The merger of transition metal and photocatalysis

Jack Twilton, Chi (Chip) Le, Patricia Zhang, Megan H. Shaw, Ryan W. Evans and David W. C. MacMillan

Abstract | The merger of transition metal catalysis and photocatalysis, termed metallaphotocatalysis, has recently emerged as a versatile platform for the development of new, highly enabling synthetic methodologies. Photoredox catalysis provides access to reactive radical species under mild conditions from abundant, native functional groups, and, when combined with transition metal catalysis, this feature allows direct coupling of non-traditional nucleophile partners. In addition, photocatalysis can aid fundamental organometallic steps through modulation of the oxidation state of transition metal complexes or through energy-transfer-mediated excitation of intermediate catalytic species. Metallaphotocatalysis provides access to distinct activation modes, which are complementary to those traditionally used in the field of transition metal catalysis, thereby enabling reaction development through entirely new mechanistic paradigms. This Review discusses key advances in the field of metallaphotocatalysis over the past decade and demonstrates how the unique mechanistic features permit challenging, or previously elusive, transformations to be accomplished.

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, USA.

Correspondence to D.W.C.M. dmacmill@princeton.edu

doi:10.1038/s41570-017-0052

Transition metal catalysis has long been recognized for its scientific and societal impact, as exemplified by the Nobel Prizes awarded in 2001 (to Knowles, Noyori and Sharpless for stereoselective catalysis)[1], 2005 (to Chauvin, Grubbs and Schrock for olefin metathesis)[2] and 2010 (to Heck, Negishi and Suzuki for palladium-catalysed cross-coupling)[3]. Although they span more than 40 years of research, these processes all share a common characteristic in that they can enable the rapid construction of valuable organic molecules from relatively simple materials. Perhaps more important, transition metal chemistry has continually delivered new modes of chemical activation that enable bond-forming or bond-breaking pathways that are often unprecedented within organic chemistry. This remarkable capacity for 'new reactivity' has made transition metal catalysis an invaluable platform for organic synthesis and, more generally, for the production of organic molecules for the benefit of society.

From a historical perspective, the use of transition metal complexes as catalysts for organic reactions has been a research practice for more than two centuries. During this span, research into transition metal catalysts, and moreover the field of metal catalysis, has grown and evolved in remarkable ways. However, three fundamental aspects of catalyst structure have remained consistent as a focus: ligand design, manipulation of available oxidation states and electronic excitation have all continued to be fruitful areas of research in catalysis (FIG. 1a).

Ligand design

It has long been appreciated that coordinating ligands can significantly alter the reactivity of metal complexes[4]. Indeed, this concept has continually motivated chemists to understand the relationship between the structure and activity of ligands for any given transformation. Moreover, for any given transition metal-catalysed organic reaction that has become widely adopted, there exists a foundation of extensive ligand design and development studies that underpin the final general catalyst system. As one prominent example, the Buchwald–Hartwig amination, in which the palladium-catalysed synthesis of anilines is achieved through the coupling of amines and aryl halides, has become a mainstay transformation in pharmaceutical synthesis[5]. Indeed, given the common presence of amine functionalities in biologically active molecules, this reaction has been widely adopted across the entire field of organic chemistry. Although palladium is an essential catalytic component of this powerful coupling pathway, numerous rounds of ligand evolution were essential to arrive at the successful catalyst complexes that are commonly used today for aryl aminations.

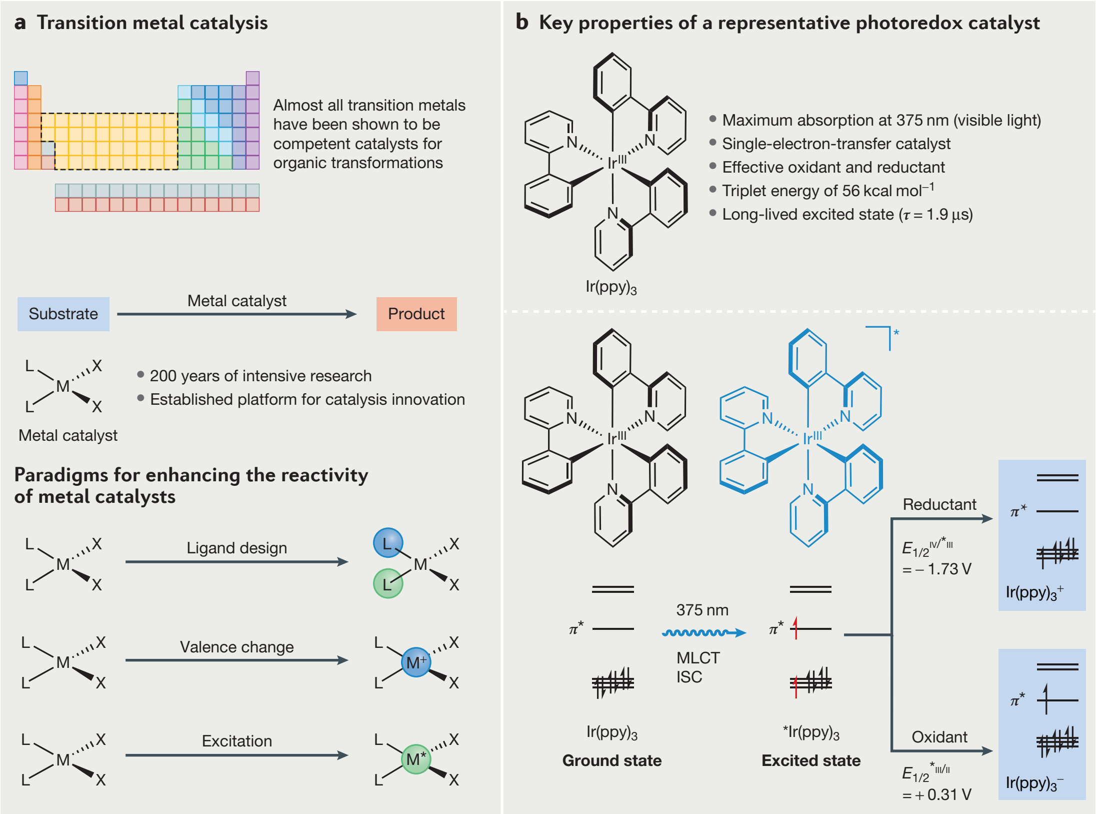


Figure 1 | **Key features of transition metal and photoredox catalysis that provide access to elusive reactivity.** **a** | The reactivity of transition metal catalysts can be enhanced and modified using three key design principles: ligand design, oxidation state modulation and catalyst excitation. **b** | The photophysical properties of photoredox catalysts allow visible light-mediated access to excited species that behave as both an oxidant and a reductant, thereby providing opportunities for the development of new chemical transformations. ISC, intersystem crossing; MLCT, metal-to-ligand charge transfer; ppy, 2-phenylpyridine.

Change of oxidation state

The importance of the metal oxidation state in transition metal catalysis is well established. Indeed, it has long been noted that the acceleration of several elementary steps in coupling protocols can be observed on modulation of the oxidation state of the metal catalyst. For example, in a stoichiometric setting, Hillhouse and others have demonstrated that oxidation of a metal centre can vastly increase the rate of reductive elimination, thereby allowing the rapid formation of C–N and C–O bonds[6–9]. More recently, these concepts have been exploited in catalytic variants: for example, the Chan–Evans–Lam reaction, in which oxidation of a copper intermediate enables a rapid reductive elimination step to forge aryl–heteroatom bonds[10–12]. Reductive elimination from Cu(II) is itself sluggish, but reductive elimination from a Cu(III) intermediate, which can be accessed using readily available and benign oxidants (such as atmospheric oxygen), is facile. Indeed, Sanford and co-workers have shown that this strategy of oxidation and subsequent reductive elimination from Cu(III) can also be used to construct C(sp^2)–F bonds using nucleophilic fluoride as the fluorine source[13], thereby providing a solution to the long-standing challenge of C–F bond formation. As a second example, Yu and co-workers have demonstrated that oxidation of cyclometallated Pd(II) intermediates to form Pd(IV) species can greatly accelerate C–C and C–X bond-forming reductive elimination steps[14–16], which have often been found to be problematic at Pd(II) centres. Overall, these results are mechanistically consistent, given that reductive elimination steps formally represent an oxidation of the pendant substituent by the metal centre. As such, a metal centre that is in a higher oxidation state would have a greater thermodynamic driving force to participate in reductive elimination. Not surprisingly, these findings have inspired a renaissance in high-valent metal catalysis, which in turn has led to the development of valuable new bond-forming reactions[17,18].

Excitation

The photophysical and photochemical properties of metal complexes have been extensively studied for more than 50 years[19]. In fact, the properties of transition metal species in their excited states have been exploited in many important applications: energy storage[20,21], organic light-emitting diodes[22] and dye-sensitized solar cells[23], to name only a few. Interestingly, with the exception of photoredox catalysis (see below)[24], the invocation of the excited state of a transition metal in organic transformations remains limited[25–28]. As a recent exception, Fu and Peters have demonstrated that photoexcitation can be exploited to achieve room-temperature Ullmann coupling of amines and aryl halides[29], a protocol that overcomes the harsh operating conditions of traditional non-light-mediated variants[30]. Mechanistic studies indicate that on exposure to irradiation, the active copper catalyst can more readily participate in a formal oxidative addition step, rendering the transformation thermodynamically feasible under ambient conditions. These findings have triggered a resurgence of interest in identifying new bond-forming processes that proceed via the intermediacy of an excited state of a transition metal catalyst[31,32].

The development of transition metal-catalysed reactions continues to change the way that chemists approach the construction of organic molecules. In this context, photoredox catalysis has proved to be highly effective in enabling catalytic access to high-energy oxidation levels and electronically excited states of transition metal complexes. The ability of dual photoredox–transition metal catalysis, termed metallaphotoredox catalysis, to enable new mechanistic paradigms has only recently been recognized. Many of these newly developed methodologies have been rapidly adopted by the broader organic community.

