challenging five-membered heteroaryl bromide substrates (**61–64**, 60%–80% yield). This heterogeneous reaction was subsequently translated to gram-scale synthesis in a continuous stirred-tank reactor by Jensen and co-workers.<sup>134</sup> Furthermore,

Flanagan and co-workers have adapted this mode of activation toward bio-relevant applications by employing the use of a pyridyl bis(carboxamide) ligand that has enabled the water-compatible nickel-catalyzed coupling of alkyl bromides and DNA-tagged aryl iodides for the preparation of DNA-encoded libraries.<sup>135</sup>

This mode of activation was then applied toward the difluoromethylation of bromoarenes by our laboratory,<sup>136</sup> a transformation of substantial interest to the medicinal chemistry community (Scheme 12a). Bromodifluoromethane,

### Scheme 12. Silyl Radical-Mediated Nickel Metallaphotoredox Transformations



used as a solution in DME, was readily converted to difluoromethyl radical via silyl-radical activation and coupled to a variety of aryl bromides to afford pharmaceutically relevant difluoromethylarenes. Thereafter, a silyl-radical-enabled C(sp<sup>3</sup>)-C(sp<sup>3</sup>) cross-electrophile coupling for the derivatization of complex, druglike alkyl bromides with a variety of small alkyl electrophiles was developed (Scheme 12b).<sup>137</sup> When run with an excess of the small alkyl fragment, good yields of cross-coupled product were observed, with competing heterodimerization leading to volatile byproducts easily removed during workup. Silyl radical activation was also successfully employed in the cross-electrophile α-arylation of α-chloro carbonyls with aryl bromides in a dual-catalytic manifold (Scheme 12c).<sup>138</sup> Notably, the strategy afforded a variety of valuable α-aryl carbonyls in the absence of strong base, and provided a

method for the  $\alpha$ -arylation of amides, ketones, esters, and even unprotected carboxylic acids. Under a related set of conditions, this transformation was rendered asymmetric by Mao, Walsh, and co-workers,<sup>139</sup> a longstanding challenge enabled by the mild photoredox conditions. A milestone achievement in the activation of alkyl chlorides was likewise born from silyl radical activation. We postulated that the principles of polarity matching should apply to halogen abstraction events. Specifically, we expected that a more electron-rich silyl radical species should be able to engage kinetically inert alkyl chlorides in this exothermic halide-abstraction event via transition-state charge stabilization.<sup>96</sup> By incorporating a nitrogen atom adjacent to the silyl radical center, a number of primary and secondary alkyl chlorides were successfully activated, and the corresponding radicals were coupled in good efficiency to a variety of (hetero)aryl chlorides (Scheme 12d).<sup>140</sup>

Concurrent with the disclosure of our initial silyl-radical-mediated coupling, Lei and co-workers demonstrated the use of simple tertiary amines as sacrificial reductants in a photoredox catalysis-promoted cross-electrophile coupling of alkyl bromides with aryl bromides.<sup>141</sup> While no mechanism was explicitly proposed, a number of potential pathways could be operative.<sup>142,143</sup> The cross-coupling of vinyl bromides with alkyl bromides was later achieved under a similar set of conditions by Fu.<sup>144</sup> In a separate report, Chu and co-workers demonstrated the coupling of allylic carbonate electrophiles with vinyl triflates, enabled by a Hantzsch ester reductant to provide access to traditionally elusive skipped dienes.<sup>145</sup> The stereoselectivity of the resultant products was found to be determined by photocatalyst triplet energy, and divergent conditions to access either *E* or *Z* isomeric products in good selectivities were developed.

In an effort to incorporate amines, another native functionality widely available to the modern chemist, as veiled carbon fragments, Katritzky salts have recently been employed in a number of contexts.<sup>146–148</sup> Given the propensity of these reagents for photoinduced electron transfer, coupled with their established utility as electrophiles in cross-coupling reactions, Molander and co-workers targeted a metallaphotocatalytic cross-electrophile coupling.<sup>149</sup> SET-mediated activation of the alkyl amine-derived electrophiles provided versatile carbon-centered radical intermediates, which were subsequently integrated into a familiar nickel-based catalytic platform and coupled to a variety of aryl bromide electrophiles. Concomitant reports from the Pan and Rueping groups disclose a similar protocol for the nickel-catalyzed activation of C–N bonds toward deaminative cross-electrophile coupling and reductive cross-coupling with aryl halides, respectively.<sup>150,151</sup>

The introduction of a carboxylic acid functionality onto aromatic and aliphatic bromides and triflates using  $K_2CO_3$  as the source of  $CO_2$  has been demonstrated by König and co-workers.<sup>152</sup> The reaction is compatible with a variety of functional groups including unactivated cyclic alkyl bromides, and was applied to the synthesis and derivatization of biologically active molecules. Spectroscopic investigations indicate the mechanism proceeds via ligand substitution of neocuproine followed by reduction to generate the active Ni(0) catalyst. In a subsequent study, the group reported the ligand-controlled Markovnikov and anti-Markovnikov hydrocarboxylation of styrenes, in which neocuproine forms the Markovnikov product exclusively, while 1,4-bis-(diphenylphosphino)butane (dppb) favors formation of the anti-Markovnikov product.<sup>153</sup> Preliminary mechanistic inves-

tigation indicates the irreversible addition of a Ni(II)–H intermediate, generated *in situ*, into the styrene.

Recently, Zhang, Niu, and co-workers reported the nickel photoredox-catalyzed cross-electrophile coupling of glycosyl chlorides with aryl bromides for the highly stereoselective synthesis of C-aryl glycosides.<sup>154</sup>

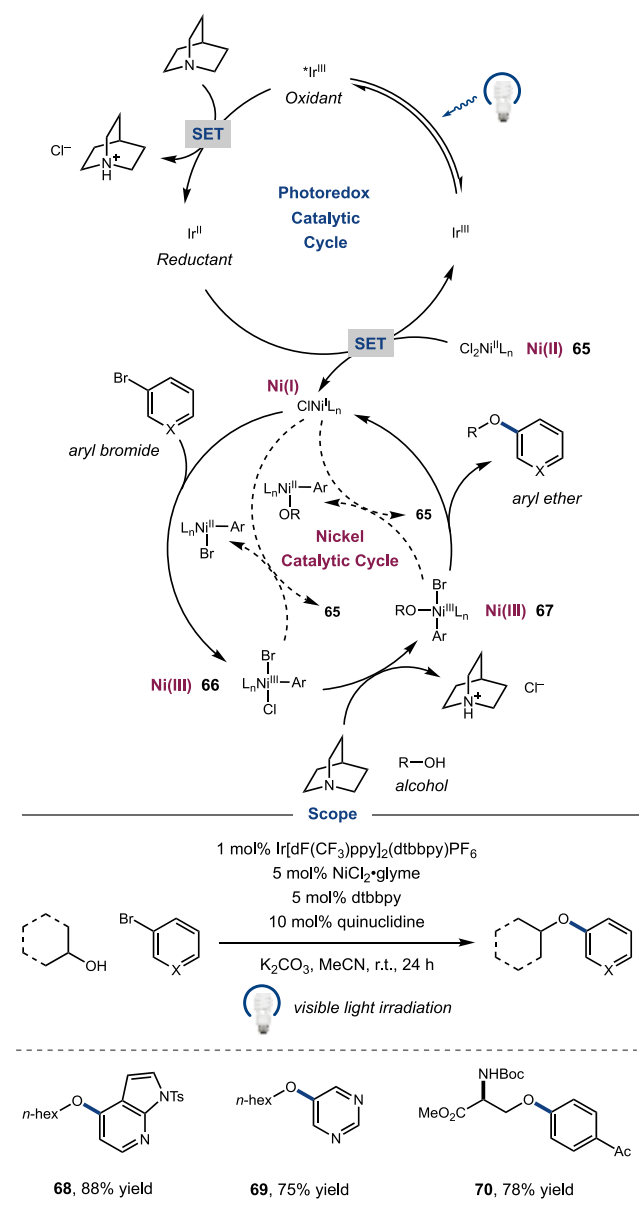
## 2.2. Carbon–Heteroatom Bond Formation

Transition metal catalysis has dramatically reshaped the landscape of chemical synthesis not only in the construction of all-carbon frameworks, but in the forging of carbon–heteroatom bonds as well. Given the competence of photoredox catalysis to enable nickel to forge historically challenging carbon–carbon bonds through energy-transfer and/or electron-transfer mechanisms, similar elementary steps have been shown to enable otherwise elusive carbon–heteroatom bond formations.

**2.2.1. C–O Bond Formation.** The construction of C–O bonds by both palladium and copper catalysis represents a well-established class of methods for the synthesis of ethers.<sup>155–157</sup> However, the assembly of this valuable linkage by nickel catalysis has remained an unrealized goal. Foundational studies by Hillhouse and co-workers have demonstrated the recalcitrant nature of reductive elimination from nickel(II)-alkyl-alkoxide metallacycles.<sup>14,158</sup> However, the key finding that exposure of this species to molecular oxygen results in desired product formation<sup>15</sup> suggests that a higher-valent nickel species can perform the otherwise sluggish bond-forming step. Given the well-documented capacity for photoredox catalysts to directly oxidize Ni(II) species to Ni(III) intermediates,<sup>107</sup> and the demonstrated capacity for related Ni(III) complexes to undergo productive C( $sp^3$ )–O bond formation,<sup>159</sup> we hypothesized that photoredox catalysis could enable the use of nickel catalysis in ether synthesis. Indeed, a broad array of alcohols underwent successful coupling with a number of (hetero)aryl bromides by the action of a simple nickel(II) bipyridyl precatalyst and a photocatalyst under blue light irradiation.<sup>160</sup> The proposed mechanism for this transformation is shown in Scheme 13. Activation of the nickel(II) chloride precatalyst **65** to the active Ni(I) species proceeds via reduction by the iridium(II) photocatalyst. Quinuclidine is hypothesized to serve as a sacrificial reductant of the excited-state iridium(III) to generate the active iridium(II) species, turning over the photocatalyst. Oxidative addition with aryl bromide produces a high-valent aryl Ni(III) complex **66** that undergoes ligand exchange with an alcohol coupling partner to form the resultant Ni(III) aryl alkoxide intermediate **67**. An exothermic reductive elimination step forges the desired bond (**68–70**, 75%–88% yield). This Ni(I)/Ni(III) self-sustained cycle is operative to achieve reactivity in the absence of photocatalysis.<sup>161</sup> Lee and co-workers applied this platform to the C( $sp^2$ )–O coupling of peptides, including both alcohol- and bromo-containing residues, achieving intermolecular etherification and side-chain-to-tail macrocyclization.<sup>162</sup>

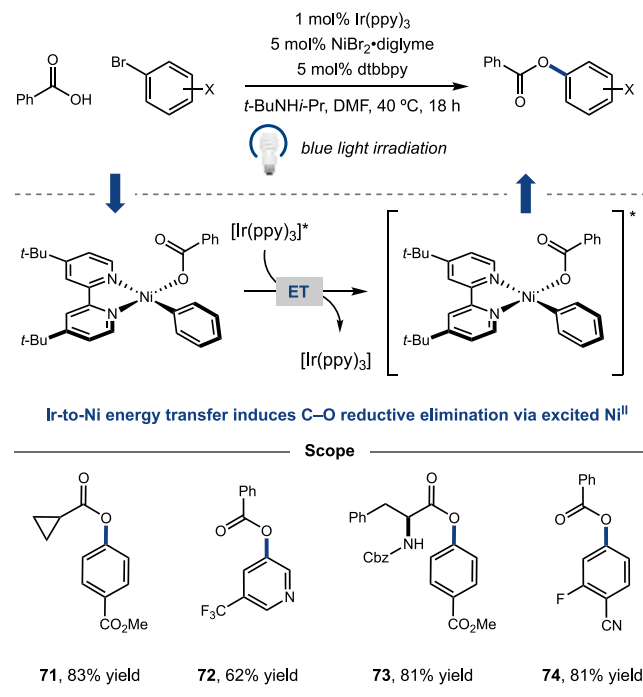
Given that electron transfer to yield a high-valent organometallic species prone to reductive elimination represents an effective strategy for challenging bond formations, we questioned whether other photocatalytic modes of activation could likewise enable novel chemistry at nickel centers. Inspired by numerous instances of direct excitation of organometallics to afford excited-state metal centers with unprecedented reactivity,<sup>106,107,163,164</sup> we questioned if an

Scheme 13. Nickel- and Photoredox-Catalyzed Etherification



energy-transfer mechanism could access similar high-energy organometallic intermediates without relying on the individual species' spectrochemical properties. In collaboration with McCusker and co-workers, we targeted the formation of aryl esters by energy-transfer-induced reductive elimination from nickel(II)-aryl-carboxylate complexes (Scheme 14).<sup>165</sup> Utilizing a photocatalyst of suitable triplet energy, a broad range of aryl and alkyl carboxylates were coupled with aryl and heteroaryl bromides in good efficiencies (71–74, 62%–83% yield). Importantly, stoichiometric experiments provided evidence for the suggested energy-transfer pathway, and calculations indicated that an electron-transfer-mediated pathway (oxidation to a Ni(III) aryl carboxylate) was nearly 15 kcal/mol higher in energy than the proposed mechanism. Subsequent transient absorption spectroscopic studies in collaboration with Scholes and co-workers confirmed the energy-transfer pathway, demonstrating the mechanism of the reductive elimination is a unimolecular process that occurs on

Scheme 14. Energy-Transfer C–O Coupling

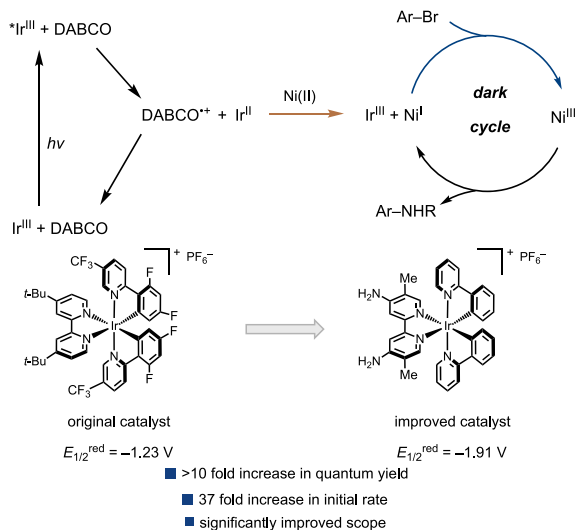
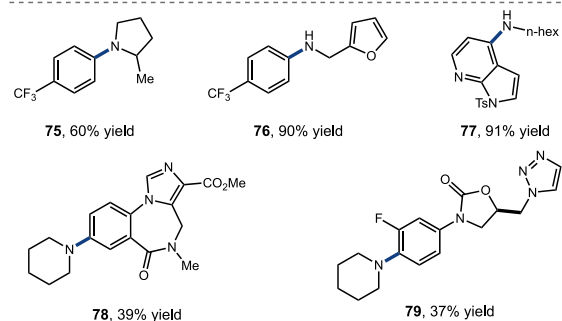
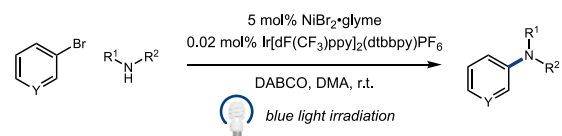


the long-lived excited state of the Ni(II) complex via diffusion-controlled energy transfer from the photocatalyst.<sup>166</sup>

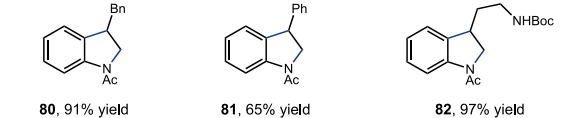
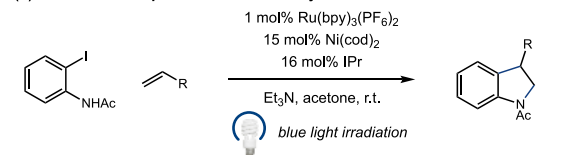
**2.2.2. C–N Bond Formation.** As metallaphotoredox catalysis has developed as an enabling platform for molecular construction, the concept of utilizing this powerful technique to circumvent traditional, often laborious strategies for reaction design and optimization has gained traction. Given that the evolution of C–N coupling has largely been confined to developments in palladium catalysis, with ligand design remaining the dominant variable in the advancement of new methodologies,<sup>11</sup> we envisioned that photoredox could provide a unique approach to unlock new C–N coupling reactions. In collaboration with the Buchwald lab, we hypothesized that dual nickel and photoredox catalysis could enable a C(sp<sup>2</sup>)-N coupling without the need for complex ancillary ligands, permitted by simple oxidation-state-modulation at the nickel center.<sup>167</sup> This objective was successfully realized, wherein a simple nickel precatalyst and a photoredox catalyst together enabled the union of aryl and heteroaryl halides with aliphatic amines in good yields under blue light irradiation, notably in the complete absence of added ligand (Scheme 15a, 75–79, 37%–91% yield). Low photocatalyst loading (0.02 mol %) was sufficient for optimal reactivity, and hits were generated for the amination of 14 of the 18 members of the chemistry informer aryl halide library, a benchmark for reaction generality developed by Krska and Dreher.<sup>168</sup> The reaction has since been adapted to flow for the large-scale synthesis of arylamines.<sup>169,170</sup> Subsequent mechanistic studies, carried out by our lab in collaboration with the Scholes lab, painted a complex mechanistic picture.<sup>171</sup> Transient absorption spectroscopy, combined with kinetic and stoichiometric experiments elucidated several key features of the reaction. Namely, (i) formation of reduced iridium photocatalyst proceeds via reductive quenching of the excited state by the 1,4-diazabicyclo[2.2.2]octane base (DABCO), (ii) reduction of the resting Ni(II) catalyst to a catalytically active Ni(I) species by this reduced Ir(II) complex is rate determining, and (iii) a

## Scheme 15. Early Developments in Metallaphotoredox Amination

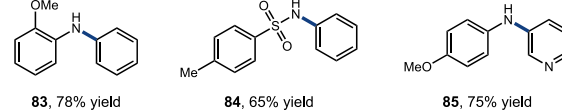
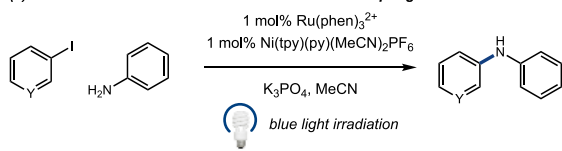
## (a) MacMillan and Buchwald Aryl Amination



## (b) Jamison Metallaphotoredox Indoline Synthesis



## (c) Vannucci Substrate Oxidation-mediated C–N Coupling



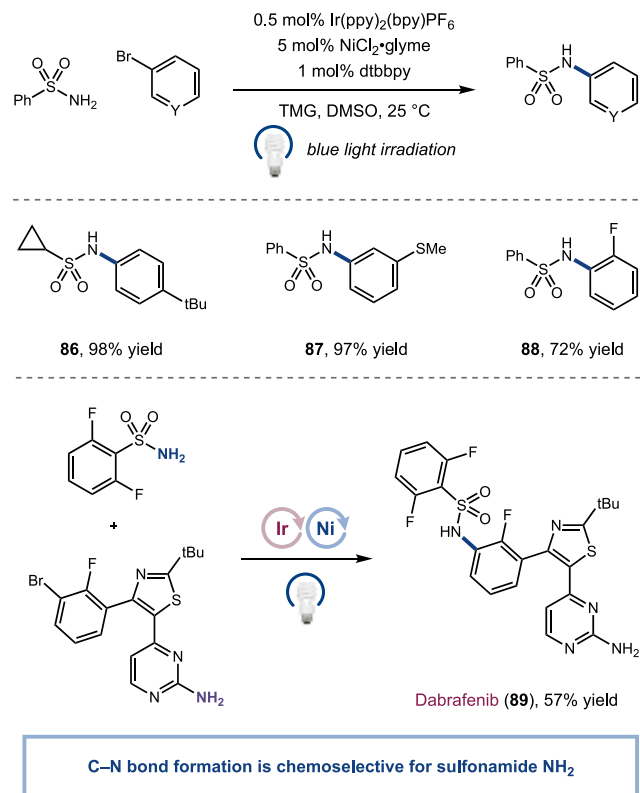
majority of product formation occurs in a dark Ni(I)–Ni(III) cycle,<sup>161</sup> with many deactivation pathways operative for the catalytically active Ni(I) species. With these key insights in mind, a more efficient photocatalyst was designed, synthesized, and tested. The new photocatalyst was found to outperform the originally published catalyst in both quantum yield and rate of product formation, and the improved conditions also generated more robust hits in the aryl halide informer library than those of the original publication.<sup>167</sup>

In a milestone advancement for the synthesis of cyclic amines, Jamison and co-workers developed a facile synthesis of indolines proceeding via a metallaphotoredox-mediated C–N bond formation (Scheme 15b).<sup>172</sup> It was proposed that in the presence of 2-iodoaniline derivatives and simple alkene coupling partners, a Ni(0) species would undergo an oxidative addition to the halide electrophile, migratory insertion to first form the aryl–alkyl bond. Thereafter, the nickel alkyl species would coordinate the pendant aniline, undergo SET with an excited photocatalyst, and perform the product-forming reductive elimination from the high-valent Ni(III) metallacycle. The group recognized the importance of a dual nickel- and photoredox-catalyzed approach for two key steps in the proposed mechanism. Particularly, the nickel alkyl species invoked should be significantly more stable to deleterious  $\beta$ -hydride elimination than the corresponding palladium alkyl species invoked as an intermediate in Heck-type cross-couplings.<sup>37,173</sup> Moreover, the intramolecular C( $sp^3$ )–N reductive elimination must outcompete  $\beta$ -hydride elimination, an inherently challenging step<sup>174</sup> which would benefit from a photochemically oxidized, high-valent nickel center. This approach to indoline synthesis afforded a broad scope of *N*-acyl protected products with a variety of substitution tolerated on the aromatic ring. Moreover, a variety of terminal olefins served as adequate coupling partners, affording indoline products in good yields (80–82, 65–97% yield). Another SET-mediated strategy for nickel- and photoredox-catalyzed C–N coupling emerged from the Vannucci laboratory. While most approaches for high-valent nickel-mediated C–N bond formation involve oxidation of a Ni(II) amido complex to the corresponding Ni(III) adduct, Vannucci and co-workers recognized that oxidative radical capture of a transient aminyl radical by a Ni(II) oxidative addition complex should afford the same key Ni(III) amido complex (Scheme 15c).<sup>175</sup> With this strategy, a number of disubstituted amines were synthesized from simple anilines and aryl iodides (83–85, 65%–78% yield), where the catalytically generated aminyl radicals act to modulate the oxidation state at nickel directly via oxidative radical capture. On the other hand, Johannes and co-workers invoke a reductive pathway in the C–N coupling of (hetero)aryl electrophiles such as iodides, bromides, chlorides and triflates with aryl azides.<sup>176</sup> Photoreduction of the aryl azide is proposed to proceed via an arylnickel–azide complex, which upon SET and loss of nitrogen, generates a Ni(III) species. Facile reductive elimination affords the desired medicinally relevant biarylamine products.

While SET-mediated generation of a critical Ni(III) intermediate has enabled a majority of nickel metallaphotocatalytic C–N bond formation, our laboratory next questioned if an energy-transfer mechanism could also be effective in forging these valuable bonds. We targeted the synthesis of *N*-aryl sulfonamides, a prevalent functionality in the pharmaceutical industry, by means of an energy-transfer mechanism.<sup>177</sup> Indeed, a broad scope of aryl and heteroaryl sulfonamides

was found to be accessible from their corresponding halide congeners (Scheme 16, 86–88, 72%–98% yield), which was

### Scheme 16. Energy Transfer in Metallaphotocatalytic C–N Cross-Coupling

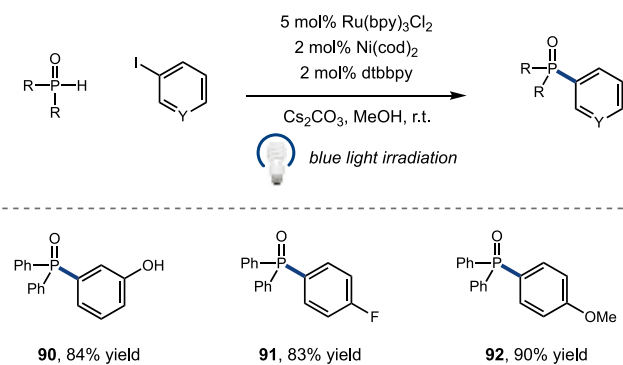


highlighted in a C–N fragment-coupling approach to the B-Raf kinase inhibitor dabrafenib (89, 57% yield). Notably, the transformation can proceed in low levels of efficiency in the absence of a photocatalyst, demonstrating that a direct excitation pathway is also possible for nickel-catalyzed C–N coupling, a result that has since been showcased in an independent report by Miyake and co-workers.<sup>178</sup> In a subsequent spectroscopic study, the group reported the Förster-type energy transfer from excited-state photocatalysts to Ni(II)-amine complexes.<sup>179</sup> Application of this knowledge toward the selection of an organic phenoxazine photocatalyst enabled the efficient C–N coupling of a diverse selection of amines and aryl halides. Finally, the transformation was applied toward the expedient synthesis *N*-(hetero)aryl sulfamides by Roizen and co-workers.<sup>180</sup>

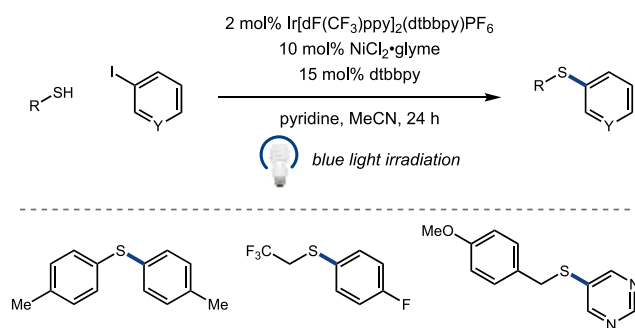
**2.2.3. Other Heteroatomic Nucleophiles.** The advancement of metallaphotocatalysis has brought numerous breakthroughs in the construction of carbon–carbon, carbon–oxygen, and carbon–nitrogen bonds. The single-electron-transfer and energy-transfer mechanisms which enable these conventionally challenging bond formations at nickel can likewise be applied to other classes of heteroatomic nucleophiles (Scheme 17). Lu and Xiao recognized that the photocatalytic oxidation of diarylphosphine oxides to the corresponding P-centered radical could enable a facile C–P bond formation in combination with nickel catalysis.<sup>181</sup> In the presence of suitable nickel and photocatalysts, a number of triarylphosphine oxides were generated from corresponding diarylphosphine oxides and aryl iodides (90–92, 83%–90%

### Scheme 17. Other Heteroatomic Nucleophiles in Nickel Metallaphotocatalysis

#### (a) Metallaphotoredox phosphorylation of aryl iodides



#### (b) Metallaphotoredox C–S bond formation from thiol and aryl halides



yield). Mechanistically, the groups hypothesized that the oxidative radical generation at phosphorus could substitute for the corresponding steps for carbon-centered radical generation disclosed by our lab (from carboxylic acids) and the Molander lab (from trifluoroborate salts). This general strategy for C–P bond formation was later elaborated to a protocol for the phosphorylation of aryl and vinyl tosylates through a similar mechanistic approach.<sup>182</sup>

Molander later demonstrated the cross-coupling of alkyl thiols enabled by dual catalysis.<sup>183</sup> Though traditionally catalyst poisons, thiols were productively engaged in cross-coupling through an unexpected mechanism. While exploring the scope of their base-free silicate chemistry,<sup>78</sup> Molander and co-workers found that the presence of an unprotected thiol on an alkyl silicate nucleophile resulted in a complete switch in reactivity, affording the desilylated thioether instead of the C(*sp*<sup>3</sup>)-linked product. It was proposed that upon oxidative decomposition of the alkyl silicate to the carbon-centered radical, a polarity-matched HAT event between the thiol and the open-shell carbon nucleophile afforded the thiyl radical,<sup>96</sup> which then engaged productively with the nickel catalytic manifold. A broad range of thiols and (hetero)aryl bromides were tolerated as coupling partners in this transformation (93–95, 85%–92% yield), including substrates bearing unprotected alcohols and amines. In a contemporaneous report, Oderinde and Johannes likewise demonstrated the coupling of aryl iodides with alkyl and aryl thiols.<sup>184</sup> Access to the critical thiyl radical intermediate was proposed to take place via an electron-transfer/proton-transfer mechanism. This work by Oderinde, Johannes, and Molander was subsequently

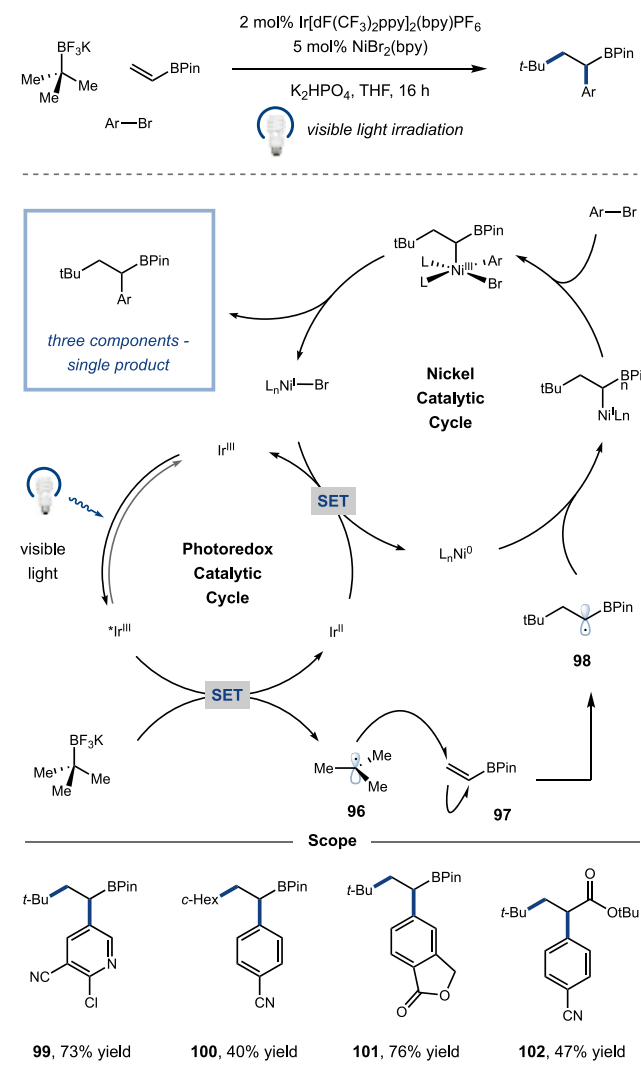
examined in a heterogeneous setting.<sup>185</sup> Lin and co-workers developed a nickel- and photocatalyst-doped metal–organic framework (MOF), and under reaction conditions similar to those reported previously, a significant improvement in catalytic activity was demonstrated. The group suggested that the proximity of the catalysts enforced by the MOF dramatically accelerated necessary SET and thyl radical-transfer steps, improving the turnover number nearly 10-fold from the homogeneous conditions.

**2.2.4. Multicomponent Reactions and 1,2-Difunctionalization.** As the number of disconnections available to the modern synthetic chemist continues to grow, so does the interest and capability for accelerating the synthesis of molecular complexity through multicomponent reactions (MCRs). In this regard, photoredox catalysis has become indispensable in the forging of multiple bonds to simple feedstock chemicals in a single step. Broadly, nickel and photoredox-mediated MCRs can be conceptualized as simple two-component cross-coupling reactions interrupted by addition across a suitable SOMOphilic  $\pi$ -unsaturate.<sup>186</sup>

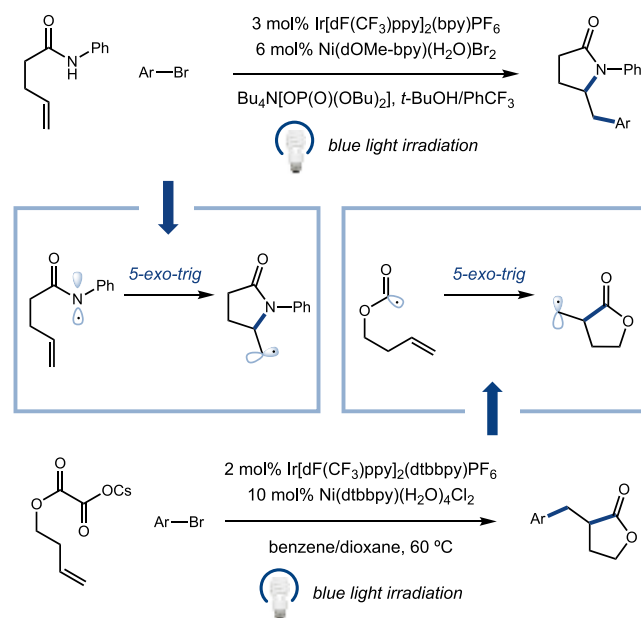
To this end, Molander and co-workers explored the application of electron-deficient alkenes in an MCR with alkyl trifluoroborate radical precursors and aryl halide electrophiles.<sup>187</sup> A mechanism is shown in Scheme 18. Addition of the borate-derived radical **96** to a vinyl boronic ester (**97**) affords the electron-deficient open-shell intermediate **98**. Thereafter, capture by a low-valent nickel species, followed by oxidative addition and reductive elimination forges the complex,  $sp^3$ -rich product. An extensive range of alkyl trifluoroborates and heteroaryl halides were joined across the unsaturated boronic ester, and a small selection of additional electron-deficient alkenes were explored as viable radical acceptors (**99–102**, 40%–76% yield). A similar strategy was disclosed by Martin and co-workers, with alkyl bromides instead serving as alkyl precursors, activated by photocatalysis in combination with an organic reductant.<sup>188</sup> Analogous reports of carbofunctionalization of olefins emerged from a number of other laboratories under a similar mechanistic paradigm, with oxalate esters,<sup>189</sup> alkyl bis(catecholato)silicates,<sup>190</sup> and  $\alpha$ -(trimethylsilyl)amines<sup>191</sup> each serving as radical precursors in separate three-component coupling protocols with (hetero)aryl halides and electronically activated alkenes. Recently, the dual-catalytic MCR of electronically biased alkenes has been rendered asymmetric by Chu and Gutierrez.<sup>192</sup> Capitalizing on key mechanistic insights from previous work,<sup>55</sup> an enantioselective carboarylation of alkenes was demonstrated, forging complex, enantioenriched products in a single, high-yielding step. Recently, Molander and co-workers disclosed the diaryl ketone HAT-catalyzed chemoselective activation of native C–H bonds toward the nickel metallaphotoredox-catalyzed multicomponent dicarbofunctionalization of alkenes.<sup>193</sup> This mode of HAT circumvents the necessity for prefunctionalized radical precursors, an inherent limitation to achieve chemoselectivity in multicomponent reactions.

Several reports on the intramolecular 1,2-difunctionalization of olefins have recently been disclosed (Scheme 19).<sup>117,172</sup> Oxidative generation of a radical distal to a pendant olefin followed by cyclization, radical capture at nickel, and subsequent coupling has been shown to afford a number of complex, often polycyclic products from accessible starting materials. Specifically, Molander and co-workers engaged amidyl radicals for the intramolecular amidarylation of

### Scheme 18. Three-Component Coupling via Nickel Metallaphotoredox Catalysis



### Scheme 19. Intramolecular Olefin Difunctionalization



alkenes to afford a range of heterocycles joined with (hetero)arenes.<sup>194</sup> Starting from oxalate-protected allylic alcohols, Overman demonstrated a facile dual-catalytic approach to spirolactones via monodecarboxylation to the formyl radical, 5-*exo* cyclization, and interception by a suitable nickel catalyst.<sup>195</sup>

Nickel metallaphotocatalytic MCRs are not strictly limited to alkenes. Chu and co-workers have likewise explored alkyne SOMOphiles, detailing an efficient protocol for the synthesis of sterically encumbered trisubstituted alkenes from heteroaryl electrophiles, alkynes, and tertiary oxalate esters.<sup>196</sup> In a complementary report, Rueping and Cavallo explored the 1,2-difunctionalization of aryl acetylenes with aryl halides and an extensive array of radical precursors.<sup>197</sup> Alkyl radical precursors such as Katritzky salts, carboxylic acids,<sup>198</sup> and  $\alpha$ -amino C–H bonds were all suitable coupling partners in this dual-catalytic MCR. Moreover, the reaction was not restricted to carbonyl functionalization; sulfinate salts were also found to smoothly provide the corresponding sulfone products in a regioselective fashion.

### 3. COPPER METALLAPHOTOCATALYSIS

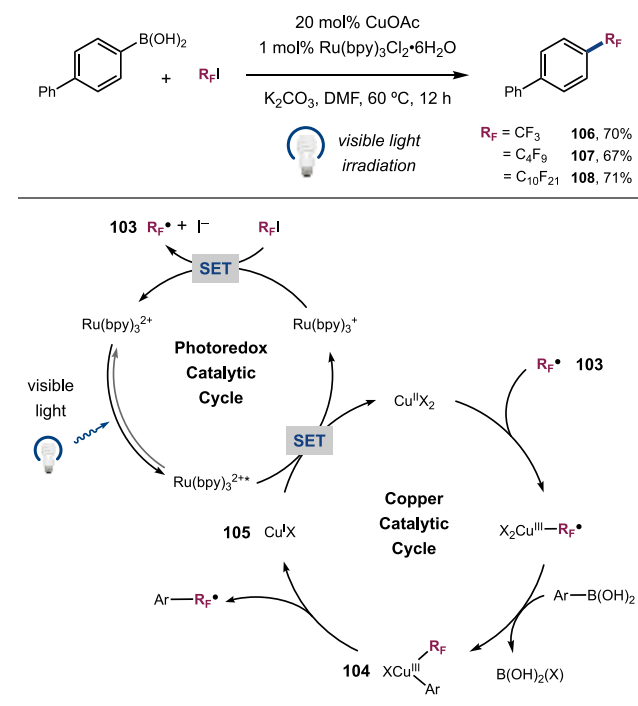
The use of copper as a catalyst in an organic transformation predates the employment of any other metal in the same context.<sup>199</sup> The low toxicity of copper, coupled with its abundance in the Earth's crust, makes copper an especially attractive candidate for catalyzing organic transformations.<sup>200</sup>

As such, advancements in copper-mediated reactions comprise a considerable fraction of developments in the arena of chemical methodology.<sup>201</sup> Nevertheless, limitations remain with respect to the mechanism of substrate activation in the realm of copper catalysis. Namely, high temperatures are often required for activation of traditional electrophiles, and nucleophiles are limited to those which can easily coordinate or transmetalate onto the metal center.<sup>201</sup> Given the efficacy of photoredox catalysis in generating highly reactive radical intermediates, and the well-established capability of copper catalysts to interact with radicals,<sup>202</sup> a growing body of work in the merging of copper and photoredox catalysis has brought forth a number of novel applications in carbon–carbon and carbon–heteroatom bond-forming reactions.

#### 3.1. C–C Bond Formation: Fluoroalkylation

Copper-mediated C–C bond formations represent a well-studied class of reactions, with a multitude of coupling partners and innumerable conditions emerging over the past 150 years.<sup>203</sup> In particular, in the forging of bonds to challenging perfluoroalkyl groups, copper has served a privileged role.<sup>20,204</sup> Recently, as photoredox catalysis has become indispensable in the mild conversion of common functional groups into highly reactive open-shell intermediates, a number of reports have detailed the merger of photoredox with copper catalysis in an endeavor to reap the benefits of both catalytic manifolds. Given the prominence of fluoroalkyl groups in medicinal chemistry,<sup>205</sup> and the importance of copper intermediates in facilitating traditionally challenging reductive eliminations,<sup>206</sup> Sanford and co-workers targeted the photoredox- and copper-catalyzed trifluoromethylation of arylboronic acids to synthesize valuable trifluoromethylarenes.<sup>207</sup> A proposed mechanism (Scheme 20) wherein reduction of trifluoroiodomethane to trifluoromethyl radical (**103**) by a photoredox catalyst would circumvent traditional two-electron pathways invoked for generation of the catalytically relevant Cu–CF<sub>3</sub> species.<sup>208–210</sup>

#### Scheme 20. Copper- and Photoredox-Catalyzed Perfluoroalkylation



The mechanism continues via addition of this reductively generated trifluoromethyl radical to a suitable Cu(II) species, followed by transmetalation with an arylboronic acid nucleophile to generate a key Cu(III)-aryl-CF<sub>3</sub> species **104**. Reductive elimination from this high-valent copper complex forges the desired product, and SET between the excited photocatalyst and reduced Cu(I) complex **105** regenerates both active catalysts. Under this mechanistic paradigm, the authors demonstrated the trifluoromethylation of a number of diverse (hetero)arylboronic acids, including substrates bearing free phenols, unprotected aldehydes, and aryl iodides. Moreover, the protocol was extended to other perfluoroalkyl iodide electrophiles in similar efficiencies (**106–108**, 61%–71% yield).

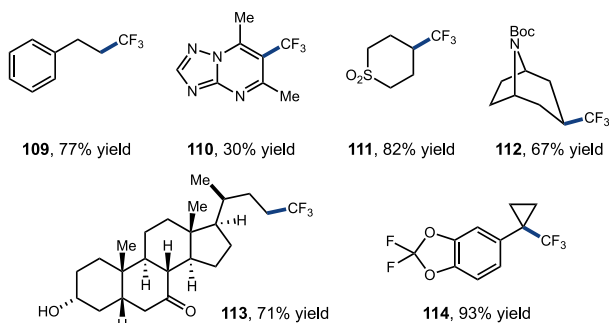
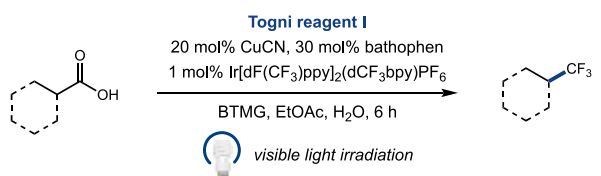
Several additional contributions to copper-catalyzed fluoroalkylation have been developed in recent years. Liu and co-workers reported the decarboxylative difluoroacetylation of cinnamic acid derivatives promoted by dual copper and photoredox catalysis.<sup>211</sup> The authors proposed the reductive generation of the difluoroacetyl radical from the corresponding iodide starting material, and a copper-mediated oxidative decarboxylation to generate the desired difluoromethylene-homologated product. A range of  $\alpha,\beta$ -unsaturated acids were expediently converted to the desired difluoroalkyl-bearing alkenes in good yields with moderate to excellent *E/Z* selectivity.

In our laboratory's initial foray into dual copper and photoredox catalysis, we likewise targeted decarboxylative fluoroalkylation of carboxylic acids. Namely, we sought to develop a metallaphotoredox-catalyzed decarboxylative trifluoromethylation of native aliphatic carboxylic acids (Scheme 21a).<sup>212</sup> Indeed, utilizing commercially available Togni reagent I in combination with a bathophenanthroline-ligated copper species and an iridium photocatalyst, a diverse range of primary and secondary carboxylic acids were trifluoromethylated in moderate to good efficiencies. Moreover, a small

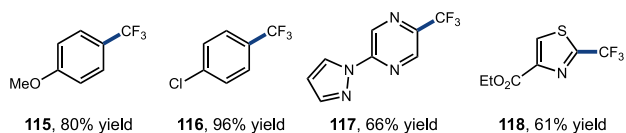
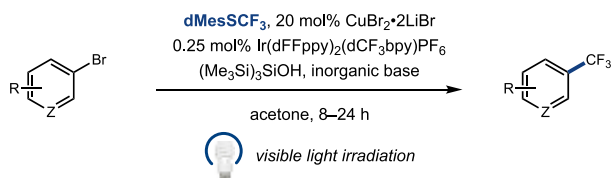


## Scheme 21. Photoredox Trifluoromethylation

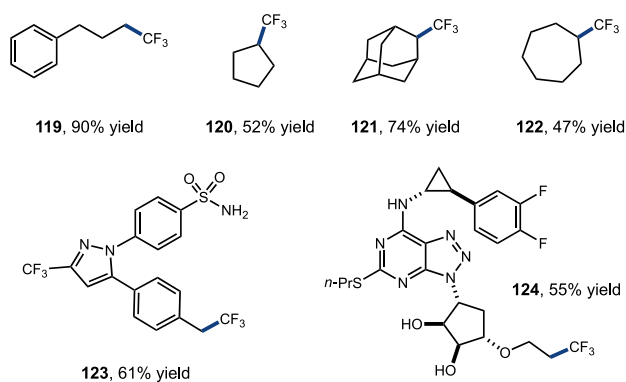
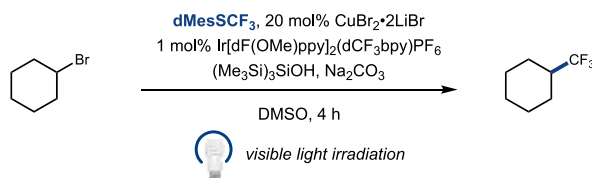
## (a) Decarboxylative trifluoromethylation of aliphatic carboxylic acids



## (b) Trifluoromethylation of aryl bromides with silyl radical halogen abstraction



## (c) Cu-catalyzed trifluoromethylation of alkyl bromides



selection of strained tertiary carboxylic acids were found to be viable substrates, and the transformation was extended to a collection of natural products and pharmaceutical agents (109–114, 30%–93% yield). Our group thereafter reported

the first copper-catalyzed trifluoromethylation of bromoarenes (Scheme 21b).<sup>213</sup> In an effort to circumvent oxidative addition at the copper center, a recalcitrant step often rate-limiting in copper-catalyzed haloarene functionalizations,<sup>214,215</sup> we employed silyl radical-mediated halogen atom abstraction to separate electrophile activation from the specific electronic properties of the catalyst. With this strategy, a broad range of aryl and heteroaryl bromides were trifluoromethylated in good efficiencies, with a number of five-membered heterocycles and other highly nitrogenous aromatic bromides performing adequately as coupling partners (115–118, 61%–96% yield). The method was extended to the trifluoromethylation of pharmaceutical analogues, and initial mechanistic studies indicated the silyl-radical activation step proceeded through a radical mechanism independent of the copper catalytic cycle. This platform was later elaborated to the trifluoromethylation of alkyl bromides (Scheme 21c).<sup>216</sup> A spectrum of alkyl bromide electrophiles, including multiple pharmaceutical derivatives, were expediently converted to trifluoromethyl analogues in good yields with this silyl-radical-mediated strategy to overcome copper's sluggish oxidative addition step (119–124, 47%–90% yield).

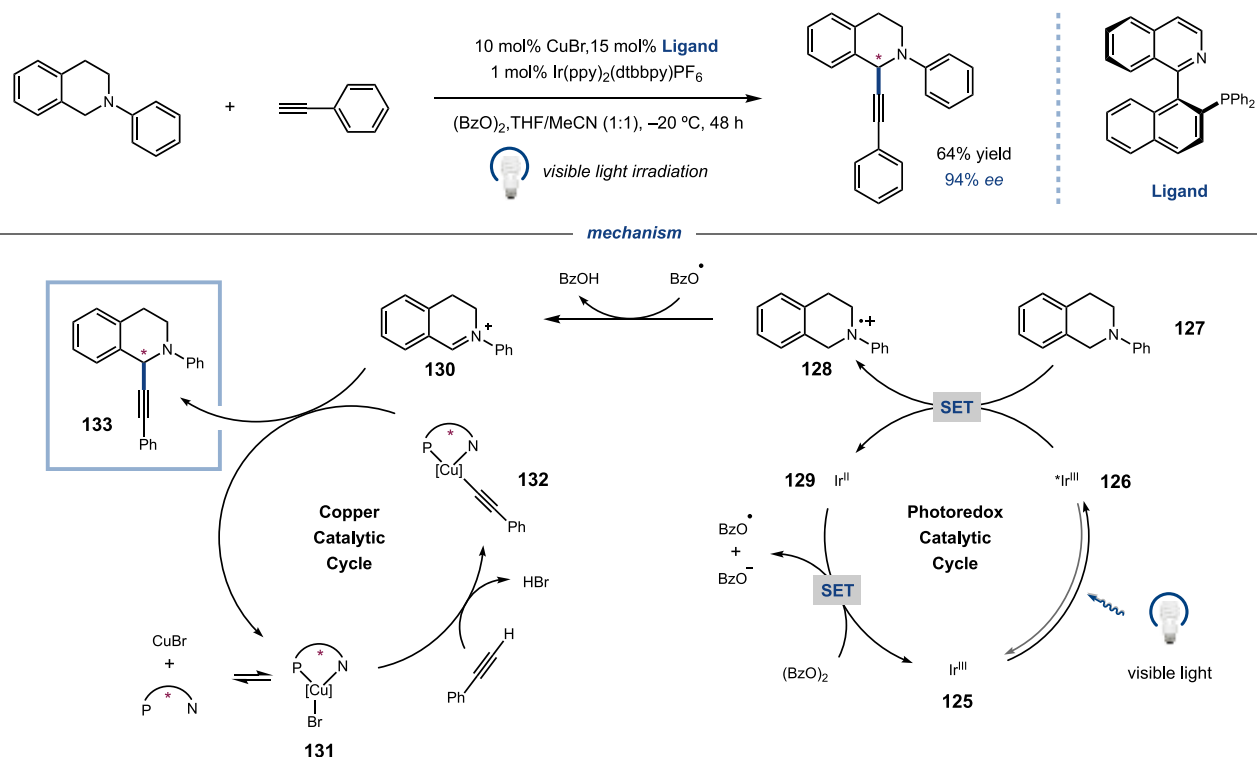
Our laboratory has recently disclosed the merger of decatungstate catalysis with copper catalysis to enable the trifluoromethylation of unactivated aliphatic C(sp<sup>3</sup>)-H bonds.<sup>217</sup> By combining the powerful C–H cleavage capability of the highly oxidizing excited state of decatungstate<sup>114</sup> with copper catalysis, our laboratory was able to append trifluoromethyl groups to a number of pharmaceutically important aliphatic amines, which were notably the limiting reagent in the reaction mixture. No protecting groups at nitrogen were employed, with the aqueous acidic conditions acting both to mask the free amines from deleterious SET events as well as influence HAT selectivity toward distal positions by virtue of polarity matching.<sup>96</sup> A range of benzylic C–H bonds were likewise trifluoromethylated in good efficiencies, in addition to a variety of pharmaceutical compounds. Studies were undertaken to elucidate the mechanism of this novel transformation, and shed light on copper-catalyzed trifluoromethylation reactions as a whole.<sup>19F</sup> NMR experiments suggested a catalytically relevant Cu(III)–CF<sub>3</sub> intermediate was formed upon exposure of a copper(I) salt to the electrophilic trifluoromethyl source Togni reagent II, while electron paramagnetic resonance (EPR) studies revealed a signal consistent with a Cu(II)–CF<sub>3</sub> intermediate. Moreover, it was shown that coordination of the copper species (either by chloride anion or diamine ligand) could affect both the diastereo- and enantioselectivity of the reaction, supporting the critical role of copper in the bond-forming step.

## 3.2. C(sp)–C Bond Formation

The intermediacy of copper acetylides (formed from copper salts and terminal alkynes) as catalytically relevant species has been invoked in cross-coupling mechanisms for over four decades.<sup>218</sup> The propensity for these transient species to act as nucleophilic organometallics has recently been exploited in a variety of light-promoted contexts.

The first dual photoredox- and copper-catalyzed alkyne-ations targeted the C–H functionalization of 1,2,3,4-tetrahydroisoquinoline (THIQ) derivatives, a well-studied system which proceeds through the iminium cation upon two-electron oxidation, mediated either by an exogenous strong oxidant<sup>219</sup> or via photocatalysis<sup>220</sup> followed by 1,2-addition of a suitable

Scheme 22. C–H Alkynylation via Copper Metallaphotoredox Catalysis



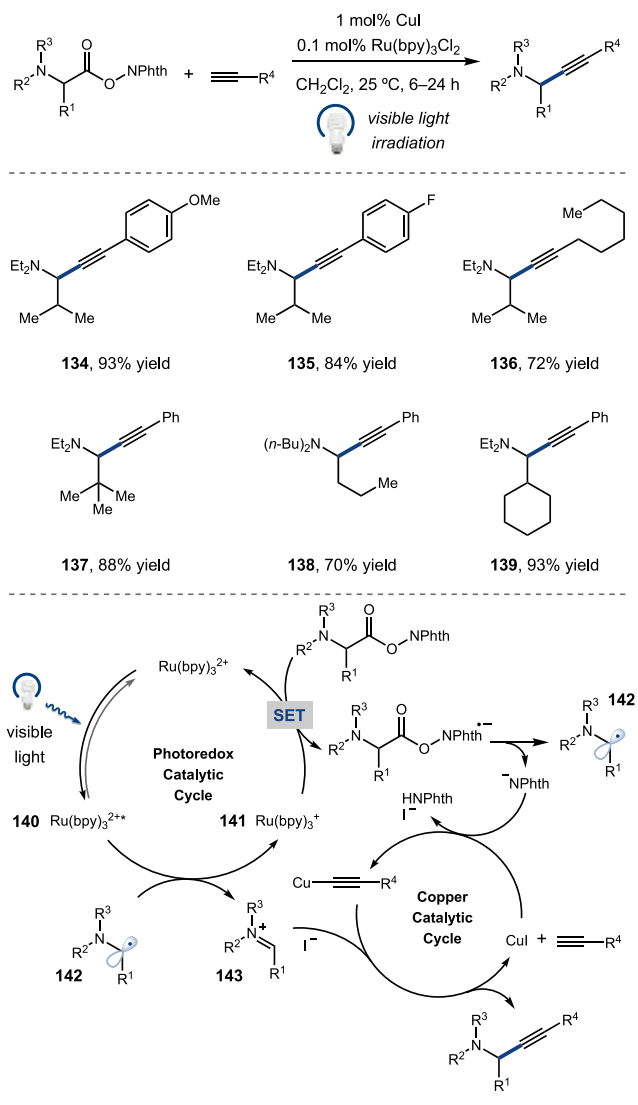
nucleophile. In light of pioneering work by Li and co-workers,<sup>219</sup> Rueping targeted the dual-catalytic alkylation of THIQ analogues under mild photoredox conditions.<sup>221</sup> The authors were able to induce copper-mediated nucleophilic addition of a range of aryl and alkyl acetylenes into photocatalytically generated iminium intermediates in moderate to excellent yields. Notably, modulation of the THIQ scaffold was well tolerated, and both *N*-aryl and *N*-alkyl substitution did not impede product formation. The authors made note of the delicate balance required for all catalytic cycles to cooperate productively, and as such, changing from high-intensity blue LEDs to a 5 W lamp resulted in vastly improved reaction efficiencies. Studies by the Li laboratory built upon the work disclosed by Rueping and co-workers, and ultimately an asymmetric C–H alkylation was disclosed.<sup>222</sup> Li and co-workers described the use of a chiral ligated copper complex in the asymmetric cross-dehydrogenative coupling of terminal alkynes with THIQs. The authors propose a mechanism detailed in Scheme 22. Iridium photocatalyst 125, upon excitation by visible light and intersystem crossing, arrives at excited state 126. Subsequent SET between the excited photocatalyst and THIQ substrate 127 is proposed to generate an amine radical cation (128) and reduced photocatalyst 129, which could undergo SET with the benzoylperoxide oxidant. The resultant benzoyl radical is proposed to undergo a second electron-transfer event with amine radical cation 128, generating the key iminium intermediate (130). Simultaneously, chiral ligated copper species 131, formed *in situ* from the isoquinoline ligand and CuBr, can coordinate the terminal alkyne substrate, and upon loss of HBr, generate copper acetylide species 132. At this point, asymmetric 1,2-addition of the organometallic intermediate into the iminium could generate the desired enantioenriched product (133). Operating under this mechanistic proposal, Li and co-workers were able to generate a library of products varied at both the

acetylene partner and at the *N*-aryl substitution of the THIQ fragment in moderate to excellent efficiencies and enantioselectivities.

A decarboxylative alkylation was disclosed thereafter by Fu and co-workers.<sup>223</sup> While related mechanistically to previous copper metallaphotocatalytic C(sp<sup>3</sup>)-C(sp) couplings, the authors instead elected to utilize  $\alpha$ -amino carboxylic acids, prefunctionalized as *N*-hydroxyphthalimide (NHPI) redox-active esters, as electrophiles in lieu of an added chemical oxidant. Despite these differences, 1,2-addition of the copper acetylide intermediate into a photocatalytically generated iminium cation remained a key feature of this alkylation protocol. A number of tertiary  $\alpha$ -amino NHPI esters were productively engaged as coupling partners with a range of aryl and alkyl acetylene derivatives (134–139, 70%–93% yield). EPR studies demonstrated the presence of radical intermediates generated under the reaction conditions, and a mechanism was proposed involving initiation by reductive quenching of excited photocatalyst 140 by a sacrificial equivalent of the tertiary amine substrate. The reduced photocatalyst 141 was then postulated to unveil a carbon-centered radical (142) by reductive decomposition of the NHPI redox-active ester, which could be oxidized to the electrophilic iminium intermediate by the excited photocatalyst. Subsequent copper-mediated 1,2-addition would complete the catalytic cycle as before (Scheme 23).

In a recent report, Pan and co-workers demonstrated a related copper-catalyzed decarboxylative cross-coupling method to access alkyl substituted alkynes, without the use of noble metal photocatalysts.<sup>224</sup> Direct photoexcitation of copper(I) acetylide with electron-rich NEt<sub>3</sub> ligands provided access to alkyl radicals from NHPI esters of carboxylic acids via SET. The alkyl radicals readily coupled with aromatic alkynes, as well as aliphatic alkynes and alkynyl silanes upon the addition of catalytic amounts of preformed copper-phenylacetylide.

### Scheme 23. Copper Metallaphotoredox Decarboxylative Alkynylation



DFT calculations revealed the importance of NEt<sub>3</sub> and acetylacetonate ligands in inhibiting homocoupling of the alkyne.

Hwang and co-workers capitalized on LMCT enabled by the direct photoexcitation of copper to develop a copper-catalyzed Sonogashira cross-coupling of aryl halides and alkyl- or aryl-substituted terminal alkynes.<sup>225</sup> The key light-absorbing copper acetylide species is formed upon deprotonation and coordination of the alkyne. Subsequent photoinduced ligand-to-metal charge transfer generates an electron-deficient acetylene moiety, favoring nucleophilic attack of electron-rich aryl halides, followed by dissociation to afford the C–C coupled products.

The highly reducing nature of a photoexcited copper acetylide species to generate copper(II)-phenylacetylide and superoxide *in situ* under aerobic conditions has since been leveraged in the denitrogenative oxidative coupling of hydrazinylpyridines with terminal alkynes,<sup>226</sup> oxidative C–N coupling of anilines with terminal alkynes for the synthesis of  $\alpha$ -ketoamides,<sup>227</sup> oxidative C–N coupling of 2-aminopyridine with terminal alkynes via C–C triple bond cleavage,<sup>228</sup> direct oxidative couplings of phenols and terminal alkynes to generate

aromatic ketones,<sup>229</sup> and oxidative C(sp)–C(sp) homo- and cross-couplings of terminal alkynes.<sup>230,231</sup>

In addition to molecular oxygen, benzoquinones can also serve as efficient external oxidants to transform photoexcited copper(I)–alkyne complexes into their copper(II) counterparts with the formation of benzoquinone radical anions. Hwang and co-workers applied this strategy to two three-component coupling protocols, the C–H annulation of anilines with terminal alkynes and benzoquinones for the synthesis of multisubstituted indoles,<sup>232</sup> as well as the construction of propargylic amines via the A3' coupling of anilines, terminal alkynes, and alcohols.<sup>233</sup>

Lalic and co-workers reported a light-mediated dehalogenative alkynylation, with aryl and alkyl acetylenes coupling efficiently to a range of primary, secondary, and bridged-bicyclic tertiary alkyl iodides in moderate to excellent yields.<sup>234</sup> Given no photocatalyst is present in the reaction mixture, the authors proposed a photoexcited copper acetylide species as the key reducing catalyst in the reaction mixture, capable of reducing a broad range of alkyl iodides to the corresponding radical intermediate, and copper is subsequently invoked in the bond-forming step.

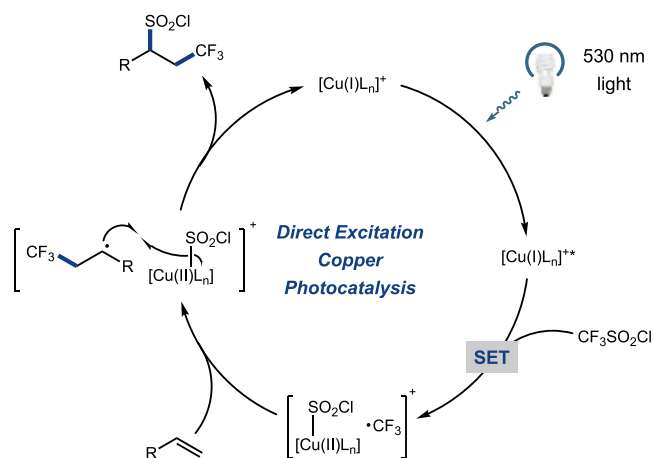
Copper metallaphotocatalyzed cross-coupling to *sp*-hybridized carbon centers is not exclusive to alkynylation. Liu and Lin developed a decarboxylative, enantioselective cyanation of benzylic carboxylic acids, prefunctionalized as NHPI redox-active esters.<sup>235</sup> The group suggested a mechanism by which photocatalytic reduction of the redox-active ester generates a stabilized benzylic radical species. Thereafter, capture of this radical by a chirally ligated copper-cyanide species (generated *in situ* from trimethylsilylcyanide and a copper(II) intermediate) generates the key high-valent Cu(III) alkyl cyanide complex prone to product-forming reductive elimination. SET between the reduced metal catalyst and oxidized photocatalyst closes both catalytic cycles simultaneously, without the need for exogenous oxidants or reductants. The authors were able to provide an array of enantioenriched tertiary benzylic nitriles from the corresponding racemic esters in good yields and enantioselectivities. Notably, due to the prevalence of the benzylic carboxylic acid motif throughout the pharmaceutical sector, six commercial pharmaceuticals were functionalized to the enantioenriched nitrile adducts, with three of these pharmaceutical compounds shown to be proficient coupling partners in a one pot procedure (condensation followed by coupling) directly from the free acid.

Wang and co-workers leveraged a similar mechanistic regime for the asymmetric ring-opening cyanation of four- and five-membered cycloketone oxime esters.<sup>236</sup> C–C bond cleavage of less strained five-membered cyclopentanones required dual photoredox/copper catalysis, while bond cleavage of strained four-membered cyclobutanone was realized with single copper catalysis. Radical capture of the *in situ*-generated benzylic cyanoalkyl radicals by chiral copper catalysts, and subsequent stereoselective reductive elimination afforded chiral 1,5- and 1,6-dinitriles. Further derivatization furnished optically active diamides and diamines. Recently, Yu and co-workers merged copper-catalyzed cyanation with photoinduced and nitrogen-centered radical-mediated intermolecular 1,5-HAT for the enantioselective C(sp<sup>3</sup>)–H cyanation of carboxamides to furnish enantioenriched cyanated amides.<sup>237</sup>

### 3.3. 1,2-Difunctionalization of $\pi$ -Unsaturates

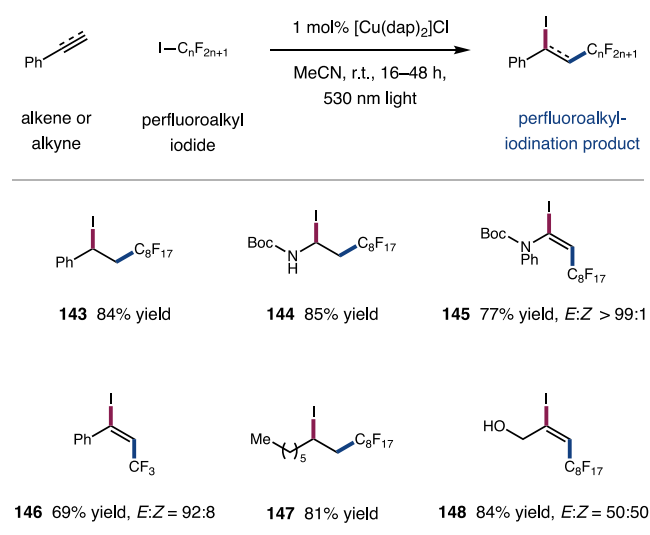
Early reports of copper- and photoredox-catalyzed olefin difunctionalization emerged from the Reiser laboratory in 2015. Using an established copper-based photocatalyst,  $\text{Cu}(\text{dap})_2$  ( $\text{dap} = 2,9$ -bis(*para*-anisyl)-1,10-phenanthroline),<sup>238</sup> the group engaged triflyl chloride in a trifluoromethylchlorosulfonylation of alkenes.<sup>239</sup> If not for key observations by Reiser and co-workers, this reaction easily could have been erroneously proposed to operate through an atom-transfer radical addition (ATRA) mechanism.<sup>240</sup> However, the authors recognized that traditional photoredox ATRA reactions employing triflyl chloride afford trifluoromethylchlorinated products.<sup>241</sup> This omission of  $\text{SO}_2$  from the final product is a consequence of outer-sphere SET from a traditional excited-state ruthenium- or iridium-based photocatalyst followed by the facile decomposition of  $[\text{SO}_2\text{Cl}]^-$  to chloride anion and sulfur dioxide.<sup>242</sup> In contrast, Reiser and co-workers propose the incorporation of  $\text{SO}_2$  in the product suggests an inner-sphere mechanism of triflyl chloride decomposition (Scheme 24). This essential insight implies that the copper catalyst plays

**Scheme 24. Evidence for Inner-Sphere Electrophile Activation by Reiser and Co-workers**



a dual-role in the reaction, both activating the electrophile as well as participating in critical ligand-stabilizing interactions prior to C–S bond formation. Moreover, the choice of copper photocatalyst was demonstrated to affect selectivity between the desired trifluoromethylchlorosulfonylation product and the undesired chlorinated adduct. The Reiser laboratory extended this concept to another longstanding challenge in ATRA catalysis, perfluoroalkyliodination of styrenes.<sup>243</sup> Using  $[\text{Cu}(\text{dap})_2]\text{Cl}$ , the authors found success, performing the reaction with a small collection of perfluoroalkyl iodides and a broad range of substituted styrenes and phenylacetylenes. The reaction was extended to other alkenes including enamines and unprotected allylic alcohols (Scheme 25, 143–148, 69%–85% yield). Mechanistic experiments ruled out the possibility for a radical chain mechanism by which the benzylic radical would abstract an iodine atom in the propagation step, a result consistent with previous failures by ruthenium- and iridium-based photocatalysts.<sup>240</sup> Reiser and co-workers propose two possible mechanisms for the formation of the previously elusive benzylic C–I bond. Specifically, (i) oxidation of the secondary benzylic radical to the benzylic cation by the  $[\text{Cu}(\text{dap})_2]^{2+}$  species, followed by capture of iodide anion, or (ii) inner-sphere reductive elimination from a Cu(III) alkyl

**Scheme 25. Iodoperfluoroalkylation of Olefins and Alkynes**



iodide complex. Both mechanisms serve to highlight the dual role of the transition metal catalyst in both electrophile reduction and bond formation.

Recently, Yu and co-workers have reported a series of azidation/difunctionalization protocols to furnish a variety of amido-azidation, benzyloxy-azidation, and diaziation products from styrene starting materials.<sup>244</sup> The success of these transformations hinge on the highly reducing nature of  $[\text{Cu}(\text{dap})_2]\text{PF}_6$  that enables the SET to azidobenzodioxole generating an azidyl radical.

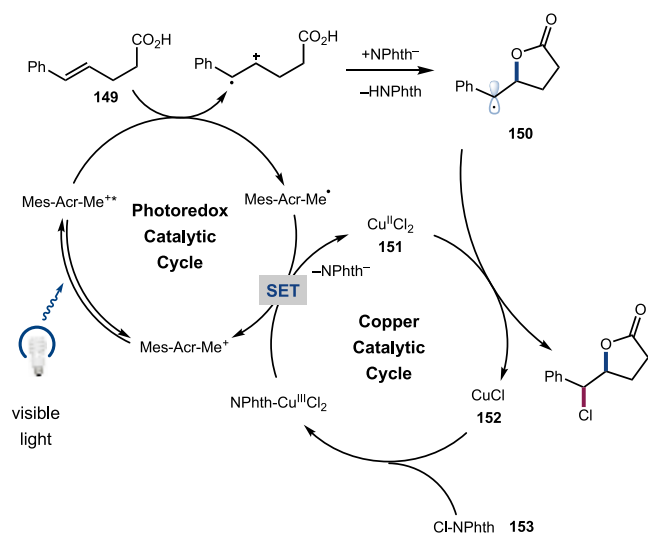
In addition to homoleptic copper complexes, heteroleptic copper-based photocatalysts have also been applied to the difunctionalization of alkenes and alkynes. Hu and co-workers recently described the preparation, characterization, and synthetic utilities of two heteroleptic  $[\text{Cu}(\text{N}^{\wedge}\text{N})(\text{P}^{\wedge}\text{P})][\text{PF}_6]$  complexes, where  $\text{N}^{\wedge}\text{N}$  represents a 4,6-disubstituted 2,2'-bipyridine ligand and  $\text{P}^{\wedge}\text{P}$  represents a bisphosphine ligand. Compared to the commonly employed  $[\text{Cu}(\text{dap})_2]\text{Cl}$  catalyst, these newly designed complexes exhibit longer excited-state lifetimes and lower reduction potentials. These copper photocatalysts have been utilized for a variety of difunctionalizations, including chlorotrifluoromethylation of terminal olefins<sup>245</sup> and chlorosulfonylation of both alkenes and alkynes.<sup>246</sup>

Qing and co-workers reported a related copper- and photoredox-catalyzed bromodifluoromethylation of terminal olefins using a difluoromethyltriphenylphosphonium bromide electrophile.<sup>247</sup> The authors found that in the absence of a copper salt additive, a mixture of bromo- and hydrodifluoromethylation was observed, but addition of catalytic quantities of  $\text{CuBr}_2$  provided the bromodifluoromethylated alkenes in good yields. This improvement in product distribution was attributed again to a role of copper in the bond-forming step. It was postulated that copper could be facilitating oxidation of the secondary radical formed after addition of the open-shell fluoroalkyl intermediate to the terminal olefin, or promoting a reductive elimination from a Cu(III) alkyl bromide intermediate. Qing and co-workers were able to apply the bromodifluoromethylation to a diverse set of terminal olefins with good functional group tolerance, and the laboratory developed a one-pot elimination procedure to afford difluoromethyl alkenes in a formal  $\text{C}(\text{sp}^2)\text{--H}$  difluoromethylation protocol. Additional olefin difunctionalization reactions

have since been reported by Li and Yu for the fluorotri-fluoromethylation of unactivated olefins, wherein a bimetallic copper fluoride species is proposed to act as a fluorine-atom-transfer reagent.<sup>248</sup> An example from Fu and Peters describes the trifluoromethylthioalkylation of olefins.<sup>249</sup> A range of electron-deficient alkyl bromides and iodides capable of photoreduction were engaged as coupling partners, and the reaction was demonstrated on other (pseudo)halogen nucleophiles, including bromide, cyanide, and azide. These contributions from Li, Yu, Fu, and Peters notably operate in the presence of visible light but without an added photocatalyst, yet again suggesting a dual role for the copper species in these three-component reactions.

Nicewicz and co-workers employed a dual copper and photoredox strategy in the intramolecular halofunctionalization of olefins.<sup>250</sup> A reversal of the traditionally observed Markovnikov selectivity for electrophilic halogenation of olefins was achieved by exploiting a strongly oxidizing acridinium photocatalyst. As shown in Scheme 26, the authors

**Scheme 26. Intramolecular Halofunctionalization of Olefins**



proposed a mechanism wherein olefin substrate **149** is oxidized to the corresponding radical cation. Thereafter, a pendant nucleophile can cyclize onto the carbocation, affording a five- or six-membered open-shell intermediate (**150**). The resultant radical is halogenated by a copper(II) halide complex **151**, via an inner-sphere Cu(III)-mediated mechanism or an outer-sphere atom-transfer reaction. The resultant reduced copper species **152**, together with an electrophilic halogenating reagent **153**, can serve to turn over the photocatalytic cycle and regenerate the active copper(II) species. Nicewicz and co-workers detailed efficient intramolecular vicinal functionalization of a number of styrenes, as well as unactivated olefins bearing pendant acid nucleophiles. Both bromination and chlorination were demonstrated, and a number of other nucleophiles including alcohols and amines were found to be effective in the trapping of the radical cation species, in both an intra- and intermolecular capacity.

Mei and Han extended the enantioselective cyanation reported by Liu and Lin<sup>235</sup> into the realm of three component couplings.<sup>251</sup> The authors described a 1,2-difunctionalization of styrenes utilizing redox-active esters as unstabilized radical precursors, which were proposed to add into the olefin

coupling partner. Capture of the resultant secondary benzylic radical by a copper cyanide species and subsequent reductive elimination is proposed to furnish the desired three-component coupling product. The authors engaged a variety of redox-active esters and styrene derivatives in this MCR, with a range of complex nitrile products provided in a single step in good efficiencies and enantioselectivities.

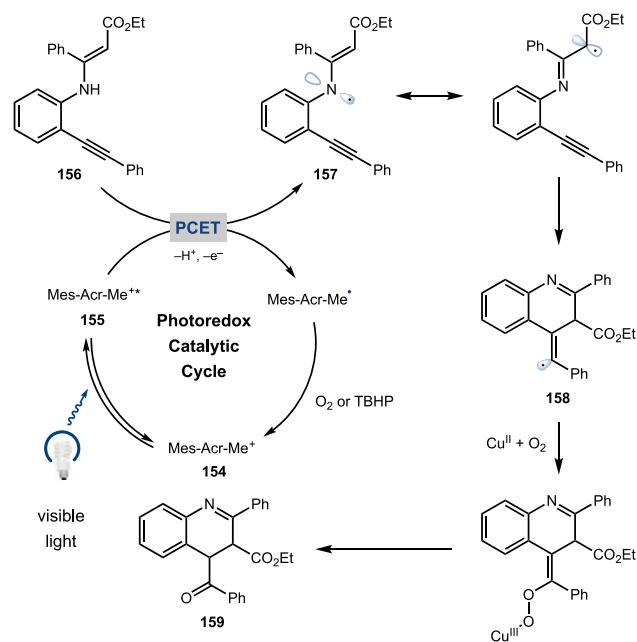
Three-component radical cross-coupling reactions to achieve olefin difunctionalization with two consecutive C–C bond formation events are valuable tools for the connection of small building blocks to build molecular complexity. Xiao and co-workers have realized this strategy in developing a redox-active oxime ester, styrene, and boronic acid three-component coupling protocol.<sup>252</sup> Under photoredox conditions, oxime esters can undergo SET followed by C–C bond cleavage to generate an alkyl radical, which is rapidly trapped by styrene. The resulting benzylic radical from this C–C bond formation event, can be efficiently captured by an aryl copper(II) species, derived from the transmetalation of aryl boronic acids with a copper(II) catalyst. The high-energy copper(III) complex can undergo facile reductive elimination to form a second C–C bond and regenerate the copper(I) catalyst. The overall result is the formation of two C–C bonds with the olefin double bond. Following this success, the same researchers extended this system to a new three-component coupling protocol, in which boronic acid is replaced with a terminal alkyne, enabling the formation of a C(sp<sup>3</sup>)–C(sp) bond.<sup>253</sup>

Olefin difunctionalization reactions are not strictly limited to C–C bond formation, however. Rehbein and Reiser demonstrated the conversion of vinyl arenes to  $\alpha$ -azido ketones.<sup>254</sup> Using [Cu(dap)<sub>2</sub>]Cl and trimethylsilyl azide under green light irradiation and aerobic conditions, a range of styrenes were capable substrates for this 1,2-functionalization, and sensitive functionalities such as an unprotected terminal olefin and a benzylic chloride were preserved under the reaction conditions. The authors characterized a photoactive copper(II) azide dimer found to be present in the reaction mixture, which, upon absorption of 530 nm light, would undergo homolytic dissociation of an azide radical. Thereafter, addition of this open-shell species into an activated olefin, followed by capture with molecular oxygen (or TEMPO, in a mechanistic probe), ultimately affords the ketone product.

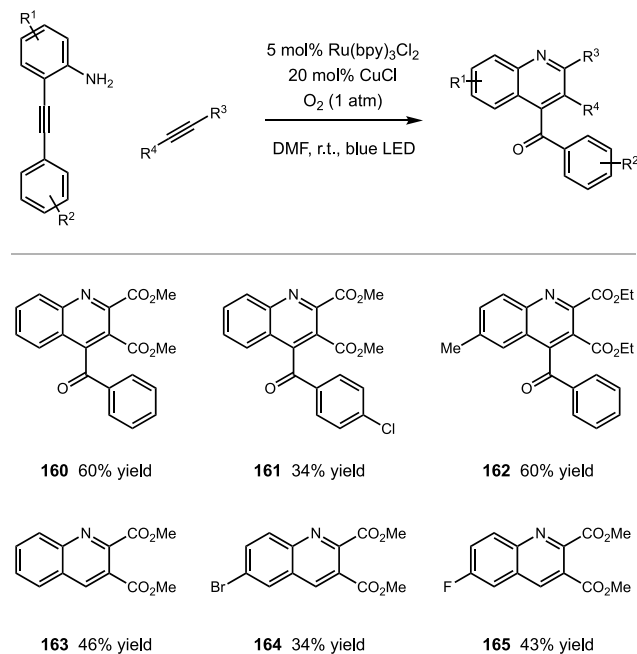
Copper has likewise been implicated in the difunctionalization of alkynes. The earliest work in this arena comes from Xia and co-workers, wherein an oxidative cyclization of alkynes with pendant enamines provides differentially substituted quinoline derivatives.<sup>255</sup> The authors postulate a radical cascade mechanism shown in Scheme 27a. Excitation of acridinium photocatalyst **154** provides highly oxidizing excited state **155**. SET followed by deprotonation of substrate **156** affords enaminy radical **157**, which can readily undergo a 6-*exo-dig* radical cyclization into a pendant alkyne. The copper catalyst, in concert with molecular oxygen, is postulated to oxidize the resulting vinyl radical (**158**) to the ketone product **159**, simultaneously regenerating a copper(II) species. Finally, the active acridinium photocatalyst is reformed by action of a terminal oxidant. Xia and co-workers also adapted this reaction to an intermolecular setting, constructing quinoline derivatives bearing 2,3-diester substitution from electron-deficient alkynes and 2-amino-phenylacetylenes (Scheme 27b, **160–165**, 34%–60% yield).

### Scheme 27. Dual-Catalytic Alkyne Difunctionalization by Xia and Co-workers

(a) Mechanism of dual photocatalytic, copper alkyne difunctionalization



(b) Scope of intermolecular quinoline formation



### 3.4. Copper as a Lewis Acid

While the merger of photoredox catalysis and copper catalysis has mainly relied on the well-established redox reactivity of copper with radicals and in bond-forming reductive elimination, copper also has a rich history of Lewis acid catalysis which has recently been exploited in a number of photoredox contexts. The first of these reports, detailed by Guo, involves the photoredox-assisted Lewis-acid activation of alkynes as electrophiles for remarkably weak nucleophiles.<sup>256</sup> Guo and co-workers proposed that upon coordination of Cu(II) to an alkyne, SET with an excited photocatalyst would generate a

three-center one-electron cation capable of reacting with weak nucleophiles. Indeed, the authors demonstrated that a number of phenanthrene derivatives could be synthesized in a single step from biarylacetylene substrates, mediated by organic photocatalyst Eosin Y.

Tao and co-workers then demonstrated dual Lewis acid- and photoredox-mediated aerobic oxidation of primary alkylamines to nitriles.<sup>257</sup> The reaction proceeds through Lewis acid activation of the amine nucleophile by copper and sequential oxidation by the excited photocatalyst and molecular oxygen to the nitrile proceeding through the copper imido complex. Under these mild aerobic conditions, a number of benzylic amines were oxidized to the corresponding cyanoarenes in good yield, and aliphatic amines were likewise shown to be competent substrates to afford alkyl nitriles.

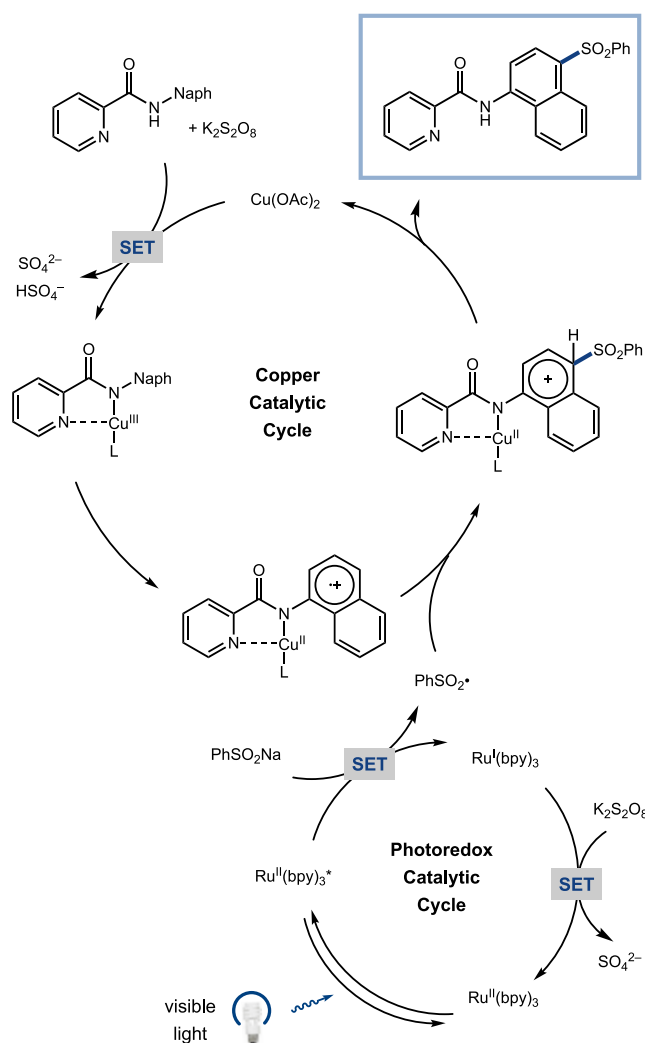
Copper-based Lewis acid catalysis has likewise enabled the C–H sulfonylation of 1-naphthylamides in concert with photocatalysis.<sup>258</sup> Wu, Wu, and Fang demonstrated the copper and photocatalyzed oxidative sulfonylation of naphthyl derivatives bearing chelating functionality, and proposed a copper coordination, oxidation, and intramolecular SET event to generate a key aryl radical cation species capable of trapping a sulfinate nucleophile (Scheme 28). The authors observed exquisite selectivity for 4-sulfonyl products, and a number of arylsulfonates functioned well as sulfur-centered nucleophiles.

Fan, Wu, and co-workers later reported the three-component coupling of potassium alkyltrifluoroborates, sulfur dioxide and alkynes for the synthesis of (*E*)-vinyl sulfones with excellent regio- and stereoselectivity via a dual photoredox/copper-catalyzed platform.<sup>259</sup> The presence of the copper catalyst is reported to assist in the addition of the alkylsulfonyl radical generated *in situ* to the alkyne.

### 3.5. Other Nucleophiles

While copper catalysis has seen a variety of methods for the construction of C–C bonds enabled by photoredox catalysis, milestone advancements in the synthesis of C–O and C–N bonds have likewise been enabled by developments in light-driven processes. The earliest demonstration in this regard comes from Fu and Peters, who disclosed a report detailing an ultraviolet light-induced Ullman coupling.<sup>163</sup> This landmark publication demonstrated the viability of an SET pathway for oxidative addition of copper into aryl halide electrophiles. A preformed copper(I)–carbazolide complex was found to facilitate bond formation between the *N*-ligand and an aryl iodide electrophile under irradiation by a 100 W Hg lamp. Evidence for an aryl radical intermediate was obtained by conducting the reaction on an aryl iodide with a pendant olefin (Scheme 29). Upon SET and loss of iodide anion, aryl radical species **166** can undergo a 5-*exo-trig* cyclization. The subsequent radical (**167**) can be captured by copper(I)-carbazolide species **168**, and C–N bond formation takes place without diastereoselectivity, ruling out a metal-mediated *syn*-insertion step facilitating ring-closure. While the authors did not suggest an SET mechanism for oxidative addition was operative across all Ullman couplings, they did remark on the significance of copper facilitating the critical C–N bond-forming step from an aryl radical intermediate generated under such mild conditions. Fu and Peters went on to accurately predict that copper may play an integral role in the formation of new bonds to nitrogen and other nucleophiles as methods for radical generation become increasingly abundant. The joint effort between the laboratories of Fu and Peters continued as

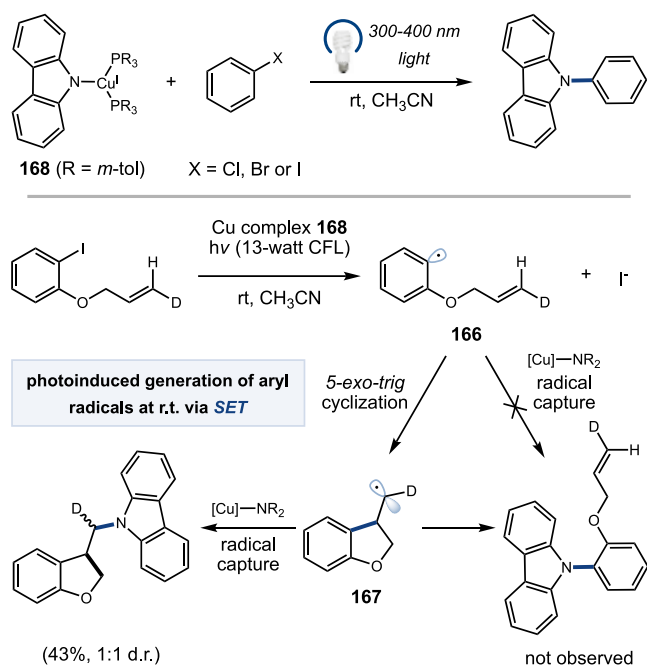
Scheme 28. Dual-Catalytic Oxidative Sulfonation of Naphthalenes



the group extended this method to alkyl iodides, relying again on radical generation by a carbazole-ligated copper complex.<sup>260</sup> A small scope of carbazole nucleophiles were alkylated in good efficiencies with primary and secondary alkyl iodides. The laboratories later disclosed an asymmetric amination of tertiary, racemic  $\alpha$ -chloroamides.<sup>164</sup> Under visible light irradiation and ligated by a chiral monophosphine ligand, copper facilitated the bond formation between a range of tertiary alkyl chlorides and conjugated amine nucleophiles in good to excellent yields and selectivities.

Fu and Peters have likewise developed protocols for C–S and C–O bond formation. Under similar conditions to previous work, the authors found that biaryl thioethers can be expeditiously generated from the corresponding (hetero)-aryl iodides and thiophenol derivatives. A diverse range of aryl and heteroaryl thiols were found to be suitable coupling partners.<sup>261</sup> Despite their lower reduction potential, aryl bromides were also competent electrophiles for the transformation. Given the absence of both photocatalyst and highly conjugated ligand, the authors were interested in identifying the photoactive species in the reaction mixture. Intriguingly, a polymetallic copper thiolate species was characterized and found to be catalytically active in the transformation. Fu and Peters later demonstrated C–O bond formation between

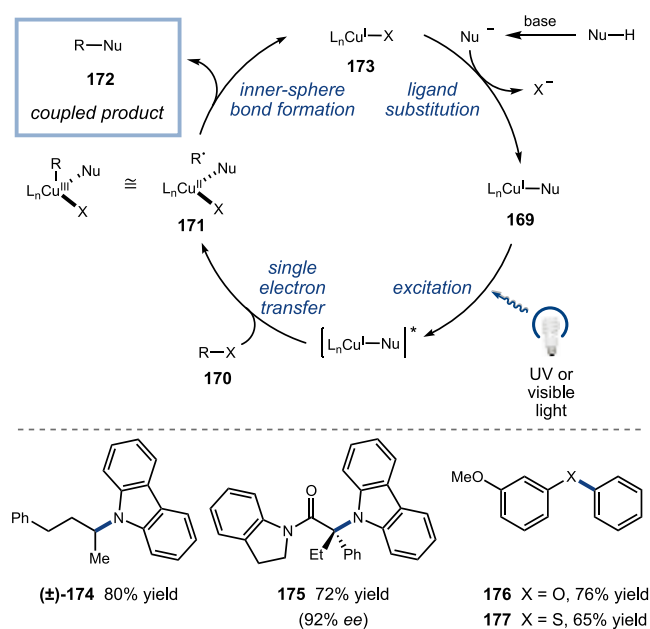
Scheme 29. Evidence for a Radical Mechanism in Photoinduced Ullman Coupling



phenols and aryl iodides.<sup>262</sup> However, 254 nm light was found to be necessary to provoke SET events between the monometallic copper catalyst and the aryl halide electrophiles.

The aforementioned work by the laboratories of Fu and Peters operates in the absence of a photocatalyst, and the mechanism proposed throughout is shown in Scheme 30. The copper precatalyst associates with a deprotonated nucleophile, generating the photoactive species **169**. Upon excitation (by UV or visible light), the copper(I) species reduces the halide electrophile (**170**) via an SET event. Loss of halide anion and association with the resultant radical affords radical pair **171**.

Scheme 30. Mechanism of the Photoinduced Ullman Coupling



Thereafter, bond formation provides the desired coupled product **172**, simultaneously regenerating the starting Cu(I) species (**173**). A broad range of both alkyl and aryl electrophiles and conjugated nucleophiles have been explored in this context (Scheme 30, 174–177, 65%–80% yield).