Photoredox catalysis tutorial

Over the past century, photochemistry has aided the development of a wide range of previously inaccessible transformations in the field of organic chemistry. Broadly, photocatalysis encompasses several mechanistic pathways (for example, energy transfer and single-electron transfer (SET)) by which photonic energy is converted into usable chemical energy[33–38]. In recent years, a generic mode of photocatalysis, termed photoredox catalysis, has been rapidly developed and adopted by the organic chemistry community[24,39–44]. In this mechanistic paradigm, a light-absorbing catalyst can, on excitation, either remove an electron from or donate an electron to an organic or organometallic substrate. This SET event both facilitates access to highly reactive radical species under exceptionally mild conditions and can effectively 'switch on' other catalysts that are non-functional in the absence of a photocatalyst and visible light.

Interestingly, the most commonly used photocatalysts within the field of organic synthesis were originally developed more than half a century ago for synthetic inorganic applications such as water splitting[22], carbon dioxide reductions[45] and new solar cell materials[23]. Despite a few early, yet seminal, reports on the use of photoredox catalysis to forge organic bonds[46–50], it is only relatively recently that this mode of catalysis has seen widespread adoption. Near-simultaneous reports from our laboratory[51], the Yoon[52] group and the Stephenson[53] group helped to initiate interest in the field of organic photoredox catalysis. Over the past ten years, the application of photoredox catalysis to synthetic organic chemistry has been reported by many research groups, and a search of the Web of Science database for the keyword "photoredox catalysis" (and derivatives) leads us to a conservative estimate of more than 700 publications on this topic so far.

Key to the rapid development of this catalytic platform has been the recognition that readily available metal–polypyridyl complexes and organic dyes have unique electronic properties when promoted to an excited state. More specifically, irradiation with low-energy visible light (at wavelengths at which common organic molecules do not absorb) allows targeted excitation of these catalytic chromophores. For commonly used metal–polypyridyl complexes, absorption corresponds to a metal-to-ligand charge transfer event in which an electron is promoted from a non-bonding metal-centred orbital to the π system of the ligand framework (FIG. 1b). Subsequent intersystem crossing leads to the formation of a long-lived triplet excited state. In this configuration, the catalyst possesses both a high-energy electron in a ligand-centred π^* orbital and a vacancy in an orbital that is predominantly located on the metal centre. As a result, these excited-state catalysts are simultaneously reducing and oxidizing, an unusual electronic property that provides a powerful tool for the development of new reactivity. Indeed, the excited state can readily donate a high-energy electron from the ligand π^* orbital (function as a reductant) or accept an electron into the low-energy metal-centred hole (function as an oxidant). Moreover, the resultant reduced or oxidized catalyst retains a strong thermodynamic driving force to return to the original oxidation state. As such, a second electron-transfer event can occur, thereby enabling access to transformations that are redox-neutral in nature. Importantly, the well-defined relationship between the structural characteristics and redox properties of the photocatalyst allows for the rational design of these catalysts by modification of the ligand framework and the metal used[54].

Photoredox catalysis provides access to a distinct reaction environment, with both oxidation and reduction of organic and organometallic species simultaneously possible. This duality stands in direct contrast to traditional redox reaction manifolds, in which the reaction conditions can be singly neutral, oxidative or reductive. As such, this key feature has enabled the development of a wide range of previously inaccessible redox-neutral transformations that would be energetically unfeasible under non-irradiative conditions. One interesting feature of the photoredox reaction manifold is the ability to continuously regenerate the excited-state catalyst. As a result, unproductive electron-transfer events or quenching pathways may not lead to diminished yields as the photocatalyst can simply be re-excited to the triplet state, albeit at the expense of the quantum yield (ratio of photons absorbed per reaction turnover) of the transformation. Recently, several groups have noted that a small number of photoredox transformations proceed with quantum yields in excess of unity; this indicates that each photon that is absorbed enables more than one molecule of product to be formed, which is consistent with a radical chain mechanism[55].

One area of research that has been particularly fruitful within the field of photoredox catalysis is its merger with alternative modes of catalysis. These dual catalytic platforms have attracted attention from many research laboratories[56,57]. Early publications in the area of organic photoredox catalysis demonstrated the potentially diverse nature of this dual activation strategy through the combination of photoexcited complexes with both organocatalysts and Lewis acids[51,52]. More recently, the application of photoredox to the field of transition metal catalysis has received broad attention from the synthetic community and has enabled the development of many useful new C–C and C–heteroatom bond-forming protocols[58,59]. The purpose of this Review is to highlight the key advances that have occurred in this new dual 'metallaphotocatalysis' area over the past decade.

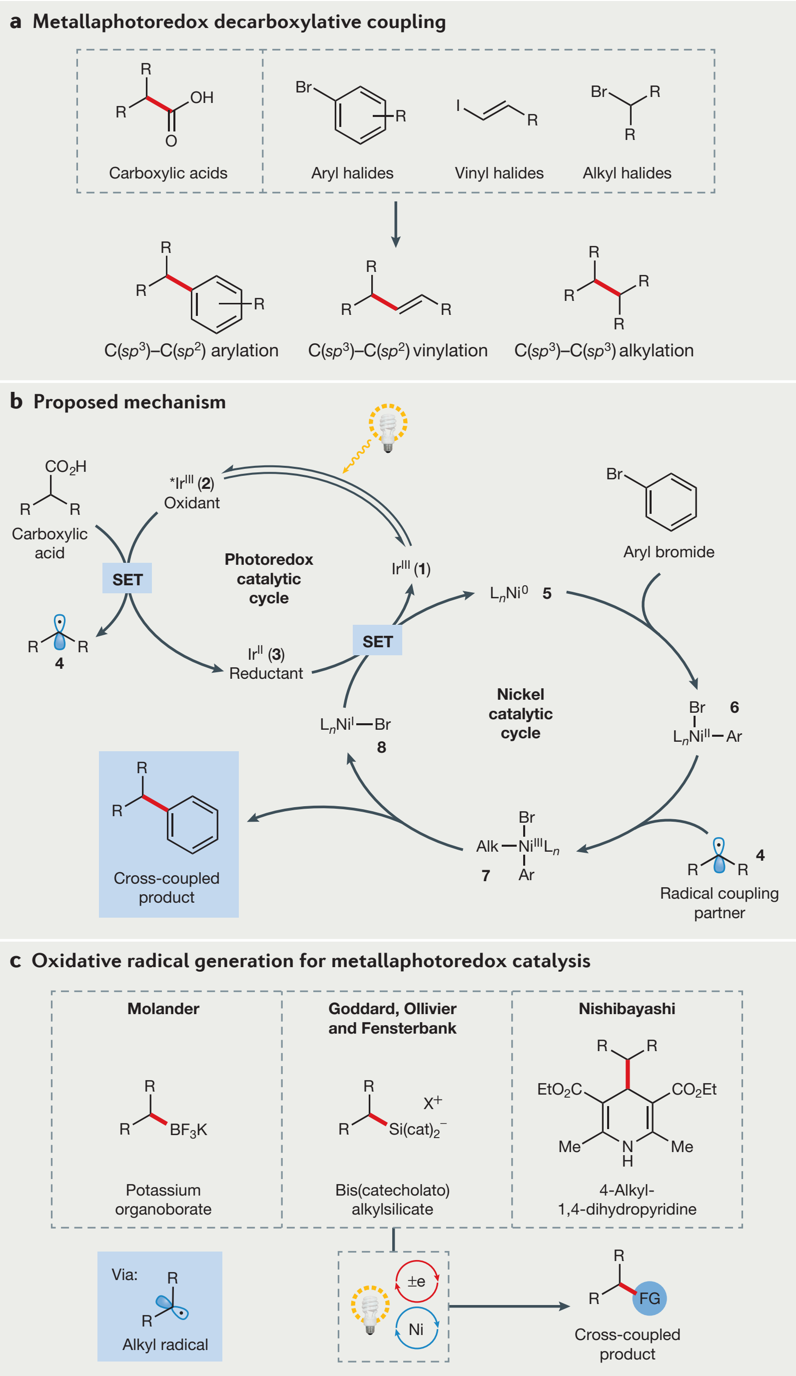


Figure 2 | **Dual photoredox nickel-catalysed C–C bond formation through oxidative radical generation. a** | Photoredox-mediated decarboxylation of carboxylic acids provides access to alkyl radicals that can engage in nickel-catalysed cross-couplings with a range of electrophilic partners. **b** | Proposed mechanism for decarboxylative arylation of aliphatic carboxylic acids. **c** | Alkyl radical coupling partners can be oxidatively generated from alkyl trifluoroborate salts, alkyl silicates and 4-alkyl-1,4-dihydropyridines. Left to right, coupling partners described in REFS 77, 84, 89, respectively. cat, catecholato; SET, single-electron transfer.

Nickel metallaphotocatalysis

Nickel metallaphotocatalysis for carbon–carbon bond formation. Over the past 50 years, the ability to rapidly assemble molecular complexity has been greatly accelerated by the development of transition metal-mediated cross-coupling methodologies. The landmark discoveries of Stille, Negishi, Heck and Suzuki have enabled modular construction of complex molecules from readily accessible fragments[60]. Since the inception of these powerful transformations, considerable effort has been dedicated towards expanding the repertoire of coupling partners. Despite advances, the coupling of C(sp^3) fragments remains challenging. Nickel catalysis has provided several elegant solutions to this challenge, in part owing to the ability of nickel complexes to undergo facile oxidative addition with alkyl electrophiles[61]. Moreover, the reduced capacity of nickel alkyl species to undergo β-hydride elimination (compared with their palladium analogues) prevents detrimental side reactions and enhances the efficiency of C(sp^3) coupling protocols[62].

Expanding the toolbox of coupling partners for transition metal-catalysed protocols to encompass abundant native functional groups (for example, C–H bonds) has garnered considerable attention in recent years. Here, photoredox-mediated radical generation has proved to be an effective strategy for activating non-traditional cross-coupling nucleophiles. Recently, we reported that simple carboxylic acids can undergo visible light-mediated oxidative decarboxylation to yield the corresponding carbon-centred radicals[63–65]. Given the well-established ability of nickel to engage in SET and radical-capture mechanisms[61], we hypothesized that interfacing this decarboxylation platform with nickel catalysis would provide entry to a general C(sp^3) cross-coupling manifold (FIG. 2a). In collaboration with the Doyle laboratory, we demonstrated the successful merger of nickel and photoredox catalysis in the decarboxylative coupling of carboxylic acids and aryl halides[66]. One potential mechanism for this dual catalytic protocol is shown in FIG. 2b. Upon excitation of photocatalyst **1** by visible light, the highly oxidizing species **2** can facilitate oxidative decarboxylation of a carboxylic acid to yield the corresponding carbon-centred radical **4**. Concurrently, Ni(0) complex **5** can undergo oxidative addition with an aryl halide to give a Ni(II)-aryl complex (**6**), which can subsequently trap the acid-derived radical **4**, resulting in formation of Ni(III) complex **7**. Rapid reductive elimination forges the desired C(sp^3)–C(sp^2) bond in the cross-coupled product. Finally, the two catalytic cycles are simultaneously closed via a SET event between Ir(II) species **3** and Ni(I) complex **8**.

This general catalytic platform enables readily available carboxylic acids to be used in place of conventional organometallic reagents. Benzylic, α-amino and α-oxy as well as simple alkyl carboxylic acids have all been demonstrated as competent substrates. Moreover, the outlined decarboxylative arylation can be rendered asymmetric through the use of a chiral nickel catalyst. Together with the Fu group, we disclosed a highly efficient asymmetric protocol which furnishes the desired benzylic amines with good levels of enantioselectivity[67]. Exploration of the electrophilic coupling partner revealed that vinyl halides are also compatible with this dual catalytic platform, and the desired vinylation products are obtained in good yields[68]. In addition to providing new approaches to C(sp^3)–C(sp^2) coupling, the merger of nickel and photoredox catalysis has also begun to address the long-standing challenge of alkyl–alkyl coupling. The distinct compatibility of nickel catalysis and C(sp^3) coupling has been demonstrated through development of a decarboxylative cross-coupling protocol between alkyl halides and carboxylic acids[69]. Here, the combination of nickel and photoredox catalysis provides a complementary approach to current alkyl–alkyl coupling technologies, which are often accomplished through the use of organometallic nucleophiles[70].

Photoredox-mediated oxidation of carboxylate groups has recently been explored as a general strategy for activation of native functional groups via CO_2-extrusion[63]. In the context of metallaphotoredox catalysis, this mode of activation has been successfully applied to a range of coupling protocols, including the synthesis of aryl and aliphatic ketones. In a mechanistically analogous manner to carboxylic acids (FIG. 2b), keto acids can be used as the nucleophile coupling partner to yield diverse ketone products through generation and trapping of the corresponding acyl radical species[71]. An alternative CO_2-extrusion–recombination strategy enables the conversion of mixed anhydrides to ketones[72]. Here, dual nickel photoredox catalysis allows the Tsuji–Saegusa decarboxylative coupling platform to be expanded beyond the classical scope of allylic and benzylic esters[73,74]. Notably, the requisite anhydrides can be readily generated *in situ* from carboxylic acids and acyl chlorides, eliminating the need for isolation of these moisture-sensitive compounds. Photoredox-mediated decarboxylation has also been applied to the challenging goal of C–O bond activation and functionalization. Alcohols, a ubiquitous native functional group, can be activated towards C–O bond cleavage through double decarboxylation of the corresponding, readily accessible oxalate salts[75]. Accordingly, combination of this activation mode with the metallaphotoredox platform provides a general strategy for C–C cross-coupling of alcohols via oxalate generation. Indeed, our laboratory recently reported that a wide variety of primary and secondary alcohols can be used as radical precursors for C(sp^3)–C(sp^2) cross-coupling with (hetero)aromatic bromides[76].

Concurrent with our initial report that outlined the metallaphotoredox decarboxylative arylation[66], Molander and co-workers disclosed a dual nickel photoredox protocol that used benzyl potassium trifluoroborate salts as radical precursors[77] (FIG. 2c). Although Suzuki–Miyaura cross-coupling with potassium trifluoroborate salts represents a pre-eminent technology for C(sp^2)–C(sp^2) coupling, the slow rate of transmetallation of alkyl trifluoroborate salts has hindered development of a generally applicable C(sp^3)–C(sp^2) bond-forming protocol. It was hypothesized[77] that generation of carbon-centred radicals through SET-mediated activation of the corresponding alkyl trifluoroborate salts would circumvent the long-standing challenge of slow two-electron transmetallation. Indeed, the combination of a nickel catalyst and an iridium-based photocatalyst enabled efficient cross-coupling of benzylic trifluoroborates and aryl halides. Following this report, it was demonstrated that this coupling paradigm is also amenable to α-amino[78], α-oxy[79] and secondary alkyl coupling partners[80]. In addition, the synthesis of ketones has been achieved by using acyl chlorides as the electrophilic coupling partner[81].

It is worth noting that the dual nickel photoredox manifold is not limited to the use of iridium-based and ruthenium-based photocatalysts; organic donor–acceptor fluorophores have emerged as competent alternatives[82]. In particular, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (REF. 83) was demonstrated as a highly efficient photocatalyst for both the decarboxylative arylation methodology and the trifluoroborate coupling manifold described above[82].

A common feature of the outlined nickel metallaphotoredox methodologies is generation of the nucleophilic radical coupling partner by single electron oxidation. Alternative oxidative radical generation strategies can be readily incorporated into this cross-coupling manifold. Goddard, Ollivier and Fensterbank reported that potassium alkylbis(catecholato)silicates undergo oxidation in the presence of an iridium photocatalyst and visible light to yield alkyl radicals and can be used as coupling partners for nickel-catalysed C(sp^3)–C(sp^2) bond-forming reactions[84] (FIG. 2c). In separate reports, the Molander group demonstrated that the metallaphotoredox cross-coupling of ammonium alkylbis(catecholato) silicates with aryl or vinyl halides shows broad functional group tolerance and high efficiency[85,86]. Perhaps the most notable feature of this system is the ability to generate carbon-centred radicals under neutral or slightly acidic conditions. The extremely mild reaction conditions allow coupling of silicates that have unprotected amine functionality — a notoriously problematic motif for transition metal-catalysed cross-couplings. Interestingly, Nishibayashi and co-workers recently demonstrated that, under the influence of visible light photoredox catalysis, 4-alkyl-1,4-dihydropyridines provide access to carbon-centred radicals[87]. Before this report, 1,4-dihydropyridines had been widely used as hydride donors but had found limited use with respect to the generation of carbon fragments[88]. In a similar manner to the previously discussed C–C bond-forming technologies, Nishibayashi[89] and Molander[90] have demonstrated that this oxidative radical generation strategy is compatible with the dual photoredox nickel cross-coupling platform. Mechanistic studies[89] suggested that radical capture occurs before oxidative addition, as no product formation was observed when a preformed Ni(II)–aryl complex was subjected to the optimized reaction conditions.

The mechanism of many of these dual nickel photoredox-catalysed C–C bond-forming protocols has not yet been unambiguously established, and the Ni(0)–Ni(II)–Ni(III)–Ni(I) cycle shown in FIG. 2b represents one potential pathway. An alternate Ni(0)–Ni(I)–Ni(III)–Ni(I) cycle has been proposed[77]. Density functional theory calculations provide support for this alternative mechanism, although it should be noted that these calculations relate specifically to the cross-coupling of stabilized benzylic radical coupling partners[91]. It is likely that the exact sequence of steps (radical capture then oxidative addition, or the alternative) depends on the identities of both the electrophilic and nucleophilic coupling partners.