Under this mechanistic regime, choice of nucleophile often remains restricted to highly conjugated systems or nucleophiles which facilitate aggregation into absorptive polymetallic structures. Fu and Peters recognized that judicious choice of ligand on copper should provide an organometallic complex which absorbs visible light, and can act as a potent photoreductant, even in the absence of nucleophiles with large extinction coefficients. The first report on this concept targeted the alkylation of primary, aliphatic amines by alkyl iodides.<sup>263</sup> The authors remarked on the inefficiency of the traditional  $S_N2$  approach to alkylation, with overalkylation and elimination often competing with formation of the desired product. A number of secondary alkyl iodides underwent facile product formation with a range of primary alkylamines in good yields without overalkylation. A preliminary mechanistic proposal deemed the BINOL-ligated copper complex the light-absorbing species, with the more conjugated bis-(phenolate) capable of absorbing lower energy light than Fu and Peter's previously described UV-active copper phenolate complexes.<sup>262</sup>

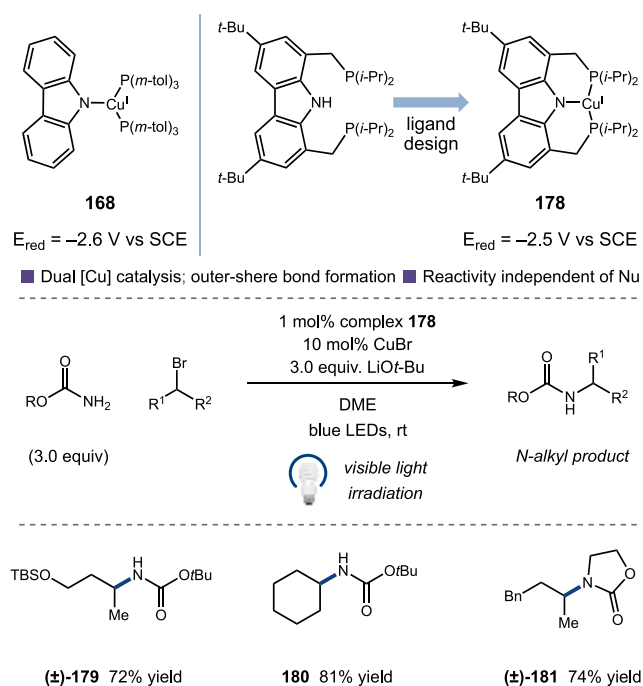
Fu and Peters sought to further expand the scope of available nucleophiles by separating the roles of photocatalyst from bond-forming catalyst. To this end, a novel, highly conjugated Cu(I)-based photocatalyst was developed to act as a powerful electron donor, while a secondary copper species could facilitate the critical steps of nucleophile ligation, radical capture, and reductive elimination.<sup>264</sup> The laboratories arrived at a carbazole-based PNP pincer-type ligand, which upon complexation with excess Cu(I), afforded novel photocatalyst **178** (Scheme 31). This *in situ*-generated photocatalyst was

competent in the facile reduction of secondary alkyl bromides to carbon-centered radicals, irrespective of nucleophile structure or conjugation. A number of carbamates were competent nucleophiles, providing the corresponding protected amines from alkyl bromides in good yields (179–181, 72%–81% yield). The transformation was proposed to operate in an analogous manner to previous transformations, with the remaining unligated copper serving to facilitate bond formation between nucleophile and radicals generated via SET from complex **178** in a dual-copper catalyst system. The estimated excited-state reduction potential of photocatalyst **178** (–2.5 V vs SCE) is similar to that of the copper(I)-carbazolide species **168** (–2.6 V vs SCE), suggesting that quenching is likely due to single electron transfer from its excited state to the alkyl bromide coupling partner.

In an effort to expand the electrophile scope beyond alkyl halides, Fu and Peters next explored NHPI redox-active esters as electrophiles in a decarboxylative amination.<sup>265</sup> A ligated copper(I) complex served as a capable photoreductant and catalyst for converting redox-active esters into alkylated phthalimides in good efficiencies. The reaction demonstrated broad functional group tolerance, with other redox-sensitive functionalities such as  $sp^2$ - and  $sp^3$ -hybridized organohalides undergoing selective decarboxylative coupling without undesired dehalogenation. Both primary and secondary redox-active esters were capable alkylating agents for the *in situ*-generated phthalimide nucleophile. The authors also examined the effect of various additives on reaction efficiency and found no deleterious effects to the reaction nor recovery of the additive across a variety of traditionally problematic functional groups including aldehydes, nitroalkanes, aryl sulfonates, and thioethers.

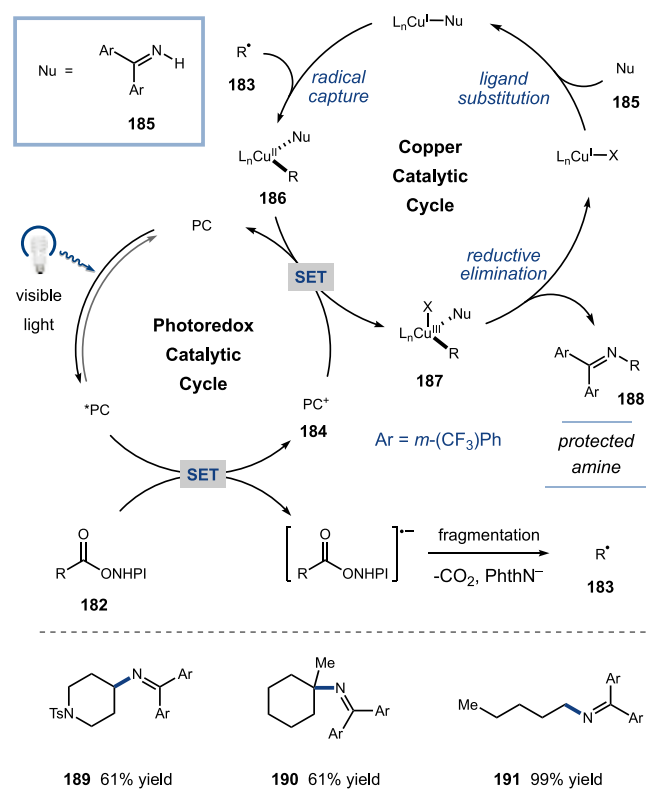
Expanding the scope of decarboxylative amination nucleophiles to benzophenone imines, Hu and co-workers employed redox-active esters with copper catalysis and an independent photocatalyst to facilitate the necessary electron-transfer steps in lieu of a dual-role photoactive copper species.<sup>266</sup> The proposed mechanism is detailed in Scheme 32. SET from the excited-state photocatalyst with redox-active ester substrate **182**, followed by fragmentation and loss of  $CO_2$ , affords alkyl-centered radical **183** and oxidized photocatalyst **184**. Simultaneously, coordination and deprotonation of benzophenone imine substrate **185** to Cu(I), followed by radical capture, affords Cu(II) intermediate **186**. SET between photocatalyst **184** and this species provides high-valent Cu(III) alkyl imido complex **187**, after which reductive elimination forges novel amine **188**. Primary, secondary, and tertiary acids, prefunctionalized as NHPI esters, were all capable coupling partners in this decarboxylative amination (189–191, 61%–99% yield) with a small number of electronically distinct benzophenone imine derivatives. Advances in ligand development by Hu and co-workers extended the scope of the dual copper- and photoredox-catalyzed decarboxylative amination to include anilines.<sup>267</sup> Under the same mechanistic assumptions as before, primary and secondary redox-active esters smoothly alkylated anilines by the action of copper and photoredox catalysis. A range of primary anilines with a variety of substitution were successful substrates, and the authors were able to extend the platform to a small subset of additional nucleophiles including a benzenesulfonamide, several benzamides, and a urea substrate. Subsequent work from the same group extends their original protocol to the decarboxylative C–N coupling with imines,<sup>266</sup>

**Scheme 31. Carbamate Alkylation with Dual Copper Catalytic System**





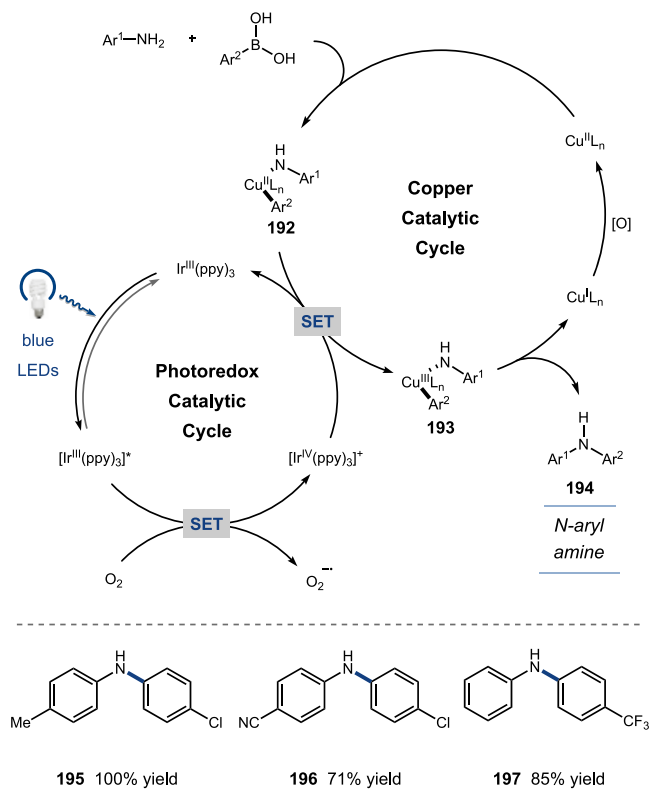
Scheme 32. Synthesis of Protected Primary Amines by Decarboxylative Amination



as well as the replacement of iridium photocatalysts with more economically efficient and abundant organic photoredox catalysts.<sup>268</sup> Hu and co-workers later incorporated phenolic nucleophiles, with alkyl NHPI redox-active esters undergoing decarboxylative C–O bond formation to forge a range of aryl alkyl ethers.<sup>269</sup> Larionov and co-workers have also applied this decarboxylative strategy to the formation of C–S bonds.<sup>270</sup> They report the amidosulfonation of carboxylic acids to access *N*-alkyl and *N*-aryl sulfonamides, as well as sulfonyl azides via dual copper/photoredox catalysis.

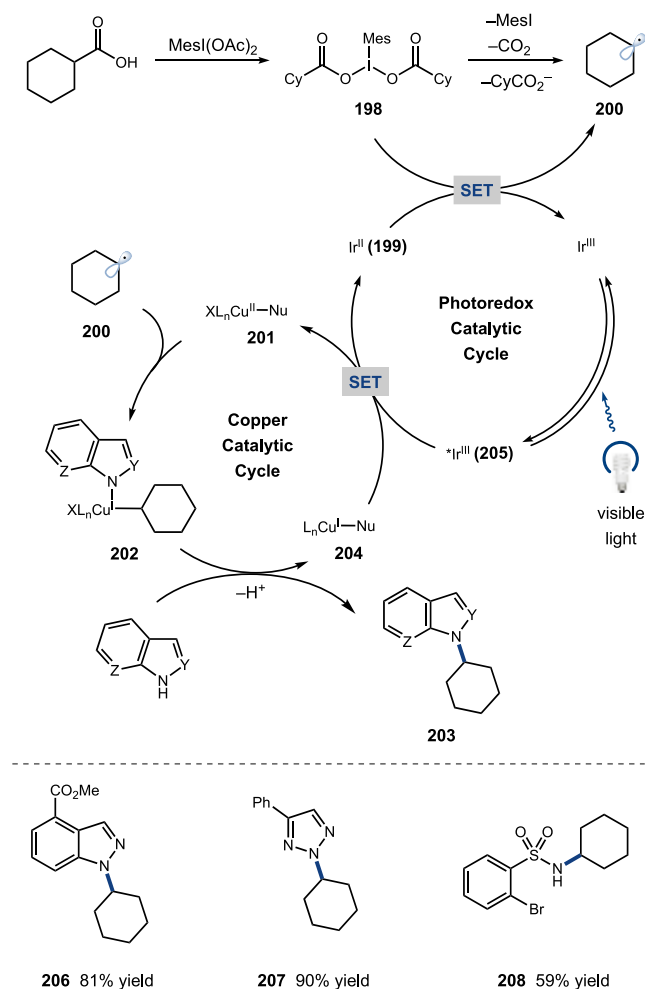
Copper-catalyzed amination reactions are not restricted to electrophilic partners such as redox-active esters and organohalides. Kobayashi and co-workers developed a photoredox-assisted Chan–Lam coupling for the mild synthesis of biaryl amines from anilines and arylboronic acids.<sup>271</sup> The authors report an open-to-air procedure, and propose that photoexcited  $\text{Ir}(\text{ppy})_3$  is oxidatively quenched by molecular oxygen (Scheme 33). The resultant Ir(IV) species then undergoes SET with Cu(II) aryl amido complex **192** to Cu(III) intermediate **193**. Reductive elimination provides the desired biarylamine (**194**), and that catalytically relevant Cu(II) intermediate is regenerated by boronic acid transmetalation and coordination of aniline nucleophile. This protocol was successful in the incorporation of electron-deficient arylboronic acid nucleophiles as coupling partners (**195–197**, 71%–100% yield). The authors attribute the improvement in efficiency to more robust photocatalyst-mediated electron-transfer steps providing access to the key Cu(III) intermediate **193** with greater efficiency than relying on SET with oxygen alone. The same authors later reported a visible-light-mediated Ullman-type C–N coupling method using carbazoles as nucleophiles and aryl iodides as substrates.<sup>272</sup> Although  $\text{Ir}(\text{ppy})_3$  was again utilized as the

Scheme 33. Photoredox-Assisted Chan–Lam Coupling



photocatalyst in this study, these researchers claimed that the iridium complex is functioning as an energy-transfer catalyst rather than a photoredox catalyst in this system. Photoexcitation of a copper carbazolate species is believed to be achieved via energy transfer from the excited-state iridium photocatalyst to the ground-state copper carbazolate complex. The excited-state copper carbazolate can then undergo further SET with aryl iodides to generate aryl radical intermediates, which then react to furnish the desired C–N bond.

Our laboratory has recently broadened our copper catalysis program to include carbon–heteroatom bond formation. Our initial report detailed the decarboxylative amination of alkyl carboxylic acids with a broad scope of *N*-nucleophiles.<sup>273</sup> In lieu of traditional NHPI redox-active esters to convert carboxylates to electrophiles capable of accepting an electron, we instead utilized hypervalent iodine-activated carboxylates as alkyl radical precursors. Our proposed mechanism, detailed in Scheme 34, begins with reduction of iodomesitylene dicarboxylate electrophile **198**, preformed without purification from commercially available iodomesitylene diacetate, by Ir(II) species **199**. Fragmentation affords a carboxylate anion, iodomesitylene,  $\text{CO}_2$ , and alkyl radical **200**. Capture of this open-shell species by nucleophile-ligated Cu(II) complex **201** affords Cu(III) intermediate **202**. Reductive elimination gives desired *N*-alkylated heterocyclic product **203**, and ligand exchange generates Cu(I) species **204**. Thereafter, SET between the reduced copper catalyst and excited-state photocatalyst **205** regenerates iridium species **199** and the initial copper complex, closing both catalytic cycles simultaneously. Ultimately, an extensive collection of acids provided product in good to excellent yields, and primary, secondary, and bridged-bicyclic tertiary alkyl fragments were well-tolerated. Altogether, 15 classes of nitrogen nucleophiles

Scheme 34. Dual-Catalytic Decarboxylative Amination of *N*-Heterocycles

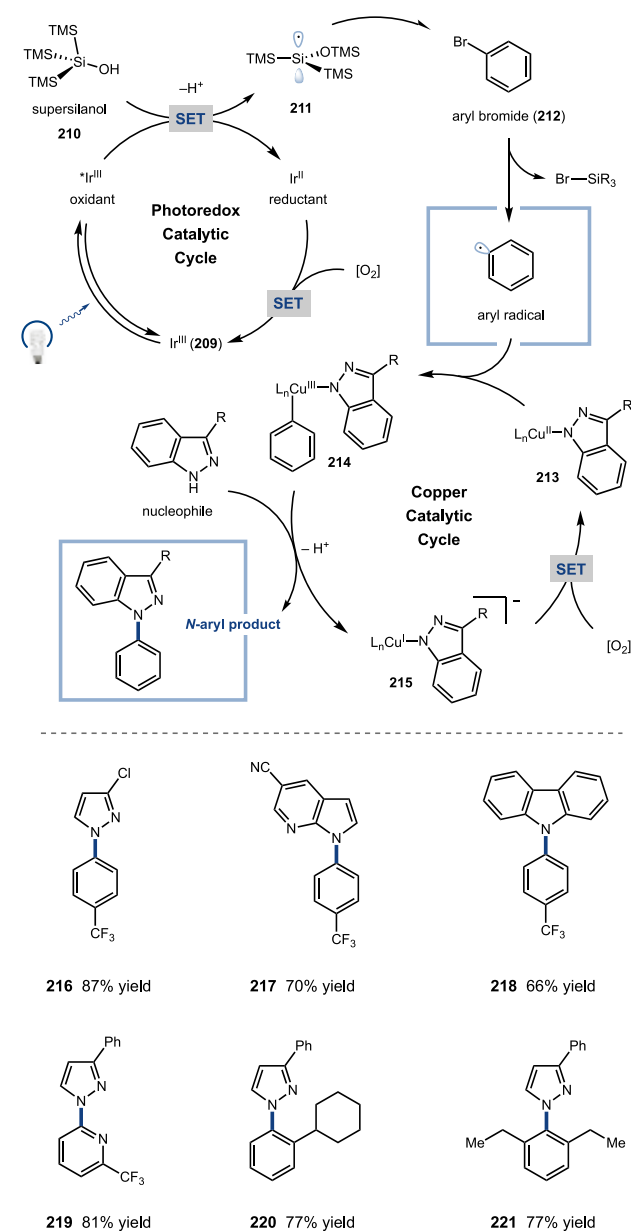
served as efficient partners in this decarboxylative amination (206–208, 59%–90% yield). Interestingly, with select classes of nucleophiles, the corresponding phenanthroline- and nucleophile-ligated Cu(I) complexes were capable of undergoing SET with iodonium electrophiles directly, and catalysis could be achieved in the absence of light and photocatalyst. A recent computational study of this system was disclosed by Zhang and co-workers, in which the experimental observations were verified with theoretical studies.<sup>274</sup> These researchers employed DFT calculations to help explain the excellent regioselectivity and chemoselectivity observed in the original report.

A similar strategy was employed by our laboratory for the synthesis of drug-like [1.1.1]-bicyclopentane (BCP) derivatives.<sup>275</sup> We reasoned that interception of reductively generated radicals by well-established SOMOPhile [1.1.1]-propellane<sup>276</sup> would transiently generate a range of substituted bicyclopentyl radicals, which could undergo further copper-mediated coupling with a range of nucleophiles as before.<sup>273</sup> This  $\sigma$ -bond-interrupted cross-coupling ultimately provided a broad range of BCP derivatives, a motif that has recently garnered interest in the pharmaceutical setting,<sup>277</sup> from readily accessible fragments. Iodine(III)-activated primary, secondary, and tertiary carboxylic acids along with activated alkyl bromides all served as viable electrophilic radical precursors. Thirteen classes of nitrogenous nucleophilic coupling partners

were demonstrated to provide product in good efficiency, while phosphorus and sulfur fragments were also employed to provide the corresponding C–P and C–S coupled BCP products, respectively. The method's utility was demonstrated in the synthesis of several BCP analogues of bioactive molecules, and a subsequent bioassay revealed marked improvements in metabolic stability for a Leflunomide BCP analogue.

Very recently, we disclosed a photoredox-promoted Ullmann–Goldberg coupling, utilizing silyl radical activation to bypass traditionally challenging oxidative addition of copper into aryl bromide electrophiles via a halogen abstraction–radical capture (HARC) sequence.<sup>278</sup> A brief mechanistic proposal is shown in Scheme 35. Iridium photocatalyst 209, upon photoexcitation and intersystem crossing, is expected to oxidize silyl radical precursor 210, which then undergoes rearrangement to silicon-centered radical intermediate 211.

## Scheme 35. Metallaphotocatalytic Ullmann–Goldberg Coupling Enabled by Halogen Abstraction–Radical Capture



Thereafter, facile abstraction of a bromine atom from aryl bromide **212** by the silyl radical provides the corresponding aryl radical. At the same time, coordination and deprotonation of an *N*-heterocycle to Cu(II) affords the copper amido species **213**, which intercepts the aryl radical to form key Cu(III) intermediate **214**. Reductive elimination and ligand exchange forges the desired C–N-coupled product and Cu(I) amido species **215**, respectively. Atmospheric oxygen, delivered to the reaction mixture through a pierced septum, regenerates both active photocatalyst **209** and Cu(II) amido species **213** to close both catalytic cycles. This HARC strategy was successful in preparing an extensive scope of *N*-arylated heterocycles in good yields under mild, room-temperature conditions (**216**–**220**, 66%–87% yield). Moreover, the absence of a sterically and electronically sensitive oxidative addition step allowed the amination of numerous *ortho*-substituted (hetero)aryl bromides, notably including examples of 2,6-disubstituted bromoarenes (**221**, 77% yield).

## 4. PALLADIUM METALLAPHOTOCATALYSIS

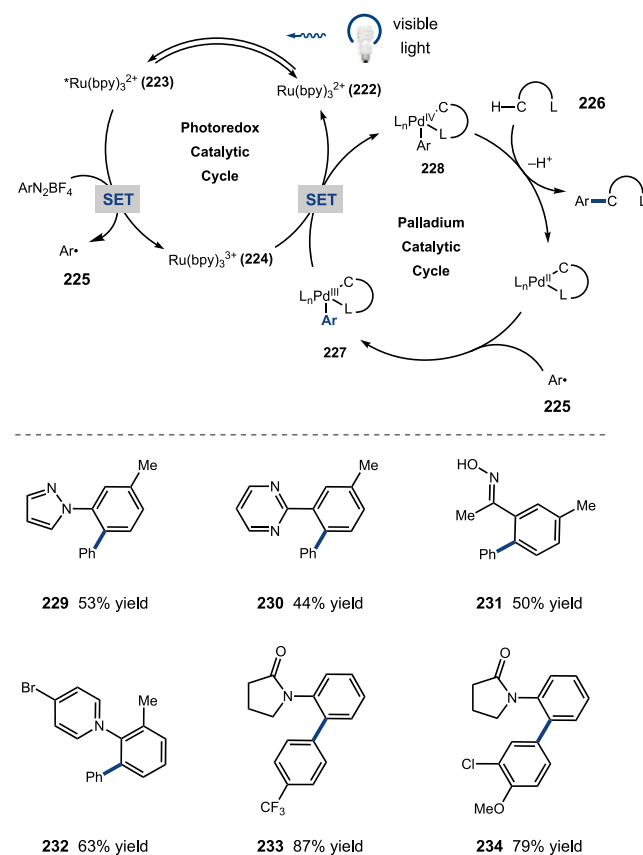
### 4.1. Early Work

Despite recent focus on first row transition metals in metallaphotoredox catalysis, the first example of transition metal and photoredox co-catalysis emerged in 2007 from the Osawa laboratory.<sup>279</sup> The authors found that introduction of [Ru(2,2'-bipyridine)<sub>3</sub>]<sup>2+</sup> to a copper-free Sonogashira coupling reaction under irradiative conditions dramatically accelerated the rate of product formation. While no specific mechanism for this result was postulated, experiments with traditionally sluggish aryl chloride electrophiles suggested that the oxidative addition step was promoted by photocatalysis. Osawa and co-workers contemplated that reductive quenching of the excited photocatalyst provided a reduced Ru species capable of assisting oxidative addition of low-valent palladium into *sp*<sup>2</sup>-hybridized electrophiles. However, the underlying implications of this finding, and thus the broader development of metallaphotoredox catalysis, would not be realized for several years.

### 4.2. C–H Activation

Sanford and co-workers were perhaps the first to recognize the potential of merging photoredox catalysis with transition metal catalysis broadly, and published a room-temperature, directed C–H arylation reaction promoted by palladium and photoredox catalysis.<sup>280</sup> While non-photonic methods for this transformation have been reported,<sup>281</sup> mechanistic studies revealed the necessity of high reaction temperatures for oxidative breakup of an inert Pd dimer.<sup>282</sup> Given this information, the authors proposed that photoredox catalysis could assist both in substrate activation and in challenging electron-transfer steps at the metal, rendering the transformation viable at room temperature with broad substrate scope and functional group tolerance. Indeed, a number of substrate classes were efficiently arylated under the dual-catalytic conditions. The authors propose a mechanism depicted in Scheme 36. The reaction begins with photoexcitation of ruthenium photocatalyst **222** to excited species **223**. SET between this excited-state complex and an arene diazonium substrate affords oxidized Ru species **224**, and, upon loss of dinitrogen, aryl radical **225**. Concurrently, a suitable Pd(II) species can undergo concerted metalation–deprotonation (CMD) into directing group-bearing C–H substrate **226**. Thereafter, capture of aryl radical to forge

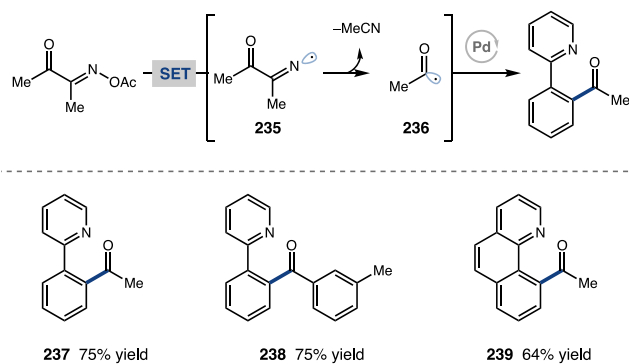
### Scheme 36. Palladium and Photoredox-catalyzed C–H Arylation



Pd(III) biaryl species **227**, followed by SET with **224**, provides the key Pd(IV) complex (**228**) and regenerates the Ru(II) photocatalyst **222**. Reductive elimination then reestablishes the Pd(II) complex and forges the desired biaryl product. Arenes with pendant directing groups including pyridines, pyrimidines, pyrazoles, amides, and oximes were all functionalized in good efficiency (**229**–**232**, 44%–63% yield). The scope of electrophilic coupling partners, aryl diazonium tetrafluoroborate salts, was equally broad, with electron-rich and electron-deficient aryl diazonium salts smoothly undergoing biaryl formation (**233** and **234**, 87% and 79% yield, respectively). The Sanford laboratory's insight into the role of photocatalysis both in substrate activation and metal oxidation-state modulation has laid the groundwork for the field of metallaphotocatalysis. Sanford and co-workers reported a C(*sp*<sup>2</sup>)–H arylation with diaryliodonium electrophiles.<sup>283</sup> Using a more strongly reducing iridium photocatalyst, the authors were able to employ iodine(III)-based aryl radical precursors, and found complementarity with respect to nucleophile scope when compared to aryl diazonium electrophiles. In both of these reports, particularly electron-deficient aryl electrophiles could provide product in the absence of photocatalyst, suggesting a direct metal-to-substrate SET event could be operative under some sets of conditions. Guo would later extend Sanford's work to include pharmaceutically important purine nucleosides as suitable C–H substrates.<sup>284</sup> Additionally, Xu and Balaraman independently adapted Sanford's diazonium C(*sp*<sup>2</sup>)–H arylation for use with organic photocatalysts.<sup>285,286</sup> Moreover, Spencer and co-workers employed Sanford's conditions to the directed C–H arylation

of benzodiazepines,<sup>287</sup> and Gopinath and co-workers engaged aryldiazonium electrophiles with *N*-phenylureas.<sup>288</sup> In a departure from aryl electrophiles, Chen and Liu employed redox-active oxime esters as acyl radical precursors for the dual palladium- and photoredox-catalyzed C–H acylation of 2-arylpyridines.<sup>289</sup> The unique mechanism of radical generation is depicted in Scheme 37. Photocatalytic reduction of the

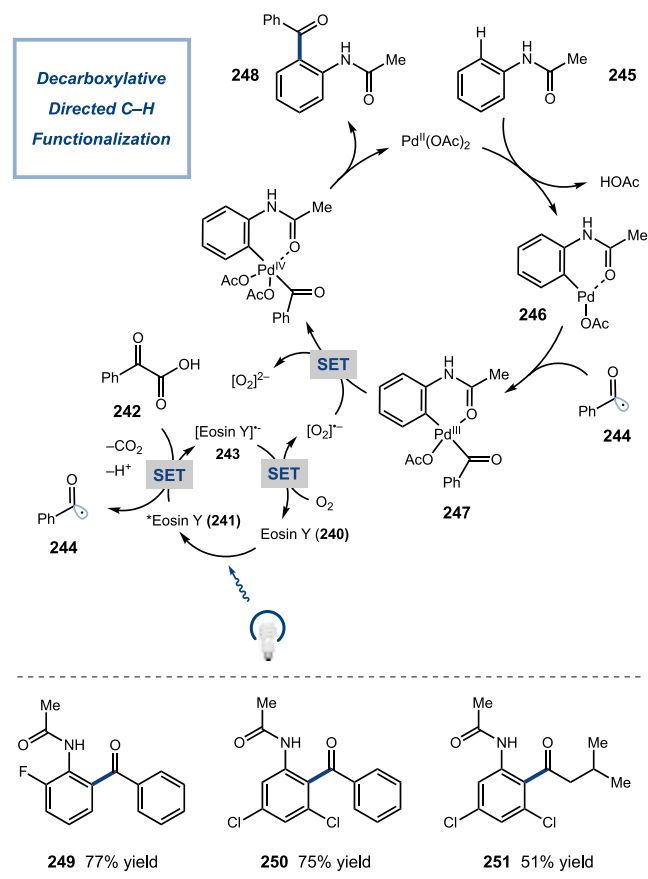
**Scheme 37. Palladium Metallaphotocatalytic C–H Acylation**



oxime ester N–O bond initially affords iminyl radical **235**.  $\beta$ -scission and loss of acetonitrile unveils acyl radical **236**, which can then interface with the transition metal catalytic cycle to provide the C–C linked products (**237–239**, 64%–75% yield).

Rueping and co-workers likewise invoked photocatalytic metal oxidation-state modulation in an intramolecular indole synthesis from *N*-aryl enamines.<sup>290</sup> A range of vinylogous amides underwent sequential palladium-mediated CMD events to provide six-membered palladacycles, from which reductive elimination forges the desired highly substituted indole products. Thereafter, the authors propose photocatalytic oxidation of the Pd(0) species back to the catalytically active Pd(II) intermediate, mediated by superoxide anion derived from atmospheric O<sub>2</sub>, obviating the use of an added stoichiometric oxidant. Several additional oxygen-promoted metallaphotoredox-catalyzed C–H functionalizations emerged from Wang and co-workers.<sup>291,292</sup> The laboratory disclosed the Pd-catalyzed C–H *ortho*-acylation of acetanilides or azobenzene nucleophiles by photocatalytic decarboxylation of  $\alpha$ -oxocarboxylic acids. The mechanistic proposal suggested by Wang and co-workers is outlined in Scheme 38. Photoexcitation of organic photocatalyst Eosin Y (**240**) affords excited-state species **241**, which can undergo SET with  $\alpha$ -oxocarboxylic acid substrate **242** to provide reduced photocatalyst species **243** and, after decarboxylation, acyl radical intermediate **244**. Simultaneously, a Pd(II) complex can undergo CMD with *N*-aryl amide substrate **245**, providing organometallic complex **246**. Subsequently, acyl radical capture provides Pd(III) species **247**. Oxidation to Pd(IV) and reductive elimination provides the C–H-functionalized product **248**. Akin to the report by Rueping and co-workers,<sup>290</sup> oxygen and photocatalyst-mediated turnover of the metal catalyst was suggested, with O<sub>2</sub> acting as a terminal oxidant in the regeneration of both the active Pd(II) species and Eosin Y. A broad range of aryl ketone products were generated in good efficiency, and substitution was well-tolerated on both coupling partners (**249–251**, 51%–77% yield). An oxidative acylation of indoles was later reported by Jana and co-workers, with a

**Scheme 38. Decarboxylative *ortho*-Acylation of Acetanilides**



peroxide additive acting both as an oxidant and a C–H abstractor, activating the aldehyde coupling partner via an HAT event.<sup>293</sup>

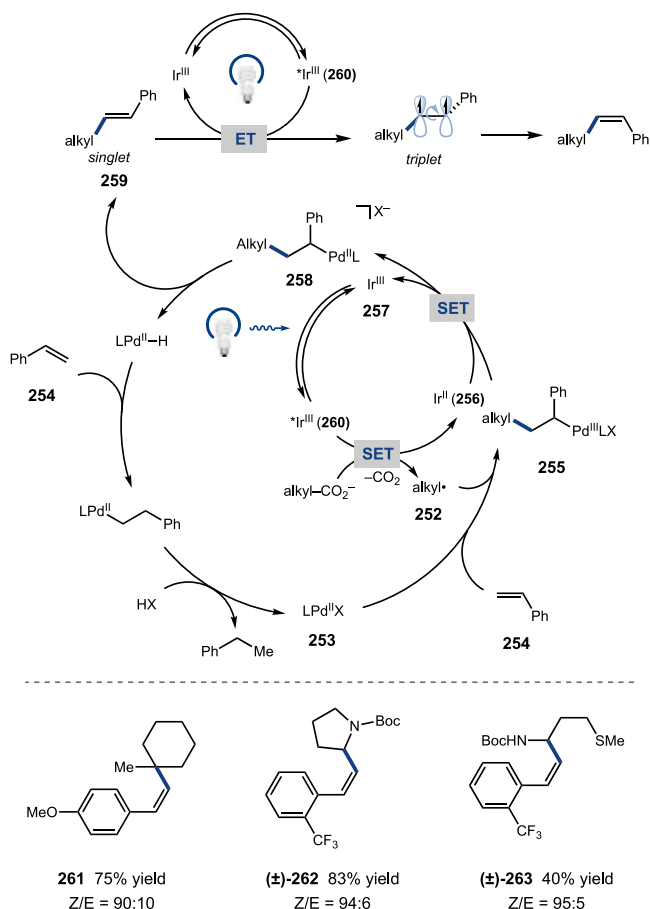
A metallaphotocatalytic C(*sp*<sup>2</sup>)–H amination reported by You and Cho offers an approach to benzo-fused heterocycles orthogonal to Rueping's indole synthesis.<sup>290,294</sup> Starting from 2-amidobiaryls, the authors detailed an expedient dual-catalytic protocol for the synthesis of carbazoles. A range of electronically diverse substituents were tolerated on both aromatic rings, forging single regioisomers of substituted *N*-sulfonyl or *N*-acyl carbazoles in good to excellent yields. Dual palladium- and photoredox-catalyzed C–O bond formation has also been demonstrated. Capitalizing on early C–H oxidation work reported by Sanford and co-workers,<sup>295</sup> Singh reported methods for the directed oxygenation of C–H bonds *ortho* to a number of heterocyclic and oxime ester directing groups.<sup>296,297</sup>

C–H functionalization by palladium metallaphotoredox catalysis is not strictly limited to *sp*<sup>2</sup>-hybridized systems. Polyzos and co-workers developed an aminoquinoline-directed C–H arylation of pendant quaternary methyl groups.<sup>298</sup> The proposed mechanism was analogous to Sanford's earlier work, with Pd-mediated C–H activation taking place now selectively at *sp*<sup>3</sup>-hybridized methyl groups. Pivalate-protected 8-aminoquinolines were arylated in moderate yields, generating mixtures of mono- and diarylated products in moderate efficiencies. However, substrates bearing a single  $\alpha$ -methyl group were selectively arylated at the sterically demanding primary site. A range of aryldiazonium salts functioned effectively as aryl radical precursors, although in stoichiometric

studies, an electron-deficient aryl iodide was also a viable coupling partner.

While mechanistically distinct from C–H metalation approaches, Heck reactions also represent a broadly used class of C( $sp^2$ )–H functionalizations. As such, several developments in photoredox-assisted Heck-type reactions have recently been disclosed. The first of these reports comes from Huang and co-workers, where it was found that the inclusion of a photocatalyst and visible light irradiation promoted a room temperature, ligand-free Heck reaction with dramatic rate enhancements over both dark and non-photocatalyzed approaches.<sup>299</sup> A broad range of aryl iodides were coupled to activated alkenes in exceptional yields, with free phenols, anilines, and other halogen functionalities remaining untouched by the mild conditions. While no specific mechanism was proposed, the authors did make note of exclusive (*E*)-selectivity in all cases except in the use of styrene nucleophiles, in which case a flip in selectivity to exclusive (*Z*)-alkene was observed as a result of stilbene triplet sensitization by the ruthenium-based photocatalyst. Na and Shang later expanded on this finding, demonstrating a decarboxylative vinylation with good levels of *cis*-selectivity promoted by the higher triplet energy iridium-based photocatalyst.<sup>300</sup> The unique mechanism of this transformation is shown in Scheme 39. The authors propose that oxidatively generated alkyl radical **252** interfaces with palladium complex **253** and styrene substrate **254** to forge Pd(III) alkyl complex **255**. SET from the reduced iridium photocatalyst **256** regenerates the photoactive Ir(III) complex (**257**) and Pd(II) alkyl inter-

Scheme 39. *Cis*-Selective Decarboxylative Alkenylation

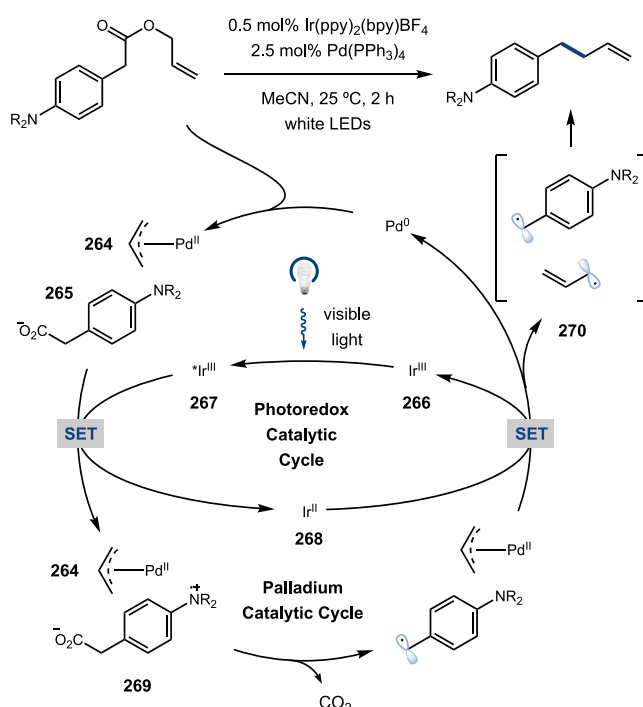


mediate **258**. At this point,  $\beta$ -hydride elimination provides the traditionally favored *trans*-alkene (**259**), and triplet energy transfer from excited photocatalyst **260** isomerizes the product to the observed *cis* product (**261–263**, 40%–83% yield). Notably, this transformation takes place in the absence of an added oxidant or electrophile, and the active Pd(II) species is thought to be regenerated via hydropalladation of a sacrificial equivalent of styrene **254** and subsequent protodemetalation.

### 4.3. Allylation

Since the first reports on palladium-catalyzed allylation,<sup>48,301,302</sup> the reaction has long been recognized for its remarkable synthetic utility in the synthesis of complex molecules.<sup>303</sup> Naturally, the advent of photoredox catalysis has provided opportunities for new developments in the arena of palladium-catalyzed allylation. Early work by Tunge and co-workers employed photoredox catalysis in palladium-catalyzed decarboxylative allylations of traditionally recalcitrant electron-rich carboxylate nucleophiles.<sup>304</sup> Given that decarboxylation of electron-rich alkanolic acids is often rate-limiting in allylations as the step trends with  $pK_a$ ,<sup>305</sup> the authors sought to employ photoredox catalysis to generate electron-deficient, open-shell intermediates, which should undergo facile decarboxylation. Indeed, a number of amine-bearing allyl esters were successfully engaged as substrates in the dual-catalytic reaction, with both benzylic and aliphatic amino esters affording the desired terminal alkene products in moderate to good efficiency. Tertiary alkyl and arylamines were well tolerated under the reaction conditions, and the protocol was extended to intermolecular couplings between free benzylic carboxylic acids and allyl methyl carbonate. While the authors conclude that a variety of reaction mechanisms could be operative, a general mechanistic proposal is given in Scheme 40. Coordination and oxidative addition of Pd(0) catalyst into the allyl ester electrophile affords cationic Pd- $\pi$ -allyl species **264**, and corresponding carboxylate nucleophile **265**. Simulta-

Scheme 40. Photoredox-Assisted Decarboxylative Allylation



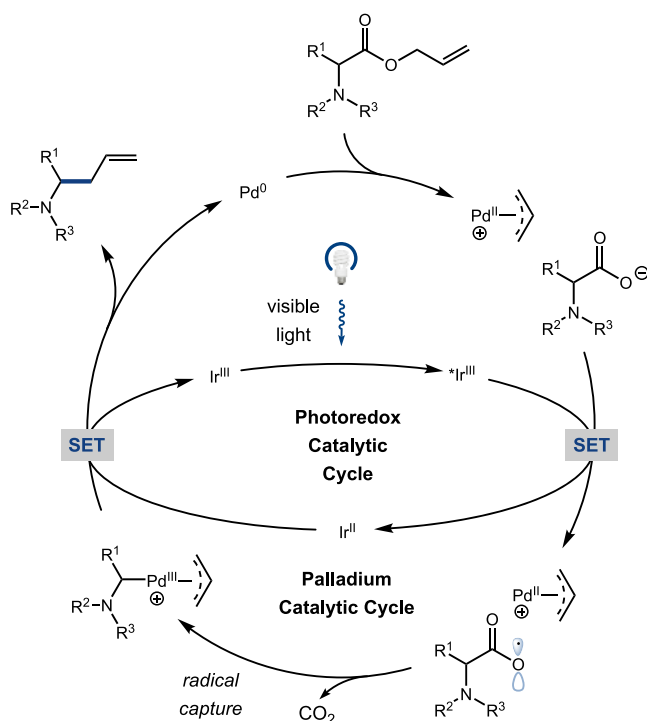
neous excitation of the photocatalyst **266** by visible light provides excited-state iridium species **267**, which upon SET with amine-bearing carboxylate nucleophile **265** unveils reduced Ir(II) species **268** and amine radical zwitterion **269**. Decarboxylation and Ir(II)-mediated reduction of the cationic Pd-allyl species, followed by homolysis, provides the benzyl-allyl radical pair (**270**). Thereafter, radical recombination forges the desired C–C bond. However, Tunge and co-workers also postulated that benzyl radical capture by palladium to afford a Pd(III) bis(alkyl) species could likewise be an operative pathway, where instead reductive elimination could lead to product formation. Very recently, Glorius and co-workers developed a decarboxylative 1,4-aminoalkylation for the difunctionalization of butadienes, proposed to proceed through a Pd- $\pi$ -allyl species generated via Pd(I) allylic radical capture.<sup>306</sup> A related three-component coupling was reported by the Glorius group recently, relying on a radical-to-polar cascade via Pd- $\pi$ -allyl nucleophilic capture.<sup>307</sup> Very recently, Breit and co-workers detailed an enantioselective decarboxylative allylation, relying on formation of the key Pd- $\pi$ -allyl complex via hydropalladation of the allene electrophile.<sup>308</sup>

Xiao and Lu extended metallaphotoredox allylation to a number of different allyl electrophiles in the C–H alkylation of THIQ derivatives.<sup>309</sup> Allylic acetates, carbonates, phosphates, halides, and even alcohols served as competent electrophiles. Notably,  $\alpha$ -amino ketones and esters were also suitable nucleophiles for the protocol, affording  $\alpha$ -allylated carbonyls in moderate efficiency. Analogous to Tunge, Xiao and Lu suggested a radical–radical coupling mechanism, given the stability of the two open-shell species. In a follow-up publication, Tunge explored potential divergence in the mechanism of bond formation, finding that less stabilized radicals tend lead to products with greater enantioselectivity when combined with a chiral ligand.<sup>310</sup> The authors attributed this to a change in mechanism from homolysis/recombination, as postulated previously by Tunge, Xiao, and Lu, to metal-mediated bond formation as a function of reduced free-radical stability (Scheme 41). Accordingly, a broad scope of  $\alpha$ -amino allyl esters were converted to corresponding homoallylic amines in good yields, with the reaction tolerating free alcohols and unprotected amides and carbamates.

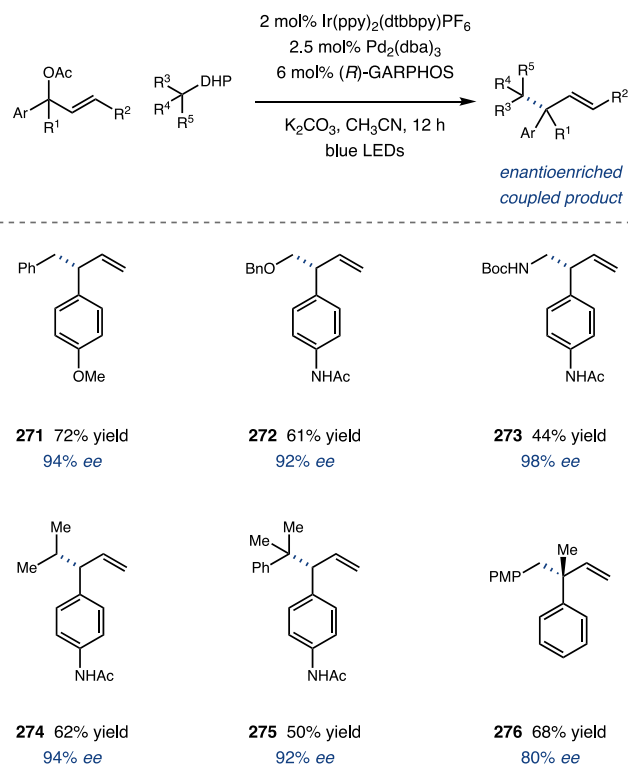
Kleij and co-workers leveraged dual palladium photoredox catalysis in the decarboxylative asymmetric allylic alkylation of vinyl cyclic carbonates using Hantzsch-type esters as radical precursors affording vicinal  $\alpha,\beta$ -tri/tetra- or  $\alpha,\beta$ -tetrasubstituted homoallylic alcohols.<sup>311</sup>

Yu and co-workers developed dual-catalytic conditions for the enantioselective allylation of stabilized radicals, coupling racemic allylic acetates and 1,4-DHP radical precursors to afford the corresponding enantioenriched C–C coupled products in good yields and high levels of enantioselectivity.<sup>312</sup> The authors proposed that precedented radical generation from 1,4-DHP derivatives<sup>84,85,88</sup> could smoothly interface with a palladium oxidative addition, radical capture, and reductive elimination mechanism, with enantioselectivity induced by a chiral diphosphine ligand in the first highly enantioselective dual palladium- and photoredox-catalyzed coupling. Yu and co-workers demonstrated the coupling across a range of stabilized allylic acetates with good efficiency (Scheme 42). Benzylic,  $\alpha$ -heteroatom, as well as unstabilized secondary and tertiary alkyl radicals all provided product in moderate to good yield and excellent levels of enantioselectivity (**271**–**275**, 44%–72% yield, 92%–98% ee). Impressively, tertiary allylic acetates

**Scheme 41. Mechanism of Decarboxylation of Less Stabilized Radicals**



**Scheme 42. Dual-Catalytic Enantioselective Allylation**



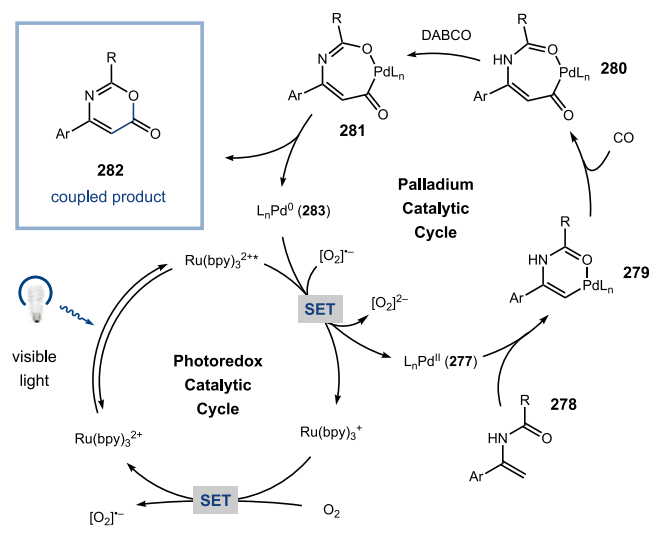
could be engaged to forge challenging enantioenriched quaternary centers in moderate yield and selectivity (**276**, 68% yield, 80% ee). Yu extended this enantioselective cross-coupling to include secondary benzylic carbonates as electrophiles,<sup>313</sup> and expanded the scope of radical precursor to simple anilines bearing  $\alpha$ -amino C–H bonds via an oxidation–

deprotonation mechanism.<sup>92,314</sup> Murakami likewise advanced a method for C–H allylation of anilines by dual palladium and photoredox catalysis, but demonstrated the direct engagement of unprotected allylic alcohols as feedstock allylic fragments.<sup>315</sup> Targeting the introduction of highly unsaturated carbon fragments, Chen and Liang developed a racemic yet exceptionally regioselective propargylic benzylation of propargylic carbonates, yet again engaging 1,4-DHP derivatives as radical precursors.<sup>316</sup>

#### 4.4. Carbonylation and Carboxylation

The incorporation of feedstock gases as coupling partners in transition metal catalysis represents an ideal approach to the installation of small fragments in an atom economical manner. In this regard, Lei and co-workers recognized that aerobic palladium and photoredox catalysis, previously demonstrated to be successful in the construction of heterocycles the need for added chemical oxidants,<sup>290,294</sup> could provide a platform for carbonylative ring closure. The authors proposed carbonylation of enamides via the mechanism shown in Scheme 43.<sup>317</sup> Pd(II) catalyst **277** was suggested to undergo

**Scheme 43. Oxidative Carbonylation of Enamides by Dual Palladium and Photoredox Catalysis**



coordination and CMD with enamide substrate **278**, forging vinyl palladium intermediate **279**. Subsequent insertion of CO into **279** affords homologated organometallic species **280**, which upon deprotonation by DABCO provides intermediate **281**. Subsequent reductive elimination forges the carbonylated heterocycle **282**, and as with previous reports by Rueping and co-workers,<sup>290</sup> oxidation of the resultant Pd(0) species **283** to the active catalyst occurs via photocatalyst and oxygen-mediated SET events. Under balloon pressure of CO and O<sub>2</sub>, a library of substituted 1,3-oxazin-6-ones was generated with carbon substitution at both the 2- and 4-positions tolerated.

Iwasawa and Martin disclosed a dual palladium- and photoredox-catalyzed carboxylation of aryl halides.<sup>318</sup> While traditional methods for carboxylation of aryl electrophiles employ strong organometallic or metal-based reductants,<sup>319,320</sup> the authors recognized the utility of excited-state photocatalysts in mediating the challenging electron-transfer steps necessary in employing carbon dioxide in a synthetic context. In a one-pot procedure under an atmosphere of CO<sub>2</sub>, a range

of electronically distinct aryl bromides were converted first to benzoic acids, then to the corresponding benzoate methyl esters in good to excellent yields. The reaction performed well on particularly sterically encumbered aryl bromides, and likewise on a small selection of aryl chlorides. Iwasawa and Jana independently extended this strategy to include aryl and vinyl triflate electrophiles,<sup>321,322</sup> and difluoroalkene electrophiles were later incorporated by Feng and co-workers.<sup>323</sup>

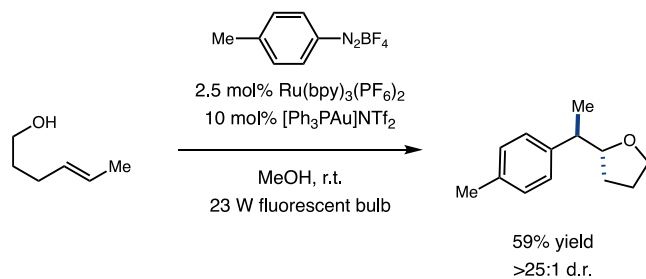
## 5. GOLD METALLAPHOTOCATALYSIS

Over the last five decades, gold catalysis has emerged as a powerful synthetic platform, predominantly for the functionalization of unsaturated carbon–carbon bonds, driven by the carbophilic  $\pi$ -acidity of gold complexes.<sup>324</sup> While applications of this reactivity toward the hydrofunctionalization of olefins and alkynes has been broadly adopted across the synthetic community, advancing gold as a catalyst in the context of redox chemistry has remained largely underdeveloped. Progress has been slowed by the challenge of accessing high-oxidation-state Au(III) from Au(I) intermediates under catalytically relevant conditions, with methods often employing strong, stoichiometric oxidants.<sup>325–327</sup> Recently, with the advent of metallaphotoredox catalysis enabling oxidation-state-modulation of transition metal catalysts under mild, irradiative conditions, speculation began to arise around the possible beneficial role photoredox catalysis could play in gold chemistry.

### 5.1. Alkene Functionalization

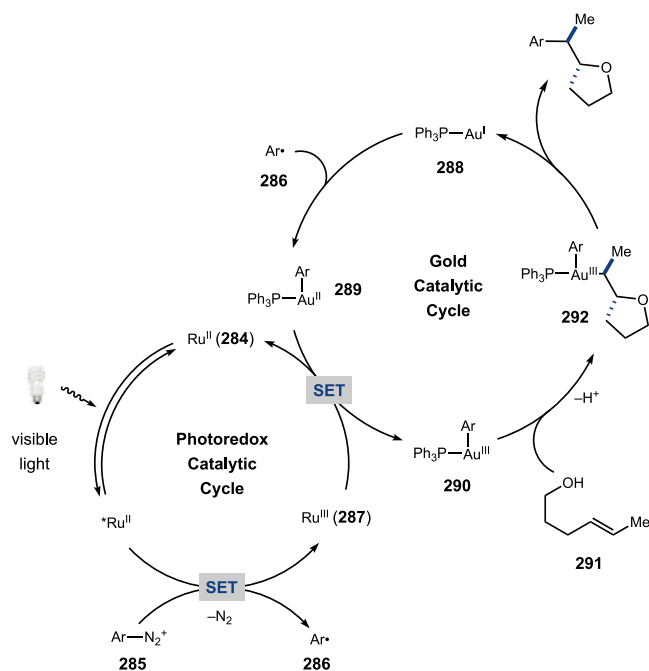
The first report detailing cooperative gold and photoredox catalysis emerged from the Glorius group in 2013.<sup>328</sup> The authors reported a dual-catalytic system for the oxy- and aminoarylation of alkenes (Scheme 44). While the originally

**Scheme 44. Early Gold Metallaphotocatalysis Reported by Glorius and Coworkers**



proposed mechanism begins with a gold(I)-mediated 5-*exo-trig* cyclization of the olefin substrate, subsequent studies by Glorius<sup>329</sup> support the mechanism shown in Scheme 45. The transformation begins with photoexcitation of ruthenium catalyst **284** by visible light, followed by reduction of aryl diazonium electrophile **285** to furnish aryl radical intermediate **286** and Ru(III) complex **287**. Capture of **286** by phosphine-ligated Au(I) complex **288** provides Au(II) species **289**, which is expected to rapidly reduce the oxidized photocatalyst **287** to furnish Au(III) aryl intermediate **290**. Coordination of this cationic organometallic complex to olefin substrate **291**, followed by cyclization forges gold(III) aryl alkyl species **292**. Reductive elimination furnishes the desired difunctionalized alkene, concurrently regenerating the catalytically active gold(I) complex. The independent synthesis of well-defined (C,N)-cyclometalated gold(III) complexes via photoredox-catalyzed oxidative addition of aryl diazonium salts

Scheme 45. Proposed Mechanism of the Gold Metallaphotocatalytic Olefin Oxyarylation

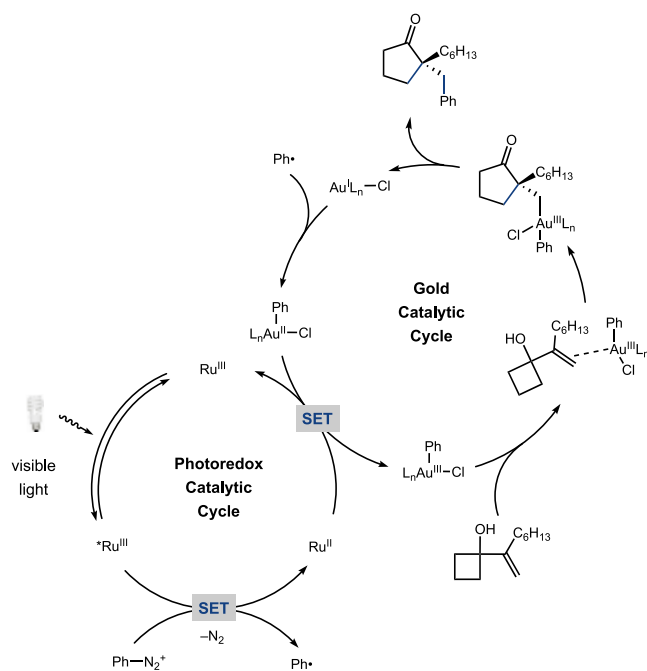


to gold(I) complexes provides experimental evidence validating the key aryl radical-induced oxidation step.<sup>330,331</sup> Glorius and co-workers were able to access oxyarylation products with a range of substitution tolerated both on the aromatic electrophile and the olefin coupling partner. Moreover, several examples of aminoarylation were reported, starting from the corresponding tosyl-protected amine bearing a distal olefin. The authors later reported an intermolecular oxyarylation of olefins, generating ether products derived from the alcohol solvent in good efficiencies,<sup>332</sup> a transformation which was later modified to utilize more stable diaryliodonium electrophiles.<sup>329</sup> This reactivity is not restricted to olefins, however. A study by Shin demonstrated the difunctionalization of allenes in a mechanistically related approach, providing smooth access to functionalized butenolide products.<sup>333</sup>

Shortly after Glorius's initial forays into gold metallaphotoredox catalysis, Toste reported an arylyative ring expansion of strained cyclic alcohols enabled by gold and photoredox catalysis.<sup>334</sup> The proposed mechanism bares resemblance to that proposed by Glorius, with the key photogenerated Au(III)–aryl electrophile facilitating alkene functionalization by coordination and, in this case, ring expansion by alkyl group migration (Scheme 46). This mechanistic proposal, probed by both time-resolved FT-IR spectroscopy and labeling experiments, provided access to a range of  $\alpha$ -functionalized ketones derived from allylic cyclopropanols and cyclobutanols. Extrapolating on Toste's results with strained allenols, Alcaide and Almendros later found that acyclic, unstrained allenols underwent cyclative arylation under similar conditions to instead forge 2,5-dihydrofuran products by nucleophilic capture at oxygen.<sup>335</sup>

Toste and co-workers report the independent synthesis of stable and catalytically active gold(III) complexes in an effort to better understand the reactivity of high-valent transition-metal catalysts.<sup>336</sup> Insertion of a cationic gold(I) complex into the strained C–C bond of biphenylene via mild oxidative addition achieves the desired oxidation and introduction of a

Scheme 46. Arylyative Ring Expansion via Gold Metallaphotoredox



stabilized biphenyl ligand. The stable gold(III) complex exhibits hard, oxophilic Lewis acidity rendering it capable of activating  $\alpha,\beta$ -unsaturated and  $\alpha,\beta,\gamma,\delta$ -diunsaturated aldehydes for selective conjugate additions, as well as an unsaturated aldehyde-allene for a [2+2] cycloaddition reaction. The ligand environment of these gold(III) complexes imposes a sterically defined binding pocket, dictating the high selectivity of additions.

While cyclization of pendant nucleophiles into gold-activated  $\pi$ -systems represents a powerful strategy for forging multiple bonds, Patil and co-workers recognized that leaving groups adjacent to alkenes could afford a novel entry point into forging bonds to  $sp^3$ -hybridized scaffolds in gold metallaphotocatalysis. The authors found that allyltrimethylsilane was a competent nucleophile for cross-coupling, with a range of electron-rich and electron-deficient aryldiazonium salts undergoing smooth allylation under the dual-catalytic manifold delivering allyl arenes in moderate to good yields.<sup>337</sup>

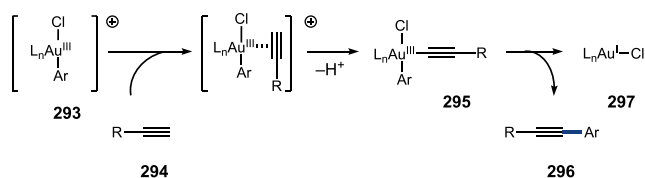
## 5.2. Alkyne Functionalization

Glorius and co-workers demonstrated the C( $sp$ )–H arylation of alkynes by dual gold and photoredox catalysis, once again relying on a key cationic arylgold(III) species as an *in situ*-generated electrophile.<sup>338</sup> An abridged mechanism is shown in Scheme 47a. Gold(III)–aryl species **293**, generated via the steps previously depicted in Scheme 45, is proposed to undergo coordination to terminal alkyne substrate **294**, after which loss of a proton generates key Au(III) intermediate **295**. At this point, reductive elimination forges the desired C( $sp$ )–C( $sp^2$ ) product (**296**), simultaneously regenerating gold(I) catalyst **297**. However, citing a quantum yield greater than 1, the authors proposed a secondary pathway by which the Au(II) intermediate afforded after radical capture could directly reduce an aryl electrophile, with the photocatalyst acting in this case as a radical initiator in a chain pathway. A range of aryl acetylenes underwent productive bond formation with diazonium electrophiles in moderate to good yield.

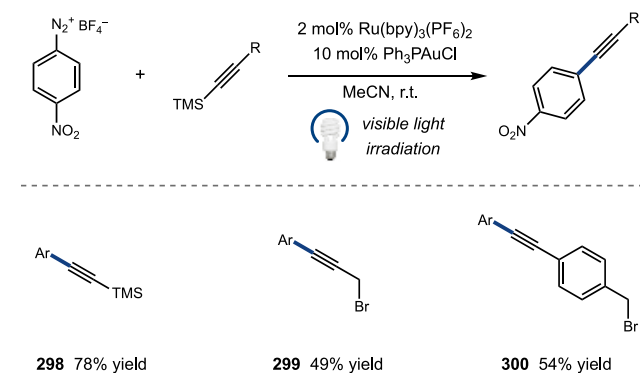


### Scheme 47. Dual Gold- and Photoredox-Catalyzed Alkynylations

#### (a) Glorius – Alkynylation of arenes with terminal acetylenes



#### (b) Toste – Desilylative arylation of protected alkynes

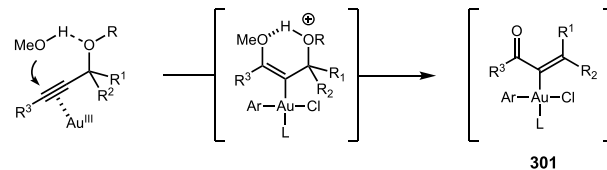


Simultaneously to this report, Toste and co-workers published the arylation of TMS-protected alkynes.<sup>339</sup> A range of alkyne coupling partners underwent smooth arylation with diazonium electrophiles under the dual-catalytic platform, with sensitive functionalities including benzylic and propargylic halides tolerated well under the mild reaction conditions (Scheme 47b, 298–300, 49%–78% yield).

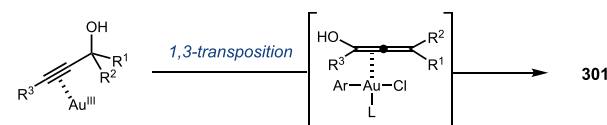
In 2016, three independent reports of dual gold- and photoredox-catalyzed arylyative Meyer–Schuster rearrangements surfaced from the laboratories of Shin,<sup>340</sup> Glorius,<sup>341</sup> and Alcaide and Almandros.<sup>342</sup> While all three reports vary in substrate scope and mechanistic proposal, a key alkenyl–gold intermediate is conserved across the three publications (Scheme 48). Shin's report relies on a hydrogen bond-guided addition of solvent methanol into the gold(III)-ligated alkyne to ultimately access key alkenyl–gold intermediate 301 (Scheme 48a); however, the reports from the groups of Glorius and Alcaide/Almandros suggest a 1,3-hydroxide transposition to access the same intermediate (48b). While Shin utilized tertiary propargyl alcohols to access tetrasubstituted olefins, Alcaide and Almandros instead demonstrated the rearrangement's compatibility with primary propargyl alcohols to access 1,1-disubstituted terminal olefin products in good efficiencies (Scheme 48c, 302–304, 55%–77% yield). In their report, Glorius and co-workers simultaneously demonstrated an extension of the method to alkyne hydration (a result that was later published by Hashmi in the absence of photocatalysis),<sup>343</sup> in addition to the intramolecular oxyarylation of *ortho*-alkynylphenols in the same report. Notably, this latter result was expounded upon by Ollivier and Fensterbank and independently by Zhu in the expedient synthesis of benzo-fused heterocycles.<sup>344,345</sup> Thereafter, Alcaide, Almandros, and Busto leveraged the domino gold-photocatalyzed reaction platform in developing a selective bisarylation protocol of TMS-terminated alkynols to furnish

### Scheme 48. Arylyative Meyer–Schuster Rearrangements

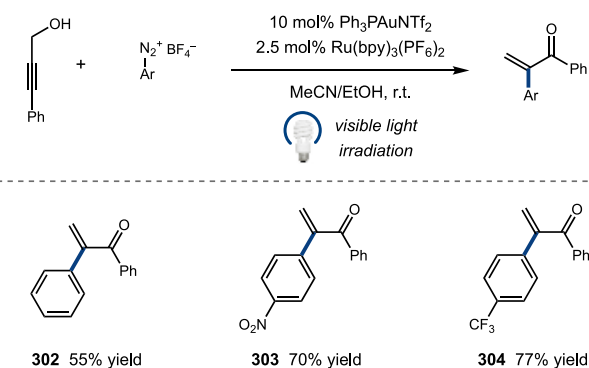
#### (a) Proposed hydrogen bond-guided solvent addition to activated alkyne



#### (b) Alcaide/Almandros proposed 1,3-hydroxide transposition



#### (c) Domino Meyer–Schuster arylation

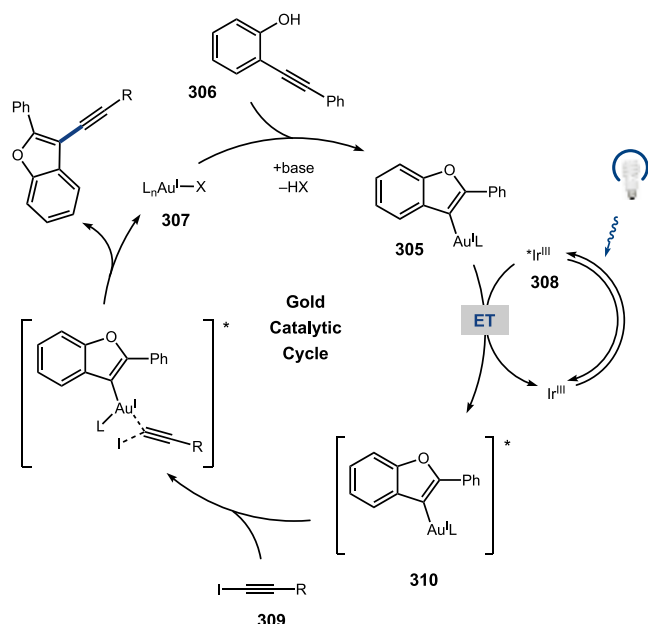


diarylated  $\alpha,\beta$ -unsaturated ketones and 2,3-diarylbenzofurans.<sup>346</sup> Upon modification of the gold catalyst from  $\text{Ar}_3\text{PAuCl}$  salts to  $[\text{Ph}_3\text{PAuNTf}_2]$ , Almandros and co-workers report the catalyst-controlled direct alkoxyarylation of alkynes for the stereoselective synthesis of enol ethers.<sup>347</sup>

In a mechanistically distinct transformation, Ollivier, Fensterbank, and Mouriés-Mansuy reported the alkynylyative cyclization of *ortho*-alkynylphenols via a unique energy-transfer mechanism.<sup>348</sup> As shown in Scheme 49, the authors propose triplet-sensitization of Au(I)–aryl species 305, formed via coordination and cyclization of 2-alkynylphenol substrate 306 with ground-state Au(I) catalyst 307, by excited-state iridium photocatalyst 308. Thereafter, calculations suggest several possible mechanisms of activation of iodoalkyne electrophile 309 by excited-state Au(I) complex 310, which ultimately leads to the desired alkynylated benzofuran. Patil and co-workers leveraged a similar energy-transfer mechanism in a dual gold/organophotoredox platform toward the *ortho*-oxygenative 1,2-difunctionalization of diarylalkynes to access highly functionalized 2-(2-hydroxyaryl)-2-alkoxy-1-arylethan-1-ones, as well as benzofurans.<sup>349</sup> Energy transfer from photoexcited Eosin Y generates a necessary singlet oxygen to undergo a formal [4+2] cycloaddition with an enol ether generated *in situ* via gold-catalyzed hydroalkoxylation.

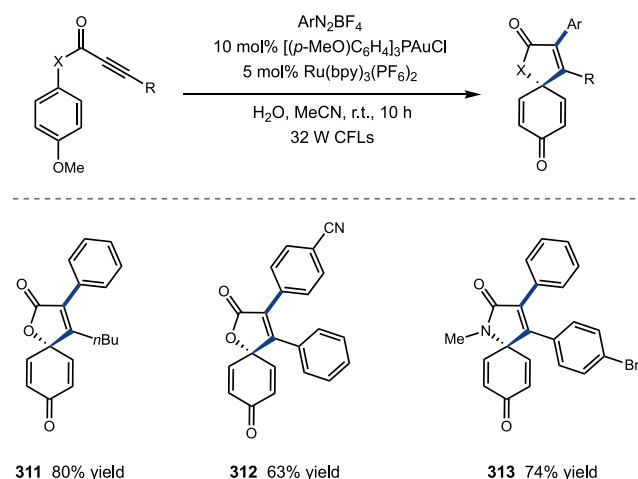
In addition to heteroatom and strain release-based quenching of Au(III)-coordinated unsaturated molecules, such electrophilic intermediates have also been quenched with carbon nucleophiles. Patil and co-workers demonstrated dearomative carboarylation of alkynes as depicted in Scheme 50.<sup>350</sup> Alkynes with a pendant *para*-methoxybenzene substituent underwent coordination to a photocatalytically

### Scheme 49. Photosensitizer-Mediated Electrophile Activation by Gold

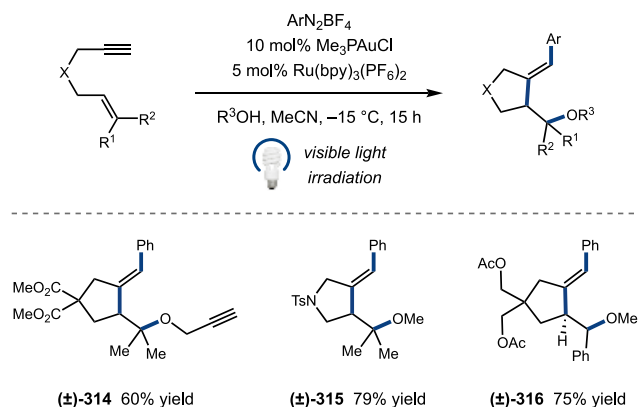


### Scheme 50. Carbocyclization by Gold Metallaphotoredox Catalysis

#### (a) Photoredox-gold intramolecular ipso-arylation cyclization



#### (b) Photoredox-gold arylation alkoxy cyclization of 1,6-enynes



generated Au(III)–aryl complex followed by *ipso*-spirocyclization and reductive elimination to forge a diverse range of spirocyclized products in good efficiency (Scheme 50a, 311–313, 63%–80% yield). Echavarren and co-workers recently demonstrated that even simple pendant olefins can serve as nucleophiles in dual photoredox and gold catalysis, forging five-membered exocyclic alkene products functionalized by alcohol solvent in a cascade of bond formations (Scheme 50b, 314–316, 60%–79% yield).<sup>473</sup>

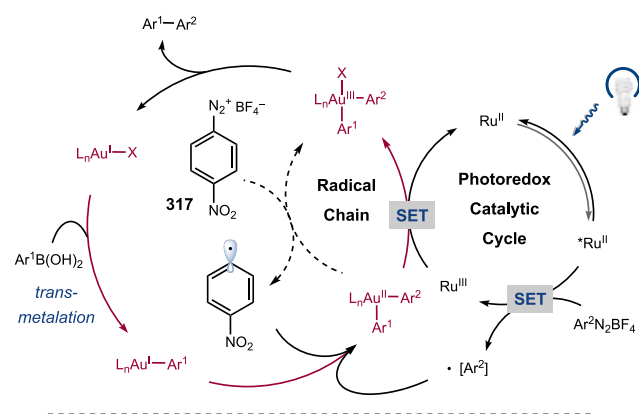
A range of multicomponent reactions have since been developed for the polyfunctionalization of alkyne starting materials. Combining a number of transformations of functionalized alkynes,<sup>338–342</sup> Alcaide and Almandros developed the arylation/oxyarylation of bifunctional alkyne starting materials. Thereafter, the authors developed a diarylation of *ortho*-heteroatomic phenylacetylenes to afford a broad range of complex and highly substituted heterocyclic functionality.<sup>351</sup> Ye and co-workers extended this reactivity to chiral homopropargyl sulfonamides, bringing forth a method for the construction of bisarylated 2,3-dihydropyrroles in good yields with excellent retention of starting material stereochemistry.<sup>352</sup>

### 5.3. Biaryl Coupling

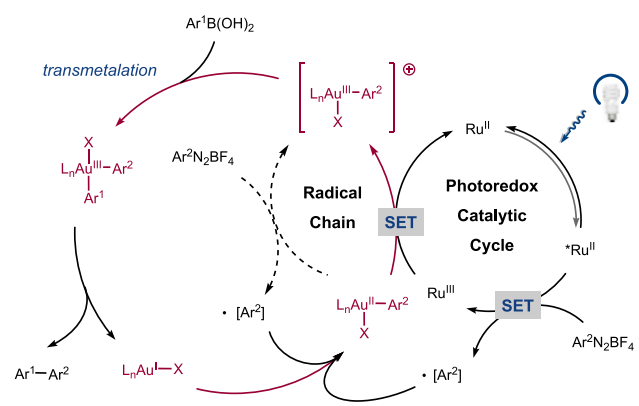
While gold catalysis overwhelmingly relies on coordination by cationic gold(III) complexes to unsaturated carbon–carbon bonds as a means of substrate activation, several reports on the use of aryl nucleophiles have been disclosed for the formation of biaryls. The first two examples, independently generated from the laboratories of Fouquet, Hermange,<sup>353</sup> and Lee<sup>354</sup> described the use of arylboronic acids in a novel approach to biaryl synthesis. Fouquet and Hermange first detailed a mechanism by which an electrophilic Au(III)–aryl species, generated via the photoredox chain mechanism previously described with a phosphine-ligated gold chloride precatalyst, underwent transmetalation with an arylboronic acid facilitated by a fluoride additive (Scheme 51a). A range of substituted biaryls were synthesized with good efficiency from the corresponding aryl electrophiles and nucleophiles. Interestingly, the authors found that particularly oxidizing electrophiles such as 4-nitrobenzenediazonium tetrafluoroborate (317) could facilitate the reaction in the absence of photocatalyst and light. Moreover, nucleophile electronics were found to dramatically influence the reaction mechanism, with electron-rich arylboronic acids leading to more efficient chain propagation and, accordingly, a higher quantum yield. In their nearly simultaneous report, Lee and co-workers described instead the use of a cationic triflimide gold precatalyst, and proposed a “transmetalation-first” mechanism wherein an Au(I)–aryl complex was generated from the boronic acid nucleophile, which then underwent oxidation and performed the coupling (Scheme 51b). The authors found the necessity of water as an additive, carefully balancing the transmetalation to gold(I) against protodeboration. <sup>1</sup>H NMR experiments suggested that the nature of the gold complex (cationic or chloride-bound) played a significant role in the order of the transmetalation and photoassisted oxidative addition steps. In a follow-up report, Fouquet and Hermange conducted mechanistic investigations, and found three possible mechanistic regimes.<sup>355</sup> Depending on specific substrate electronics, transmetalation first, oxidation first, and ligand exchange between Au(I) and Au(III) were all possible under a related set of reaction conditions (Scheme 51c).

## Scheme 51. Gold Metallaphotocatalytic Biaryl Synthesis

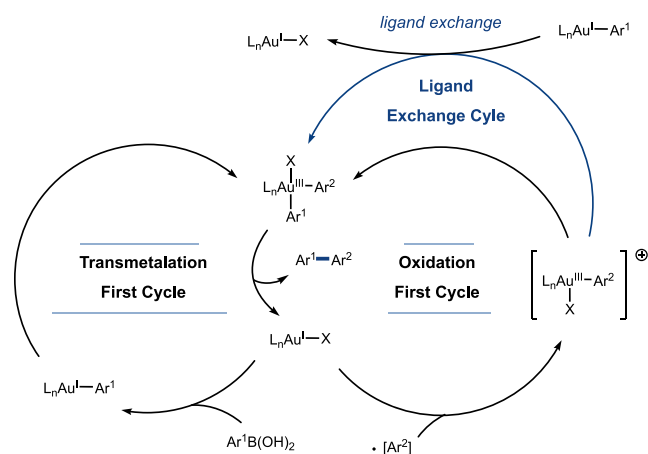
## (a) Transmetalation first



## (b) Oxidation first

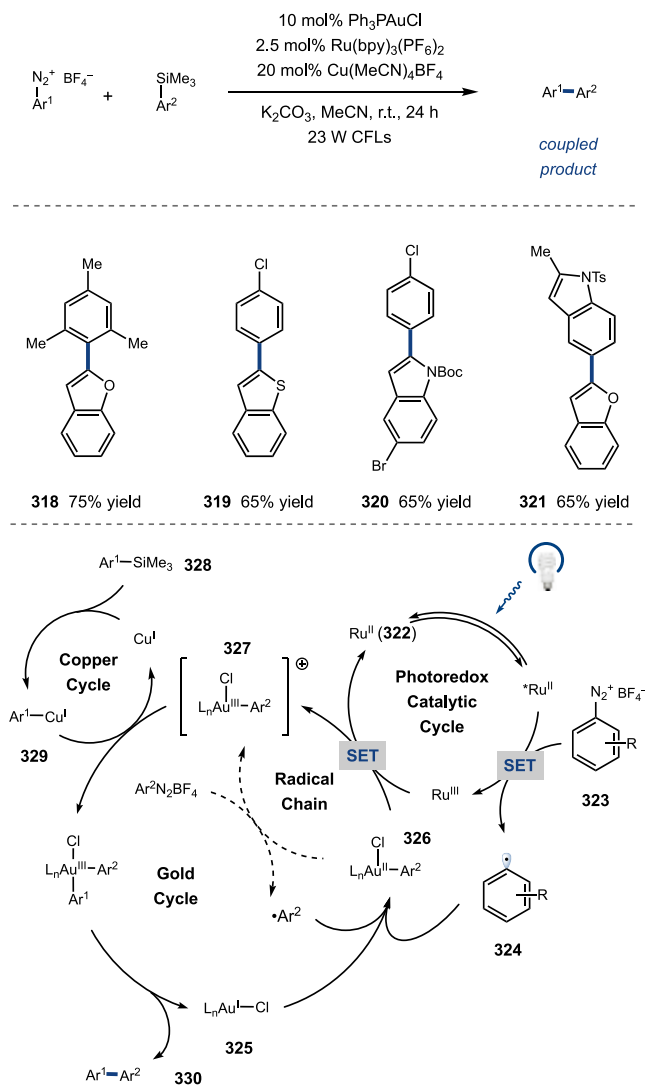


## (c) Potential mechanisms



Patil and co-workers, following up their initial work on gold-catalyzed desilylative couplings,<sup>337</sup> reported a triply catalytic system for biaryl formation from trimethylsilylarenes and aryl diazonium salts.<sup>356</sup> The authors recognized the privileged role of copper catalysis in the activation of arylsilanes to transient organometallic complexes, and demonstrated the copper-, gold-, and photocatalyzed arylation on a range of benzofuran, benzothiophene, indole, and arene silyl-based nucleophiles (Scheme 52, 318–321, 65%–75% yield). The proposed mechanism begins with photoexcitation of ruthenium-

## Scheme 52. Gold and Copper Metallaphotocatalytic Biaryl Synthesis



ium-based photocatalyst 322, which can promptly reduce arene electrophile 323 to the corresponding aryl radical (324). Capture of this open-shell species by Au(I) complex 325 affords the Au(II) organometallic 326, which can either reduce the oxidized photocatalyst via SET, or propagate a radical chain mechanism via direct reduction of the diazonium electrophile to afford Au(III)–aryl species 327. At this point, Cu(I) is proposed to undergo transmetalation with arylsilane nucleophile 328 to forge arylcopper complex 329. Transmetalation with Au(III) complex 327, followed by reductive elimination provides biaryl product 330.

## 5.4. Miscellaneous Transformations

Toste and co-workers realized the utility of accessing high-valent gold complexes under mild conditions in the coupling of arenes to H-phosphonates.<sup>357</sup> Taking advantage of the mild, redox-neutral formation of Au(III)–aryl complexes from diazonium electrophiles and photoredox catalysis, the authors were able to form valuable C–P linkages for the first time with gold catalysis. The lack of stoichiometric chemical oxidant in the reaction mixture, traditionally required for gold(I)/(III) redox activity, allowed for use of sensitive phosphonate nucleophiles. Notably, the transformation tolerated an aryl

electrophile bearing an alkyne in good efficiency, further highlighting the orthogonal reactivity of this system to traditional gold catalysis.

The laboratory of Xu, likewise interested in exploring substrates beyond the scope of traditional gold catalysis, targeted the bifunctionalization of alkenes through a dual-catalytic atom-transfer reaction. Xu and co-workers targeted the thiosulfonylation of alkenes in a rare example of gold metallaphotocatalysis in the absence of arenediazonium electrophile.<sup>358</sup> A range of styrene coupling partners were functionalized in a 1,2-fashion by a disulfide electrophile in tandem with gold and photoredox co-catalysis in moderate to good yields with good diastereoselectivity.

### 5.5. Direct Excitation

While outside the scope of this Review, a number of transformations and mechanistic studies<sup>359</sup> have detailed the direct excitation of gold complexes in the absence of a photocatalyst. The chain mechanism suggested for many of the above transformations has led chemists to question the need for a dedicated photocatalyst, with numerous mechanisms possible for the direct activation of substrates by photoexcited gold. Pioneering work by Hashmi<sup>331,343</sup> inspired a computational investigation into the mechanism of substrate activation by Zhang and co-workers.<sup>360</sup> Since Hashmi's early reports, a number of synthetic transformations have been developed without the aid of photocatalysis, with a primary focus on the synthesis of biaryls<sup>361–364</sup> and functionalization of carbon–carbon multiple bonds.<sup>363,365–369</sup>

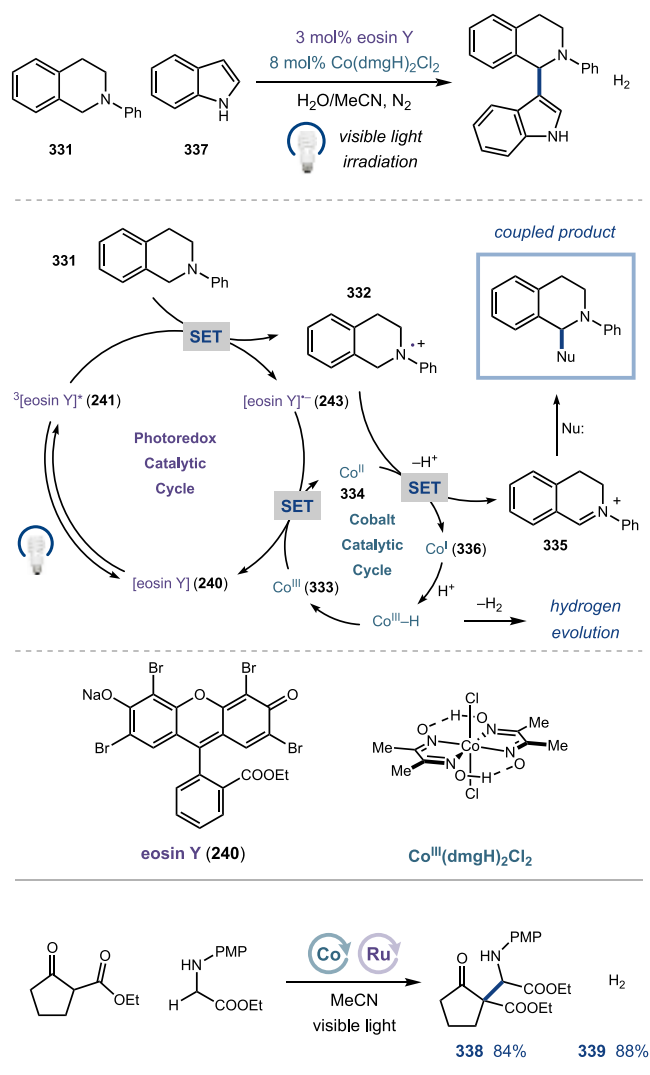
## 6. COBALT METALLAPHOTOCATALYSIS

The catalytic splitting of water into its constituent elements, hydrogen and oxygen, represents a longstanding challenge in the field of inorganic photochemistry.<sup>370</sup> While a broad range of systems have been investigated to emulate nature's conversion of sunlight into chemical energy, cobalt has remained at the forefront of these efforts for several decades.<sup>371</sup> In the context of synthetic chemistry, only recently has attention shifted toward engaging cobalt in light-enabled transformations of organic molecules. This is due to the surge in the development of metallaphotoredox catalysis using first-row transition metals. While a substantial diversity of transformations have been developed over the past decade, cobalt's well-established roots in hydrogen evolution have guided much of the developments in the area of cobalt and photoredox co-catalysis.

### 6.1. Cross-Dehydrogenative Coupling

The first report of cobalt and photoredox dual catalysis emerged in 2014 from the Wu group.<sup>372</sup> The authors reported a cobalt-catalyzed cross-coupling hydrogen evolution (CCHE) reaction, building on a previous heterogeneous ruthenium-based system for the coupling of indoles with tetrahydroisoquinolines (THIQs).<sup>373</sup> Wu and co-workers reported the use of  $\text{Co}(\text{dmgH})_2\text{Cl}_2$  ( $\text{dmgH}$  = dimethylglyoximate) in tandem with an organic photocatalyst in a noble metal-free  $\text{C}(\text{sp}^3)\text{--}\text{C}(\text{sp}^2)$  cross-coupling. As shown in Scheme 53, the proposed mechanism begins with photoexcitation of eosin Y (240) to triplet excited state 241. SET with *N*-aryl-THIQ substrate 331 affords radical cation 332 and reduced catalyst 243. Co(III) species 333 is proposed to regenerate the active photocatalyst, and subsequent oxidation of amine radical cation 332 by resultant Co(II) complex 334 affords, after loss of a proton, iminium ion 335 and Co(I) catalyst 336. Addition

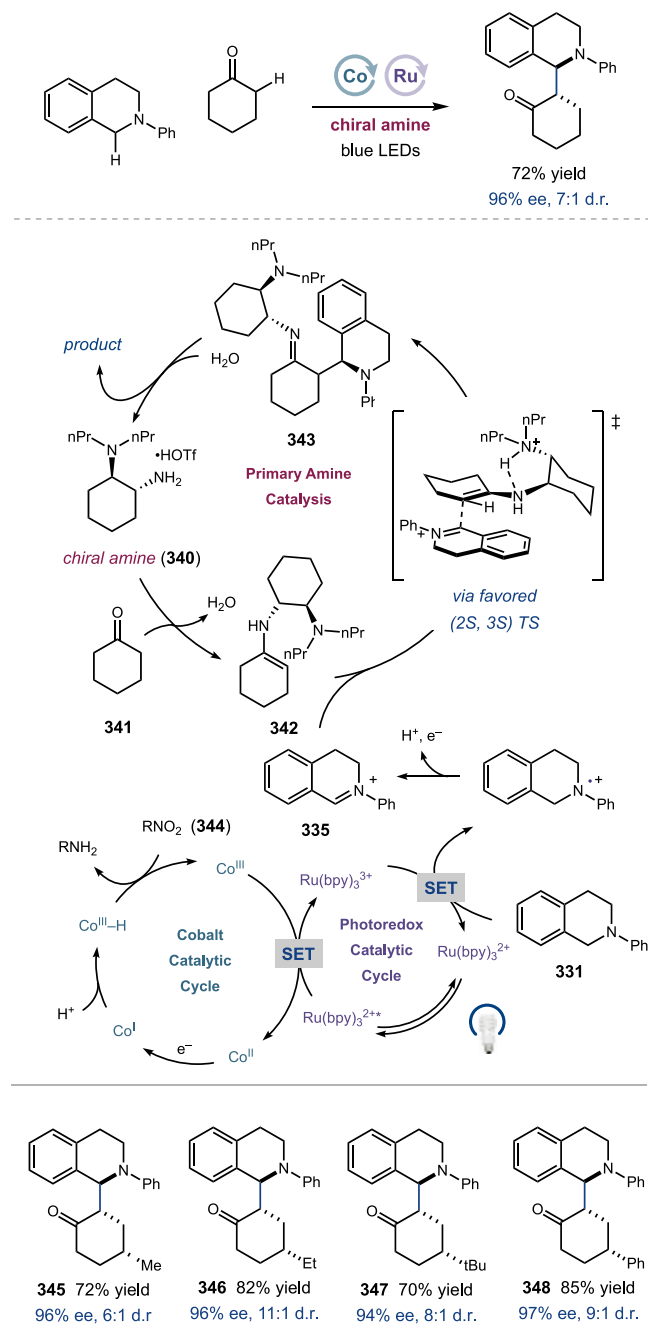
### Scheme 53. Photocatalytic Cobalt-Mediated Cross-Coupling Hydrogen Evolution



of indole nucleophile 337 into this iminium cation, followed by rearomatization affords the product. Thereafter, protonation of Co(I) complex 336 and loss of hydrogen gas would close the transition metal catalytic cycle. A notable feature of this mechanism is the propensity for cobalt to oxidize intermediates in an SET fashion sequentially, followed by proton reduction to hydrogen to carry out transformations entirely in the absence of external oxidant. In this initial disclosure, Wu and co-workers demonstrated the successful application of this CCHE reaction to a variety of substituted indoles, affording C–C linked products (and concomitant hydrogen evolution) in near quantitative yields. In follow-up publications, the Wu laboratory described the addition of indole and  $\beta$ -ketoester nucleophiles into transiently generated imine and oxonium electrophiles, once again reporting good to excellent efficiency in both formation of coupled products and evolution of hydrogen (Scheme 53, 338 and 339, 84% and 88% yield, respectively).<sup>374,375</sup> Moreover, Lei and co-workers demonstrated the quenching of these transiently generated iminium electrophiles with trialkylphosphites, likewise under oxidant-free conditions enabled by cobalt and photoredox dual catalysis.<sup>376</sup>

In a collaborative effort with the lab of Luo, Wu demonstrated a triply catalytic system for the asymmetric  $\alpha$ -functionalization of ketones (via enamine catalysis) with THIQ derivatives.<sup>377</sup> A potential mechanism for the transformation is shown in Scheme 54. Chiral amine catalyst **340** is

**Scheme 54. Triply Catalytic Enantioselective Alkylation of Ketones**

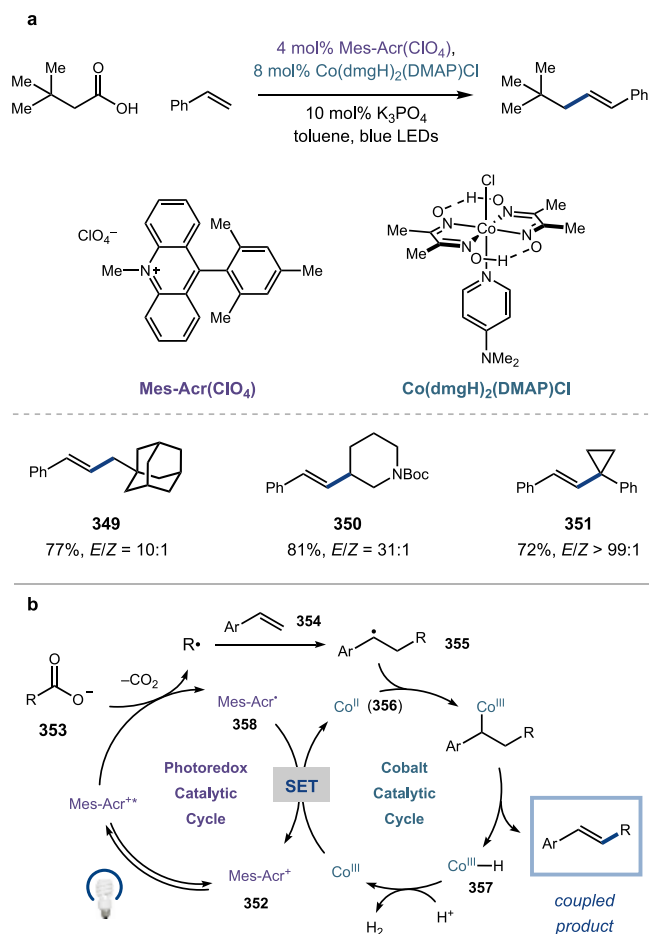


proposed to undergo condensation with ketone substrate **341**, furnishing electron-rich enamine **342**. Iminium **335**, generated as before via photoredox and cobalt catalysis from THIQ substrate **331**, can capture enamine nucleophile **342** in an enantio- and diastereoselective fashion. Thereafter, hydrolysis of the resultant iminium (**343**) provides the product. Notably, Wu, Luo, and co-workers found that addition of a substoichiometric nitroarene additive (**344**) was critical for

useful reaction efficiencies, functioning as a hydrogen acceptor. A range of cyclic ketones were effective substrates in the cross-dehydrogenative coupling, providing products with vicinal tertiary stereocenters in good diastereoselectivity and excellent enantioselectivity (**345**–**348**, 70%–85% yield,  $\geq 6.1$  d.r., 94%–97% ee).