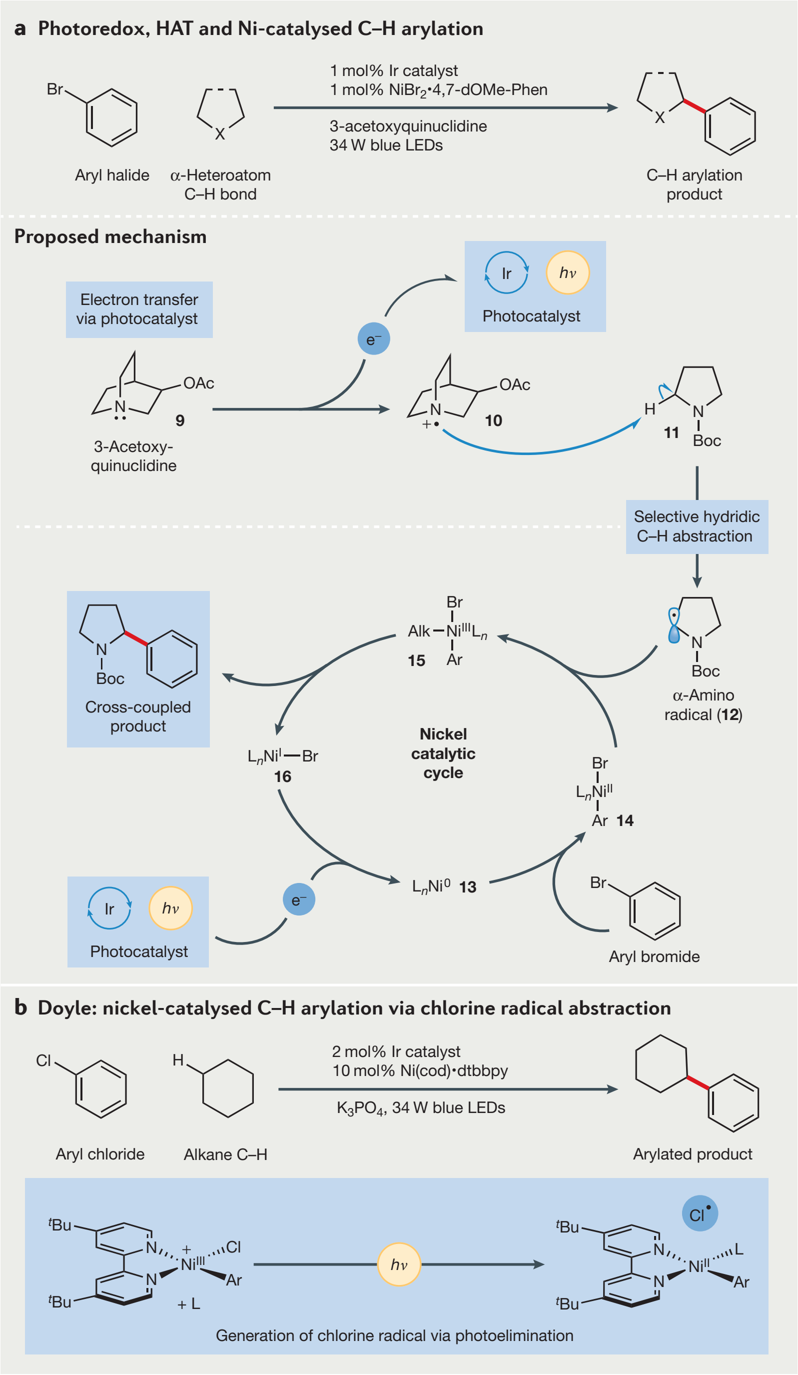


Figure 3 | **C–H arylation by dual nickel photoredox catalysis. a** | Proposed catalytic cycle for the photoredox nickel-catalysed functionalization of α-heteroatom C–H bonds; this reaction proceeds by means of a hydrogen atom transfer (HAT) event, mediated by an amine radical cation[94]. **b** | Nickel-catalysed C–H functionalization by means of chlorine radical hydrogen abstraction is proposed to proceed through photoelimination of a halogen radical from a Ni(III)-halide complex upon exposure to visible light[96]. cod, cyclooctadiene; 4,7-dOMe-phen, 4,7-dimethoxy-1,10-phenanthroline; dtbbpy, 4,4′-di(*tert*-butyl)-2,2′-bipyridine.

The direct cross-coupling of unactivated C–H bonds poses an extremely desirable, but challenging, goal for synthetic chemists. Recent studies have established photoredox catalysis as a powerful tool for the generation of radicals from native functional groups (such as carboxylic acids and alcohols), and this platform has been expanded to encompass neutral and hydridic C–H bonds through hydrogen atom transfer (HAT) catalysis. In our initial metallaphotoredox publication with the Doyle group, direct C(*sp*^{3})–H arylation of dimethylaniline was described via an oxidation–deprotonation sequence for radical generation[66]. This concept has been expanded by Doyle and co-workers and applied to a wide range of *N*-aryl amines[92]. In an effort to dissociate the capacity for C–H functionalization from the oxidation potential of the substrate, we recently targeted the development of a general, selective C–H coupling manifold through the use of a HAT catalyst. Here, it was found that highly electrophilic tertiary amine radical cations selectively abstract hydridic C–H bonds to yield carbon-centred radicals[93]. Incorporation of the outlined HAT activation mode with metallaphotoredox resulted in the development of a triple catalytic reaction platform that enables the selective arylation of electron-rich C–H bonds[94]. The proposed mechanism for this arylation protocol is depicted in FIG. 3a. Initially, 3-acetoxyquinuclidine (**9**) undergoes oxidation by the excited photocatalyst to yield amine radical cation **10**. Under the polarity match–mismatch paradigm[95], hydrogen abstraction with electrophilic radical **10** is selective for the most hydridic site on *N*-Boc-pyrrolidine (**11**), affording α-amino radical **12**. Concurrently, Ni–aryl complex **14** is generated and can rapidly trap the α-amino radical, resulting in formation of Ni(III) species **15**. Facile reductive elimination then furnishes the desired benzylic amine product. Finally, turnover of both the nickel and photoredox catalytic cycles is completed by a SET event. A wide variety of aryl halides and α-amino C–H nucleophiles were tolerated in this HAT metallaphotoredox platform. Additionally, α-oxy and benzylic C–H arylation was feasible using this coupling protocol.

In addition to amine radical cations, halogen radicals have been demonstrated as competent HAT reagents for nickel photoredox-mediated α-oxy C–H arylation[96] (FIG. 3b). More specifically, Doyle and co-workers reported that aryl chlorides can function as both the electrophile coupling partner and an *in situ* source of halogen radical in this metallaphotocatalysis manifold[96]. Generation of a chlorine radical is proposed to occur by a sequential 'two-photon capture' mechanism that involves photocatalyst-mediated oxidation of a Ni(II)–aryl-chloride complex to deliver a Ni(III) species. This is followed by visible light excitation of the high-valent Ni(III) complex, thereby promoting extrusion of a chlorine atom. Arylation of the C–H nucleophile occurs via HAT with the halogen radical and subsequent rebound of the C(sp^3)-radical species to the Ni(II)–aryl complex. Mechanistic studies[96] revealed that the extrusion of a chlorine radical from the Ni(II)–aryl-chloride complex requires both an oxidant and visible light. These observations support the proposed mechanism and are consistent with studies by Nocera and co-workers regarding the extrusion of chlorine radicals from Ni(III) trichloride complexes[97–99]. The outlined protocol is applicable to a wide range of aryl chlorides and, although the C–H nucleophile coupling partners were typically used as the reaction medium, preliminary studies indicate that good efficiencies can also be achieved with only 10 equivalents of substrate. Notably, simple unfunctionalized alkanes, such as cyclohexane, were shown to be competent coupling partners, delivering the arylated products in moderate yield. Concurrent with this report[96], the Molander group[100] established that catalytic generation of bromine radicals (from the aryl bromide coupling partner) allows development of a similar α-oxy and benzylic arylation protocol, although a mechanistically distinct pathway was proposed for this transformation. Preliminary mechanistic studies are consistent with the hypothesis that extrusion of a bromine radical occurs from an electronically excited Ni(II)–aryl-bromide complex that is generated through energy transfer with the iridium photocatalyst.

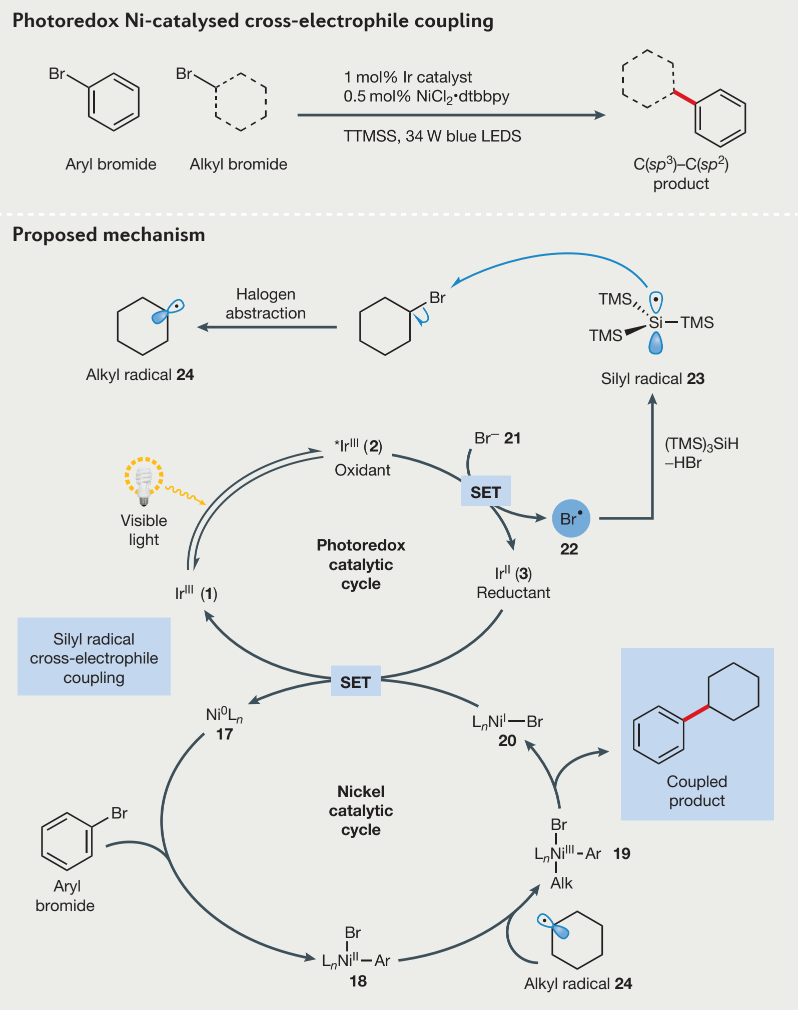


Figure 4 | **Cross-electrophile coupling mediated by a silyl radical.** Dual photoredox nickel-catalysed C(sp^3)–C(sp^2) cross-electrophile coupling between aryl bromides and alkyl bromides is proposed to occur by silyl radical-mediated halogen abstraction from the alkyl bromide coupling partner to generate the corresponding alkyl radical. SET, single-electron transfer; TMS, trimethylsilyl; TTMSS, tris(trimethylsilyl)silane.

Recently, our group sought to implement the dual nickel photoredox catalysis platform in the development of a cross-electrophile coupling between aryl halides and alkyl halides[101]. Here, a key design element for promoting efficient hetero-coupling was differential activation of the bromide coupling partners. Selective activation of the aryl and alkyl bromide components was accomplished through the synergistic behaviour of a nickel catalyst and a photoredox-generated silyl radical species. As shown in the proposed mechanism in FIG. 4, Ni(0) undergoes preferential oxidative addition with the aryl halide to yield Ni(II)–aryl-bromide complex **18**. Luminescence quenching studies showed that bromide (**21**) can be oxidized by the excited state of the photocatalyst (**2**) to give bromine radical **22**. Subsequent HAT between **22** and tris(trimethylsilyl)silane yields the corresponding silyl radical (**23**), and selective bromine atom abstraction from the alkyl bromide then occurs to deliver carbon-centred radical **24**. The 'activated' aryl and alkyl bromide components (**18** and **24**) then combine to deliver the desired hetero-coupled product upon reductive elimination. The outlined cross-electrophile strategy was found to be applicable to a range of structurally diverse aryl and alkyl bromides, and notably exhibited high efficiencies for both sterically encumbered tertiary alkyl bromides and medicinally relevant heteroaromatic bromides.

Nickel metallaphotocatalysis for carbon–heteroatom bond formation. The ability of metallaphotocatalysis to mediate challenging, or previously elusive, bond constructions has been highlighted by recent publications describing valuable carbon–heteroatom bond-forming technologies. From a mechanistic viewpoint, several reports in this area describe proposed reaction pathways that are centred on an oxidative radical generation manifold, analogous to those discussed in the previous section. Moreover, in a distinct mechanistic paradigm, the excited photocatalyst has also been implicated in direct modulation of the electronic configuration of the metal centre through electron or energy transfer. For example, our laboratory recently targeted the nickel-catalysed coupling of aryl halides and alcohols. Although palladium-catalysed[102,103] and copper-catalysed[104] etherification of aryl halides is well documented in the literature, analogous catalytic nickel-mediated transformations had not been reported. Seminal studies by Hillhouse and others indicated that C–O reductive elimination from Ni(II)–aryl-alkoxide complexes is unfavourable[6,7,105]. However, exposure of such complexes to molecular oxygen resulted in productive ether formation, which suggests the involvement of a hypervalent nickel species[8]. Given the capacity of photoredox catalysts to modulate the oxidation state of organometallic intermediates (for example, the reduction of Ni(I) complexes to Ni(0); see FIG. 2b), and the fact that C–heteroatom reductive elimination from hypervalent nickel complexes has been observed[8,9,106], it was hypothesized that the merger of nickel and photoredox catalysis could facilitate C–O reductive elimination through oxidation of the intermediate Ni(II) complex **27** to a high-valent Ni(III) species (**28**)[107] (FIG. 5a). Indeed, in the presence of a photocatalyst, a nickel–bipyridyl complex and visible light, a wide range of primary and secondary alcohols underwent efficient coupling with aryl halides[107]. Notably, this protocol allowed direct access to phenols by using water as the nucleophile. Electrochemical studies indicated that oxidation of a catalytically relevant bipyridyl–Ni(II)–aryl-alkoxide complex by the photocatalyst is feasible[107,108]. Moreover, exposure of this complex to the photocatalyst and visible light resulted in reductive elimination to produce the desired aryl ether. Together, these observations lend support to the intermediacy of a Ni(III) complex.

Transition metal catalysis promoted by visible light photoredox catalysis, in which SET promotes vital elementary steps (for example, radical generation and reductive elimination), has been established as a powerful, highly predictable strategy over the past 6 years. However, the concept of energy-transfer-mediated organometallic cross-coupling has been little explored for organic bond-forming reactions. Although elegant examples from Fu and Peters[29,32], Nocera[97], and Doyle[96] demonstrate the feasibility of promoting organometallic transformations by direct excitation of transition metal complexes with ultraviolet or visible light, it was anticipated that this approach would have limited generality because of the inherent relationship between the coupling partners used and the absorption cross-section of the corresponding organometallic species. As such, we recently reported that light-harvesting photocatalysts (**30**) can facilitate triplet sensitization of Ni(II)–aryl-carboxylate complexes (**34**) via an energy-transfer mechanism to promote the previously elusive cross-coupling of aryl halides and carboxylic acids[109] (FIG. 5b). Here, the use of a discrete photosensitizer separates the roles of the transition metal complex and the light-harvesting species — a strategy that could provide a general platform for excited-state transition metal catalysis[100,109–111]. Preliminary mechanistic studies revealed that productive C–O bond formation occurs in the absence of a photocatalyst, albeit at significantly reduced reaction rates, demonstrating that direct visible light excitation of the metal species can occur. During mechanistic investigations, several key experiments provided support for the mechanism outlined in FIG. 5b (versus an electron-transfer pathway). Namely, higher reaction efficiencies were observed when photocatalysts with higher triplet energies and lower oxidation potentials were used; C–O bond formation was observed when a preformed Ni(II)–aryl-carboxylate complex was exposed to light (both with and without photocatalyst); and cyclic voltammetry revealed that single-electron oxidation of the Ni(II)–aryl-carboxylate complex by $Ir(ppy)_3$ (where ppy is 2-phenylpyridine) is thermodynamically unfavourable. The outlined energy-transfer-mediated C–O coupling protocol highlights a new, general strategy for developing metallaphotocatalysis technologies and further demonstrates the applicability of photocatalysis to the field of transition metal chemistry. At present, it is difficult to predict a priori whether a given transformation will proceed via an electron-transfer or energy-transfer pathway. Detailed mechanistic analysis can provide insight into the likely mode of catalyst activation and aid in the development of the optimal catalyst system.

In addition to C–O cross-couplings, C–N bond-forming protocols have also been developed through exploitation of a metallaphotocatalysis manifold. Recently, our laboratory collaborated with the Buchwald group and Merck Research Laboratories in the development of a mild, visible light-promoted nickel-catalysed aryl amination[112] (FIG. 5c, top). Although nickel-catalysed aminations have been reported, these systems often require elevated temperatures and/or strong bases[113–118]. In the presence of a photocatalyst and visible light, C–N bond formation could be achieved at ambient temperature with a mild organic base, 1,4-diazabicyclo[2.2.2]octane (DABCO). No exogenous ligand was required under the optimized conditions, and simple Ni(II)-halide salts promoted efficient coupling of a wide range of primary and secondary amines. With ligand design having a key role in the success of many traditional organometallic transformations, including palladium-catalysed aryl aminations[119], the realization of this ligand-free metallaphotocatalysis system highlights a complementary approach for enhancing the reactivity of transition metal catalysts. The generality of this protocol was further examined by use of a chemistry informer plate, a concept developed by Merck laboratories[120]. Here, catalysis conditions are screened against a library of complex, medicinally relevant coupling partners (such as, aryl halides and boronic acids) to allow rapid evaluation of reaction applicability. The outlined photoredox amination protocol successfully coupled piperidine with 78% of the drug-like aryl halides that were included in the informer plate, which represents one of the highest success rates observed by Merck for an amination procedure.

Jamison and co-workers have also explored the dual nickel photocatalysis framework in the context of C–N coupling technologies[121]. More specifically, the synthesis of indolines was targeted through an intermolecular coupling of iodoacetanilines and terminal olefins (FIG. 5c, bottom). It was anticipated that photoredox catalysis would facilitate oxidation of the intermediate Ni(II)–alkyl-amido complex and, in turn, promote reductive elimination to the desired indoline product in preference to generation of Heck-type products that arise from detrimental β-hydride elimination pathways. Indeed, with the addition of $Ru(bpy)_3^{2+}$ (where bpy is 2,2′-bipyridine) and visible light, nickel-catalysed indoline formation proceeded in good-to-excellent yields across a range of substrates[121] (FIG. 5c, bottom). Highly regioselective formation of the 3-substituted indoline products was observed with both styrenyl and aliphatic terminal alkenes. Stoichiometric studies and cyclic voltammetry on relevant nickel complexes indicated that oxidation of Ni(II) to Ni(III) was required for productive C–N coupling.

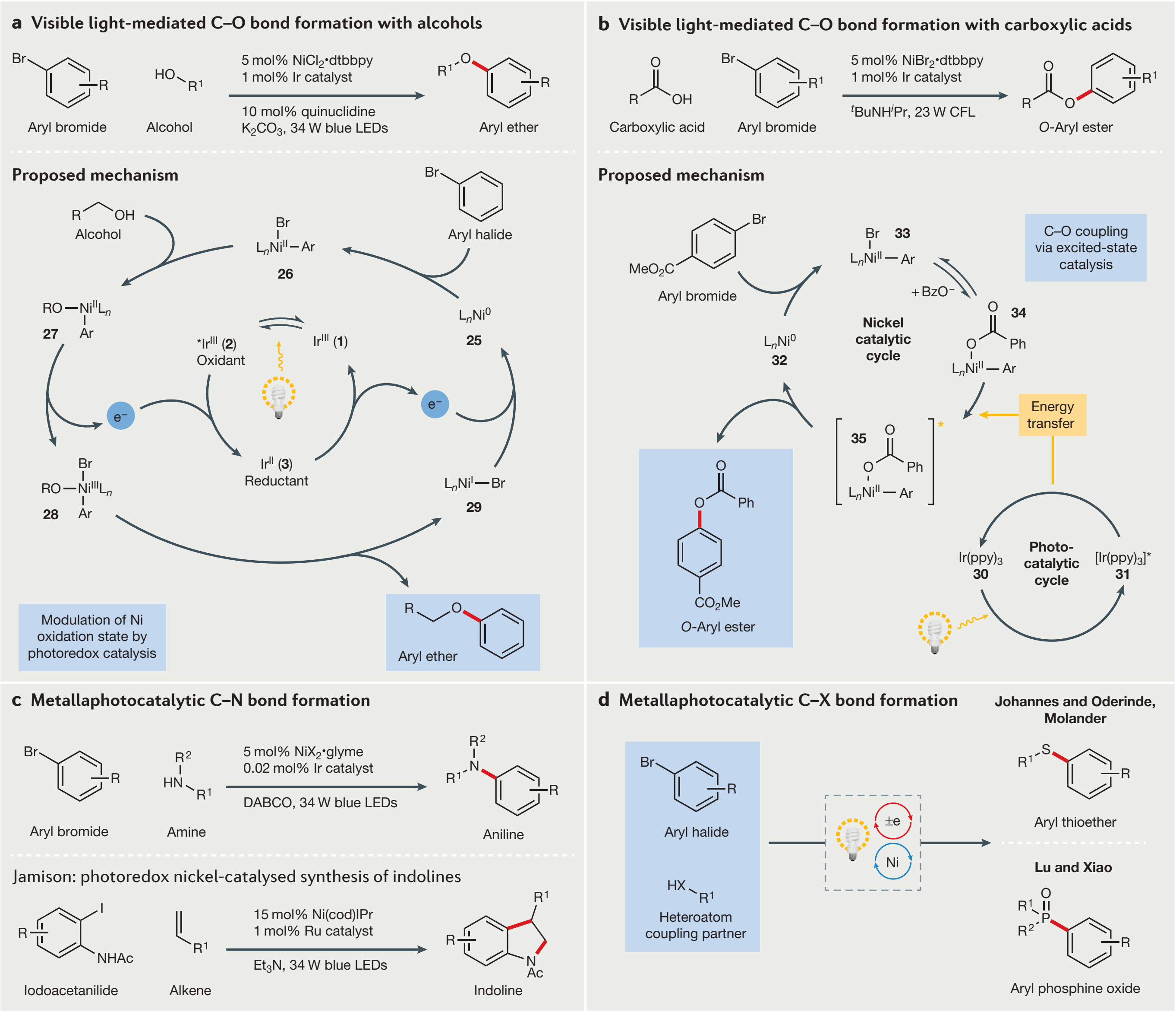


Figure 5 | **Visible light-enabled Ni-catalysed C–X bond-forming reactions. a** | Photoredox nickel-catalysed etherification of aryl halides is proposed to proceed by oxidation of a Ni(II)-alkoxide complex to a high-valent Ni(III) species[107]. **b** | Formation of aryl esters can be accomplished through energy transfer-mediated coupling of aryl halides and carboxylic acids[109]. **c** | The introduction of a photocatalyst and visible light has been demonstrated to facilitate nickel-catalysed C–N cross-couplings, thereby providing access to aniline[112] and indoline[121] products. **d** | Cross-coupling protocols for C–S (REFS 123,124) and C–P (REF. 125) bond formation have been developed using the metallaphotoredox catalysis platform. CFL, compact fluorescent light; cod, cyclooctadiene; DABCO, 1,4-diazabicyclo[2.2.2]octane; dtbbpy, 4,4′-di(*tert*-butyl)-2,2′-bipyridine; glyme, 1,2-dimethoxyethane.