A photoinduced Heck coupling of activated olefins with alkyl carboxylic acid radical precursors was reported by Wu and co-workers.<sup>378</sup> The authors found that a broad scope of primary, secondary, and tertiary acids all underwent facile bond formation with styrene electrophiles (Scheme 55a, **349**–**351**,

**Scheme 55. Photoinduced Heck Alkylation of Olefins by Cobalt Metallaphotocatalysis**

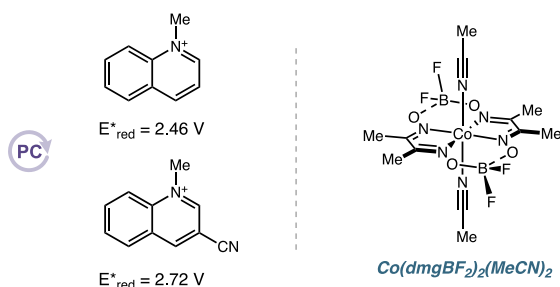
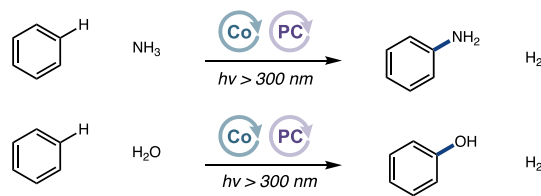


72%–81% yield). Moreover, a number of vinyl silanes and boronates were suitable radicalophiles, affording the corresponding C(*sp*<sup>3</sup>)–C(*sp*<sup>2</sup>) coupled products in moderate to good yields. A plausible mechanism, shown in Scheme 55b, begins with photoexcitation of acridinium photocatalyst **352** and subsequent SET-induced decarboxylation of alkyl carboxylate coupling partner **353**. Addition of this unstabilized alkyl radical into activated olefin coupling partner **354** provides stabilized open-shell intermediate **355**. Capture of this species by Co(II) catalyst **356** is proposed to be reversible, and ultimately abstraction of the weakened adjacent hydrogen atom provides the desired olefin product and cobalt–hydride species **357**. Thereafter, proton reduction provides hydrogen, and a Co(III) intermediate capable of oxidizing reduced acridinium species **358** to close both catalytic cycles at the same moment. A related strategy was later used to incorporate sulfur

nucleophiles into activated olefins by Lei and co-workers.<sup>379</sup> Independent reports from Ackermann<sup>380</sup> and Li<sup>381</sup> later described the decarboxylative alkylation of heterocycles mediated by cobalt and photoredox catalysis. Intriguingly, both groups simultaneously developed these methods predominantly for the installation of adamantyl fragments into azole-type heterocycles.

Cross-dehydrogenative coupling is not limited to carbon–carbon bond formations, and many desirable transformations have been developed for the construction of carbon–heteroatom bonds from simple feedstock chemicals enabled by cooperative photoredox and cobalt catalysis (Scheme 56).

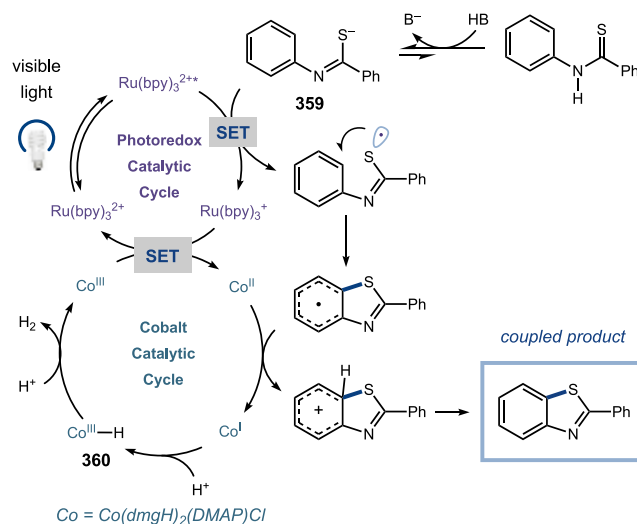
**Scheme 56. Benzene Functionalization by Cobalt and Photoredox Co-catalysis**



Wu and Tung first reported the direct hydroxylation of benzene with water, invoking cobalt catalysis to render the transformation redox-neutral alongside evolution of hydrogen.<sup>382</sup> In the same publication, the groups also reported the direct C–H amination of benzene and derivatives, with both transformations taking place under UV light irradiation. Strongly oxidizing quinolonium photocatalyst was proposed to oxidize benzene to the corresponding radical cation, which could capture a nucleophile and rearomatize via the aid of the cobalt cocatalyst. Thereafter, a range of impressive disconnections were reported following the general mechanistic outline of carbon, nitrogen, or phosphorus nucleophile capture by photocatalytically generated radical cations of arenes and alkenes.<sup>383–389</sup>

Intramolecular dehydrogenative couplings have likewise been developed, with the cobalt catalyst mediating key SET oxidations of the substrate, often relying on rearomatization as a thermodynamic driving force. The first example of such a transformation arose in 2015 from the Wu and Lei laboratories. The authors demonstrated an oxidant-free cobalt- and photoredox-catalyzed C–H thiolation reaction en route to the synthesis of benzothiazole products.<sup>390</sup> An abridged mechanism, shown in Scheme 57, depicts initial photon-mediated oxidation of thioamide substrate **359**, followed by addition of the corresponding S-centered radical to the pendant arene and rearomatization by cobalt and base. As before, proton reduction by cobalt–hydride species **360** closes the catalytic cycle in the absence of exogenous oxidant. A range of aromatic substitution was tolerated, affording a broad array

**Scheme 57. Dehydrogenative Dual-Catalytic Heterocycle Synthesis**



of 2-aryl- and 2-alkylbenzothiazoles in excellent yields. Thereafter, Xiao and Chen reported a radical cascade cyclization for the synthesis of heterocycle-fused benzosultams, similarly mediated by cobalt-catalyzed proton reduction.<sup>391</sup>

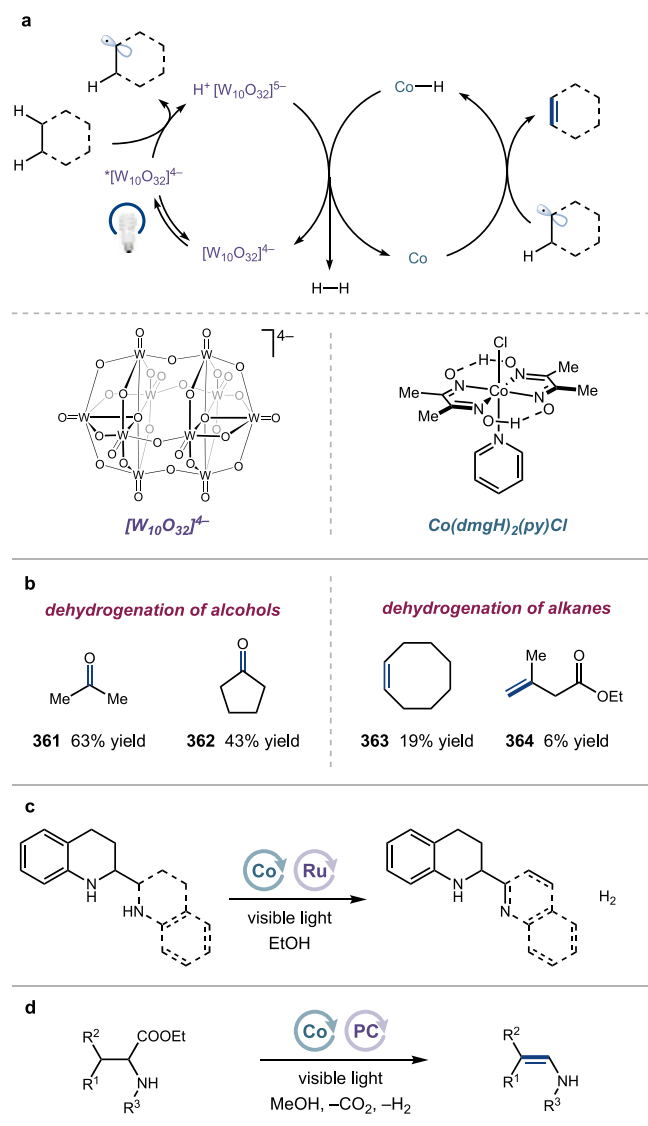
## 6.2. Dehydrogenation and Hydrogenation

Cobalt has served a privileged role in the development of metallaphotoredox-catalyzed cross-dehydrogenative couplings as a result of its unique capacity to combine the power of photoinduced electron transfer with proton reduction. Resultantly, chemists have identified dehydrogenation and transfer hydrogenation reactions enabled by cobalt metallaphotocatalysis as an attractive strategy for introducing and modifying unsaturation in organic molecules without stoichiometric oxidants or reductants.

An early report on the merger of cobalt and light-enabled catalysis in the acceptorless dehydrogenation of alkanes comes from the Sorensen laboratory. The authors found that decatungstate catalysis, well-precedented to engage aliphatic C–H bonds,<sup>114,115</sup> could be merged with cobalt catalysis to provide valuable alkene products from feedstock materials.<sup>392</sup> The proposed mechanism of this endothermic transformation invokes sequential HAT events, first by the excited-state polyoxometalate and then by a cobalt species to afford the alkene product. The cobalt–hydride could then engage with the protonated, reduced photocatalyst to evolve hydrogen (Scheme 58a). Notably, neither disproportionation nor radical coupling could result in catalyst turnover. Sorensen and co-workers demonstrated the transformation on a small collection of alkanes and alcohols, affording varying yields of the corresponding alkenes and carbonyls, respectively (Scheme 58b, **361–364**, 6%–63% yield). This catalytic system has also been leveraged toward dehydroformylation of aldehydes.<sup>393</sup>

Given the thermodynamic challenges of dehydrogenation at room temperature, several reports have opted to invoke aromaticity as a driving force for hydrogen loss from saturated carbo- and heterocycles. Li and co-workers reported the acceptorless dehydrogenation of five- and six-membered saturated heterocycles, providing access to the corresponding aromatic products in near quantitative yields with corresponding efficiency of hydrogen evolution (Scheme 58c).<sup>394</sup> This transformation has since been shown to function efficiently in

## Scheme 58. Dual-Catalytic Dehydrogenations



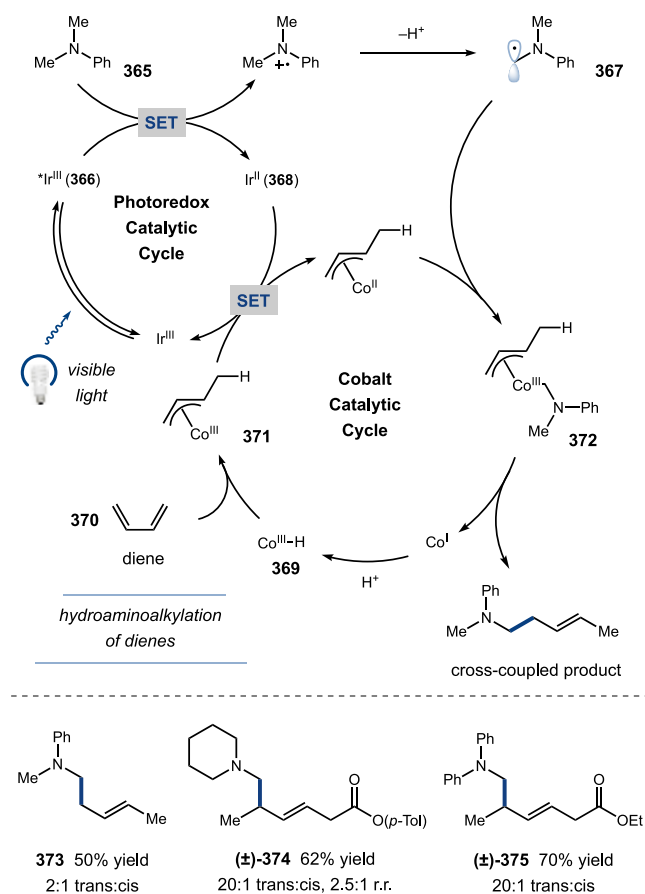
aqueous conditions by the Balaraman laboratory,<sup>395</sup> whom have similarly developed a dehydrogenation of diarylhydrazines to azobenzene derivatives.<sup>396</sup> Leonori and co-workers have likewise exploited aromaticity as a driving force in the synthesis of anilines from cyclohexanone-condensed amines via dual cobalt- and photoredox-catalyzed dehydrogenation.<sup>397</sup> Evolution of carbon dioxide has also been leveraged as a means to impart thermodynamic bias. Tunge and Cartwright first demonstrated the decarboxylative elimination of  $\alpha$ -amino acids to provide enecarbamates in an acceptorless fashion by dual photoredox and cobalt catalysis (Scheme 58d).<sup>398,399</sup> Ritter reported a dehydrogenative decarboxyolefination mediated by cobalt metallaphotocatalysis, with a broad range of natural product and pharmaceutically relevant carboxylic acids expediently converted to olefins in good to excellent yields.<sup>400</sup> Larionov and co-workers later reported a similar decarboxylative olefination, and demonstrated the direct, triple-catalytic conversion of triglycerides to olefins via combination with biocatalysis.<sup>401</sup>

In an isolated report, Lloret-Fillol and co-workers reported the reduction of aldehydes and ketones by dual cobalt and photoredox catalysis using water as a hydride source.<sup>402</sup>

## 6.3. Hydrofunctionalization of Olefins

Given cobalt's capacity to form catalytically active metal hydrides under incredibly mild photoredox conditions, interest in the hydrofunctionalization of unsaturated systems naturally followed. In this area, Rovis was first to report a hydroaminoalkylation of conjugated dienes.<sup>403</sup> The proposed mechanism for the transformation, shown in Scheme 59,

## Scheme 59. Hydroaminoalkylation of 1,3-Dienes



begins with oxidation and deprotonation of aniline substrate **365** by excited-state photocatalyst **366** to afford  $\alpha$ -amino radical **367**, and corresponding reduced photocatalyst **368**. Simultaneously, a cobalt(I) species, generated *in situ*, could be protonated by a suitable proton source such as pivalic acid, to afford Co(III) hydride complex **369**. Hydrometalation of diene substrate **370** forges  $\pi$ -allylcobalt intermediate **371**. Reduction of this complex by **368**, followed by radical capture of radical **367** forges, by way of Co(III)-alkyl complex **372**, the desired product. The authors found that a broad scope of 1,3-dienes were competent coupling partners for the hydrofunctionalization, and a number of aniline and tertiary amine substrates provided desired product in good efficiency (**373–375**, 50%–70% yield). Konig and co-workers went on to invoke a similar catalytically generated cobalt hydride for the dual-catalytic isomerization of terminal alkenes to internal alkenes.<sup>404</sup> Maji and co-workers anticipated that hydrometalation of electron-deficient alkenes would afford an organocobalt species capable of carbometalating alkynes to forge valuable C–C bonds.<sup>405</sup> Indeed, a range of internal alkynes underwent formal addition to conjugate acceptors in excellent yields, mediated by cooperative photoredox and cobalt catalysis.

## 6.4. Miscellaneous Transformations

In addition to the extensive hydrogen evolution and hydro-metalation chemistry that cobalt has made possible, a number of additional transformations have been reported capitalizing on cobalt's rich history beyond traditional cross-coupling and hydride transfer. Rovis reported a cobalt-catalyzed [2+2+2] cycloaddition enabled by visible light for the spatially and temporally controlled assembly of arenes<sup>406</sup> and later the polymerization of triyne monomers.<sup>407</sup> Follow-up studies have since indicated that a direct excitation mechanism through a metal acetylide LMCT event is operative for terminal alkyne substrates.<sup>408</sup>

Cobalt metallaphotocatalysis has also found value in the construction of complex heterocyclic frameworks, including a divergent synthesis of several oxygen-bearing heterocycles from feedstock CO<sub>2</sub>.<sup>409</sup> The annulation of benzamides with alkenes via C–H functionalization was successful in providing a range of isoquinolone products.<sup>410,411</sup>

Finally, several reports on the dual cobalt- and photoredox-catalyzed allylation of nucleophiles have recently emerged. Matsunaga and co-workers reported Tsuji–Trost allylation of malonates with allyl carbonate electrophiles, providing the branched products in excellent yields and selectivities,<sup>412</sup> now comparable to the more expensive noble-metal-catalyzed protocols.<sup>413</sup> Shortly thereafter, Li and co-workers reported the enantioselective allylic amination of carbonate electrophiles, providing valuable enantioenriched allylic amines in near quantitative yields with excellent levels of enantio- and regioselectivity.<sup>414</sup>

## 7. OTHER METALLAPHOTOCATALYSIS

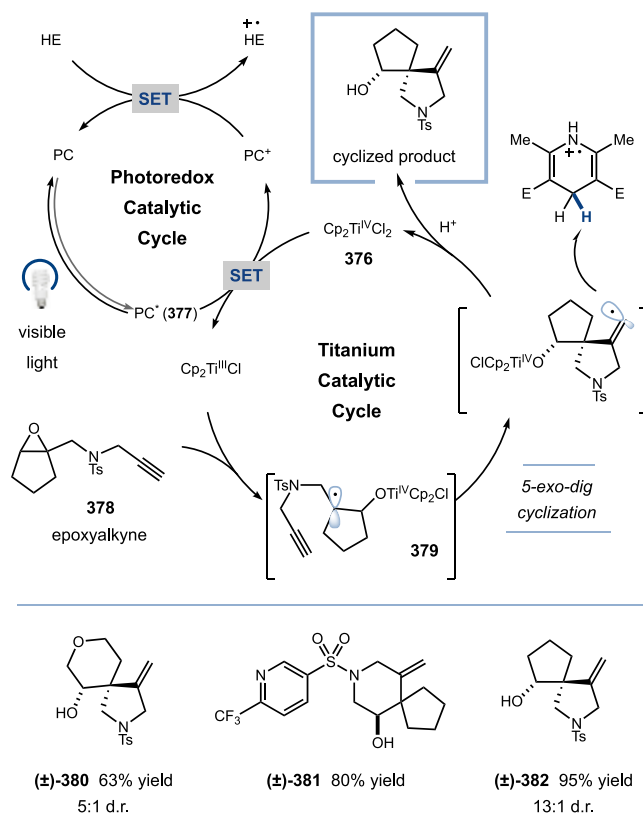
In addition to the well-established cooperativity of photoredox catalysis with the metals described above, there has been great interest in expanding the scope of metallaphotoredox catalysis to lesser studied metals in a synthetic context. Given the capacity for photoredox catalysis to both modulate oxidation states and transfer energy to metal catalysts, in recent years chemists have contemplated merging the study of less traditional catalysts with photoredox catalysis to open new avenues of chemical reactivity.

### 7.1. Titanium Metallaphotocatalysis

Titanium has a rich history of light-enabled chemistry, with titanium dioxide—or titania—the subject of intense research over the last several decades as a result of its bulk properties as a catalyst, pigment, and UV light absorber.<sup>415–417</sup> Despite these advancements in materials and inorganic photochemistry, developments in light-enabled titanium catalysis have been substantially underexplored.

Recently, Shi and co-workers became interested in accessing low-valent titanium complexes via photoinduced SET rather than traditional stoichiometric metal reductants or organometallic reagents.<sup>418,419</sup> The first report in this area emerged in late 2019 from Shi and co-workers on the reductive spirocyclization of epoxide-derived radicals into pendant alkyne SOMOphiles.<sup>420</sup> The proposed mechanism, shown in Scheme 60, begins with SET reduction of the Ti(IV) precatalyst (376) by excited-state photocatalyst 377. The resulting Ti(III) intermediate is preceded to undergo SET-mediated reduction of epoxide substrate 378, providing Ti(IV)-ligated open-shell species 379. A 5-*exo-dig* radical cyclization, followed by reduction with Hantzsch ester and protonation provides the spirocyclized alcohol product, and

Scheme 60. Titanium Metallaphotocatalytic Spirocyclization



simultaneously regenerates Ti(IV) complex 376. A range of spirocyclic scaffolds were forged in good to excellent yields, with both five- and six-membered ring products accessible via the radical cyclization (380–382, 63%–95% yield). Thereafter, Shi and others reported a number of titanium metallaphotocatalyzed protocols, relying on the transient generation of Ti(III) under mild visible light irradiation for the installation of allyl nucleophiles into carbonyls.<sup>421–423</sup> Doyle and co-workers impressively reported a triple catalytic system for the cross electrophile coupling of epoxides with aryl halides to afford valuable  $\beta$ -aryl alcohols.<sup>424</sup> The triple-catalytic system invokes the familiar oxidative addition/radical capture/reductive elimination manifold of previous nickel-catalyzed cross-electrophile couplings,<sup>130,136,137</sup> with the necessary open-shell intermediates derived from Ti(III)-mediated reductive epoxide opening.<sup>419</sup>

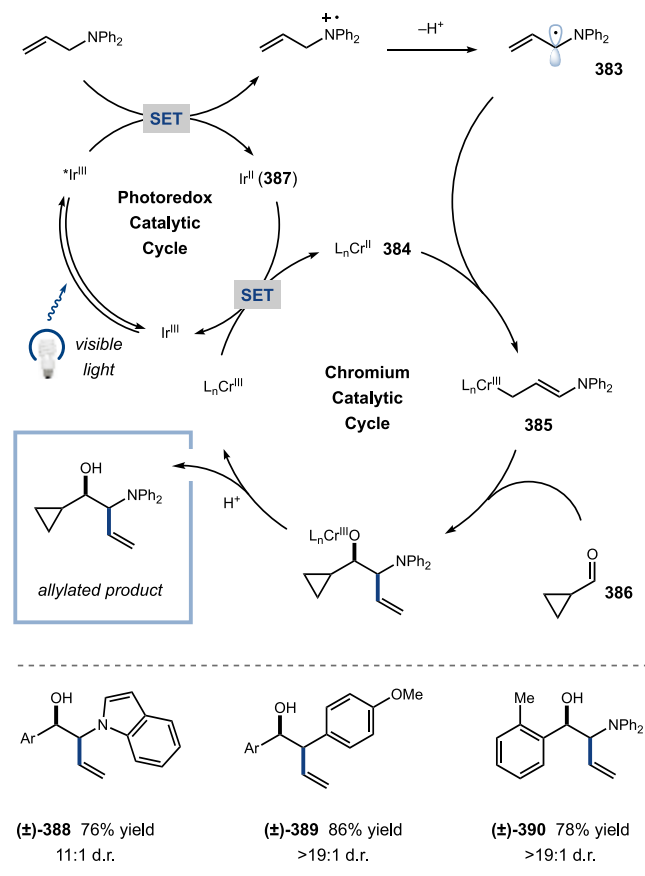
### 7.2. Chromium Metallaphotocatalysis

A hallmark of organochromium chemistry is the Nozaki–Hiyama–Kishi or NHK reaction for the allylation of aldehydes.<sup>425</sup> While early developments relied on stoichiometric chromium, a significant concern in terms of both atom economy and toxicity of the spent reaction mixture, modern advancements toward the catalytic employment Cr have been largely successful.<sup>426</sup>

Glorius reported the first application of dual chromium and photoredox catalysis in the form of an aldehyde allylation in 2018.<sup>427</sup> As detailed in Scheme 61, Glorius and co-workers envisioned a mechanism wherein oxidation/deprotonation of allylic amines and arenes provided allyl radical 383, upon which capture by Cr(II) catalyst 384 affords the organometallic intermediate 385. Addition to aldehyde substrate 386 followed by protonation provides the homoallylic alcohol



### Scheme 61. Photoredox Aldehyde Allylation by Dual Chromium and Photoredox Catalysis



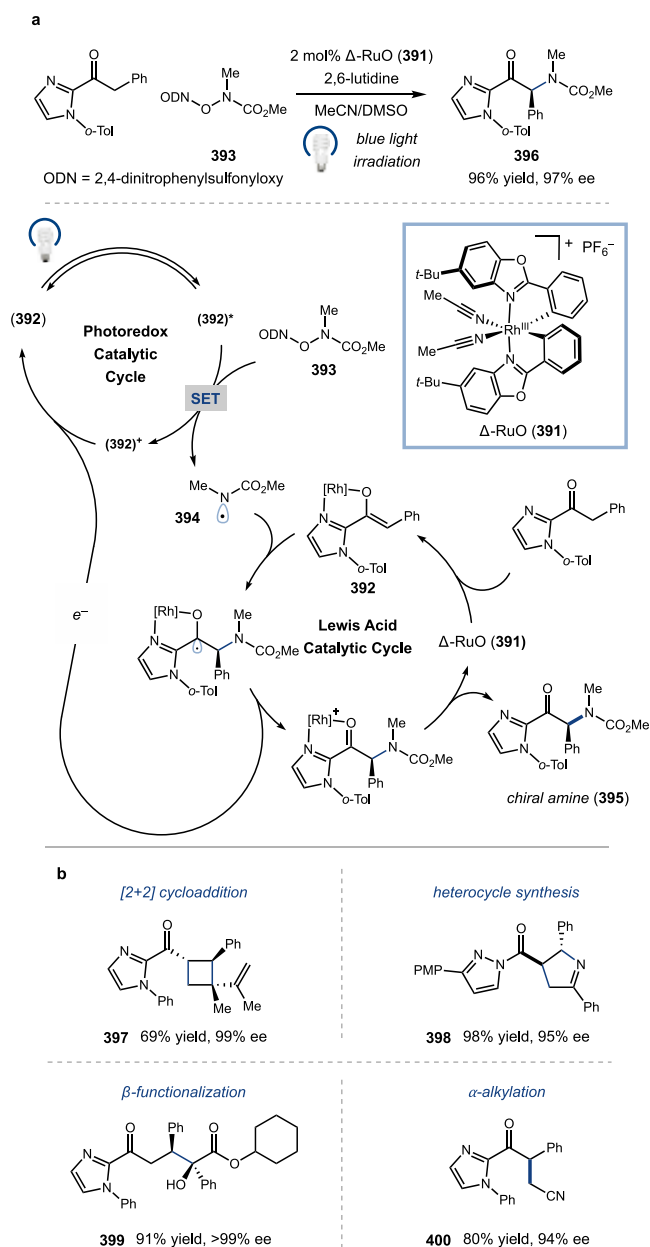
product in high diastereoselectivity, followed by Cr(III) reduction by reduced photocatalyst **387** to regenerate both active catalysts. A broad scope of aryl and alkyl aldehydes were successfully allylated under the reaction conditions, with a range of electron-rich allylbenzene and *N*-allylaniline derivatives serving as competent radical precursors (**388–390**, 76%–86% yield). Later, Kanai and co-workers developed an asymmetric allylation of aldehydes via unstabilized allyl radicals, again via oxidation deprotonation.<sup>428</sup> Judicious choice of bis(oxazoline) ligand and cationic additives provided smooth access to homoallylic alcohols with high levels of enantio- and diastereoselectivity. The group disclosed in a subsequent report the catalytic allylation of aldehydes with unactivated alkenes, as simple feedstock organic molecules, via a triple photoredox/HAT/chromium catalytic platform.<sup>429</sup>

Thereafter, Glorius reported a second highly diastereoselective allylation of aldehydes in a three-component coupling of 1,3-dienes with DHP radical precursors.<sup>430</sup> This system was subsequently extended to enyne SOMOphiles.<sup>431</sup> The Glorius laboratory also reported the synthesis of aminoalcohols under a similar dual-catalytic manifold.<sup>432</sup> Surprisingly, ketones were competent electrophiles for the transformation, possibly enabled by the *in situ* liberation of trimethylsilylium from the  $\alpha$ -silylamine radical precursors. 1,2-Diols were likewise accessible, this time from silyl-protected allylic alcohols and aldehydes in good to excellent yields and moderate diastereoselectivity.<sup>433</sup> Finally, Yahata and co-workers reported the direct addition of unactivated C–H nucleophiles into aldehydes enabled by dual decatungstate and chromium catalysis.<sup>434</sup>

### 7.3. Rhodium Metallaphotocatalysis

Like many noble metals, rhodium has a rich history in transition metal catalysis.<sup>435</sup> The combination of rhodium and photoredox catalysis emerged from the Meggers group in 2016.<sup>436</sup> Inspired by their earlier work on asymmetric alkylation with chiral, photoactive iridium complexes,<sup>437</sup> Meggers and co-workers reported a rhodium-based system for the visible-light-promoted asymmetric  $\alpha$ -amination of ketones. In their proposed mechanism, shown in Scheme 62a, the authors suggest that coordination of the substrate to

### Scheme 62. Rhodium Metallaphotoredox Catalysis



the chiral, cyclometalated rhodium complex **391** followed by deprotonation affords rhodium enolate **392**. This enolate species is proposed to act both as a radical acceptor and a viable photocatalyst for the reduction of nitrogen electrophile **393**. At this point, addition of nitrogen-centered radical **394** into Rh enolate species **392** provides, after oxidation and dissociation, the asymmetric amine product **395**. With this

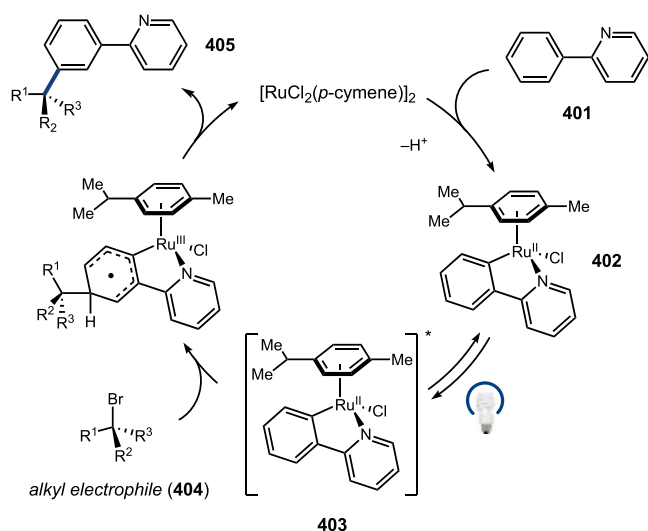
mechanistic picture, a range of 2-acylimidazoles were aminated with carbamate-protected alkylamines in good to quantitative yields with excellent enantioselectivity (396, 96% yield, 97% ee). Thereafter, the Meggers group reported asymmetric [2+2] photocycloaddition,<sup>438</sup> enantioselective heterocycle synthesis,<sup>439</sup>  $\beta$ -C–H functionalization,<sup>440</sup> and  $\alpha$ -alkylation<sup>441</sup> utilizing similar chiral photoactive rhodium complexes (Scheme 62b, 397–400, 69%–98% yield, 94%–99% ee).<sup>442</sup>

In an isolated report, Baslé and co-workers detailed the light-mediated directed C–H borylation of arenes, with a postulated direct excitation event leading to C–H oxidative addition by the ligated Rh complex.<sup>443</sup>

#### 7.4. Ruthenium Metallaphotocatalysis

While ruthenium-based complexes have been utilized as photosensitizers since the earliest reports of photoredox-mediated organic synthesis,<sup>444–448</sup> reports referencing ruthenium in the context of bond formation are few and far between. Recently, two independent publications by Ackermann and Greaney emerged simultaneously on dual-role ruthenium catalysis for the *meta*-selective alkylation of arenes.<sup>449,450</sup> The mechanism, proposed by both laboratories and shown in Scheme 63, begins with directed C–H activation

**Scheme 63. Ruthenium-Photocatalyzed *Meta*-Selective Arene Alkylation**



of the biaryl substrate **401** by  $[\text{RuCl}(\textit{p}\text{-cymene})]_2$  to afford cyclometalated Ru complex **402**. Thereafter, absorption of visible light by this complex provides excited-state Ru species **403**, which undergoes SET with alkyl electrophile **404**. Upon loss of halide anion, the corresponding alkyl radical undergoes addition to the Ru(III)-bound arene. LMCT, deprotonation, and ligand exchange provides the *meta*-alkylated product **405**, simultaneously regenerating the photoactive Ru(II) species **402**. A range of directing-group-bound benzene rings and radical precursors functioned effectively as coupling partners in this unique set of transformations.

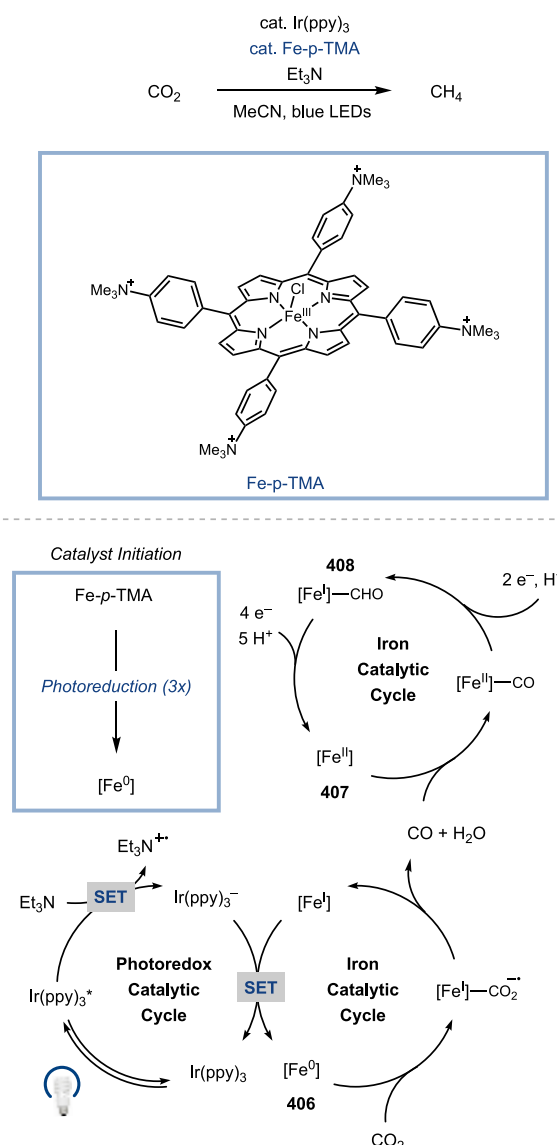
#### 7.5. Iron Metallaphotocatalysis

Interest in the use of iron catalysis stems from both the high abundance of iron in the Earth's crust in addition to the element's low toxicity. However, the reduced reactivity of iron when compared to late, electron-rich transition metals like palladium and nickel has hampered the development of iron-

catalysis in modern methods. With this in mind, several groups have become interested in iron metallaphotocatalysis, wherein reactivity can be provoked through the delivery of visible light energy to the reaction mixture.

Early work in the area of iron metallaphotocatalysis simply involved the use of visible light in the degradation of an iron precatalyst, generating an active catalyst for a non-photonic ketone reduction.<sup>451</sup> A landmark report by Robert and co-workers detailed the photocatalytic reduction of  $\text{CO}_2$  to methane by cooperative iron and photoredox catalysis.<sup>452</sup> The authors found that quantum yield for methane production reached 0.18%, with Fe(0) species **406** facilitating initial sequestration and reduction of carbon dioxide to CO and water (Scheme 64). Thereafter, CO binding by Fe(II) complex **407** and photoreduction provides iron(I) formyl species **408**, at which point successive SET reduction provides a second equivalent of water and the methane product. Robert and Miyake later extended this work to operate with improved quantum yield (0.47%) with an organic photocatalyst.<sup>453</sup>

**Scheme 64. Carbon Dioxide Reduction to Methane by Dual Iron Photocatalysis**



Noël and Alcázar reported a visible-light-promoted Kumada coupling mediated by iron in flow.<sup>454</sup> Notably, the reaction was successful for recalcitrant electron-rich aryl chlorides, which the authors attributed to a robust, photoinduced Fe(I) oxidative addition, with preliminary mechanistic studies suggesting an Fe(I)/(III) pathway. Additionally, a range of olefin difunctionalizations have likewise been reported to operate under visible light conditions, enabled by iron catalysis.<sup>455–457</sup>

### 7.6. Manganese Metallaphotocatalysis

A small collection of manganese photoredox papers have been reported to date. Most of these publications rely on the photoinduced Mn–Mn bond homolysis of dimanganese decacarbonyl and resultant Mn-centered radical chemistry.<sup>458</sup> Abstraction of halides from alkyl iodides by this photo-generated complex has been used in Minisci alkylations,<sup>459</sup> haloalkylations of alkynes,<sup>460</sup> atom-transfer radical cyclizations,<sup>461</sup> aminations,<sup>462</sup> and desulfonylative allylations (Scheme 65a).<sup>463</sup> Open-shell Mn-mediated hydrogen atom

transfer and energy-transfer processes, which in turn unveil open-shell and excited-state species which readily engage in unprecedented chemical reactivity. Transition metal catalysis has seen dramatic developments since the first cooperative metallaphotoredox papers. In this context, a variety of bench-stable and otherwise unreactive functional groups can productively engage in coupling pathways to forge chemical complexity from native functionality. Ultimately, this has resulted in significant expansion of the pool of available fragments from preformed organometallic reagents to adaptive functionalities such as carboxylic acids, alcohols, and even simple C–H bonds.

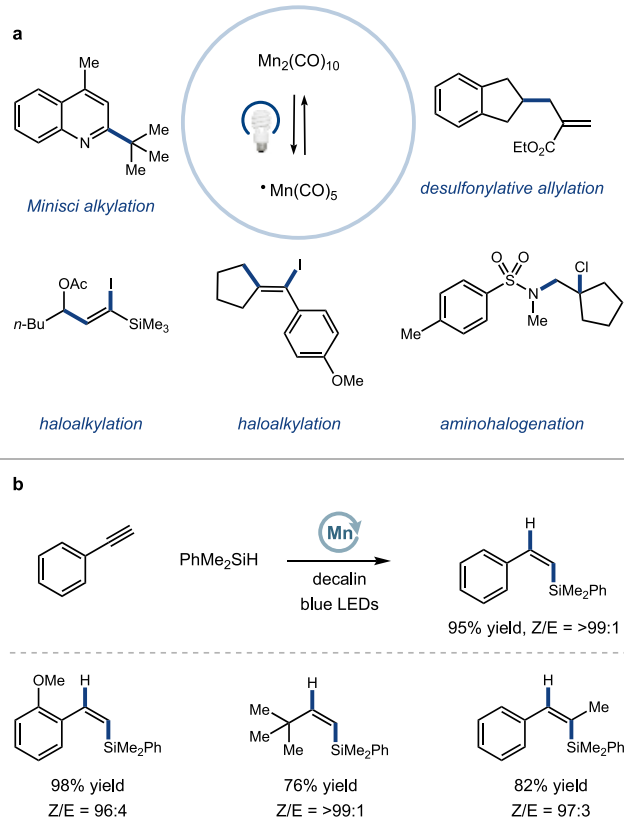
While the activation and implementation of novel starting materials for metal catalysis represents an important and continued area of exploration, photoredox catalysis can also dramatically influence the reactivity available to exploit at metal centers. The circumvention of challenging two-electron oxidative additions by means of a sequential photoinduced SET and radical capture mechanism (e.g., Au(I)/(III) and Cu(I)/(III) chemistry) has opened avenues for mild transformations which would otherwise require strongly oxidizing or forcing conditions. Additionally, the catalytic, photoinduced shuttling of electrons to and from organometallic intermediates has allowed for rapid formation of even the most challenging bonds via high-valent reductive elimination. Moreover, excited-state transition metal catalysis has become much more broadly accessible, relying instead on the well-studied photophysical properties of light harvesting complexes in lieu of the limitations imposed by a specific organometallic substrate's absorption spectrum.

While a considerable breadth of light-mediated multi-catalytic manifolds have surfaced over the past 10 years, there is much left to be uncovered. Many metals have been typecast in their cooperative reactivity with photoredox catalysis. For example, however successful radical capture and inner-sphere reductive elimination has been for the formation of bonds between radical precursors and electrophiles in late metallaphotocatalysis, it is certainly not the only mechanism by which these metals can facilitate bond construction.<sup>66,466–468</sup>

Additionally, while radicals represent logically straightforward disconnections easily accessible with photoredox catalysis, they are merely one of many potential reactive intermediates available through photonic energy absorption. As a result of continued developments in the area of photoredox catalysis, anions,<sup>469</sup> cations,<sup>470</sup> nitrenes,<sup>471</sup> and carbenes<sup>472</sup> are all readily generated under mild irradiative conditions. However, for many of these transient intermediates, the taming of their reactivity with cooperative transition metal catalysis remains underexplored.

The advent of metallaphotoredox catalysis has brought with it innumerable opportunities in the streamlining of syntheses to uncovering novel fundamental reactivity. The intersection of these two fields has thus far yielded unthinkable progress for the synthetic community, and we anticipate that continued exploration will provide enduring advances for every area of the chemical sciences.

Scheme 65. Manganese Metallaphotoredox Catalysis



abstraction has also been utilized in the hydrofunctionalization of alkynes by Zhang and Zhang (Scheme 65b).<sup>464</sup> An isolated report on photoinduced SET by excited-state Mn(acac)<sub>3</sub> by Wan and co-workers detailed the hydroxytrifluoromethylation of terminal olefins.<sup>465</sup>

## 8. CONCLUSIONS AND OUTLOOK

The merger of transition metal and photoredox catalysis has brought about an abundance of novel transformations by combining the power of light harvesting complexes with the reactivity of transition metal catalysis. Selective delivery of photonic energy into a reaction mixture permits electron-

## AUTHOR INFORMATION

### Corresponding Author

David W. C. MacMillan – Merck Center for Catalysis,  
Princeton University, Princeton, New Jersey 08544, United

States; [orcid.org/0000-0001-6447-0587](https://orcid.org/0000-0001-6447-0587);  
Email: [dmacmill@princeton.edu](mailto:dmacmill@princeton.edu)

## Authors

- Amy Y. Chan** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States
- Ian B. Perry** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States
- Noah B. Bissonnette** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States;  
[orcid.org/0000-0001-6892-5040](https://orcid.org/0000-0001-6892-5040)
- Benito F. Buksh** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States
- Grant A. Edwards** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States
- Lucas I. Frye** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States;  
[orcid.org/0000-0001-7713-7097](https://orcid.org/0000-0001-7713-7097)
- Olivia L. Garry** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States
- Marissa N. Lavagnino** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States;  
[orcid.org/0000-0001-6851-919X](https://orcid.org/0000-0001-6851-919X)
- Beryl X. Li** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States
- Yufan Liang** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States
- Edna Mao** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States
- Agustin Millet** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States
- James V. Oakley** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States
- Nicholas L. Reed** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States;  
[orcid.org/0000-0003-4234-5464](https://orcid.org/0000-0003-4234-5464)
- Holt A. Sakai** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States
- Ciaran P. Seath** – Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States

Complete contact information is available at:  
<https://pubs.acs.org/10.1021/acs.chemrev.1c00383>

## Author Contributions

<sup>†</sup>A.Y.C. and I.B.P. contributed equally.