The development of photoredox nickel-catalysed methodologies for C–C bond-formation has primarily relied on a mechanistic blueprint that involves oxidative radical generation, organometallic radical capture and reduction of an intermediate nickel species. This mechanistic paradigm has recently been exploited in the design of C–X cross-coupling protocols. In this scenario, the combination of radical capture and oxidative addition produces a high-valent Ni(III) species which, as outlined in the direct oxidation state modulation strategy (FIG. 5a), assists C–X bond formation. Johannes and Oderinde reported a photoredox nickel-catalysed amination protocol that delivers diarylanilines from aryl halides and primary aniline precursors[122]. A wide variety of anilines with different electronic properties can be used, but the coupling of primary aliphatic amines proceeded with low efficiency under these conditions. The proposed mechanism involves the generation of an aminyl radical by oxidation and deprotonation of the aniline nucleophile, followed by trapping with a Ni(I) halide complex. This metallaphotoredox strategy was also applied to the thioetherification of aryl halides[123] (FIG. 5d). In this report, concerted proton-coupled electron-transfer-mediated thiyl radical generation is postulated. This mechanistic proposal is supported by Stern–Volmer quenching studies and thiyl radical trapping experiments. Molander and co-workers also reported a dual photoredox nickel-catalysed thioetherification protocol, although thiyl radical generation is proposed to occur by an alternative HAT mechanism[124]. Single-electron oxidation of alkyl silicates has been shown to deliver alkyl radicals (FIG. 2c). This strategy was used to deliver carbon-centred radicals that could then undergo HAT with the thiol nucleophile to afford the key thiyl radical coupling partner (FIG. 5d). The outlined silicate–HAT platform enabled the development of mild, base-free reaction conditions and, consequently, excellent functional group compatibility was observed. The outlined thioetherification methodologies enable coupling of a wide variety of primary, secondary and tertiary thiols, and, interestingly, high selectivity towards C–S coupling was observed in the presence of reactive oxy and amino functional groups. In addition, Lu and Xiao reported a metallaphotoredox-catalysed C–P bond-forming protocol that is proposed to proceed through the generation of a phosphorus-centred radical[125].

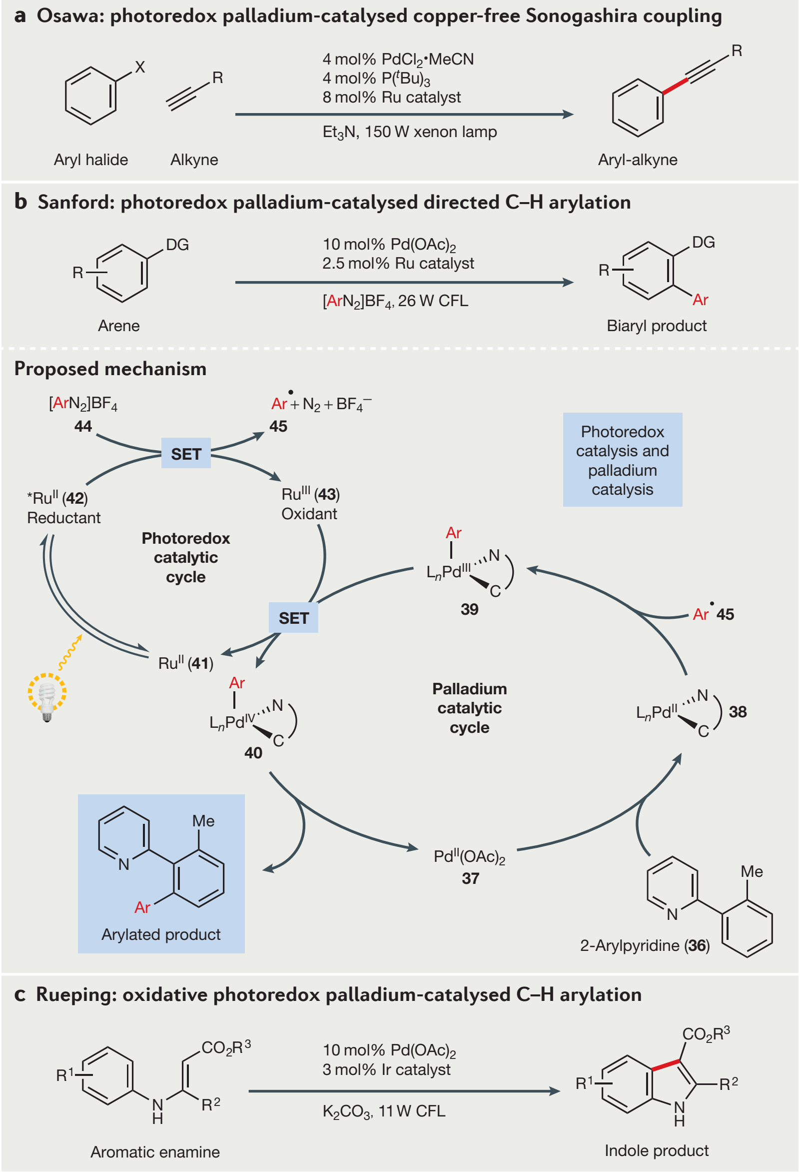


Figure 6 | **Light-enabled C–H functionalization using dual palladium photoredox catalysis. a** | Enhanced efficiencies were observed in palladium-catalysed Sonogashira couplings through addition of a photocatalyst and visible light[110]. **b** | Proposed catalytic cycle for dual photoredox palladium-catalysed C–H arylation of phenylpyridines involving aryl radical generation from aryl diazonium precursors[127]. **c** | Photoredox palladium-catalysed oxidative intramolecular C–H functionalization provides access to indoles with molecular oxygen used as the terminal oxidant[134]. CFL, compact fluorescent light; DG, directing group; SET, single-electron transfer.

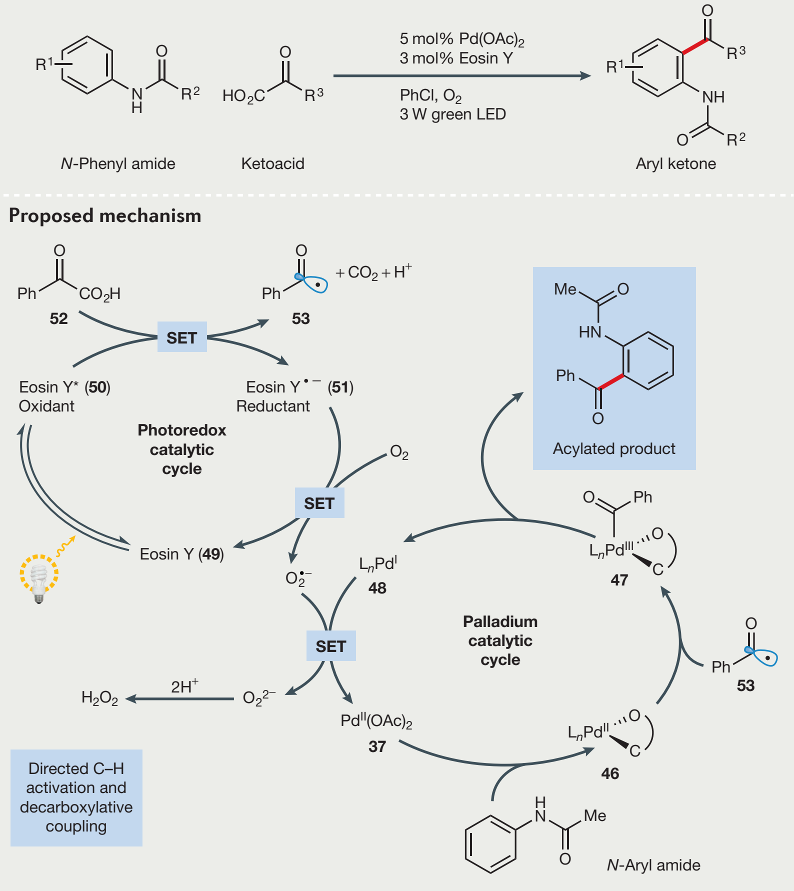
Palladium metallaphotocatalysis

The potential impact of combining light-harvesting catalysts with transition metal catalysis was first recognized by Osawa in 2007. In this seminal report, the inclusion of $Ru(bpy)_3^{2+}$ and irradiation with visible light was noted to significantly accelerate palladium-catalysed Sonogashira reactions[110] (FIG. 6a). Moreover, addition of the photocatalyst obviated the need for a copper co-catalyst, an additive traditionally used to aid activation of the alkyne partner[126]. The authors postulated that photoexcited $Ru(bpy)_3^{2+}$ facilitates oxidative addition, as enhanced efficiencies were observed for challenging aryl chloride substrates, but the precise mechanistic role of the photocatalyst was not determined.