## Notes

The authors declare no competing financial interest.

## Biographies

Amy Y. Chan was born and raised in New York City, where she gained her first experience in organic synthesis as a high school researcher in the lab of Professor Keith A. Woerpel at New York University. There she worked on the development of methods for the synthesis of organic peroxides. She obtained her B.Sc. degree in chemistry in 2019 from Yale University, conducting research on C–H functionalization in the lab of Professor Jonathan A. Ellman. Amy is currently pursuing her Ph.D. at Princeton University under the supervision of Professor David W. C. MacMillan. Her research focuses on the development and understanding of bond formations via first-row transition metal photoredox catalysis.

Ian Perry is a scientist at Pfizer in Cambridge, MA. He obtained his B.S. degree in chemistry in 2017 from the Massachusetts Institute of Technology under the supervision of Professor Stephen Buchwald, where he developed methods in the area of copper–hydride catalysis. He then moved to Princeton University, where he obtained his Ph.D. in 2021 for his work on photoredox-mediated methods for the synthesis and diversification of sp<sup>3</sup>-rich scaffolds.

Noah B. Bissonnette obtained his Bachelor's degree in chemistry from Northeastern University in 2020 (under Prof. Kirss). As an undergraduate, he completed internships at Vertex Pharmaceuticals, Celgene, and Merck. While working for these companies, he was inspired by the power of photoredox catalysis and developed several novel synthetic methodologies. For his undergraduate work in organic chemistry, he was awarded the American Chemical Society's Organic Division Undergraduate Award. He currently is pursuing his Ph.D. at Princeton (under Prof. MacMillan).

Benito F. Buksh was born in Milwaukee, Wisconsin, in 1997. He obtained a B.Sc. in chemistry with high honors from The University of Texas at Austin (2019), where he conducted research under the supervision of Professor Michael J. Krische. In fall 2019, he began his graduate studies at Princeton University under the guidance of Professor David W. C. MacMillan. His research in the MacMillan group is centered on developing new photocatalytic platforms for proximity labeling.

Grant A. Edwards obtained his B.S. in chemistry from the University of Tulsa in 2011. He completed his M.S. in chemistry in 2014 at the same institution, where he performed research under the guidance of Prof. Justin Chalker. In 2020, Grant completed his doctoral studies at North Carolina State University under the direction of Prof. Joshua Pierce. During his time in the Pierce Group, Grant developed natural-product-inspired small-molecule modulators of bacterial biofilm formation and worked toward the total synthesis of polycyclic alkaloids pretazettine and crambescidin 359. In 2020, Grant joined the laboratory of Prof. Dave MacMillan at Princeton University as a postdoctoral fellow, where he is currently developing new methods in metallaphotoredox catalysis.

Lucas Frye was born in Boone, North Carolina, in 1998. He obtained his B.Sc. in chemistry in 2020 at the University of Virginia, where he conducted research in catalytic alkene hydroarylation under the supervision of Prof. T. Brent Gunnoe. Since August 2020, he has been a Ph.D. student at Princeton University, where he studies the structure and reactivity of transition metal porphyrin complexes in the group of Prof. John T. Groves.

Olivia Garry completed her M.Chem. in chemistry from the University of Oxford in 2018. She is currently a Ph.D. student with Professor David MacMillan at Princeton University, where her research focuses on photocatalytic C–H functionalization reactions.

Marissa Lavagnino was born and raised in California. She obtained her B.S. in chemistry from the University of California, Berkeley, in 2017 after completing her Honors thesis in the lab of Prof. John Hartwig. During her undergraduate studies, she also performed research in the lab of Prof. Melanie Sanford at the University of Michigan. She is now pursuing a Ph.D. in chemistry at Princeton University in the lab of Prof. David MacMillan. Her research interests involve the development of novel bond-forming reactions via copper and iron photoredox catalysis.

Beryl X. Li was born in Beijing, China, in 1995 and raised between Beijing, Vancouver, and California. In 2016, she received her B.Sc. in chemical biology from UC Berkeley (College of Chemistry), where she worked on the total syntheses of diterpenoid alkaloids in the lab

of Prof. Richmond Sarpong. Pursuing a Ph.D. in chemistry, she then joined the group of Prof. David MacMillan at Princeton University in 2017. Her graduate work focuses on leveraging photoredox catalysis to develop new methodologies in the contexts of bioconjugation and proximity labeling.

Yufan Liang was born in China in 1988. In 2010, he received his B.Sc. in chemistry from Peking University in Beijing, China. He then continued on to graduate studies at MIT in the laboratory of Professor Gregory C. Fu, developing nickel-catalyzed asymmetric cross-coupling methods. After moving to Caltech, he completed his Ph.D. in 2016 and then began his postdoctoral studies with Professor David W. C. MacMillan at Princeton University. His research in the MacMillan group has focused on the development of novel metallaphotoredox catalysis methods.

Edna Mao received her B.Sc. in chemical biology from the University of California, Berkeley, in 2019, where she performed research in the laboratory of John Hartwig. In 2020, she joined the Macmillan research group at Princeton University to pursue her doctoral degree, where she is working on the development of metallaphotoredox reactions.

Agustin Millet is a postdoctoral researcher in the group of Prof. David W. C. MacMillan at Princeton University through BioLEC. He received his Ph.D. in inorganic chemistry, with a focus on dirhodium metal–metal bonded complexes, at Texas A&M University under the supervision of Prof. Kim R. Dunbar in 2019. Prior to that, he obtained his bachelor's degree in chemistry at the Universidad de Buenos Aires, in Argentina. His current research activity is focused on the development of a direct trifluoromethylation methodology for aliphatic alcohols through metallaphotoredox cross-couplings.

James V. Oakley obtained a B.S. in chemistry from California State University San Marcos in 2018, where he conducted undergraduate research on homogeneous gold catalysis under the advisory of Professor Robert Iafe. He is currently an NSF predoctoral fellow in the laboratory of Professor David MacMillan. His research is focused on developing novel proximity labeling technologies for the exploration of nanometer-scale biological interaction networks, or microenvironments.

Nicholas L. Reed was born in Portland, Oregon, in 1990. In 2012, he received his B.S. in chemistry from Purdue University, where he conducted research in the laboratories of Professor Chengde Mao and Professor Ei-ichi Negishi. He then earned his M.S. from the University of Pittsburgh in 2014, synthesizing bioactive small molecules for the treatment of tinnitus with Professor Peter Wipf. He completed his doctoral studies at the University of Wisconsin-Madison with Prof. Tehshik Yoon in 2020, developing a general platform for photocatalytic oxidation. He then began postdoctoral studies with Professor David W. C. MacMillan, where his research has been focused on the development of novel C–N bond-forming reactions utilizing a metallaphotoredox approach.

Holt A. Sakai was born in Honolulu, Hawaii, and received his B.S. and M.S. degrees in chemistry in 2018 from Yale University, where he worked with Professor Timothy R. Newhouse. Holt began his graduate studies in the same year under the direction of Professor David W. C. MacMillan at Princeton, where his research focuses on the development of new cross-coupling technologies using visible light photoredox catalysis.

Ciaran Seath completed his Ph.D. in chemistry from the University of Strathclyde in 2017, where he worked under the supervision of Dr. Allan Watson, investigating chemoselective transition metal catalysis. He then moved to Emory University as a postdoctoral researcher,

working in the laboratory of Professor Nathan Jui developing novel photoredox methodologies. Since 2019, Ciaran has worked with Professors David MacMillan and Tom Muir at Princeton University, where he has been exploring new photocatalytic methods for proximity labelling.

David W. C. MacMillan is the James S. McDonnell Distinguished University Chair of chemistry at Princeton University. He began his independent career at UC Berkeley in 1998, before moving to the California Institute of Technology in 2000. In 2006, he became the A. Barton Hepburn Chair of Chemistry and Director of the Merck Center for Catalysis at Princeton University. In 2012, he was elected to both the American Academy of Arts and Sciences and the Royal Society. His research interests encompass a wide range of organic chemistry, including the development of new areas in organocatalysis and photoredox catalysis.

## ACKNOWLEDGMENTS

The authors are grateful for financial support provided by the National Institute of General Medical Sciences (NIGMS), the NIH (under Award R35GM134897-01), the Princeton Catalysis Initiative, and kind gifts from Merck, Janssen, BMS, Genentech, Celgene, and Pfizer. N.B.B., L.I.F., and E.M. acknowledge Princeton University for first-year fellowships. A.Y.C., B.F.B., O.L.G., J.V.O., and H.A.S. acknowledge Princeton University, E. Taylor, and the Taylor family for an Edward C. Taylor Fellowship. J.V.O. acknowledges the NSF for a predoctoral fellowship (DGE-1656466). B.X.L. and A.M. acknowledge support from BioLEC, an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science under Award No. DE-SC0019370. We thank Vlad Bacauanu, Nathan W. Dow, Patrick J. Sarver, and Dr. Mario P. Wiesenfeldt for their assistance in preparing this manuscript.

## REFERENCES

- (1) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.
- (2) Knowles, W. S.; Sabacky, M. J. Catalytic Asymmetric Hydrogenation Employing a Soluble, Optically Active, Rhodium Complex. *Chem. Commun.* **1968**, *22*, 1445–1446.
- (3) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. 2,2'-Bis(Diphenylphosphino)-1,1'-Binaphthyl(Binap). A New Atropisomeric Bis(Triaryl)Phosphine. Synthesis and Its Use in the Rh(I)-Catalyzed Asymmetric Hydrogenation of  $\alpha$ -(Acylamino)Acrylic Acids. *Tetrahedron* **1984**, *40*, 1245–1253.
- (4) Katsuki, T.; Sharpless, K. B. The First Practical Method for Asymmetric Epoxidation. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
- (5) Hérisson, P. J.-L.; Chauvin, Y. Catalyse de transformation des oléfines par les complexes du tungstène. *Makromol. Chem.* **1971**, *141*, 161–176.
- (6) Schrock, R. R. An "Alkylcarbene" Complex of Tantalum by Intramolecular  $\alpha$ -Hydrogen Abstraction. *J. Am. Chem. Soc.* **1974**, *96*, 6796–6797.
- (7) Grubbs, R. H.; Brunck, T. K. A Possible Intermediate in the Tungsten-Catalyzed Olefin Metathesis Reaction. *J. Am. Chem. Soc.* **1972**, *94*, 2538–2540.
- (8) Heck, R. F. Arylation, Methylation, and Carboxyalkylation of Olefins by Group VIII Metal Derivatives. *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526.
- (9) Baba, S.; Negishi, E.-i. A Novel Stereospecific Alkenyl-Alkenyl Cross-Coupling by a Palladium- or Nickel-Catalyzed Reaction of Alkenylalanes with Alkenyl Halides. *J. Am. Chem. Soc.* **1976**, *98*, 6729–6731.

- (10) Miyaura, N.; Yamada, K.; Suzuki, A. A New Stereospecific Cross-Coupling by the Palladium-Catalyzed Reaction of 1-Alkenylboranes with 1-Alkenyl or 1-Alkynyl Halides. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.
- (11) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564–12649.
- (12) Tsou, T. T.; Kochi, J. K. Reductive Coupling of Organometals Induced by Oxidation. Detection of Metastable Paramagnetic Intermediates. *J. Am. Chem. Soc.* **1978**, *100*, 1634–1635.
- (13) 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<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>). *J. Am. Chem. Soc.* **1993**, *115*, 2075–2077.
- (14) Matsunaga, P. T.; Mavropoulos, J. C.; Hillhouse, G. L. Oxygen-Atom Transfer from Nitrous Oxide (NNO) to Nickel Alkyls. Syntheses and Reactions of Nickel(II) Alkoxides. *Polyhedron* **1995**, *14*, 175–185.
- (15) 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.* **1997**, *119*, 8135–8136.
- (16) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. New N- and O-Arylations with Phenylboronic Acids and Cupric Acetate. *Tetrahedron Lett.* **1998**, *39*, 2933–2936.
- (17) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. New Aryl/Heteroaryl C–N Bond Cross-Coupling Reactions via Arylboronic Acid/Cupric Acetate Arylation. *Tetrahedron Lett.* **1998**, *39*, 2941–2944.
- (18) Evans, D. A.; Katz, J. L.; West, T. R. Synthesis of Diaryl Ethers through the Copper-Promoted Arylation of Phenols with Arylboronic Acids. An Expedient Synthesis of Thyroxine. *Tetrahedron Lett.* **1998**, *39*, 2937–2940.
- (19) Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. Pd(II)-Catalyzed Hydroxyl-Directed C–H Activation/C–O Cyclization: Expedient Construction of Dihydrobenzofurans. *J. Am. Chem. Soc.* **2010**, *132*, 12203–12205.
- (20) Hickman, A. J.; Sanford, M. S. High-Valent Organometallic Copper and Palladium in Catalysis. *Nature* **2012**, *484*, 177–185.
- (21) Hickman, A. J.; Sanford, M. S. Catalyst Control of Site Selectivity in the Pd<sup>II/IV</sup>-Catalyzed Direct Arylation of Naphthalene. *ACS Catal.* **2011**, *1*, 170–174.
- (22) Ciamician, G.; Silber, P. Chemische Lichtwirkungen. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 1928–1935.
- (23) Kalyanasundaram, K.; Grätzel, M. Applications of Functionalized Transition Metal Complexes in Photonic and Optoelectronic Devices. *Coord. Chem. Rev.* **1998**, *177*, 347–414.
- (24) Takeda, H.; Ishitani, O. Development of Efficient Photocatalytic Systems for CO<sub>2</sub> Reduction Using Mononuclear and Multinuclear Metal Complexes Based on Mechanistic Studies. *Coord. Chem. Rev.* **2010**, *254*, 346–354.
- (25) Lowry, M. S.; Bernhard, S. Synthetically Tailored Excited States: Phosphorescent, Cyclometalated Iridium(III) Complexes and Their Applications. *Chem. - Eur. J.* **2006**, *12*, 7970–7977.
- (26) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363.
- (27) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898–6926.
- (28) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075–10166.
- (29) Capaldo, L.; Ravelli, D. The Dark Side of Photocatalysis: One Thousand Ways to Close the Cycle. *Eur. J. Org. Chem.* **2020**, *2020*, 2783–2806.
- (30) Arias-Rotondo, D. M.; McCusker, J. K. The Photophysics of Photoredox Catalysis: A Roadmap for Catalyst Design. *Chem. Soc. Rev.* **2016**, *45*, 5803–5820.
- (31) Hopkinson, M. N.; Sahoo, B.; Li, J. L.; Glorius, F. Dual Catalysis Sees the Light: Combining Photoredox with Organo-, Acid, and Transition-Metal Catalysis. *Chem. - Eur. J.* **2014**, *20*, 3874–3886.
- (32) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. *Chem. Rev.* **2016**, *116*, 10035–10074.
- (33) Levin, M. D.; Kim, S.; Toste, F. D. Photoredox Catalysis Unlocks Single-Electron Elementary Steps in Transition Metal Catalyzed Cross-Coupling. *ACS Cent. Sci.* **2016**, *2*, 293–301.
- (34) Twilton, J.; Le, C. C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. The Merger of Transition Metal and Photocatalysis. *Nat. Rev. Chem.* **2017**, *1*, 0052.
- (35) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085.
- (36) De Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004.
- (37) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Recent Advances in Homogeneous Nickel Catalysis. *Nature* **2014**, *509*, 299–309.
- (38) Zuo, Z.; MacMillan, D. W. C. Decarboxylative Arylation of  $\alpha$ -Amino Acids via Photoredox Catalysis: A One-Step Conversion of Biomass to Drug Pharmacophore. *J. Am. Chem. Soc.* **2014**, *136*, 5257–5260.
- (39) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. Carboxylic Acids as a Traceless Activation Group for Conjugate Additions. *J. Am. Chem. Soc.* **2014**, *136*, 10886–10889.
- (40) Ventre, S.; Petronijevic, F. R.; MacMillan, D. W. C. Decarboxylative Fluorination of Aliphatic Carboxylic Acids via Photoredox Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 5654–5657.
- (41) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. Merging Photoredox with Nickel Catalysis: Coupling of  $\alpha$ -Carboxyl Sp<sup>3</sup>-Carbons with Aryl Halides. *Science* **2014**, *345*, 437–440.
- (42) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. Enantioselective Decarboxylative Arylation of  $\alpha$ -Amino Acids via the Merger of Photoredox and Nickel Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 1832–1835.
- (43) Kölmel, D. K.; Meng, J.; Tsai, M. H.; Que, J.; Loach, R. P.; Knauber, T.; Wan, J.; Flanagan, M. E. On-DNA Decarboxylative Arylation: Merging Photoredox with Nickel Catalysis in Water. *ACS Comb. Sci.* **2019**, *21*, 588–597.
- (44) Chu, L.; Lipschultz, J. M.; MacMillan, D. W. C. Merging Photoredox and Nickel Catalysis: The Direct Synthesis of Ketones by the Decarboxylative Arylation of  $\alpha$ -Oxo Acids. *Angew. Chem., Int. Ed.* **2015**, *54*, 7929–7933.
- (45) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. Merging Photoredox and Nickel Catalysis: Decarboxylative Cross-Coupling of Carboxylic Acids with Vinyl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 624–627.
- (46) Till, N. A.; Smith, R. T.; MacMillan, D. W. C. Decarboxylative Hydroalkylation of Alkynes. *J. Am. Chem. Soc.* **2018**, *140*, 5701–5705.
- (47) Le, C. C.; MacMillan, D. W. C. Fragment Couplings via CO<sub>2</sub> Extrusion-Recombination: Expansion of a Classic Bond-Forming Strategy via Metallaphotoredox. *J. Am. Chem. Soc.* **2015**, *137*, 11938–11941.
- (48) Shimizu, I.; Yamada, T.; Tsuji, J. Palladium-Catalyzed Rearrangement of Allylic Esters of Acetoacetic Acid to Give  $\gamma,\delta$ -Unsaturated Methyl Ketones. *Tetrahedron Lett.* **1980**, *21*, 3199–3202.
- (49) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. Facile Generation of a Reactive Palladium(II) Enolate Intermediate by the Decarboxylation of Palladium(II)  $\beta$ -Ketocarboxylate and Its Utilization in Allylic Acylation. *J. Am. Chem. Soc.* **1980**, *102*, 6381–6384.
- (50) Zhou, J.; Fu, G. C. Cross-Couplings of Unactivated Secondary Alkyl Halides: Room-Temperature Nickel-Catalyzed Negishi Reactions of Alkyl Bromides and Iodides. *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727.
- (51) Zhou, J.; Fu, G. C. Suzuki Cross-Couplings of Unactivated Secondary Alkyl Bromides and Iodides. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341.

- (52) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. Metallaphotoredox-catalysed  $sp^3$ - $sp^3$  cross-coupling of carboxylic acids with alkyl halides. *Nature* **2016**, *536*, 322–325.
- (53) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417–1492.
- (54) Tellis, J. C.; Primer, D. N.; Molander, G. A. Single-Electron Transmetalation in Organoboron Cross-Coupling by Photoredox/Nickel Dual Catalysis. *Science* **2014**, *345*, 433–436.
- (55) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals: Uncovering a General Manifold for Stereoconvergence in Nickel-Catalyzed Cross-Couplings. *J. Am. Chem. Soc.* **2015**, *137*, 4896–4899.
- (56) El Khatib, M.; Serafim, R. A. M.; Molander, G. A.  $\alpha$ -Arylation/Heteroarylation of Chiral  $\alpha$ -Aminomethyltrifluoroborates by Synergistic Iridium Photoredox/Nickel Cross-Coupling Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 254–258.
- (57) Karakaya, I.; Primer, D. N.; Molander, G. A. Photoredox Cross-Coupling: Ir/Ni Dual Catalysis for the Synthesis of Benzylic Ethers. *Org. Lett.* **2015**, *17*, 3294–3297.
- (58) Tellis, J. C.; Amani, J.; Molander, G. A. Single-Electron Transmetalation: Photoredox/Nickel Dual Catalytic Cross-Coupling of Secondary Alkyl  $\beta$ -Trifluoroborato ketones and -Esters with Aryl Bromides. *Org. Lett.* **2016**, *18*, 2994–2997.
- (59) Lima, F.; Kabeshov, M. A.; Tran, D. N.; Battilocchio, C.; Sedelmeier, J.; Sedelmeier, G.; Schenkel, B.; Ley, S. V. Visible Light Activation of Boronic Esters Enables Efficient Photoredox C( $sp^2$ )-C( $sp^3$ ) Cross-Couplings in Flow. *Angew. Chem., Int. Ed.* **2016**, *55*, 14085–14089.
- (60) Karimi-Nami, R.; Tellis, J. C.; Molander, G. A. Single-Electron Transmetalation: Protecting-Group-Independent Synthesis of Secondary Benzylic Alcohol Derivatives via Photoredox/Nickel Dual Catalysis. *Org. Lett.* **2016**, *18*, 2572–2575.
- (61) Alam, R.; Molander, G. A. Direct Synthesis of Secondary Benzylic Alcohols Enabled by Photoredox/Ni Dual-Catalyzed Cross-Coupling. *J. Org. Chem.* **2017**, *82*, 13728–13734.
- (62) Amani, J.; Molander, G. A. Synergistic Photoredox/Nickel Coupling of Acyl Chlorides with Secondary Alkyltrifluoroborates: Dialkyl Ketone Synthesis. *J. Org. Chem.* **2017**, *82*, 1856–1863.
- (63) Amani, J.; Alam, R.; Badir, S.; Molander, G. A. Synergistic Visible-Light Photoredox/Nickel-Catalyzed Synthesis of Aliphatic Ketones via N–C Cleavage of Imides. *Org. Lett.* **2017**, *19*, 2426–2429.
- (64) Stache, E. E.; Rovis, T.; Doyle, A. G. Dual Nickel- and Photoredox-Catalyzed Enantioselective Desymmetrization of Cyclic Meso-Anhydrides. *Angew. Chem., Int. Ed.* **2017**, *56*, 3679–3683.
- (65) Primer, D. N.; Molander, G. A. Enabling the Cross-Coupling of Tertiary Organoboron Nucleophiles through Radical-Mediated Alkyl Transfer. *J. Am. Chem. Soc.* **2017**, *139*, 9847–9850.
- (66) Yuan, M.; Song, Z.; Badir, S. O.; Molander, G. A.; Gutierrez, O. On the Nature of C( $sp^3$ )-C( $sp^2$ ) Bond Formation in Nickel-Catalyzed Tertiary Radical Cross-Couplings: A Case Study of Ni/Photoredox Catalytic Cross-Coupling of Alkyl Radicals and Aryl Halides. *J. Am. Chem. Soc.* **2020**, *142*, 7225–7234.
- (67) Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. Oxalates as Activating Groups for Alcohols in Visible Light Photoredox Catalysis: Formation of Quaternary Centers by Redox-Neutral Fragment Coupling. *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273.
- (68) Zhang, X.; MacMillan, D. W. C. Alcohols as Latent Coupling Fragments for Metallaphotoredox Catalysis:  $sp^3$ - $sp^2$  Cross-Coupling of Oxalates with Aryl Halides. *J. Am. Chem. Soc.* **2016**, *138*, 13862–13865.
- (69) Barton, D. H. R.; McCombie, S. W. A new method for the deoxygenation of secondary alcohols. *J. Chem. Soc., Perkin Trans. 1* **1975**, *1*, 1574–1585.
- (70) Vara, B. A.; Patel, N. R.; Molander, G. A. *O*-Benzyl Xanthate Esters under Ni/Photoredox Dual Catalysis: Selective Radical Generation and  $Csp^3$ - $Csp^2$  Cross-Coupling. *ACS Catal.* **2017**, *7*, 3955–3959.
- (71) Huang, L.; Ji, T.; Rueping, M. Remote Nickel-Catalyzed Cross-Coupling Arylation via Proton-Coupled Electron Transfer-Enabled C–C Bond Cleavage. *J. Am. Chem. Soc.* **2020**, *142*, 3532–3539.
- (72) Yayla, H. G.; Wang, H.; Tarantino, K. T.; Orbe, H. S.; Knowles, R. R. Catalytic Ring-Opening of Cyclic Alcohols Enabled by PCET Activation of Strong O–H Bonds. *J. Am. Chem. Soc.* **2016**, *138*, 10794–10797.
- (73) Cong, F.; Lv, X. Y.; Day, C. S.; Martin, R. Dual Catalytic Strategy for Forging  $Sp^2$ - $Sp^3$  and  $Sp^3$ - $Sp^3$  Architectures via  $\beta$ -Scission of Aliphatic Alcohol Derivatives. *J. Am. Chem. Soc.* **2020**, *142*, 20594–20599.
- (74) Chen, Y.; Wang, X.; He, X.; An, Q.; Zuo, Z. Photocatalytic Dehydroxymethylative Arylation by Synergistic Cerium and Nickel Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 4896–4902.
- (75) Matsuoka, D.; Nishigaichi, Y. Photosubstitution of Dicyanoarenes by Hypervalent Alkylsilicon Reagents via Photoinduced Electron Transfer. *Chem. Lett.* **2014**, *43*, 559–561.
- (76) Corcé, V.; Chamoreau, L. M.; Derat, E.; Goddard, J. P.; Ollivier, C.; Fensterbank, L. Silicates as Latent Alkyl Radical Precursors: Visible-Light Photocatalytic Oxidation of Hypervalent Bis-Catecholato Silicon Compounds. *Angew. Chem., Int. Ed.* **2015**, *54*, 11414–11418.
- (77) Lévêque, C.; Cheneberg, L.; Corcé, V.; Goddard, J.-P.; Ollivier, C.; Fensterbank, L. Primary alkyl bis-catecholato silicates in dual photoredox/nickel catalysis: aryl- and heteroaryl-alkyl cross coupling reactions. *Org. Chem. Front.* **2016**, *3*, 462–465.
- (78) Jouffroy, M.; Primer, D. N.; Molander, G. A. Base-Free Photoredox/Nickel Dual-Catalytic Cross-Coupling of Ammonium Alkylsilicates. *J. Am. Chem. Soc.* **2016**, *138*, 475–478.
- (79) Patel, N. R.; Kelly, C. B.; Jouffroy, M.; Molander, G. A. Engaging Alkyl Halides with Alkylsilicates via Photoredox Dual Catalysis. *Org. Lett.* **2016**, *18*, 764–767.
- (80) Vara, B. A.; Jouffroy, M.; Molander, G. A. C( $sp^3$ ) – C( $sp^2$ ) cross-coupling of alkylsilicates with borylated aryl bromides – an iterative platform to alkylated aryl- and heteroaryl boronates. *Chem. Sci.* **2017**, *8*, 530–535.
- (81) Lévêque, C.; Corcé, V.; Cheneberg, L.; Ollivier, C.; Fensterbank, L. Photoredox/Nickel Dual Catalysis for the C( $sp^3$ )-C( $sp^3$ ) Cross-Coupling of Alkylsilicates with Alkyl Halides. *Eur. J. Org. Chem.* **2017**, *2017*, 2118–2121.
- (82) Knauber, T.; Chandrasekaran, R.; Tucker, J. W.; Chen, J. M.; Reese, M.; Rankic, D. A.; Sach, N.; Helal, C. Ru/Ni Dual Catalytic Desulfinate Photoredox  $C_{sp^2} - C_{sp^3}$  Cross-Coupling of Alkyl Sulfinate Salts and Aryl Halides. *Org. Lett.* **2017**, *19*, 6566–6569.
- (83) Zheng, C.; You, S. L. Transfer Hydrogenation with Hantzsch Esters and Related Organic Hydride Donors. *Chem. Soc. Rev.* **2012**, *41*, 2498–2518.
- (84) Nakajima, K.; Nojima, S.; Sakata, K.; Nishibayashi, Y. Visible-Light-Mediated Aromatic Substitution Reactions of Cyanoarenes with 4-Alkyl-1,4-Dihydropyridines through Double Carbon-Carbon Bond Cleavage. *ChemCatChem* **2016**, *8*, 1028–1032.
- (85) Nakajima, K.; Nojima, S.; Nishibayashi, Y. Nickel- and Photoredox-Catalyzed Cross-Coupling Reactions of Aryl Halides with 4-Alkyl-1,4-Dihydropyridines as Formal Nucleophilic Alkylation Reagents. *Angew. Chem., Int. Ed.* **2016**, *55*, 14106–14110.
- (86) Buzzetti, L.; Prieto, A.; Roy, S. R.; Melchiorre, P. Radical-Based C–C Bond-Forming Processes Enabled by the Photoexcitation of 4-Alkyl-1,4-Dihydropyridines. *Angew. Chem., Int. Ed.* **2017**, *56*, 15039–15043.
- (87) Gandolfo, E.; Tang, X.; Raha Roy, S.; Melchiorre, P. Photochemical Asymmetric Nickel-Catalyzed Acyl Cross-Coupling. *Angew. Chem., Int. Ed.* **2019**, *58*, 16854–16858.
- (88) Gutierrez-Bonet, A.; Tellis, J. C.; Matsui, J. K.; Vara, B. A.; Molander, G. A. 1,4-Dihydropyridines as Alkyl Radical Precursors:

Introducing the Aldehyde Feedstock to Nickel/Photoredox Dual Catalysis. *ACS Catal.* **2016**, *6*, 8004–8008.

(89) Matsui, J. K.; Gutiérrez-Bonet, A.; Rotella, M.; Alam, R.; Gutierrez, O.; Molander, G. A. Photoredox/Nickel-Catalyzed Single-Electron Tsuji–Trost Reaction: Development and Mechanistic Insights. *Angew. Chem., Int. Ed.* **2018**, *57*, 15847–15851.

(90) Alandini, N.; Buzzetti, L.; Favi, G.; Schulte, T.; Candish, L.; Collins, K. D.; Melchiorre, P. Amide Synthesis by Nickel/Photoredox-Catalyzed Direct Carbamoylation of (Hetero)Aryl Bromides. *Angew. Chem., Int. Ed.* **2020**, *59*, 5248–5253.

(91) Qin, Q.; Jiang, H.; Hu, Z.; Ren, D.; Yu, S. Functionalization of C–H Bonds by Photoredox Catalysis. *Chem. Rec.* **2017**, *17*, 754–774.

(92) McNally, A.; Prier, C. K.; MacMillan, D. W. C. Discovery of an  $\alpha$ -Amino C–H Arylation Reaction Using the Strategy of Accelerated Serendipity. *Science* **2011**, *334*, 1114–1117.

(93) Ahneman, D. T.; Doyle, A. G. C–H Functionalization of Amines with Aryl Halides by Nickel-Photoredox Catalysis. *Chem. Sci.* **2016**, *7*, 7002–7006.

(94) Gui, Y. Y.; Wang, Z. X.; Zhou, W. J.; Liao, L. L.; Song, L.; Yin, Z. B.; Li, J.; Yu, D. G. Arylation of Aniline C(sp<sup>3</sup>)–H Bonds with Phenols via an In Situ Activation Strategy. *Asian J. Org. Chem.* **2018**, *7*, 537–541.

(95) Joe, C. L.; Doyle, A. G. Direct Acylation of C(sp<sup>3</sup>)–H Bonds Enabled by Nickel and Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 4040–4043.

(96) Roberts, B. P. Polarity-Reversal Catalysis of Hydrogen-Atom Abstraction Reactions: Concepts and Applications in Organic Chemistry. *Chem. Soc. Rev.* **1999**, *28*, 25–35.

(97) Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C. O–H hydrogen bonding promotes H-atom transfer from  $\alpha$  C–H bonds for C-alkylation of alcohols. *Science* **2015**, *349*, 1532–1536.

(98) Cuthbertson, J. D.; MacMillan, D. W. C. The Direct Arylation of Allylic Sp<sup>3</sup> C–H Bonds via Organic and Photoredox Catalysis. *Nature* **2015**, *519*, 74–77.

(99) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. Native Functionality in Triple Catalytic Cross-Coupling: Sp<sup>3</sup> C–H Bonds as Latent Nucleophiles. *Science* **2016**, *352*, 1304–1308.

(100) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. Selective Sp<sup>3</sup> C–H Alkylation via Polarity-Match-Based Cross-Coupling. *Nature* **2017**, *547*, 79–83.

(101) Cavallo, L.; Rueping, M.; Maity, B.; Zhu, C.; Yue, H.; Huang, L.; Harb, M.; Minenkov, Y. Mechanistic Insight into the Photoredox-Nickel-HAT Triple Catalyzed Arylation and Alkylation of  $\alpha$ -Amino Csp<sup>3</sup>–H Bonds. *J. Am. Chem. Soc.* **2020**, *142*, 16942–16952.

(102) Zhang, X.; MacMillan, D. W. C. Direct Aldehyde C–H Arylation and Alkylation via the Combination of Nickel, Hydrogen Atom Transfer, and Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139* (33), 11353–11356.

(103) Twilton, J.; Christensen, M.; DiRocco, D. A.; Ruck, R. T.; Davies, I. W.; MacMillan, D. W. C. Selective Hydrogen Atom Abstraction through Induced Bond Polarization: Direct  $\alpha$ -Arylation of Alcohols through Photoredox, HAT, and Nickel Catalysis. *Angew. Chem., Int. Ed.* **2018**, *57* (19), 5369–5373.

(104) Heitz, D. R.; Tellis, J. C.; Molander, G. A. Photochemical Nickel-Catalyzed C–H Arylation: Synthetic Scope and Mechanistic Investigations. *J. Am. Chem. Soc.* **2016**, *138* (39), 12715–12718.

(105) Huang, L.; Rueping, M. Direct Cross-Coupling of Allylic C(sp<sup>3</sup>)–H Bonds with Aryl- and Vinylbromides by Combined Nickel and Visible-Light Catalysis. *Angew. Chem., Int. Ed.* **2018**, *57* (32), 10333–10337.

(106) Hwang, S. J.; Powers, D. C.; Maher, A. G.; Anderson, B. L.; Hadt, R. G.; Zheng, S. L.; Chen, Y. S.; Nocera, D. G. Trap-Free Halogen Photoelimination from Mononuclear Ni(III) Complexes. *J. Am. Chem. Soc.* **2015**, *137* (20), 6472–6475.

(107) Shields, B. J.; Doyle, A. G. Direct C(sp<sup>3</sup>)–H Cross Coupling Enabled by Catalytic Generation of Chlorine Radicals. *J. Am. Chem. Soc.* **2016**, *138*, 12719–12722.

(108) Ackerman, L. K. G.; Martinez Alvarado, J. I.; Doyle, A. G. Direct C–C Bond Formation from Alkanes Using Ni-Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 14059–14063.

(109) Nielsen, M. K.; Shields, B. J.; Liu, J.; Williams, M. J.; Zacuto, M. J.; Doyle, A. G. Mild, Redox-Neutral Formylation of Aryl Chlorides through the Photocatalytic Generation of Chlorine Radicals. *Angew. Chem., Int. Ed.* **2017**, *56*, 7191–7194.

(110) Schönherr, H.; Cernak, T. Profound Methyl Effects in Drug Discovery and a Call for New C–H Methylation Reactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256–12267.

(111) Kariofillis, S. K.; Shields, B. J.; Tekle-Smith, M. A.; Zacuto, M. J.; Doyle, A. G. Nickel/Photoredox-Catalyzed Methylation of (Hetero)Aryl Chlorides Using Trimethyl Orthoformate as a Methyl Radical Source. *J. Am. Chem. Soc.* **2020**, *142*, 7683–7689.

(112) Deng, H. P.; Fan, X. Z.; Chen, Z. H.; Xu, Q. H.; Wu, J. Photoinduced Nickel-Catalyzed Chemo- and Regioselective Hydroalkylation of Internal Alkynes with Ether and Amide  $\alpha$ -Hetero C(sp<sup>3</sup>)–H Bonds. *J. Am. Chem. Soc.* **2017**, *139*, 13579–13584.

(113) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 2056–2071.

(114) De Waele, V.; Poizat, O.; Fagnoni, M.; Bagno, A.; Ravelli, D. Unraveling the Key Features of the Reactive State of Decatungstate Anion in Hydrogen Atom Transfer (HAT) Photocatalysis. *ACS Catal.* **2016**, *6*, 7174–7182.

(115) Ravelli, D.; Fagnoni, M.; Fukuyama, T.; Nishikawa, T.; Ryu, I. Site-Selective C–H Functionalization by Decatungstate Anion Photocatalysis: Synergistic Control by Polar and Steric Effects Expands the Reaction Scope. *ACS Catal.* **2018**, *8*, 701–713.

(116) Perry, I. B.; Brewer, T. F.; Sarver, P. J.; Schultz, D. M.; DiRocco, D. A.; MacMillan, D. W. C. Direct Arylation of Strong Aliphatic C–H Bonds. *Nature* **2018**, *560*, 70–75.

(117) Fan, P.; Lan, Y.; Zhang, C.; Wang, C. Nickel/Photocatalyzed Asymmetric Acyl-Carbamoylation of Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 2180–2186.

(118) Shen, Y.; Gu, Y.; Martin, R. Sp<sup>3</sup> C–H Arylation and Alkylation Enabled by the Synergy of Triplet Excited Ketones and Nickel Catalysts. *J. Am. Chem. Soc.* **2018**, *140*, 12200–12209.

(119) Dewanji, A.; Krach, P. E.; Rueping, M. The Dual Role of Benzophenone in Visible-Light/Nickel Photoredox-Catalyzed C–H Arylations: Hydrogen-Atom Transfer and Energy Transfer. *Angew. Chem., Int. Ed.* **2019**, *58*, 3566–3570.

(120) Krach, P. E.; Dewanji, A.; Yuan, T.; Rueping, M. Synthesis of Unsymmetrical Ketones by Applying Visible-Light Benzophenone/Nickel Dual Catalysis for Direct Benzylic Acylation. *Chem. Commun.* **2020**, *56*, 6082–6085.

(121) Ishida, N.; Masuda, Y.; Imamura, Y.; Yamazaki, K.; Murakami, M. Carboxylation of Benzylic and Aliphatic C–H Bonds with CO<sub>2</sub> Induced by Light/Ketone/Nickel. *J. Am. Chem. Soc.* **2019**, *141*, 19611–19615.

(122) Si, X.; Zhang, L.; Hashmi, A. S. K. Benzaldehyde- And Nickel-Catalyzed Photoredox C(sp<sup>3</sup>)–H Alkylation/Arylation with Amides and Thioethers. *Org. Lett.* **2019**, *21*, 6329–6332.

(123) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Catalytic Alkylation of Remote C–H Bonds Enabled by Proton-Coupled Electron Transfer. *Nature* **2016**, *539*, 268–271.

(124) Chu, J. C. K.; Rovis, T. Amide-Directed Photoredox-Catalyzed C–C Bond Formation at Unactivated Sp<sup>3</sup> C–H Bonds. *Nature* **2016**, *539*, 272–275.

(125) Thullen, S. M.; Treacy, S. M.; Rovis, T. Regioselective Alkylative Cross-Coupling of Remote Unactivated C(sp<sup>3</sup>)–H Bonds. *J. Am. Chem. Soc.* **2019**, *141*, 14062–14067.

(126) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146–6159.

(127) Molander, G. A.; Traister, K. M.; O'Neill, B. T. Reductive Cross-Coupling of Nonaromatic, Heterocyclic Bromides with Aryl and Heteroaryl Bromides. *J. Org. Chem.* **2014**, *79*, 5771–5780.



- (128) Bhonde, V. R.; O'Neill, B. T.; Buchwald, S. L. An Improved System for the Aqueous Lipshutz-Negishi Cross-Coupling of Alkyl Halides with Aryl Electrophiles. *Angew. Chem., Int. Ed.* **2016**, *55*, 1849–1853.
- (129) Everson, D. A.; Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **2014**, *79*, 4793–4798.
- (130) Zhang, P.; Le, C. C.; MacMillan, D. W. C. Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 8084–8087.
- (131) Chatgililoglu, C.; Griller, D.; Lesage, M. Rate Constants for the Reactions of Tris(trimethylsilyl)silyl Radicals with Organic Halides. *J. Org. Chem.* **1989**, *54*, 2492–2494.
- (132) Chatgililoglu, C. *Organosilanes in Radical Chemistry*; Wiley: Weinheim, 2004. DOI: 10.1002/0470024755.
- (133) Walsh, R. Bond Dissociation Energy Values in Silicon-Containing Compounds and Some of Their Implications. *Acc. Chem. Res.* **1981**, *14*, 246–252.
- (134) Pomberger, A.; Mo, Y.; Nandiwale, K. Y.; Schultz, V. L.; Duvadie, R.; Robinson, R. I.; Altinoglu, E. I.; Jensen, K. F. A Continuous Stirred-Tank Reactor (CSTR) Cascade for Handling Solid-Containing Photochemical Reactions. *Org. Process Res. Dev.* **2019**, *23*, 2699–2706.
- (135) Kölmel, D. K.; Ratnayake, A. S.; Flanagan, M. E. Photoredox Cross-Electrophile Coupling in DNA-Encoded Chemistry. *Biochem. Biophys. Res. Commun.* **2020**, *533*, 201–208.
- (136) Bacuanu, V.; Cardinal, S.; Yamauchi, M.; Kondo, M.; Fernández, D. F.; Remy, R.; MacMillan, D. W. C. Metallaphotoredox Difluoromethylation of Aryl Bromides. *Angew. Chem., Int. Ed.* **2018**, *57*, 12543–12548.
- (137) Smith, R. T.; Zhang, X.; Rincón, J. A.; Agejas, J.; Mateos, C.; Barberis, M.; García-Cerrada, S.; De Frutos, O.; Macmillan, D. W. C. Metallaphotoredox-Catalyzed Cross-Electrophile C Sp<sup>3</sup>-C Sp<sup>3</sup> Coupling of Aliphatic Bromides. *J. Am. Chem. Soc.* **2018**, *140*, 17433–17438.
- (138) Chen, T. Q.; MacMillan, D. W. C. A Metallaphotoredox Strategy for the Cross-Electrophile Coupling of  $\alpha$ -Chloro Carbonyls with Aryl Halides. *Angew. Chem., Int. Ed.* **2019**, *58*, 14584–14588.
- (139) Guan, H.; Zhang, Q.; Walsh, P. J.; Mao, J. Nickel/Photoredox-Catalyzed Asymmetric Reductive Cross-Coupling of Racemic  $\alpha$ -Chloro Esters with Aryl Iodides. *Angew. Chem., Int. Ed.* **2020**, *59*, 5172–5177.
- (140) Sakai, H. A.; Liu, W.; Le, C.; MacMillan, D. W. C. Cross-Electrophile Coupling of Unactivated Alkyl Chlorides. *J. Am. Chem. Soc.* **2020**, *142*, 11691–11697.
- (141) Duan, Z.; Li, W.; Lei, A. Nickel-Catalyzed Reductive Cross-Coupling of Aryl Bromides with Alkyl Bromides: Et<sub>3</sub>N as the Terminal Reductant. *Org. Lett.* **2016**, *18*, 4012–4015.
- (142) Paul, A.; Smith, M. D.; Vannucci, A. K. Photoredox-Assisted Reductive Cross-Coupling: Mechanistic Insight into Catalytic Aryl-Alkyl Cross-Couplings. *J. Org. Chem.* **2017**, *82*, 1996–2003.
- (143) Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Juliá, F.; Leonori, D. Aminoalkyl Radicals as Halogen-Atom Transfer Agents for Activation of Alkyl and Aryl Halides. *Science (Washington, DC, U. S.)* **2020**, *367*, 1021–1026.
- (144) Yu, W.; Chen, L.; Tao, J.; Wang, T.; Fu, J. Dual Nickel- and Photoredox-Catalyzed Reductive Cross-Coupling of Aryl Vinyl Halides and Unactivated Tertiary Alkyl Bromides. *Chem. Commun.* **2019**, *55*, 5918–5921.
- (145) Song, F.; Wang, F.; Guo, L.; Feng, X.; Zhang, Y.; Chu, L. Visible-Light-Enabled Stereodivergent Synthesis of E- and Z-Configured 1,4-Dienes by Photoredox/Nickel Dual Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 177–181.
- (146) Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P. Harnessing Alkyl Amines as Electrophiles for Nickel-Catalyzed Cross Couplings via C–N Bond Activation. *J. Am. Chem. Soc.* **2017**, *139*, 5313–5316.
- (147) Klauck, F. J. R.; James, M. J.; Glorius, F. Deaminative Strategy for the Visible-Light-Mediated Generation of Alkyl Radicals. *Angew. Chem., Int. Ed.* **2017**, *56*, 12336–12339.
- (148) Wu, J.; He, L.; Noble, A.; Aggarwal, V. K. Photoinduced Deaminative Borylation of Alkylamines. *J. Am. Chem. Soc.* **2018**, *140*, 10700–10704.
- (149) Yi, J.; Badir, S. O.; Kammer, L. M.; Ribagorda, M.; Molander, G. A. Deaminative Reductive Arylation Enabled by Nickel/Photoredox Dual Catalysis. *Org. Lett.* **2019**, *21*, 3346–3351.
- (150) Ni, S.; Li, C. X.; Mao, Y.; Han, J.; Wang, Y.; Yan, H.; Pan, Y. Ni-Catalyzed Deaminative Cross-Electrophile Coupling of Katritzky Salts with Halides via CN Bond Activation. *Sci. Adv.* **2019**, *5*, eaaw9516.
- (151) Yue, H.; Zhu, C.; Shen, L.; Geng, Q.; Hock, K. J.; Yuan, T.; Cavallo, L.; Rueping, M. Nickel-Catalyzed C–N Bond Activation: Activated Primary Amines as Alkylating Reagents in Reductive Cross-Coupling. *Chem. Sci.* **2019**, *10*, 4430–4435.
- (152) Meng, Q. Y.; Wang, S.; König, B. Carboxylation of Aromatic and Aliphatic Bromides and Triflates with CO<sub>2</sub> by Dual Visible-Light–Nickel Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 13426–13430.
- (153) Meng, Q. Y.; Wang, S.; Huff, G. S.; König, B. Ligand-Controlled Regioselective Hydrocarboxylation of Styrenes with CO<sub>2</sub> by Combining Visible Light and Nickel Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 3198–3201.
- (154) Mou, Z. D.; Wang, J. X.; Zhang, X.; Niu, D. Stereoselective Preparation of C-Aryl Glycosides via Visible-Light-Induced Nickel-Catalyzed Reductive Cross-Coupling of Glycosyl Chlorides and Aryl Bromides. *Adv. Synth. Catal.* **2021**, *363*, 3025–3029.
- (155) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. An Efficient Intermolecular Palladium-Catalyzed Synthesis of Aryl Ethers [17]. *J. Am. Chem. Soc.* **2001**, *123*, 10770–10771.
- (156) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. Copper-Catalyzed Coupling of Aryl Iodides with Aliphatic Alcohols. *Org. Lett.* **2002**, *4*, 973–976.
- (157) 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.* **2002**, *67*, 5553–5566.
- (158) Matsunaga, P. T.; Hillhouse, G. L.; Rheingold, A. L. Oxygen-Atom Transfer from Nitrous Oxide to a Nickel Metallacyclic. Synthesis, Structure, and Reactions of (2,2'-Bipyridine)Ni(OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>). *J. Am. Chem. Soc.* **1993**, *115*, 2075–2077.
- (159) Zhou, W.; Schultz, J. W.; Rath, N. P.; Mirica, L. M. Aromatic Methoxylation and Hydroxylation by Organometallic High-Valent Nickel Complexes. *J. Am. Chem. Soc.* **2015**, *137*, 7604–7607.
- (160) Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C. Switching on Elusive Organometallic Mechanisms with Photoredox Catalysis. *Nature* **2015**, *524*, 330–334.
- (161) Sun, R.; Qin, Y.; Nocera, D. G. General Paradigm in Photoredox Nickel-Catalyzed Cross-Coupling Allows for Light-Free Access to Reactivity. *Angew. Chem., Int. Ed.* **2020**, *59*, 9527–9533.
- (162) Lee, H.; Boyer, N. C.; Deng, Q.; Kim, H. Y.; Sawyer, T. K.; Sciammetta, N. Photoredox Ni-Catalyzed Peptide C(Sp<sup>2</sup>)-O Cross-Coupling: From Intermolecular Reactions to Side Chain-to-Tail Macrocyclization. *Chem. Sci.* **2019**, *10*, 5073–5078.
- (163) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. Photoinduced Ullmann C–N Coupling: Demonstrating the Viability of a Radical Pathway. *Science* **2012**, *338*, 647–651.
- (164) Kainz, Q. M.; Matier, C. D.; Bartoszczewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. Asymmetric Copper-Catalyzed C–N Cross-Couplings Induced by Visible Light. *Science* **2016**, *351*, 681–685.
- (165) Welin, E. R.; Le, C.; Arias-rotondo, D. M.; Mccusker, J. K.; MacMillan, D. W. C. Photosensitized, Energy Transfer-Mediated Organometallic Catalysis through Electronically Excited Nickel(II). *Science* **2017**, *355*, 380–385.
- (166) Tian, L.; Till, N. A.; Kudisch, B.; MacMillan, D. W. C.; Scholes, G. D. Transient Absorption Spectroscopy Offers Mechanistic

Insights for an Iridium/Nickel-Catalyzed C–O Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 4555–4559.

(167) Corcoran, E. B.; Pirnot, M. T.; Lin, S.; Dreher, S. D.; Dirococo, D. A.; Davies, I. W.; Buchwald, S. L.; MacMillan, D. W. C. Aryl Amination Using Ligand-Free Ni(II) Salts and Photoredox Catalysis. *Science* **2016**, *353*, 279–283.

(168) Kutchukian, P. S.; Dropinski, J. F.; Dykstra, K. D.; Li, B.; Dirococo, D. A.; Streckfuss, E. C.; Campeau, L. C.; Cernak, T.; Vachal, P.; Davies, I. W.; Krska, S. W.; Dreher, S. D. Chemistry Informer Libraries: A Chemoinformatics Enabled Approach to Evaluate and Advance Synthetic Methods. *Chem. Sci.* **2016**, *7*, 2604–2613.

(169) Corcoran, E. B.; McMullen, J. P.; Lévesque, F.; Wismer, M. K.; Naber, J. R. Photon Equivalents as a Parameter for Scaling Photoredox Reactions in Flow: Translation of Photocatalytic C–N Cross-Coupling from Lab Scale to Multikilogram Scale. *Angew. Chem., Int. Ed.* **2020**, *59*, 11964–11968.

(170) Park, B. Y.; Pirnot, M. T.; Buchwald, S. L. Visible Light-Mediated (Hetero)Aryl Amination Using Ni(II) Salts and Photoredox Catalysis in Flow: A Synthesis of Tetracaine. *J. Org. Chem.* **2020**, *85*, 3234–3244.

(171) Till, N. A.; Tian, L.; Dong, Z.; Scholes, G. D.; MacMillan, D. W. C. Mechanistic Analysis of Metallaphotoredox C–N Coupling: Photocatalysis Initiates and Perpetuates Ni(I)/Ni(III) Coupling Activity. *J. Am. Chem. Soc.* **2020**, *142*, 15830–15841.

(172) Tasker, S. Z.; Jamison, T. F. Highly Regioselective Indoline Synthesis under Nickel/Photoredox Dual Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 9531–9534.

(173) Beletskaya, I. P.; Cheprakov, A. V. Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **2000**, *100*, 3009–3066.

(174) Hartwig, J. F. Carbon-Heteroatom Bond Formation Catalysed by Organometallic Complexes. *Nature* **2008**, *455*, 314–322.

(175) Key, R. J.; Vannucci, A. K. Nickel Dual Photoredox Catalysis for the Synthesis of Aryl Amines. *Organometallics* **2018**, *37*, 1468–1472.

(176) Konev, M. O.; McTeague, T. A.; Johannes, J. W. Nickel-Catalyzed Photoredox-Mediated Cross-Coupling of Aryl Electrophiles and Aryl Azides. *ACS Catal.* **2018**, *8*, 9120–9124.

(177) Kim, T.; McCarver, S. J.; Lee, C.; MacMillan, D. W. C. Sulfonamidation of Aryl and Heteroaryl Halides through Photosensitized Nickel Catalysis. *Angew. Chem., Int. Ed.* **2018**, *57*, 3488–3492.

(178) Lim, C. H.; Kudisch, M.; Liu, B.; Miyake, G. M. C–N Cross-Coupling via Photoexcitation of Nickel–Amine Complexes. *J. Am. Chem. Soc.* **2018**, *140*, 7667–7673.

(179) Kudisch, M.; Lim, C. H.; Thordarson, P.; Miyake, G. M. Energy Transfer to Ni–Amine Complexes in Dual Catalytic, Light-Driven C–N Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2019**, *141*, 19479–19486.

(180) Simons, R. T.; Scott, G. E.; Kanegusuku, A. G.; Roizen, J. L. Photochemically Mediated Nickel-Catalyzed Synthesis of N-(Hetero)Aryl Sulfamides. *J. Org. Chem.* **2020**, *85*, 6380–6391.

(181) Xuan, J.; Zeng, T. T.; Chen, J. R.; Lu, L. Q.; Xiao, W. J. Room Temperature C–P Bond Formation Enabled by Merging Nickel Catalysis and Visible-Light-Induced Photoredox Catalysis. *Chem. - Eur. J.* **2015**, *21*, 4962–4965.

(182) Liao, L. L.; Gui, Y. Y.; Zhang, X. B.; Shen, G.; Liu, H. D.; Zhou, W. J.; Li, J.; Yu, D. G. Phosphorylation of Alkenyl and Aryl C–O Bonds via Photoredox/Nickel Dual Catalysis. *Org. Lett.* **2017**, *19*, 3735–3738.

(183) Jouffroy, M.; Kelly, C. B.; Molander, G. A. Thioetherification via Photoredox/Nickel Dual Catalysis. *Org. Lett.* **2016**, *18*, 876–879.

(184) Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W. Photoredox Mediated Nickel Catalyzed Cross-Coupling of Thiols with Aryl and Heteroaryl Iodides via Thiyl Radicals. *J. Am. Chem. Soc.* **2016**, *138*, 1760–1763.

(185) Zhu, Y. Y.; Lan, G.; Fan, Y.; Veroneau, S. S.; Song, Y.; Micheroni, D.; Lin, W. Merging Photoredox and Organometallic Catalysts in a Metal–Organic Framework Significantly Boosts

Photocatalytic Activities. *Angew. Chem., Int. Ed.* **2018**, *57*, 14090–14094.

(186) Badir, S. O.; Molander, G. A. Developments in Photoredox/Nickel Dual-Catalyzed 1,2-Difunctionalizations. *Chem.* **2020**, *6*, 1327–1339.

(187) Campbell, M. W.; Compton, J. S.; Kelly, C. B.; Molander, G. A. Three-Component Olefin Dicarbofunctionalization Enabled by Nickel/Photoredox Dual Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 20069–20078.

(188) Sun, S. Z.; Duan, Y.; Mega, R. S.; Somerville, R. J.; Martin, R. Site-Selective 1,2-Dicarbofunctionalization of Vinyl Boronates through Dual Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 4370–4374.

(189) Guo, L.; Tu, H. Y.; Zhu, S.; Chu, L. Selective, Intermolecular Alkylarylation of Alkenes via Photoredox/Nickel Dual Catalysis. *Org. Lett.* **2019**, *21*, 4771–4776.

(190) García-Domínguez, A.; Mondal, R.; Nevado, C. Dual Photoredox/Nickel-Catalyzed Three-Component Carbofunctionalization of Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 12286–12290.

(191) Zheng, S.; Chen, Z.; Hu, Y.; Xi, X.; Liao, Z.; Li, W.; Yuan, W. Selective 1,2-Aryl-Aminoalkylation of Alkenes Enabled by Metal-laphotoredox Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59* (41), 17910–17916.

(192) Guo, L.; Yuan, M.; Zhang, Y.; Wang, F.; Zhu, S.; Gutierrez, O.; Chu, L. General Method for Enantioselective Three-Component Carboarylation of Alkenes Enabled by Visible-Light Dual Photoredox/Nickel Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 20390–20399.

(193) Campbell, M. W.; Yuan, M.; Polites, V. C.; Gutierrez, O.; Molander, G. A. Photochemical C–H Activation Enables Nickel-Catalyzed Olefin Dicarbofunctionalization. *J. Am. Chem. Soc.* **2021**, *143*, 3901–3910.

(194) Zheng, S.; Gutiérrez-Bonet, Á.; Molander, G. A. Merging Photoredox PCET with Ni-Catalyzed Cross-Coupling: Cascade Amidoarylation of Unactivated Olefins. *Chem.* **2019**, *5*, 339–352.

(195) Weires, N. A.; Slutskyy, Y.; Overman, L. E. Facile Preparation of Spirolactones by an Alkoxy-carbonyl Radical Cyclization–Cross-Coupling Cascade. *Angew. Chem., Int. Ed.* **2019**, *58*, 8561–8565.

(196) Guo, L.; Song, F.; Zhu, S.; Li, H.; Chu, L. Syn-Selective Alkylarylation of Terminal Alkynes via the Combination of Photoredox and Nickel Catalysis. *Nat. Commun.* **2018**, *9*, 4543.

(197) Zhu, C.; Yue, H.; Maity, B.; Atodiresi, I.; Cavallo, L.; Rueping, M. A Multicomponent Synthesis of Stereodefined Olefins via Nickel Catalysis and Single Electron/Triplet Energy Transfer. *Nat. Catal.* **2019**, *2*, 678–687.

(198) Yue, H.; Zhu, C.; Kancherla, R.; Liu, F.; Rueping, M. Regioselective Hydroalkylation and Arylalkylation of Alkynes by Photoredox/Nickel Dual Catalysis: Application and Mechanism. *Angew. Chem., Int. Ed.* **2020**, *59*, 5738–5746.

(199) Glaser, C. Beiträge Zur Kenntnifs Des Acetenylbenzols. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422–424.

(200) Anilkuma, G.; Saranya, S. In *Copper Catalysis in Organic Synthesis*; Anilkuma, G., Saranya, S., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2020.

(201) Evano, G.; Blanchard, N. In *Copper-Mediated Cross-Coupling Reactions*; Evano, G., Blanchard, N., Eds.; John Wiley & Sons: New York, 2014.

(202) De La Mare, H. E.; Kochi, J. K.; Rust, F. F. The Oxidation of Free Radicals by Metal Ions. *J. Am. Chem. Soc.* **1961**, *83*, 2013.

(203) Maaliki, C.; Thiery, E.; Thibonnet, J. Emergence of Copper-Mediated Formation of C–C Bonds. *Eur. J. Org. Chem.* **2017**, *2017*, 209–228.

(204) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for Fluorination and Trifluoromethylation. *Nature* **2011**, *473*, 470–477.

(205) Hagemann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369.

(206) Casitas, A.; Ribas, X. The Role of Organometallic Copper(III) Complexes in Homogeneous Catalysis. *Chem. Sci.* **2013**, *4*, 2301–2318.

(207) Ye, Y.; Sanford, M. S. Merging Visible-Light Photocatalysis and Transition-Metal Catalysis in the Copper-Catalyzed Trifluoro-

- omethylation of Boronic Acids with  $\text{CF}_3\text{I}$ . *J. Am. Chem. Soc.* **2012**, *134*, 9034–9037.
- (208) Chu, L.; Qing, F. L. Copper-Mediated Oxidative Trifluoromethylation of Boronic Acids. *Org. Lett.* **2010**, *12*, 5060–5063.
- (209) Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. Room Temperature Aryl Trifluoromethylation via Copper-Mediated Oxidative Cross-Coupling. *J. Org. Chem.* **2011**, *76*, 1174–1176.
- (210) Xu, J.; Luo, D. F.; Xiao, B.; Liu, Z. J.; Gong, T. J.; Fu, Y.; Liu, L. Copper-Catalyzed Trifluoromethylation of Aryl Boronic Acids Using a  $\text{CF}_3^+$  Reagent. *Chem. Commun.* **2011**, *47*, 4300–4302.
- (211) Zhang, H. R.; Chen, D. Q.; Han, Y. P.; Qiu, Y. F.; Jin, D. P.; Liu, X. Y. Merging Photoredox with Copper Catalysis: Decarboxylative Difluoroacetylation of  $\alpha,\beta$ -Unsaturated Carboxylic Acids with  $\text{ICF}_2\text{CO}_2\text{Et}$ . *Chem. Commun.* **2016**, *52*, 11827–11830.
- (212) Kautzky, J. A.; Wang, T.; Evans, R. W.; MacMillan, D. W. C. Decarboxylative Trifluoromethylation of Aliphatic Carboxylic Acids. *J. Am. Chem. Soc.* **2018**, *140*, 6522–6526.
- (213) Le, C.; Chen, T. Q.; Liang, T.; Zhang, P.; MacMillan, D. W. C. A Radical Approach to the Copper Oxidative Addition Problem: Trifluoromethylation of Bromoarenes. *Science* **2018**, *360*, 1010–1014.
- (214) Jones, G. O.; Liu, P.; Houk, K. N.; Buchwald, S. L. Computational Explorations of Mechanisms and Ligand-Directed Selectivities of Copper-Catalyzed Ullmann-Type Reactions. *J. Am. Chem. Soc.* **2010**, *132*, 6205–6213.
- (215) Yu, H. Z.; Jiang, Y. Y.; Fu, Y.; Liu, L. Alternative Mechanistic Explanation for Ligand-Dependent Selectivities in Copper-Catalyzed N- and O-Arylation Reactions. *J. Am. Chem. Soc.* **2010**, *132*, 18078–18091.
- (216) Kornfilt, D. J. P.; MacMillan, D. W. C. Copper-Catalyzed Trifluoromethylation of Alkyl Bromides. *J. Am. Chem. Soc.* **2019**, *141*, 6853–6858.
- (217) Sarver, P. J.; Bacauanu, V.; Schultz, D. M.; DiRocco, D. A.; Lam, Y.; Sherer, E. C.; MacMillan, D. W. C. The Merger of Decatungstate and Copper Catalysis to Enable Aliphatic  $\text{C}(\text{sp}^3)\text{-H}$  Trifluoromethylation. *Nat. Chem.* **2020**, *12*, 459–467.
- (218) Sonogashira, K.; Tohda, Y.; Hagihara, N. A Convenient Synthesis of Acetylenes: Catalytic Substitutions of Acetylenic Hydrogen with Bromalkenes, Iodoarenes, and Bromopyridines. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
- (219) Li, Z.; Li, C. J. Highly Efficient Copper-Catalyzed Nitro-Mannich Type Reaction: Cross-Dehydrogenative-Coupling between  $\text{Sp}^3$  C–H Bond and  $\text{Sp}^3$  C–H Bond. *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673.
- (220) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. Functionally Diverse Nucleophilic Trapping of Iminium Intermediates Generated Utilizing Visible Light. *Org. Lett.* **2012**, *14*, 94–97.
- (221) Rueping, M.; Koenigs, R. M.; Poschary, K.; Fabry, D. C.; Leonori, D.; Vila, C. Dual Catalysis: Combination of Photocatalytic Aerobic Oxidation and Metal Catalyzed Alkynylation Reactions-C-C Bond Formation Using Visible Light. *Chem. - Eur. J.* **2012**, *18*, 5170–5174.
- (222) Perepichka, I.; Kundu, S.; Hearne, Z.; Li, C. J. Efficient Merging of Copper and Photoredox Catalysis for the Asymmetric Cross-Dehydrogenative-Coupling of Alkynes and Tetrahydroisoquinolines. *Org. Biomol. Chem.* **2015**, *13*, 447–451.
- (223) Zhang, H.; Zhang, P.; Jiang, M.; Yang, H.; Fu, H. Merging Photoredox with Copper Catalysis: Decarboxylative Alkynylation of  $\alpha$ -Amino Acid Derivatives. *Org. Lett.* **2017**, *19*, 1016–1019.
- (224) Mao, Y.; Zhao, W.; Lu, S.; Yu, L.; Wang, Y.; Liang, Y.; Ni, S.; Pan, Y. Copper-Catalyzed Photoinduced Decarboxylative Alkynylation: A Combined Experimental and Computational Study. *Chem. Sci.* **2020**, *11*, 4939–4947.
- (225) Sagadevan, A.; Hwang, K. C. Photo-Induced Sonogashira C-C Coupling Reaction Catalyzed by Simple Copper(I) Chloride Salt at Room Temperature. *Adv. Synth. Catal.* **2012**, *354*, 3421–3427.
- (226) Charpe, V. P.; Hande, A. A.; Sagadevan, A.; Hwang, K. C. Visible-Light Induced Copper(I)-Catalyzed Denitrogenative Oxidative Coupling of Hydrazinylpyridines with Terminal Alkynes. *Green Chem.* **2018**, *20*, 4859–4864.
- (227) Sagadevan, A.; Ragupathi, A.; Lin, C.-C.; Hwu, J. R.; Hwang, K. C. Visible-Light Initiated Copper(I)-Catalyzed Oxidative C-N Coupling of Anilines with Terminal Alkynes: One-Step Synthesis of  $\alpha$ -Ketoamides. *Green Chem.* **2015**, *17*, 1113–1119.
- (228) Ragupathi, A.; Sagadevan, A.; Lin, C.-C.; Hwu, J. R.; Hwang, K. C. Copper(I)-Catalyzed Oxidative C-N Coupling of 2-Aminopyridine with Terminal Alkynes Featuring a  $\text{C}\equiv\text{C}$  Bond Cleavage Promoted by Visible Light. *Chem. Commun.* **2016**, *52*, 11756–11759.
- (229) Sagadevan, A.; Charpe, V. P.; Ragupathi, A.; Hwang, K. C. Visible Light Copper Photoredox-Catalyzed Aerobic Oxidative Coupling of Phenols and Terminal Alkynes: Regioselective Synthesis of Functionalized Ketones via  $\text{C}\equiv\text{C}$  Triple Bond Cleavage. *J. Am. Chem. Soc.* **2017**, *139*, 2896–2899.
- (230) Sagadevan, A.; Charpe, V. P.; Hwang, K. C. Copper(I) Chloride Catalyzed Room Temperature  $\text{C}_{\text{sp}}\text{-C}_{\text{sp}}$  Homocoupling of Terminal Alkynes Mediated by Visible Light. *Catal. Sci. Technol.* **2016**, *6*, 7688–7692.
- (231) Sagadevan, A.; Lyu, P.-C.; Hwang, K. C. Visible-Light-Activated Copper(I) Catalyzed Oxidative  $\text{C}_{\text{sp}}\text{-C}_{\text{sp}}$  Cross-Coupling Reaction: Efficient Synthesis of Unsymmetrical Conjugated Diynes without Ligands and Base. *Green Chem.* **2016**, *18*, 4526–4530.
- (232) Sagadevan, A.; Ragupathi, A.; Hwang, K. C. Photoinduced Copper-Catalyzed Regioselective Synthesis of Indoles: Three-Component Coupling of Arylamines, Terminal Alkynes, and Quinones. *Angew. Chem., Int. Ed.* **2015**, *54*, 13896–13901.
- (233) Sagadevan, A.; Pampana, V. K. K.; Hwang, K. C. Copper Photoredox Catalyzed  $\text{A}3'$  Coupling of Arylamines, Terminal Alkynes, and Alcohols through a Hydrogen Atom Transfer Process. *Angew. Chem., Int. Ed.* **2019**, *58*, 3838–3842.
- (234) Hazra, A.; Lee, M. T.; Chiu, J. F.; Lalic, G. Photoinduced Copper-Catalyzed Coupling of Terminal Alkynes and Alkyl Iodides. *Angew. Chem., Int. Ed.* **2018**, *57*, 5492–5496.
- (235) Wang, D.; Zhu, N.; Chen, P.; Lin, Z.; Liu, G. Enantioselective Decarboxylative Cyanation Employing Cooperative Photoredox Catalysis and Copper Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 15632–15635.
- (236) Wang, T.; Wang, Y.-N.; Wang, R.; Zhang, B.-C.; Yang, C.; Li, Y.-L.; Wang, X.-S. Enantioselective Cyanation via Radical-Mediated C–C Single Bond Cleavage for Synthesis of Chiral Dinitriles. *Nat. Commun.* **2019**, *10*, 5373.
- (237) Chen, H.; Jin, W.; Yu, S. Enantioselective Remote  $\text{C}(\text{sp}^3)\text{-H}$  Cyanation via Dual Photoredox and Copper Catalysis. *Org. Lett.* **2020**, *22*, 5910–5914.
- (238) Kern, J.-M.; Sauvage, J. Photoassisted C–C Coupling via Electron Transfer to Benzylic Halides by a Bis(Di-Imine) Copper(I) Complex. *J. Chem. Soc., Chem. Commun.* **1987**, 546–548.
- (239) Bagal, D. B.; Kachkovskiy, G.; Knorn, M.; Rawner, T.; Bhanage, B. M.; Reiser, O. Trifluoromethylchlorosulfonylation of Alkenes: Evidence for an Inner-Sphere Mechanism by a Copper Phenanthroline Photoredox Catalyst. *Angew. Chem., Int. Ed.* **2015**, *54*, 6999–7002.
- (240) Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. Visible Light-Mediated Atom Transfer Radical Addition via Oxidative and Reductive Quenching of Photocatalysts. *J. Am. Chem. Soc.* **2012**, *134*, 8875–8884.
- (241) Oh, S. H.; Malpani, Y. R.; Ha, N.; Jung, Y.-S.; Han, S. B. Vicinal Difunctionalization of Alkenes: Chlorotrifluoromethylation with  $\text{CF}_3\text{SO}_2\text{Cl}$  by Photoredox Catalysis. *Org. Lett.* **2014**, *16*, 1310–1313.
- (242) Dolbier, W. R. Fluorinated Free Radicals. In *Organofluorine Chemistry: Fluorinated Alkenes and Reactive Intermediates*; Chambers, R. D., Ed.; Springer: Berlin, Heidelberg, 1997; pp 97–163.
- (243) Rawner, T.; Lutsker, E.; Kaiser, C. A.; Reiser, O. The Different Faces of Photoredox Catalysts: Visible-Light-Mediated Atom Transfer Radical Addition (ATRA) Reactions of Perfluoroalkyl Iodides with Styrenes and Phenylacetylenes. *ACS Catal.* **2018**, *8*, 3950–3956.
- (244) Wu, D.; Cui, S.-S.; Lin, Y.; Li, L.; Yu, W. Visible Light-Driven Azidation/Difunctionalization of Vinyl Arenes with Azidobenziodoxole under Copper Catalysis. *J. Org. Chem.* **2019**, *84*, 10978–10989.

- (245) Alkan-Zambada, M.; Hu, X. Cu Photoredox Catalysts Supported by a 4,6-Disubstituted 2,2'-Bipyridine Ligand: Application in Chlorotrifluoromethylation of Alkenes. *Organometallics* **2018**, *37*, 3928–3935.
- (246) Alkan-Zambada, M.; Hu, X. Cu-Catalyzed Photoredox Chlorosulfonation of Alkenes and Alkynes. *J. Org. Chem.* **2019**, *84*, 4525–4533.
- (247) Lin, Q.-Y.; Ran, Y.; Xu, X.-H.; Qing, F.-L. Photoredox-Catalyzed Bromodifluoromethylation of Alkenes with (Difluoromethyl)Triphenylphosphonium Bromide. *Org. Lett.* **2016**, *18*, 2419–2422.
- (248) Liu, Z.; Chen, H.; Lv, Y.; Tan, X.; Shen, H.; Yu, H.-Z.; Li, C. Radical Carbofluorination of Unactivated Alkenes with Fluoride Ions. *J. Am. Chem. Soc.* **2018**, *140*, 6169–6175.
- (249) He, J.; Chen, C.; Fu, G. C.; Peters, J. C. Visible-Light-Induced, Copper-Catalyzed Three-Component Coupling of Alkyl Halides, Olefins, and Trifluoromethylthiolate to Generate Trifluoromethyl Thioethers. *ACS Catal.* **2018**, *8*, 11741–11748.
- (250) Griffin, J. D.; Cavanaugh, C. L.; Nicewicz, D. A. Reversing the Regioselectivity of Halofunctionalization Reactions through Cooperative Photoredox and Copper Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 2097–2100.
- (251) Sha, W.; Deng, L.; Ni, S.; Mei, H.; Han, J.; Pan, Y. Merging Photoredox and Copper Catalysis: Enantioselective Radical Cyanoalkylation of Styrenes. *ACS Catal.* **2018**, *8*, 7489–7494.
- (252) Yu, X.-Y.; Zhao, Q.-Q.; Chen, J.; Chen, J.-R.; Xiao, W.-J. Copper-Catalyzed Radical Cross-Coupling of Redox-Active Oxime Esters, Styrenes, and Boronic Acids. *Angew. Chem., Int. Ed.* **2018**, *57*, 15505–15509.
- (253) Chen, J.; He, B.-Q.; Wang, P.-Z.; Yu, X.-Y.; Zhao, Q.-Q.; Chen, J.-R.; Xiao, W.-J. Photoinduced, Copper-Catalyzed Radical Cross-Coupling of Cycloketone Oxime Esters, Alkenes, and Terminal Alkynes. *Org. Lett.* **2019**, *21*, 4359–4364.
- (254) Hossain, A.; Vidyasagar, A.; Eichinger, C.; Lankes, C.; Phan, J.; Rehbein, J.; Reiser, O. Visible-Light-Accelerated Copper(II)-Catalyzed Regio- and Chemoselective Oxo-Azidation of Vinyl Arenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 8288–8292.
- (255) Xia, X.-F.; Zhang, G.-W.; Wang, D.; Zhu, S.-L. Visible-Light Induced and Oxygen-Promoted Oxidative Cyclization of Aromatic Enamines for the Synthesis of Quinolines Derivatives. *J. Org. Chem.* **2017**, *82*, 8455–8463.
- (256) Jin, R.; Chen, Y.; Liu, W.; Xu, D.; Li, Y.; Ding, A.; Guo, H. Merging Photoredox Catalysis with Lewis Acid Catalysis: Activation of Carbon-Carbon Triple Bonds. *Chem. Commun.* **2016**, *52*, 9909–9912.
- (257) Tao, C.; Wang, B.; Sun, L.; Liu, Z.; Zhai, Y.; Zhang, X.; Wang, J. Merging Visible-Light Photoredox and Copper Catalysis in Catalytic Aerobic Oxidation of Amines to Nitriles. *Org. Biomol. Chem.* **2017**, *15*, 328–332.
- (258) Bai, P.; Sun, S.; Li, Z.; Qiao, H.; Su, X.; Yang, F.; Wu, Y.; Wu, Y. Ru/Cu Photoredox or Cu/Ag Catalyzed C4-H Sulfonation of 1-Naphthylamides at Room Temperature. *J. Org. Chem.* **2017**, *82*, 12119–12127.
- (259) Liu, T.; Ding, Y.; Fan, X.; Wu, J. Photoinduced Synthesis of (E)-Vinyl Sulfones through the Insertion of Sulfur Dioxide. *Org. Chem. Front.* **2018**, *5*, 3153–3157.
- (260) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. Transition-Metal-Catalyzed Alkylations of Amines with Alkyl Halides: Photoinduced, Copper-Catalyzed Couplings of Carbazoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 5129–5133.
- (261) Uyeda, C.; Tan, Y.; Fu, G. C.; Peters, J. C. A New Family of Nucleophiles for Photoinduced, Copper-Catalyzed Cross-Couplings via Single-Electron Transfer: Reactions of Thiols with Aryl Halides under Mild Conditions (0 °C). *J. Am. Chem. Soc.* **2013**, *135*, 9548–9552.
- (262) Tan, Y.; Muñoz-Molina, J. M.; Fu, G. C.; Peters, J. C. Oxygen Nucleophiles as Reaction Partners in Photoinduced, Copper-Catalyzed Cross-Couplings: O-Arylations of Phenols at Room Temperature. *Chem. Sci.* **2014**, *5*, 2831–2835.
- (263) Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C. Copper-Catalyzed Alkylation of Aliphatic Amines Induced by Visible Light. *J. Am. Chem. Soc.* **2017**, *139*, 17707–17710.
- (264) Ahn, J. M.; Peters, J. C.; Fu, G. C. Design of a Photoredox Catalyst That Enables the Direct Synthesis of Carbamate-Protected Primary Amines via Photoinduced, Copper-Catalyzed N-Alkylation Reactions of Unactivated Secondary Halides. *J. Am. Chem. Soc.* **2017**, *139*, 18101–18106.
- (265) Zhao, W.; Wurz, R. P.; Peters, J. C.; Fu, G. C. Photoinduced, Copper-Catalyzed Decarboxylative C–N Coupling to Generate Protected Amines: An Alternative to the Curtius Rearrangement. *J. Am. Chem. Soc.* **2017**, *139*, 12153–12156.
- (266) Mao, R.; Balon, J.; Hu, X. Cross-Coupling of Alkyl Redox-Active Esters with Benzophenone Imines: Tandem Photoredox and Copper Catalysis. *Angew. Chem., Int. Ed.* **2018**, *57*, 9501–9504.
- (267) Mao, R.; Frey, A.; Balon, J.; Hu, X. Decarboxylative C(sp<sup>3</sup>)-N Cross-Coupling via Synergetic Photoredox and Copper Catalysis. *Nat. Catal.* **2018**, *1*, 120–126.
- (268) Barzanò, G.; Mao, R.; Garreau, M.; Waser, J.; Hu, X. Tandem Photoredox and Copper-Catalyzed Decarboxylative C(sp<sup>3</sup>)-N Coupling of Anilines and Imines Using an Organic Photocatalyst. *Org. Lett.* **2020**, *22*, 5412–5416.
- (269) Mao, R.; Balon, J.; Hu, X. Decarboxylative C(sp<sup>3</sup>)-O Cross-Coupling. *Angew. Chem., Int. Ed.* **2018**, *57*, 13624–13628.
- (270) Nguyen, V. T.; Haug, G. C.; Nguyen, V. D.; Vuong, N. T. H.; Arman, H. D.; Larionov, O. V. Photocatalytic Decarboxylative Amidosulfonation Enables Direct Transformation of Carboxylic Acids to Sulfonamides. *Chem. Sci.* **2021**, *12*, 6429–6436.
- (271) Yoo, W.-J.; Tsukamoto, T.; Kobayashi, S. Visible-Light-Mediated Chan-Lam Coupling Reactions of Aryl Boronic Acids and Aniline Derivatives. *Angew. Chem., Int. Ed.* **2015**, *54*, 6587–6590.
- (272) Yoo, W.-J.; Tsukamoto, T.; Kobayashi, S. Visible Light-Mediated Ullmann-Type C–N Coupling Reactions of Carbazole Derivatives and Aryl Iodides. *Org. Lett.* **2015**, *17*, 3640–3642.
- (273) Liang, Y.; Zhang, X.; MacMillan, D. W. C. Decarboxylative sp<sup>3</sup> C–N Coupling via Dual Copper and Photoredox Catalysis. *Nature* **2018**, *559*, 83–88.
- (274) Zhao, X.; Liu, Y.; Zhu, R.; Liu, C.; Zhang, D. Mechanistic Study on the Decarboxylative sp<sup>3</sup> C–N Cross-Coupling between Alkyl Carboxylic Acids and Nitrogen Nucleophiles via Dual Copper and Photoredox Catalysis. *Inorg. Chem.* **2019**, *58*, 12669–12677.
- (275) Zhang, X.; Smith, R. T.; Le, C.; McCarver, S. J.; Shireman, B. T.; Carruthers, N. I.; MacMillan, D. W. C. Copper-Mediated Synthesis of Drug-like Bicyclopentanes. *Nature* **2020**, *580*, 220–226.
- (276) Kanazawa, J.; Uchiyama, M. Recent Advances in the Synthetic Chemistry of Bicyclo[1.1.1]pentane. *Synlett* **2019**, *30*, 1–11.
- (277) Mykhailiuk, P. K. Saturated Bioisosteres of Benzene: Where to Go Next? *Org. Biomol. Chem.* **2019**, *17*, 2839–2849.
- (278) Lavagnino, M. N.; Liang, T.; MacMillan, D. W. C. HARC as an Open-Shell Strategy to Bypass Oxidative Addition in Ullmann–Goldberg Couplings. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 21058–21064.
- (279) Osawa, M.; Nagai, H.; Akita, M. Photo-Activation of Pd-Catalyzed Sonogashira Coupling Using a Ru/Bipyridine Complex as Energy Transfer Agent. *J. Chem. Soc. Dalt. Trans.* **2007**, *8*, 827–829.
- (280) Kalyani, D.; McMurtrey, 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.* **2011**, *133*, 18566–18569.
- (281) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. Oxidative C–H Activation/C–C Bond Forming Reactions: Synthetic Scope and Mechanistic Insights. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331.
- (282) Deprez, N. R.; Sanford, M. S. Synthetic and Mechanistic Studies of Pd-Catalyzed C–H Arylation with Diaryliodonium Salts: Evidence for a Bimetallic High Oxidation State Pd Intermediate. *J. Am. Chem. Soc.* **2009**, *131*, 11234–11241.
- (283) Neufeldt, S. R.; Sanford, M. S. Combining Transition Metal Catalysis with Radical Chemistry: Dramatic Acceleration of

- Palladium-Catalyzed C–H Arylation with Diaryliodonium Salts. *Adv. Synth. Catal.* **2012**, *354*, 3517–3522.
- (284) Liang, L.; Xie, M.-S.; Wang, H.-X.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. Visible-Light-Mediated Monoselective Ortho C–H Arylation of 6-Arylpyridine Nucleosides with Diazonium Salts. *J. Org. Chem.* **2017**, *82*, 5966–5973.
- (285) Jiang, J.; Zhang, W.-M.; Dai, J.-J.; Xu, J.; Xu, H.-J. Visible-Light-Promoted C–H Arylation by Merging Palladium Catalysis with Organic Photoredox Catalysis. *J. Org. Chem.* **2017**, *82*, 3622–3630.
- (286) Sahoo, M. K.; Midya, S. P.; Landge, V. G.; Balaraman, E. A Unified Strategy for Silver-, Base-, and Oxidant-Free Direct Arylation of C–H Bonds. *Green Chem.* **2017**, *19*, 2111–2117.
- (287) Khan, R.; Boonseng, S.; Kemmitt, P. D.; Felix, R.; Coles, S. J.; Tizzard, G. J.; Williams, G.; Simmonds, O.; Harvey, J.-L.; Atack, J.; Cox, H.; Spencer, J. Combining Sanford Arylations on Benzodiazepines with the Nuisance Effect. *Adv. Synth. Catal.* **2017**, *359*, 3261–3269.
- (288) Babu, S. S.; Shahid, M.; Gopinath, P. Dual Palladium-Photoredox Catalyzed Chemoselective C–H Arylation of Phenylureas. *Chem. Commun.* **2020**, *56*, 5985–5988.
- (289) He, B.-Q.; Gao, Y.; Wang, P.-Z.; Wu, H.; Zhou, H.-B.; Liu, X.-P.; Chen, J.-R. Dual Photoredox/Palladium-Catalyzed C–H Acylation of 2-Arylpyridines with Oxime Esters. *Synlett* **2021**, *32*, 373–377.
- (290) Zoller, J.; Fabry, D. C.; Ronge, M. A.; Rueping, M. Synthesis of Indoles Using Visible Light: Photoredox Catalysis for Palladium-Catalyzed C–H Activation. *Angew. Chem., Int. Ed.* **2014**, *53*, 13264–13268.
- (291) Zhou, C.; Li, P.; Zhu, X.; Wang, L. Merging Photoredox with Palladium Catalysis: Decarboxylative *ortho*-Acylation of Acetanilides with  $\alpha$ -Oxocarboxylic Acids under Mild Reaction Conditions. *Org. Lett.* **2015**, *17*, 6198–6201.
- (292) Xu, N.; Li, P.; Xie, Z.; Wang, L. Merging Visible-Light Photocatalysis and Palladium Catalysis for C–H Acylation of Azo- and Azoxybenzenes with  $\alpha$ -Keto Acids. *Chem. - Eur. J.* **2016**, *22*, 2236–2242.
- (293) Manna, M. K.; Bairy, G.; Jana, R. Dual Visible-Light Photoredox and Palladium(II) Catalysis for Dehydrogenative C2-Acylation of Indoles at Room Temperature. *Org. Biomol. Chem.* **2017**, *15*, 5899–5903.
- (294) Choi, S.; Chatterjee, T.; Choi, W. J.; You, Y.; Cho, E. J. Synthesis of Carbazoles by a Merged Visible Light Photoredox and Palladium-Catalyzed Process. *ACS Catal.* **2015**, *5*, 4796–4802.
- (295) Dick, A. R.; Hull, K. L.; Sanford, M. S. A Highly Selective Catalytic Method for the Oxidative Functionalization of C–H Bonds. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301.
- (296) Shah, S. S.; Paul, A.; Bera, M.; Venkatesh, Y.; Singh, N. D. P. Metallaphotoredox-Mediated C<sub>sp2</sub>-H Hydroxylation of Arenes under Aerobic Conditions. *Org. Lett.* **2018**, *20*, 5533–5536.
- (297) Shah, S. S.; Shee, M.; Singh, A. K.; Paul, A.; Singh, N. D. P. Direct Oxygenation of C–H Bonds through Photoredox and Palladium Catalysis. *J. Org. Chem.* **2020**, *85*, 3426–3439.
- (298) Czyn, M. L.; Lupton, D. W.; Polyzos, A. Auxiliary-Directed C(sp<sup>3</sup>)-H Arylation by Synergistic Photoredox and Palladium Catalysis. *Chem. - Eur. J.* **2017**, *23*, 14450–14453.
- (299) Zhang, H.; Huang, X. Ligand-Free Heck Reactions of Aryl Iodides: Significant Acceleration of the Rate through Visible Light Irradiation at Ambient Temperature. *Adv. Synth. Catal.* **2016**, *358*, 3736–3742.
- (300) Zheng, C.; Cheng, W.-M.; Li, H.-L.; Na, R.-S.; Shang, R. Cis-Selective Decarboxylative Alkenylation of Aliphatic Carboxylic Acids with Vinyl Arenes Enabled by Photoredox/Palladium/Uphill Triple Catalysis. *Org. Lett.* **2018**, *20*, 2559–2563.
- (301) Tsuji, J.; Takahashi, H.; Morikawa, M. Organic Syntheses by Means of Noble Metal Compounds XVII. Reaction of  $\pi$ -Allylpalladium Chloride with Nucleophiles. *Tetrahedron Lett.* **1965**, *6*, 4387–4388.
- (302) Trost, B. M.; Fullerton, T. J. New Synthetic Reactions. Allylic Alkylation. *J. Am. Chem. Soc.* **1973**, *95*, 292–294.
- (303) Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921–2943.
- (304) Lang, S. B.; O'Nele, K. M.; Tunge, J. A. Decarboxylative Allylation of Amino Alkanoic Acids and Esters via Dual Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 13606–13609.
- (305) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. Transition Metal-Catalyzed Decarboxylative Allylation and Benzyl-ation Reactions. *Chem. Rev.* **2011**, *111*, 1846–1913.
- (306) Huang, H. M.; Koy, M.; Serrano, E.; Pflüger, P. M.; Schwarz, J. L.; Glorius, F. Catalytic Radical Generation of  $\pi$ -Allylpalladium Complexes. *Nat. Catal.* **2020**, *3*, 393–400.
- (307) Bellotti, P.; Koy, M.; Gutheil, C.; Heuvel, S.; Glorius, F. Three-Component Three-Bond Forming Cascade via Palladium Photoredox Catalysis. *Chem. Sci.* **2021**, *12*, 1810–1817.
- (308) Zheng, J.; Nikbakht, A.; Breit, B. Dual Palladium/Photoredox-Catalyzed Enantioselective and Regioselective Decarboxylative Hydroaminoalkylation of Allenes. *ACS Catal.* **2021**, *11*, 3343–3350.
- (309) Xuan, J.; Zeng, T.-T.; Feng, Z.-J.; Deng, Q.-H.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J.; Alper, H. Redox-Neutral  $\alpha$ -Allylation of Amines by Combining Palladium Catalysis and Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 1625–1628.
- (310) Lang, S. B.; O'Nele, K. M.; Douglas, J. T.; Tunge, J. A. Dual Catalytic Decarboxylative Allylations of  $\alpha$ -Amino Acids and Their Divergent Mechanisms. *Chem. - Eur. J.* **2015**, *21*, 18589–18593.
- (311) Xue, S.; Limburg, B.; Ghorai, D.; Benet-Buchholz, J.; Kleij, A. W. Asymmetric Synthesis of Homoallylic Alcohols Featuring Vicinal Tetrasubstituted Carbon Centers via Dual Pd/Photoredox Catalysis. *Org. Lett.* **2021**, *23*, 4447–4451.
- (312) Zhang, H.-H.; Zhao, J.-J.; Yu, S. Enantioselective Allylic Alkylation with 4-Alkyl-1,4-Dihydro-Pyridines Enabled by Photoredox/Palladium Cocatalysis. *J. Am. Chem. Soc.* **2018**, *140*, 16914–16919.
- (313) Shen, X.; Qian, L.; Yu, S. Photoredox/Palladium-Cocatalyzed Enantioselective Alkylation of Secondary Benzyl Carbonates with 4-Alkyl-1,4-Dihydropyridines. *Sci. China: Chem.* **2020**, *63*, 687–691.
- (314) Zhang, H.-H.; Zhao, J.-J.; Yu, S. Enantioselective  $\alpha$ -Allylation of Anilines Enabled by a Combined Palladium and Photoredox Catalytic System. *ACS Catal.* **2020**, *10*, 4710–4716.
- (315) Masuda, Y.; Ito, M.; Murakami, M. Dehydrative Allylation of  $\alpha$  C(sp<sup>3</sup>)-H Bonds of Alkylamines with Allylic Alcohols. *Org. Lett.* **2020**, *22*, 4467–4470.
- (316) Zhou, Z.-Z.; Jiao, R.-Q.; Yang, K.; Chen, X.-M.; Liang, Y.-M. Photoredox/Palladium Co-Catalyzed Propargylic Benzyl-ation with Internal Propargylic Carbonates. *Chem. Commun.* **2020**, *56*, 12957–12960.
- (317) Liu, K.; Zou, M.; Lei, A. Aerobic Oxidative Carbonylation of Enamides by Merging Palladium with Photoredox Catalysis. *J. Org. Chem.* **2016**, *81*, 7088–7092.
- (318) Shimomaki, K.; Murata, K.; Martin, R.; Iwasawa, N. Visible-Light-Driven Carboxylation of Aryl Halides by the Combined Use of Palladium and Photoredox Catalysts. *J. Am. Chem. Soc.* **2017**, *139*, 9467–9470.
- (319) Correa, A.; Martín, R. Palladium-Catalyzed Direct Carboxylation of Aryl Bromides with Carbon Dioxide. *J. Am. Chem. Soc.* **2009**, *131*, 15974–15975.
- (320) Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. Nickel-Catalyzed Carboxylation of Aryl and Vinyl Chlorides Employing Carbon Dioxide. *J. Am. Chem. Soc.* **2012**, *134*, 9106–9109.
- (321) Shimomaki, K.; Nakajima, T.; Caner, J.; Toriumi, N.; Iwasawa, N. Palladium-Catalyzed Visible-Light-Driven Carboxylation of Aryl and Alkenyl Triflates by Using Photoredox Catalysts. *Org. Lett.* **2019**, *21*, 4486–4489.
- (322) Bhunia, S. K.; Das, P.; Nandi, S.; Jana, R. Carboxylation of Aryl Triflates with CO<sub>2</sub> Merging Palladium and Visible-Light-Photoredox Catalysts. *Org. Lett.* **2019**, *21*, 4632–4637.
- (323) Zhu, C.; Zhang, Y.-F.; Liu, Z.-Y.; Zhou, L.; Liu, H.; Feng, C. Selective C–F Bond Carboxylation of gem-Difluoroalkenes with CO<sub>2</sub>