In 2011, Sanford and co-workers further investigated the concept of merging photoredox and transition metal catalysis, and a dual photoredox palladium catalyst system was designed that enabled $C(sp^2)$–H arylation of 2-arylpyridines with aryl diazonium salts[127] (FIG. 6b). Prior to this report, palladium-catalysed C–H arylation protocols typically required the presence of strong oxidants and/or elevated temperatures[128–130]. By merging photoredox and palladium catalysis, the outlined C–H arylation could be conducted at ambient temperature and in the absence of strong external oxidants, thereby providing greater functional group tolerance than would be exhibited using traditional reaction conditions.

Perhaps more importantly, it was proposed[127] that the photocatalyst was implicated in both reductive radical generation and modulation of the oxidation state of the palladium catalyst. These key mechanistic proposals provided a blueprint for the design of alternative metallaphotoredox platforms and instigated significant growth in the field. Specifically, Sanford hypothesized that concerted metallation–deprotonation of 2-phenylpyridine (**36**) by $Pd(OAc)_2$ (**37**) delivers palladacycle **38** (FIG. 6b). Simultaneously, the excited ruthenium photocatalyst **42** can reduce aryl diazonium salt **44** to afford aryl radical **45** and dinitrogen upon fragmentation. The aryl radical can then intercept palladacycle **38** to afford the Pd(III) intermediate **39**. Subsequent oxidation of **39** by the Ru(III) complex **43** generates a high-valent Pd(IV) species (**40**) that undergoes rapid reductive elimination to yield the arylated product. An alternative mechanism that involves reductive elimination from Pd(III) and subsequent oxidation of the Pd(I) species by the oxidized photocatalyst has been proposed and is supported by computational studies[131]. Other palladium-catalysed C–H functionalization protocols have been proposed to proceed via a similar Pd(III)–Pd(I) mechanism[132]. Interestingly, when electron-deficient aryl diazonium salts were coupled with 1-phenylpyrrolidin-2-one, high yields of the C–H arylated products were obtained in the absence of a photocatalyst. Here, it was postulated that the palladacyclic intermediate (analogous to **38**) could engage in photoinduced electron transfer (PET) with the aryl diazonium coupling partner. Indeed, the Che lab recently reported that cyclometallated palladium(II) complexes can function as efficient photocatalysts on exposure to visible light[133]. Rueping and co-workers[134] have exploited the capacity of palladium catalysts (i) to activate strong alkenyl and aromatic C–H bonds, and (ii) to undergo photocatalyst-mediated oxidation state modulation, to develop a dual catalytic synthesis of indoles from aromatic enamines (FIG. 6c). The terminal oxidant in this direct C–H olefination methodology is molecular oxygen, further demonstrating that photoredox catalysis can aid the development of mild protocols for transition metal-catalysed reactions, which typically demand strong stoichiometric oxidants.

a **Wang: oxidative photoredox palladium-catalysed C–H acylation**



b **Tunge: photoredox palladium-catalysed decarboxylative allylation**

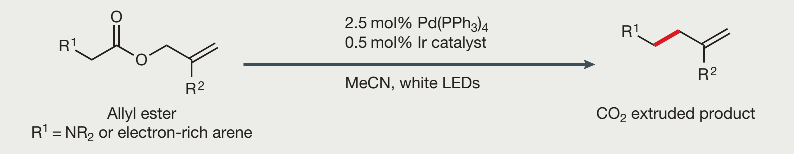


Figure 7 | **Visible light-enabled decarboxylative coupling using metallaphotoredox catalysis. a** | Photoredox-mediated acyl radical generation can be merged with palladium-catalysed directed C–H functionalization to accomplish C(sp^2)–C(sp^2) cross-coupling[136,137]. **b** | Photoredox palladium-catalysed intramolecular decarboxylative allylation is proposed to proceed through radical decarboxylation from an intermediate palladium–carboxylate complex[139,140]. LED, light emitting diode; SET, single-electron transfer.

Intermolecular and intramolecular transition metal-mediated decarboxylative technologies allow simple carboxylates to be used as coupling partners for valuable C–C bond-forming reactions. Since the early work of Tsuji and Saegusa[73,74] on decarboxylative cross-coupling, palladium catalysts have been widely used for these transformations and, although many elegant strategies have been developed by Gooßen and others[135], metal-mediated decarboxylation of aliphatic carboxylates remains challenging. Recently, our laboratory developed a general catalysis platform for cross-coupling of aliphatic carboxylic acids through the merger of photoredox and nickel catalysis (FIG. 2a). Subsequently, the Wang group demonstrated that the aforementioned photoredox-mediated decarboxylation strategy could be interfaced with palladium catalysis to accomplish direct C–H acylation of *N*-phenyl amides[136,137]. As depicted in FIG. 7a, the proposed mechanism involves initial amide-directed C–H activation to deliver palladacycle **46**. Oxidative decarboxylation of keto acid **52** by the excited organic photocatalyst **50** provides acyl radical **53**. Palladacycle **46** intercepts radical **53** to form a Pd(III) intermediate (**47**), which then undergoes C–C bond-forming reductive elimination to provide the acylated adduct and a Pd(I) species (**48**). Finally, molecular oxygen facilitates closure of both catalytic cycles through sequential single-electron oxidation of the reduced photocatalyst (**51**) and Pd(I) complex **48** to regenerate photocatalyst **49** and Pd(II) catalyst **37**. The outlined decarboxylative keto acid activation mode and palladium catalysis was used by Fu and Shang to cross-couple nucleophilic acyl radicals with aryl halides — presumably in a mechanistically analogous manner to the previously discussed nickel-mediated protocol[71,138]. In an intramolecular setting, Tunge and co-workers established that photoredox catalysis can enable expansion of the classic Tsuji–Trost system to encompass new substrate classes such as α-amino allyl esters[139,140] (FIG. 7b). Here, radical decarboxylation overcomes the inherent difficulties that are associated with anionic metal-mediated decarboxylation of aliphatic acids, and the protocol could be extended to allow intermolecular coupling of amino acids and allyl carbonates. Xiao and Lu demonstrated that C–H allylation of *N*-aryl amines could also be achieved by interfacing photoredox-mediated oxidative generation of α-amino radicals with palladium-mediated π-allyl formation[141].

Copper metallaphotocatalysis

Following on from pioneering work in the field of photoredox palladium catalysis, the Sanford laboratory successfully demonstrated that copper catalysis could also be integrated into the metallaphotoredox manifold. The key design elements outlined in the dual photoredox palladium-catalyst system, namely reductive radical generation and oxidative modulation of the transition metal oxidation state, were elegantly applied to the development of a copper-catalysed trifluoromethylation protocol[142]. Selective trifluoromethylation strategies are highly desirable because of the enhanced metabolic stability that is often exhibited by drug-like molecules that are substituted with this functional group[143]. As such, this dual photoredox copper-catalysed methodology provides a mild, efficient catalyst system for cross-coupling boronic acids and perfluoroalkyl iodides[142] (FIG. 8a). In the proposed mechanism, the trifluoromethyl radical is generated through reduction of CF$_3$I by Ru(I) complex **54** (REF. 144), and, subsequently, this radical is trapped by a Cu(II) complex (**55**). The resultant Cu(III) species **56** can undergo transmetallation with the boronic acid (to form **57**) and reductive elimination to furnish the desired trifluoromethylated product. Finally, SET between the copper and photoredox catalysts (**58** and **42**) closes both catalytic cycles. Although the dual photoredox copper- and palladium-catalysed methodologies that have been reported by the Sanford group use similar key mechanistic principles, the discrete transformations that are enabled by these catalyst systems highlight the potential for developing a vast array of highly valuable bond-forming methodologies through creative manipulation of the core concepts of metallaphotocatalysis.

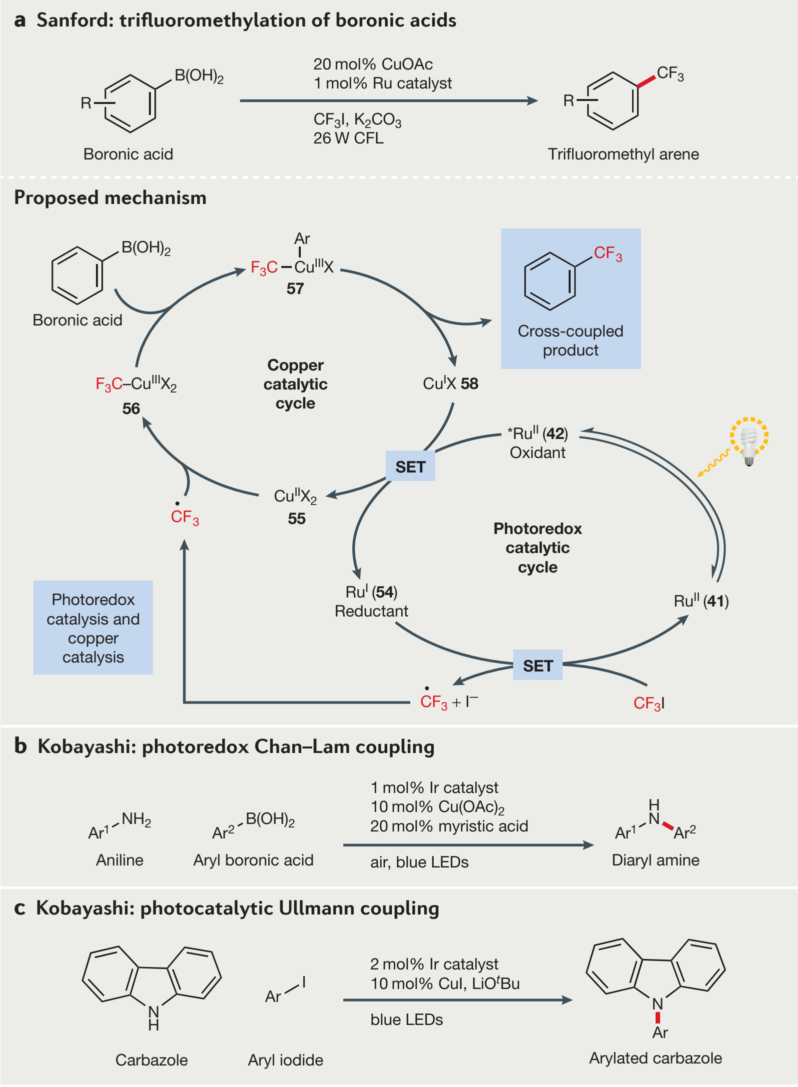


Figure 8 | **Formation of C–C and C–N bonds using dual copper photoredox catalysis. a** | Seminal studies demonstrated the feasibility of combining photoredox and copper catalysis, with the photocatalyst mediating radical generation and modulating the metal oxidation state[142]. **b** | Copper-catalysed Chan–Lam couplings benefit from combination with photoredox catalysis, owing to enhanced catalyst turnover efficiency[145]. **c** | Photocatalytic copper-catalysed Ullmann couplings are proposed to proceed through excitation of the *in situ* generated copper–carbazolide complex[111]. SET, single-electron transfer.