- by Photoredox/Palladium Dual Catalysis. *Chem. Sci.* **2019**, *10*, 6721–6726.
- (324) Hashmi, A. S. K. Gold-Catalyzed Organic Reactions. *Chem. Rev.* **2007**, *107*, 3180–3211.
- (325) Hashmi, A. S. K.; Ramamurthi, T. D.; Rominger, F. Synthesis, Structure and Reactivity of Organogold Compounds of Relevance to Homogeneous Gold Catalysis. *J. Organomet. Chem.* **2009**, *694*, 592–597.
- (326) Wang, W.; Jasinski, J.; Hammond, G. B.; Xu, B. Fluorine-Enabled Cationic Gold Catalysis: Functionalized Hydration of Alkynes. *Angew. Chem., Int. Ed.* **2010**, *49*, 7247–7252.
- (327) Hopkinson, M. N.; Gee, A. D.; Gouverneur, V. Au<sup>I</sup>/Au<sup>III</sup> Catalysis: An Alternative Approach for C-C Oxidative Coupling. *Chem. - Eur. J.* **2011**, *17*, 8248–8262.
- (328) Sahoo, B.; Hopkinson, M. N.; Glorius, F. Combining Gold and Photoredox Catalysis: Visible Light-Mediated Oxy- and Aminoylation of Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 5505–5508.
- (329) Hopkinson, M. N.; Tlahuext-Aca, A.; Glorius, F. Merging Visible Light Photoredox and Gold Catalysis. *Acc. Chem. Res.* **2016**, *49*, 2261–2272.
- (330) Tlahuext-Aca, A.; Hopkinson, M. N.; Daniliuc, C. G.; Glorius, F. Oxidative Addition to Gold(I) by Photoredox Catalysis: Straightforward Access to Diverse (C,N)-Cyclometalated Gold(III) Complexes. *Chem. - Eur. J.* **2016**, *22*, 11587–11592.
- (331) Huang, L.; Rominger, F.; Rudolph, M.; Hashmi, A. S. K. A General Access to Organogold(III) Complexes by Oxidative Addition of Diazonium Salts. *Chem. Commun.* **2016**, *52*, 6435–6438.
- (332) Hopkinson, M. N.; Sahoo, B.; Glorius, F. Dual Photoredox and Gold Catalysis: Intermolecular Multicomponent Oxyarylation of Alkenes. *Adv. Synth. Catal.* **2014**, *356*, 2794–2800.
- (333) Patil, D. V.; Yun, H.; Shin, S. Catalytic Cross-Coupling of Vinyl Golds with Diazonium Salts under Photoredox and Thermal Conditions. *Adv. Synth. Catal.* **2015**, *357*, 2622–2628.
- (334) Shu, X.-Z.; Zhang, M.; He, Y.; Frei, H.; Toste, F. D. Dual Visible Light Photoredox and Gold-Catalyzed Arylative Ring Expansion. *J. Am. Chem. Soc.* **2014**, *136*, 5844–5847.
- (335) Alcaide, B.; Almendros, P.; Aparicio, B.; Lázaro-Milla, C.; Luna, A.; Faza, O. N. Gold-Photoredox-Cocatalyzed Tandem Oxyacylation/Coupling Sequence of Allenols and Diazonium Salts with Visible Light Mediation. *Adv. Synth. Catal.* **2017**, *359*, 2789–2800.
- (336) Wu, C.-Y.; Horibe, T.; Jacobsen, C. B.; Toste, F. D. Stable Gold(III) Catalysts by Oxidative Addition of a Carbon–Carbon Bond. *Nature* **2015**, *517*, 449–454.
- (337) Akram, M. O.; Mali, P. S.; Patil, N. T. Cross-Coupling Reactions of Aryldiazonium Salts with Allylsilanes under Merged Gold/Visible-Light Photoredox Catalysis. *Org. Lett.* **2017**, *19*, 3075–3078.
- (338) Tlahuext-Aca, A.; Hopkinson, M. N.; Sahoo, B.; Glorius, F. Dual Gold/Photoredox-Catalyzed C(sp)-H Arylation of Terminal Alkynes with Diazonium Salts. *Chem. Sci.* **2016**, *7*, 89–93.
- (339) Kim, S.; Rojas-Martin, J.; Toste, F. D. Visible Light-Mediated Gold-Catalysed Carbon(sp<sup>2</sup>)–Carbon(sp) Cross-Coupling. *Chem. Sci.* **2016**, *7*, 85–88.
- (340) Um, J.; Yun, H.; Shin, S. Cross-Coupling of Meyer-Schuster Intermediates under Dual Gold-Photoredox Catalysis. *Org. Lett.* **2016**, *18*, 484–487.
- (341) Tlahuext-Aca, A.; Hopkinson, M. N.; Garza-Sanchez, R. A.; Glorius, F. Alkyne Difunctionalization by Dual Gold/Photoredox Catalysis. *Chem. - Eur. J.* **2016**, *22*, 5909–5913.
- (342) Alcaide, B.; Almendros, P.; Busto, E.; Luna, A. Domino Meyer-Schuster/Arylation Reaction of Alkynols or Alkynyl Hydroperoxides with Diazonium Salts Promoted by Visible Light under Dual Gold and Ruthenium Catalysis. *Adv. Synth. Catal.* **2016**, *358*, 1526–1533.
- (343) Huang, L.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Photosensitizer-Free Visible-Light-Mediated Gold-Catalyzed 1,2-Difunctionalization of Alkynes. *Angew. Chem., Int. Ed.* **2016**, *55*, 4808–4813.
- (344) Xia, Z.; Khaled, O.; Mouriès-Mansuy, V.; Ollivier, C.; Fensterbank, L. Dual Photoredox/Gold Catalysis Arylative Cyclization of o-Alkynylphenols with Aryldiazonium Salts: A Flexible Synthesis of Benzofurans. *J. Org. Chem.* **2016**, *81*, 7182–7190.
- (345) Qu, C.; Zhang, S.; Du, H.; Zhu, C. Cascade Photoredox/Gold Catalysis: Access to Multisubstituted Indoles via Aminoarylation of Alkynes. *Chem. Commun.* **2016**, *52*, 14400–14403.
- (346) Alcaide, B.; Almendros, P.; Busto, E.; Lázaro-Milla, C. Photoinduced Gold-Catalyzed Domino C(sp) Arylation/Oxyarylation of TMS-Terminated Alkynols with Arenediazonium Salts. *J. Org. Chem.* **2017**, *82*, 2177–2186.
- (347) Lázaro-Milla, C.; Busto, E.; Burgos, I.; Nieto Faza, O.; Almendros, P. Gold-Catalyzed Reaction of Alkynes with Diazonium Salts under Photoirradiation Revisited: New Alkoxyarylation Variant Leading to Enol Ethers. *J. Catal.* **2020**, *391*, 48–55.
- (348) Xia, Z.; Corcé, V.; Zhao, F.; Przybylski, C.; Espagne, A.; Jullien, L.; Le Saux, T.; Gimbert, Y.; Dossman, H.; Mouriès-Mansuy, V.; Ollivier, C.; Fensterbank, L. Photosensitized Oxidative Addition to Gold(I) Enables Alkynylative Cyclization of o-Alkynylphenols with Iodoalkynes. *Nat. Chem.* **2019**, *11*, 797–805.
- (349) Sancheti, S. P.; Akram, M. O.; Roy, R.; Bedi, V.; Kundu, S.; Patil, N. T. Ortho-Oxygenative 1,2-Difunctionalization of Diarylalkynes under Merged Gold/Organophotoredox Relay Catalysis. *Chem. - Asian J.* **2019**, *14*, 4601–4606.
- (350) Bansode, A. H.; Shaikh, S. R.; Gonnade, R. G.; Patil, N. T. Intramolecular: Ipso -Arylative Cyclization of Aryl-Alkynoates and N -Arylpropiolamides with Aryldiazonium Salts through Merged Gold/Visible Light Photoredox Catalysis. *Chem. Commun.* **2017**, *53*, 9081–9084.
- (351) Alcaide, B.; Almendros, P.; Busto, E.; Herrera, F.; Lázaro-Milla, C.; Luna, A. Photopromoted Entry to Benzothiophenes, Benzoselenophenes, 3H-Indoles, Isocoumarins, Benzosultams, and (Thio)Flavones by Gold-Catalyzed Arylative Heterocyclization of Alkynes. *Adv. Synth. Catal.* **2017**, *359*, 2640–2652.
- (352) Wang, Z.-S.; Tan, T.-D.; Wang, C.-M.; Yuan, D.-Q.; Zhang, T.; Zhu, P.; Zhu, C.; Zhou, J.-M.; Ye, L.-W. Dual Gold/Photoredox-Catalyzed Bis-Arylative Cyclization of Chiral Homopropargyl Sulfonamides with Diazonium Salts: Rapid Access to Enantioenriched 2,3-Dihydropyrroles. *Chem. Commun.* **2017**, *53*, 6848–6851.
- (353) Cornilleau, T.; Hermange, P.; Fouquet, E. Gold-Catalysed Cross-Coupling between Aryldiazonium Salts and Arylboronic Acids: Probing the Usefulness of Photoredox Conditions. *Chem. Commun.* **2016**, *52*, 10040–10043.
- (354) Gauchot, V.; Lee, A.-L. Dual Gold Photoredox C(sp<sup>2</sup>)–C(sp<sup>2</sup>) Cross Couplings-Development and Mechanistic Studies. *Chem. Commun.* **2016**, *52*, 10163–10166.
- (355) Tabey, A.; Berlande, M.; Hermange, P.; Fouquet, E. Mechanistic and Asymmetric Investigations of the Au-Catalysed Cross-Coupling between Aryldiazonium Salts and Arylboronic Acids Using (P,N) Gold Complexes. *Chem. Commun.* **2018**, *54*, 12867–12870.
- (356) Chakrabarty, I.; Akram, M. O.; Biswas, S.; Patil, N. T. Visible Light Mediated Desilylative C(sp<sup>2</sup>)–C(sp<sup>2</sup>) Cross-Coupling Reactions of Arylsilanes with Aryldiazonium Salts under Au(I)/Au(III) Catalysis. *Chem. Commun.* **2018**, *54*, 7223–7226.
- (357) He, Y.; Wu, H.; Toste, F. D. A Dual Catalytic Strategy for Carbon-Phosphorus Cross-Coupling via Gold and Photoredox Catalysis. *Chem. Sci.* **2015**, *6*, 1194–1198.
- (358) Li, H.; Shan, C.; Tung, C. H.; Xu, Z. Dual Gold and Photoredox Catalysis: Visible Light-Mediated Intermolecular Atom Transfer Thiosulfonylation of Alkenes. *Chem. Sci.* **2017**, *8*, 2610–2615.
- (359) Bhattacharjee, R.; Datta, A. Understanding Thermal and Photochemical Aryl–Aryl Cross-Coupling by the Au<sup>I</sup>/Au<sup>III</sup> Redox Couple. *Chem. - Eur. J.* **2018**, *24*, 13636–13646.
- (360) Zhang, Q.; Zhang, Z.-Q.; Fu, Y.; Yu, H. Z. Mechanism of the Visible Light-Mediated Gold-Catalyzed Oxyarylation Reaction of Alkenes. *ACS Catal.* **2016**, *6*, 798–808.

- (361) Witzel, S.; Xie, J.; Rudolph, M.; Hashmi, A. S. K. Photosensitizer-Free, Gold-Catalyzed C–C Cross-Coupling of Boronic Acids and Diazonium Salts Enabled by Visible Light. *Adv. Synth. Catal.* **2017**, *359*, 1522–1528.
- (362) Xie, J.; Sekine, K.; Witzel, S.; Krämer, P.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Light-Induced Gold-Catalyzed Hiyama Arylation: A Coupling Access to Biarylboronates. *Angew. Chem., Int. Ed.* **2018**, *57*, 16648–16653.
- (363) Witzel, S.; Sekine, K.; Rudolph, M.; Hashmi, A. S. K. New Transmetalation Reagents for the Gold-Catalyzed Visible Light-Enabled C(sp or sp<sup>2</sup>)–C(sp<sup>2</sup>) Cross-Coupling with Aryldiazonium Salts in the Absence of a Photosensitizer. *Chem. Commun.* **2018**, *54*, 13802–13804.
- (364) Sherborne, G. J.; Gevondian, A. G.; Funes-Ardoiz, I.; Dahiya, A.; Fricke, C.; Schoenebeck, F. Modular and Selective Arylation of Aryl Germanes (C–GeEt<sub>3</sub>) over C–Bpin, C–SiR<sub>3</sub> and Halogens Enabled by Light-Activated Gold Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 15543–15548.
- (365) Liu, Y.; Yang, Y.; Zhu, R.; Liu, C.; Zhang, D. The Dual Role of Gold(I) Complexes in Photosensitizer-Free Visible-Light-Mediated Gold-Catalyzed 1,2-Difunctionalization of Alkynes: A DFT Study. *Chem. - Eur. J.* **2018**, *24*, 14119–14126.
- (366) Deng, J. R.; Chan, W. C.; Chun-Him Lai, N.; Yang, B.; Tsang, C. S.; Chi-Bun Ko, B.; Lai-Fung Chan, S.; Wong, M. K. Photosensitizer-Free Visible Light-Mediated Gold-Catalyzed Cis-Difunctionalization of Silyl-Substituted Alkynes. *Chem. Sci.* **2017**, *8*, 7537–7544.
- (367) Liu, Y.; Yang, Y.; Zhu, R.; Liu, C.; Zhang, D. DFT Study on Photosensitizer-Free Visible-Light-Mediated Au-Catalyzed Cis-Difunctionalization of Alkynes: Mechanism and Selectivities as Compared to Rh Catalysis. *J. Org. Chem.* **2019**, *84*, 16171–16182.
- (368) Taschinski, S.; Döpp, R.; Ackermann, M.; Rominger, F.; de Vries, F.; Menger, M. F. S. J.; Rudolph, M.; Hashmi, A. S. K.; Klein, J. E. M. N. Light-Induced Mechanistic Divergence in Gold(I) Catalysis: Revisiting the Reactivity of Diazonium Salts. *Angew. Chem., Int. Ed.* **2019**, *58*, 16988–16993.
- (369) Tang, H. J.; Zhang, X.; Zhang, Y. F.; Feng, C. Visible-Light-Assisted Gold-Catalyzed Fluoroarylation of Allenates. *Angew. Chem., Int. Ed.* **2020**, *59*, 5242–5247.
- (370) Kärkäs, M. D.; Verho, O.; Johnston, E. V.; Åkermark, B. Artificial Photosynthesis: Molecular Systems for Catalytic Water Oxidation. *Chem. Rev.* **2014**, *114*, 11863–12001.
- (371) Eckenhoff, W. T.; McNamara, W. R.; Du, P.; Eisenberg, R. Cobalt Complexes as Artificial Hydrogenases for the Reductive Side of Water Splitting. *Biochim. Biophys. Acta, Bioenerg.* **2013**, *1827*, 958–973.
- (372) Zhong, J. J.; Meng, Q. Y.; Liu, B.; Li, X. B.; Gao, X. W.; Lei, T.; Wu, C. J.; Li, Z. J.; Tung, C. H.; Wu, L. Z. Cross-Coupling Hydrogen Evolution Reaction in Homogeneous Solution without Noble Metals. *Org. Lett.* **2014**, *16*, 1988–1991.
- (373) Meng, Q. Y.; Zhong, J. J.; Liu, Q.; Gao, X. W.; Zhang, H. H.; Lei, T.; Li, Z. J.; Feng, K.; Chen, B.; Tung, C. H.; Wu, L. Z. A Cascade Cross-Coupling Hydrogen Evolution Reaction by Visible Light Catalysis. *J. Am. Chem. Soc.* **2013**, *135*, 19052–19055.
- (374) Gao, X. W.; Meng, Q. Y.; Li, J. X.; Zhong, J. J.; Lei, T.; Li, X. B.; Tung, C. H.; Wu, L. Z. Visible Light Catalysis Assisted Site-Specific Functionalization of Amino Acid Derivatives by C–H Bond Activation without Oxidant: Cross-Coupling Hydrogen Evolution Reaction. *ACS Catal.* **2015**, *5*, 2391–2396.
- (375) Xiang, M.; Meng, Q. Y.; Li, J. X.; Zheng, Y. W.; Ye, C.; Li, Z. J.; Chen, B.; Tung, C. H.; Wu, L. Z. Activation of C–H Bonds through Oxidant-Free Photoredox Catalysis: Cross-Coupling Hydrogen-Evolution Transformation of Isochromans and  $\beta$ -Keto Esters. *Chem. - Eur. J.* **2015**, *21*, 18080–18484.
- (376) Niu, L.; Wang, S.; Liu, J.; Yi, H.; Liang, X. A.; Liu, T.; Lei, A. Visible Light-Mediated Oxidative C(sp<sup>3</sup>)-H Phosphonylation for  $\alpha$ -Aminophosphonates under Oxidant-Free Conditions. *Chem. Commun.* **2018**, *54*, 1659–1662.
- (377) Yang, Q.; Zhang, L.; Ye, C.; Luo, S.; Wu, L. Z.; Tung, C. H. Visible-Light-Promoted Asymmetric Cross-Dehydrogenative Coupling of Tertiary Amines to Ketones by Synergistic Multiple Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 3694–3698.
- (378) Cao, H.; Jiang, H.; Feng, H.; Kwan, J. M. C.; Liu, X.; Wu, J. Photo-Induced Decarboxylative Heck-Type Coupling of Unactivated Aliphatic Acids and Terminal Alkenes in the Absence of Sacrificial Hydrogen Acceptors. *J. Am. Chem. Soc.* **2018**, *140*, 16360–16367.
- (379) Zhang, G.; Zhang, L.; Yi, H.; Luo, Y.; Qi, X.; Tung, C. H.; Wu, L. Z.; Lei, A. Visible-Light Induced Oxidant-Free Oxidative Cross-Coupling for Constructing Allylic Sulfones from Olefins and Sulfinic Acids. *Chem. Commun.* **2016**, *52*, 10407–10410.
- (380) Koeller, J.; Gandeeppan, P.; Ackermann, L. Visible-Light-Induced Decarboxylative C–H Adamantylation of Azoles at Ambient Temperature. *Synthesis* **2019**, *51*, 1284–1292.
- (381) Tian, W. F.; Hu, C. H.; He, K. H.; He, X. Y.; Li, Y. Visible-Light Photoredox-Catalyzed Decarboxylative Alkylation of Heteroarenes Using Carboxylic Acids with Hydrogen Release. *Org. Lett.* **2019**, *21*, 6930–6935.
- (382) Zheng, Y. W.; Chen, B.; Ye, P.; Feng, K.; Wang, W.; Meng, Q. Y.; Wu, L. Z.; Tung, C. H. Photocatalytic Hydrogen-Evolution Cross-Couplings: Benzene C–H Amination and Hydroxylation. *J. Am. Chem. Soc.* **2016**, *138*, 10080–10083.
- (383) Zhang, M.; Ruzi, R.; Li, N.; Xie, J.; Zhu, C. Photoredox and Cobalt Co-Catalyzed C(sp<sup>2</sup>)-H Functionalization/C–O Bond Formation for Synthesis of Lactones under Oxidant- and Acceptor-Free Conditions. *Org. Chem. Front.* **2018**, *5*, 749–752.
- (384) Shao, A.; Zhan, J.; Li, N.; Chiang, C. W.; Lei, A. External Oxidant-Free Dehydrogenative Lactonization of 2-Arylbenzoic Acids via Visible-Light Photocatalysis. *J. Org. Chem.* **2018**, *83*, 3582–3589.
- (385) Zhang, G.; Hu, X.; Chiang, C. W.; Yi, H.; Pei, P.; Singh, A. K.; Lei, A. Anti-Markovnikov Oxidation of  $\beta$ -Alkyl Styrenes with H<sub>2</sub>O as the Terminal Oxidant. *J. Am. Chem. Soc.* **2016**, *138*, 12037–12040.
- (386) Niu, L.; Yi, H.; Wang, S.; Liu, T.; Liu, J.; Lei, A. Photo-Induced Oxidant-Free Oxidative C–H/N–H Cross-Coupling between Arenes and Azoles. *Nat. Commun.* **2017**, *8*, 14226.
- (387) Yi, H.; Niu, L.; Song, C.; Li, Y.; Dou, B.; Singh, A. K.; Lei, A. Photocatalytic Dehydrogenative Cross-Coupling of Alkenes with Alcohols or Azoles without External Oxidant. *Angew. Chem., Int. Ed.* **2017**, *56*, 1120–1124.
- (388) Niu, L.; Liu, J.; Yi, H.; Wang, S.; Liang, X. A.; Singh, A. K.; Chiang, C. W.; Lei, A. Visible-Light-Induced External Oxidant-Free Oxidative Phosphonylation of C(sp<sup>2</sup>)-H Bonds. *ACS Catal.* **2017**, *7*, 7412–7416.
- (389) Zhang, G.; Lin, Y.; Luo, X.; Hu, X.; Chen, C.; Lei, A. Oxidative [4 + 2] Annulation of Styrenes with Alkynes under External-Oxidant-Free Conditions. *Nat. Commun.* **2018**, *9*, 1225.
- (390) Zhang, G.; Liu, C.; Yi, H.; Meng, Q.; Bian, C.; Chen, H.; Jian, J. X.; Wu, L. Z.; Lei, A. External Oxidant-Free Oxidative Cross-Coupling: A Photoredox Cobalt-Catalyzed Aromatic C–H Thiolation for Constructing C–S Bonds. *J. Am. Chem. Soc.* **2015**, *137*, 9273–9280.
- (391) Zhao, Q. Q.; Hu, X. Q.; Yang, M. N.; Chen, J. R.; Xiao, W. J. A Visible-Light Photocatalytic N-Radical Cascade of Hydrazones for the Synthesis of Dihydropyrazole-Fused Benzosultams. *Chem. Commun.* **2016**, *52*, 12749–12752.
- (392) West, J. G.; Huang, D.; Sorensen, E. J. Acceptorless Dehydrogenation of Small Molecules through Cooperative Base Metal Catalysis. *Nat. Commun.* **2015**, *6*, 10093.
- (393) Abrams, D. J.; West, J. G.; Sorensen, E. J. Toward a Mild Dehydroformylation Using Base-Metal Catalysis. *Chem. Sci.* **2017**, *8*, 1954–1959.
- (394) He, K. H.; Tan, F. F.; Zhou, C. Z.; Zhou, G. J.; Yang, X. L.; Li, Y. Acceptorless Dehydrogenation of N-Heterocycles by Merging Visible-Light Photoredox Catalysis and Cobalt Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 3080–3084.
- (395) Sahoo, M. K.; Balaraman, E. Room Temperature Catalytic Dehydrogenation of Cyclic Amines with the Liberation of H<sub>2</sub> Using Water as a Solvent. *Green Chem.* **2019**, *21*, 2119–2128.

- (396) Sahoo, M. K.; Saravanakumar, K.; Jaiswal, G.; Balaraman, E. Photocatalysis Enabling Acceptorless Dehydrogenation of Diaryl Hydrazines at Room Temperature. *ACS Catal.* **2018**, *8*, 7727–7733.
- (397) Dighe, S. U.; Juliá, F.; Luridiana, A.; Douglas, J. J.; Leonori, D. A Photochemical Dehydrogenative Strategy for Aniline Synthesis. *Nature* **2020**, *584*, 75–81.
- (398) Cartwright, K. C.; Tunge, J. A. Decarboxylative Elimination of *N*-Acyl Amino Acids via Photoredox/Cobalt Dual Catalysis. *ACS Catal.* **2018**, *8*, 11801–11806.
- (399) Cartwright, K. C.; Joseph, E.; Comadoll, C. G.; Tunge, J. A. Photoredox/Cobalt Dual-Catalyzed Decarboxylative Elimination of Carboxylic Acids: Development and Mechanistic Insight. *Chem. - Eur. J.* **2020**, *26*, 12454–12471.
- (400) Sun, X.; Chen, J.; Ritter, T. Catalytic Dehydrogenative Decarboxyolefination of Carboxylic Acids. *Nat. Chem.* **2018**, *10*, 1229–1233.
- (401) Nguyen, V. T.; Nguyen, V. D.; Haug, G. C.; Dang, H. T.; Jin, S.; Li, Z.; Flores-Hansen, C.; Benavides, B. S.; Arman, H. D.; Larionov, O. V. Alkene Synthesis by Photocatalytic Chemoenzymatically Compatible Dehydrodecarboxylation of Carboxylic Acids and Biomass. *ACS Catal.* **2019**, *9*, 9485–9498.
- (402) Call, A.; Casadevall, C.; Acuña-Parés, F.; Casitas, A.; Lloret-Fillol, J. Dual Cobalt-Copper Light-Driven Catalytic Reduction of Aldehydes and Aromatic Ketones in Aqueous Media. *Chem. Sci.* **2017**, *8*, 4739–4749.
- (403) Thullen, S. M.; Rovis, T. A Mild Hydroaminoalkylation of Conjugated Dienes Using a Unified Cobalt and Photoredox Catalytic System. *J. Am. Chem. Soc.* **2017**, *139*, 15504–15508.
- (404) Meng, Q. Y.; Schirmer, T. E.; Katou, K.; König, B. Controllable Isomerization of Alkenes by Dual Visible-Light-Cobalt Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 5723–5728.
- (405) Rai, P.; Maji, K.; Maji, B. Photoredox/Cobalt Dual Catalysis for Visible-Light-Mediated Alkene-Alkyne Coupling. *Org. Lett.* **2019**, *21*, 3755–3759.
- (406) Ruhl, K. E.; Rovis, T. Visible Light-Gated Cobalt Catalysis for a Spatially and Temporally Resolved [2+2+2] Cycloaddition. *J. Am. Chem. Soc.* **2016**, *138*, 15527–15530.
- (407) Ravetz, B. D.; Ruhl, K. E.; Rovis, T. External Regulation of Cobalt-Catalyzed Cycloaddition Polymerization with Visible Light. *ACS Catal.* **2018**, *8*, 5323–5327.
- (408) Ravetz, B. D.; Wang, J. Y.; Ruhl, K. E.; Rovis, T. Photoinduced Ligand-to-Metal Charge Transfer Enables Photocatalyst-Independent Light-Gated Activation of Co(II). *ACS Catal.* **2019**, *9*, 200–204.
- (409) Hou, J.; Ee, A.; Feng, W.; Xu, J. H.; Zhao, Y.; Wu, J. Visible-Light-Driven Alkyne Hydro-/Carboxylation Using CO<sub>2</sub> via Iridium/Cobalt Dual Catalysis for Divergent Heterocycle Synthesis. *J. Am. Chem. Soc.* **2018**, *140*, 5257–5263.
- (410) Kalsi, D.; Dutta, S.; Barsu, N.; Rueping, M.; Sundararaju, B. Room-Temperature C-H Bond Functionalization by Merging Cobalt and Photoredox Catalysis. *ACS Catal.* **2018**, *8*, 8115–8120.
- (411) Kalsi, D.; Barsu, N.; Chakrabarti, S.; Dahiya, P.; Rueping, M.; Sundararaju, B. C-H and N-H Bond Annulation of Aryl Amides with Unactivated Olefins by Merging Cobalt(III) and Photoredox Catalysis. *Chem. Commun.* **2019**, *55*, 11626–11629.
- (412) Takizawa, K.; Sekino, T.; Sato, S.; Yoshino, T.; Kojima, M.; Matsunaga, S. Cobalt-Catalyzed Allylic Alkylation Enabled by Organophotoredox Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 9199–9203.
- (413) Turnbull, B. W. H.; Evans, P. A. Asymmetric Rhodium-Catalyzed Allylic Substitution Reactions: Discovery, Development and Applications to Target-Directed Synthesis. *J. Org. Chem.* **2018**, *83*, 11463–11479.
- (414) Ghorai, S.; Chirke, S. S.; Xu, W.-B.; Chen, J.-F.; Li, C. Cobalt-Catalyzed Regio- and Enantioselective Allylic Amination. *J. Am. Chem. Soc.* **2019**, *141*, 11430–11434.
- (415) Pfaff, G.; Reynders, P. Angle-Dependent Optical Effects Deriving from Submicron Structures of Films and Pigments. *Chem. Rev.* **1999**, *99*, 1963–1981.
- (416) Dahl, M.; Liu, Y.; Yin, Y. Composite Titanium Dioxide Nanomaterials. *Chem. Rev.* **2014**, *114*, 9853–9889.
- (417) Ma, Y.; Wang, X.; Jia, Y.; Chen, X.; Han, H.; Li, C. Titanium Dioxide-Based Nanomaterials for Photocatalytic Fuel Generations. *Chem. Rev.* **2014**, *114*, 9987–10043.
- (418) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. New, Efficient Method for the Synthesis of Allyltitanium Compounds from Allyl Halides or Allyl Alcohol Derivatives via Oxidative Addition. A Highly Efficient and Practical Synthesis of Homoallyl Alcohols. *J. Am. Chem. Soc.* **1995**, *117*, 3881–3882.
- (419) Gansäuer, A.; Bluhm, H.; Pierobon, M. Emergence of a Novel Catalytic Radical Reaction: Titanocene-Catalyzed Reductive Opening of Epoxides. *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.
- (420) Lin, S.; Chen, Y.; Li, F.; Shi, C.; Shi, L. Visible-Light-Driven Spirocyclization of Epoxides: Via Dual Titanocene and Photoredox Catalysis. *Chem. Sci.* **2020**, *11*, 839–844.
- (421) Li, F. S.; Chen, Y. Q.; Lin, S. J.; Shi, C. Z.; Li, X. Y.; Sun, Y. C.; Guo, Z. W.; Shi, L. Visible-Light-Mediated Barbier Allylation of Aldehydes and Ketones: Via Dual Titanium and Photoredox Catalysis. *Org. Chem. Front.* **2020**, *7*, 3434–3438.
- (422) Gualandi, A.; Calogero, F.; Mazzarini, M.; Guazzi, S.; Fermi, A.; Bergamini, G.; Cozzi, P. G. Cp<sub>2</sub>TiCl<sub>2</sub>-Catalyzed Photoredox Allylation of Aldehydes with Visible Light. *ACS Catal.* **2020**, *10*, 3857–3863.
- (423) Li, F.; Lin, S.; Chen, Y.; Shi, C.; Yan, H.; Li, C.; Wu, C.; Lin, L.; Duan, C.; Shi, L. Photocatalytic Generation of  $\pi$ -Allyltitanium Complexes via Radical Intermediates. *Angew. Chem., Int. Ed.* **2021**, *60*, 1561–1566.
- (424) Parasram, M.; Shields, B. J.; Ahmad, O.; Knauber, T.; Doyle, A. G. Regioselective Cross-Electrophile Coupling of Epoxides and (Hetero)Aryl Iodides via Ni/Ti/Photoredox Catalysis. *ACS Catal.* **2020**, *10*, 5821–5827.
- (425) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. Grignard-Type Carbonyl Addition of Allyl Halides by Means of Chromous Salt. A Chemospecific Synthesis of Homoallyl Alcohols. *J. Am. Chem. Soc.* **1977**, *99*, 3179–3181.
- (426) Fürstner, A.; Shi, N. Nozaki-Hiyama-Kishi Reactions Catalytic in Chromium. *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357.
- (427) Schwarz, J. L.; Schäfers, F.; Tlahuext-Aca, A.; Lückemeier, L.; Glorius, F. Diastereoselective Allylation of Aldehydes by Dual Photoredox and Chromium Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 12705–12709.
- (428) Mitsunuma, H.; Tanabe, S.; Fuse, H.; Ohkubo, K.; Kanai, M. Catalytic Asymmetric Allylation of Aldehydes with Alkenes through Allylic C(sp<sup>3</sup>)-H Functionalization Mediated by Organophotoredox and Chiral Chromium Hybrid Catalysis. *Chem. Sci.* **2019**, *10*, 3459–3465.
- (429) Tanabe, S.; Mitsunuma, H.; Kanai, M. Catalytic Allylation of Aldehydes Using Unactivated Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 12374–12381.
- (430) Schwarz, J. L.; Huang, H. M.; Paulisch, T. O.; Glorius, F. Dialkylation of 1,3-Dienes by Dual Photoredox and Chromium Catalysis. *ACS Catal.* **2020**, *10*, 1621–1627.
- (431) Huang, H. M.; Bellotti, P.; Daniliuc, C. G.; Glorius, F. Radical Carbonyl Propargylation by Dual Catalysis. *Angew. Chem., Int. Ed.* **2021**, *60*, 2464–2471.
- (432) Schwarz, J. L.; Kleinmans, R.; Paulisch, T. O.; Glorius, F. 1,2-Amino Alcohols via Cr/Photoredox Dual-Catalyzed Addition of  $\alpha$ -Amino Carbanion Equivalents to Carbonyls. *J. Am. Chem. Soc.* **2020**, *142*, 2168–2174.
- (433) Schäfers, F.; Quach, L.; Schwarz, J. L.; Saladrigas, M.; Daniliuc, C. G.; Glorius, F. Direct Access to Monoprotected Homoallylic 1,2-Diols via Dual Chromium/Photoredox Catalysis. *ACS Catal.* **2020**, *10*, 11841–11847.
- (434) Yahata, K.; Sakurai, S.; Hori, S.; Yoshioka, S.; Kaneko, Y.; Hasegawa, K.; Akai, S. Coupling Reaction between Aldehydes and Non-Activated Hydrocarbons via the Reductive Radical-Polar Cross-over Pathway. *Org. Lett.* **2020**, *22*, 1199–1203.



- (435) *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005.
- (436) Shen, X.; Harms, K.; Marsch, M.; Meggers, E. A Rhodium Catalyst Superior to Iridium Congeners for Enantioselective Radical Amination Activated by Visible Light. *Chem. - Eur. J.* **2016**, *22*, 9102–9105.
- (437) Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L. A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. Asymmetric Photoredox Transition-Metal Catalysis Activated by Visible Light. *Nature* **2014**, *515*, 100–103.
- (438) Huang, X.; Quinn, T. R.; Harms, K.; Webster, R. D.; Zhang, L.; Wiest, O.; Meggers, E. Direct Visible-Light-Excited Asymmetric Lewis Acid Catalysis of Intermolecular [2+2] Photocycloadditions. *J. Am. Chem. Soc.* **2017**, *139*, 9120–9123.
- (439) Huang, X.; Li, X.; Xie, X.; Harms, K.; Riedel, R.; Meggers, E. Catalytic Asymmetric Synthesis of a Nitrogen Heterocycle through Stereocontrolled Direct Photoreaction from Electronically Excited State. *Nat. Commun.* **2017**, *8*, 2245.
- (440) Ma, J.; Rosales, A. R.; Huang, X.; Harms, K.; Riedel, R.; Wiest, O.; Meggers, E. Visible-Light-Activated Asymmetric  $\beta$ -C-H Functionalization of Acceptor-Substituted Ketones with 1,2-Dicarbonyl Compounds. *J. Am. Chem. Soc.* **2017**, *139*, 17245–17248.
- (441) Steinlandt, P. S.; Zuo, W.; Harms, K.; Meggers, E. Bis-Cyclometalated Indazole Chiral-at-Rhodium Catalyst for Asymmetric Photoredox Cyanoalkylations. *Chem. - Eur. J.* **2019**, *25*, 15333–15340.
- (442) Huang, X.; Meggers, E. Asymmetric Photocatalysis with Bis-Cyclometalated Rhodium Complexes. *Acc. Chem. Res.* **2019**, *52*, 833–847.
- (443) Thongpaen, J.; Manguin, R.; Dorcet, V.; Vives, T.; Duhayon, C.; Mauduit, M.; Baslé, O. Visible Light Induced Rhodium(I)-Catalyzed C–H Borylation. *Angew. Chem., Int. Ed.* **2019**, *58*, 15244–15248.
- (444) Pac, C.; Ihama, M.; Yasuda, M.; Miyauchi, Y.; Sakurai, H. Ru(bpy)<sub>3</sub><sup>2+</sup>-Mediated Photoreduction of Olefins with 1-Benzyl-1,4-Dihydronicotinamide: A Mechanistic Probe for Electron-Transfer Reactions of NAD(P)H-Model Compounds. *J. Am. Chem. Soc.* **1981**, *103*, 6495–6497.
- (445) Cano-Yelo, H.; Deronzier, A. Photo-Oxidation of Some Carbinols by the Ru(II) Polypyridyl Complex-Aryl Diazonium Salt System. *Tetrahedron Lett.* **1984**, *25*, 5517–5520.
- (446) Nicewicz, D. A.; MacMillan, D. W. C. Merging Photoredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes. *Science* **2008**, *322*, 77–80.
- (447) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. Efficient Visible Light Photocatalysis of [2+2] Enone Cycloadditions. *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887.
- (448) 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.* **2009**, *131*, 8756–8757.
- (449) Gandeepan, P.; Koeller, J.; Korvorapun, K.; Mohr, J.; Ackermann, L. Visible-Light-Enabled Ruthenium-Catalyzed Meta-C–H Alkylation at Room Temperature. *Angew. Chem., Int. Ed.* **2019**, *58*, 9820–9825.
- (450) Sagadevan, A.; Greaney, M. F. Meta-Selective C–H Activation of Arenes at Room Temperature Using Visible Light: Dual-Function Ruthenium Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 9826–9830.
- (451) Castro, L. C. M.; Bézier, D.; Sortais, J. B.; Darcel, C. Iron Dihydride Complex as the Pre-Catalyst for Efficient Hydrosilylation of Aldehydes and Ketones under Visible Light Activation. *Adv. Synth. Catal.* **2011**, *353*, 1279–1284.
- (452) Rao, H.; Schmidt, L. C.; Bonin, J.; Robert, M. Visible-Light-Driven Methane Formation from CO<sub>2</sub> with a Molecular Iron Catalyst. *Nature* **2017**, *548*, 74–77.
- (453) Rao, H.; Lim, C. H.; Bonin, J.; Miyake, G. M.; Robert, M. Visible-Light-Driven Conversion of CO<sub>2</sub> to CH<sub>4</sub> with an Organic Sensitizer and an Iron Porphyrin Catalyst. *J. Am. Chem. Soc.* **2018**, *140*, 17830–17834.
- (454) Wei, X. J.; Abdiaj, I.; Sambiagio, C.; Li, C.; Zysman-Colman, E.; Alcázar, J.; Noël, T. Visible-Light-Promoted Iron-Catalyzed C(sp<sup>2</sup>)–C(sp<sup>3</sup>) Kumada Cross-Coupling in Flow. *Angew. Chem., Int. Ed.* **2019**, *58*, 13030–13034.
- (455) Ye, J. H.; Miao, M.; Huang, H.; Yan, S. S.; Yin, Z. B.; Zhou, W. J.; Yu, D. G. Visible-Light-Driven Iron-Promoted Thiocarboxylation of Styrenes and Acrylates with CO<sub>2</sub>. *Angew. Chem., Int. Ed.* **2017**, *56*, 15416–15420.
- (456) Xu, R.; Cai, C. Three-Component Difluoroalkylation-Thiolation of Alkenes by Iron-Facilitated Visible-Light Photoredox Catalysis. *Chem. Commun.* **2019**, *55*, 4383–4386.
- (457) Ouyang, X. H.; Li, Y.; Song, R. J.; Hu, M.; Luo, S.; Li, J. H. Intermolecular Dialkylation of Alkenes with Two Distinct C(sp<sup>3</sup>)H Bonds Enabled by Synergistic Photoredox Catalysis and Iron Catalysis. *Sci. Adv.* **2019**, *5*, eaav9839.
- (458) Suslick, K. S.; Schubert, P. F. Sonochemistry of Dimanganese Decacarbonyl (Mn<sub>2</sub>(CO)<sub>10</sub>) and Dirhenium Decacarbonyl (Re<sub>2</sub>(CO)<sub>10</sub>). *J. Am. Chem. Soc.* **1983**, *105*, 6042–6044.
- (459) Nuhant, P.; Oderinde, M. S.; Genovino, J.; Juneau, A.; Gagné, Y.; Allais, C.; Chinigo, G. M.; Choi, C.; Sach, N. W.; Bernier, L.; Fobian, Y. M.; Bundesmann, M. W.; Khunte, B.; Frenette, M.; Fadeyi, O. O. Visible-Light-Initiated Manganese Catalysis for C–H Alkylation of Heteroarenes: Applications and Mechanistic Studies. *Angew. Chem., Int. Ed.* **2017**, *56*, 15309–15313.
- (460) Wang, L.; Lear, J. M.; Rafferty, S. M.; Fosu, S. C.; Nagib, D. A. Ketyl Radical Reactivity via Atom Transfer Catalysis. *Science* **2018**, *362*, 225–229.
- (461) Weng, W. Z.; Liang, H.; Liu, R. Z.; Ji, Y. X.; Zhang, B. Visible-Light-Promoted Manganese-Catalyzed Atom Transfer Radical Cyclization of Unactivated Alkyl Iodides. *Org. Lett.* **2019**, *21*, 5586–5590.
- (462) Liu, R. Z.; Li, J.; Sun, J.; Liu, X. G.; Qu, S.; Li, P.; Zhang, B. Generation and Reactivity of Amidyl Radicals: Manganese-Mediated Atom-Transfer Reaction. *Angew. Chem., Int. Ed.* **2020**, *59*, 4428–4433.
- (463) Wang, X.; Dong, J.; Li, Y.; Liu, Y.; Wang, Q. Visible-Light-Mediated Manganese-Catalyzed Allylation Reactions of Unactivated Alkyl Iodides. *J. Org. Chem.* **2020**, *85*, 7459–7467.
- (464) Liang, H.; Ji, Y. X.; Wang, R. H.; Zhang, Z. H.; Zhang, B. Visible-Light-Initiated Manganese-Catalyzed E-Selective Hydrosilylation and Hydrogermylation of Alkynes. *Org. Lett.* **2019**, *21*, 2750–2754.
- (465) Long, W.; Lian, P.; Li, J.; Wan, X. Mn-Catalyzed Photoredox Hydroxytrifluoromethylation of Aliphatic Alkenes Using CF<sub>3</sub>SO<sub>2</sub>Na. *Org. Biomol. Chem.* **2020**, *18*, 6483–6486.
- (466) Dodd, D.; Johnson, M. D.; Lockman, B. L. Kinetics and Mechanism of Apparent Alkyl Transfer from Alkylcobaloximes to Cobaloxime(I), Cobaloxime(II), and Cobaloxime(III) Reagents. *J. Am. Chem. Soc.* **1977**, *99*, 3664–3673.
- (467) Johnson, M. D. Bimolecular Homolytic Displacement of Transition-Metal Complexes from Carbon. *Acc. Chem. Res.* **1983**, *16*, 343–349.
- (468) Bour, J. R.; Ferguson, D. M.; McClain, E. J.; Kampf, J. W.; Sanford, M. S. Connecting Organometallic Ni(III) and Ni(IV): Reactions of Carbon-Centered Radicals with High-Valent Organonickel Complexes. *J. Am. Chem. Soc.* **2019**, *141*, 8914–8920.
- (469) Pitzer, L.; Schwarz, J. L.; Glorius, F. Reductive Radical-Polar Crossover: Traditional Electrophiles in Modern Radical Reactions. *Chem. Sci.* **2019**, *10*, 8285–8291.
- (470) Zhu, Q.; Gentry, E. C.; Knowles, R. R. Catalytic Carbocation Generation Enabled by the Mesolytic Cleavage of Alkoxyamine Radical Cations. *Angew. Chem., Int. Ed.* **2016**, *55*, 9969–9973.
- (471) Scholz, S. O.; Farney, E. P.; Kim, S.; Bates, D. M.; Yoon, T. P. Spin-Selective Generation of Triplet Nitrenes: Olefin Aziridination through Visible-Light Photosensitization of Azidoformates. *Angew. Chem., Int. Ed.* **2016**, *55*, 2239–2242.
- (472) Geri, J. B.; Oakley, J. V.; Reyes-Robles, T.; Wang, T.; McCarver, S. J.; White, C. H.; Rodriguez-Rivera, F. P.; Parker, D. L.; Hett, E. C.; Fadeyi, O. O.; Oslund, R. C.; MacMillan, D. W. C.

Microenvironment Mapping via Dexter Energy Transfer on Immune Cells. *Science* **2020**, *367*, 1091–1097.

(473) Mayans, J. G.; Suppo, J.-S.; Echavarren, A. M. Photoredox-Assisted Gold-Catalyzed Arylative Alkoxy cyclization of 1,6-Enynes. *Org. Lett.* **2020**, *22*, 3045–3049.