Light-promoted copper catalysis — initiated either by direct ultraviolet excitation or by photocatalyst-mediated visible light sensitization — has recently gained considerable attention in the context of carbon–heteroatom bond formation. Chan–Lam cross-couplings represent a powerful strategy for copper-mediated C–X bond formation, with molecular oxygen typically functioning as the terminal oxidant. In this regard, Kobayashi[145] reported a photoredox Chan–Lam procedure based on reaction conditions previously described by Buchwald[146] for the coupling of aryl boronic acids and anilines (FIG. 8b). The combination of copper and photoredox catalysis both eliminated the requirement for a large headspace and vigorous stirring (a practical constraint that is associated with oxygen-mediated catalyst turnover) and expanded the substrate scope to include electron-deficient aryl boronic acids. As such, it was proposed[145] that the role of the photocatalyst is related to efficient turnover of the copper catalyst, and photoredox-mediated generation of a high valent Cu(III) complex was tentatively postulated. In a subsequent report, Kobayashi and co-workers described a photocatalytic copper-mediated Ullmann coupling for the synthesis of arylated carbazoles[111] (FIG. 8c). This visible light-mediated protocol may proceed in a mechanistically similar manner to the C–N couplings reported previously by Fu and Peters[29]; here, irradiation by high-energy ultraviolet light is proposed to initiate a SET pathway through excitation of an *in situ* generated Cu–carbazolide complex. In the dual catalytic, visible light-activated reaction, triplet sensitization of a copper amide complex by energy transfer from the photoexcited iridium catalyst is postulated[111]. In the absence of mechanistic studies, alternative SET and direct excitation pathways are also outlined as potential reaction mechanisms. The activation of organometallic complexes by energy transfer from a visible light-harvesting catalyst represents a little-explored, but potentially powerful, strategy for developing challenging transition metal-mediated technologies.

Gold metallaphotocatalysis

The application of photocatalysis to the field of transition metal cross-coupling has provided new strategies for accomplishing traditionally challenging elementary mechanistic steps such as reductive elimination (for example, electron-transfer or energy-transfer activation of organometallic intermediates; see FIG. 5), transmetallation (for example, radical generation from alkyl trifluoroborate salts; see FIG. 2c) and oxidative addition (see below). In this regard, metallaphotoredox catalysis can enable metal species that typically engage in polar oxidative additions to partake in single-electron radical capture mechanisms. For example, Sanford reported that cyclometallated Pd(II) complexes can intercept aryl radicals to afford Pd(III)–aryl species[127]. Glorius, Toste and others have employed this radical capture strategy to design mild gold-catalysed arylation protocols — desirable coupling processes that typically require harsh oxidants. Although the carbophilic Lewis acidic nature of Au(I) complexes has enabled the development of a wide array of alkene and alkyne functionalization technologies, a key challenge has been to expand beyond hydrofunctionalization protocols to enable efficient terminal arylation[147–150]. Here, the difficulty of polar oxidative additions between Au(I) species and aryl halides presents a key challenge[151–153], and photoredox catalysis has provided one solution for addressing this issue (FIG. 9a). Under the dual photoredox gold catalysis manifold, reductive generation of aryl radicals from aryl diazonium salts can provide rapid access to Au(II)–aryl species (**61**). Subsequent oxidation of the Au(II) complex either by SET with the oxidized photocatalyst or through a radical chain pathway[154,155] produces a Au(III)–aryl complex that can readily engage a variety of π-unsaturates. Recent stoichiometric studies by Glorius and co-workers support this mechanistic proposal[156]. Importantly, this strategy disfavours protodeauration by installing the aryl group before substrate complexation; assists in substrate activation by generation of a highly activated cationic Au(III) complex; and overcomes the challenge of unfavourable two-electron oxidative addition through mediating an alternative aryl radical trapping pathway.

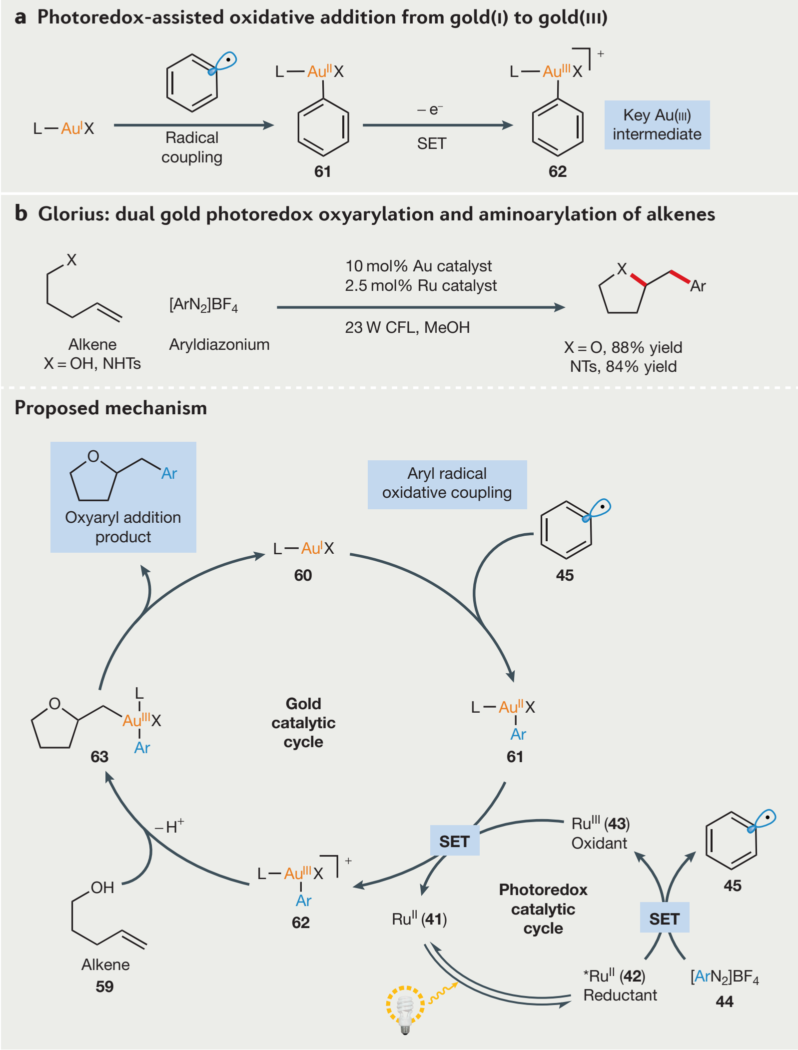


Figure 9 | **Oxyarylation and aminoarylation of alkenes through dual gold photoredox catalysis. a** | The challenge of generating Au(III)-aryl complexes through polar oxidative addition can be overcome by photoredox-mediated aryl radical generation/gold-trapping followed by single-electron oxidation. **b** | The merger of photoredox and gold catalysis assists in oxyarylation of alkenes through generation of a highly activated cationic Au(III)–aryl complex[157]. CFL, compact fluorescent light; SET, single-electron transfer; Ts, tosyl.

The merger of photoredox and gold catalysis was first reported by Glorius and co-workers in 2013 (REF. 157). Here, the outlined aryl radical capture strategy facilitated highly efficient intramolecular oxyarylation and aminoarylation of alkenes (FIG. 9b). Selective 5-exo-trig and 6-exo-trig cyclizations provide access to arylated tetrahydrofuran, tetrahydropyran and pyrrolidine ring systems. Although, in the initial publication, aryl radical capture was tentatively proposed to occur after Au(I)-mediated alkene cyclization, subsequent computational and stoichiometric studies[158,156,154] lend support to the mechanism outlined in FIG. 9b. As previously discussed, photoexcited ruthenium catalyst **42** facilitates reductive generation of aryl radical **45**, and the resultant oxidized Ru(III) species **43** mediates oxidation of *in situ* generated Au(II)–aryl complex **61**. This stepwise oxidative addition generates the key cationic Au(III)–aryl complex **62**, and intermediate **62** mediates rapid cyclization of alkene substrate **59** to yield the oxyaryl addition product upon reductive elimination. Notably, high diastereoselectivities were observed when internal alkenes were used, consistent with trans-selective oxyauration and stereoretentive reductive elimination from the Au(III)–alkyl–aryl complex. In addition, this strategy could be expanded to accomplish intermolecular, three-component couplings of alkenes, methanol and aryldiazonium (or diaryliodonium) salts[159]. Following on from this report, Toste and co-workers demonstrated that dual photoredox gold catalysis can facilitate arylative ring expansions of allylic cyclopropanol and cyclobutanol precursors to afford cyclobutanone and cyclopentanone scaffolds, respectively[160] (FIG. 10). In this report, the intermediacy of the key cationic Au(III) aryl species was postulated, and preliminary mechanistic investigations provided support for this hypothesis.

The dual photoredox gold catalysis platform is not restricted to alkene functionalization protocols. Indeed, Shin and co-workers reported the arylative cyclization of *tert*-butyl allenoates to provide a range of structurally diverse butenolides[161]. Interestingly, high efficiencies could be achieved under both photoredox and thermal conditions, and it was postulated that a radical chain mechanism could be operative. It should be noted that

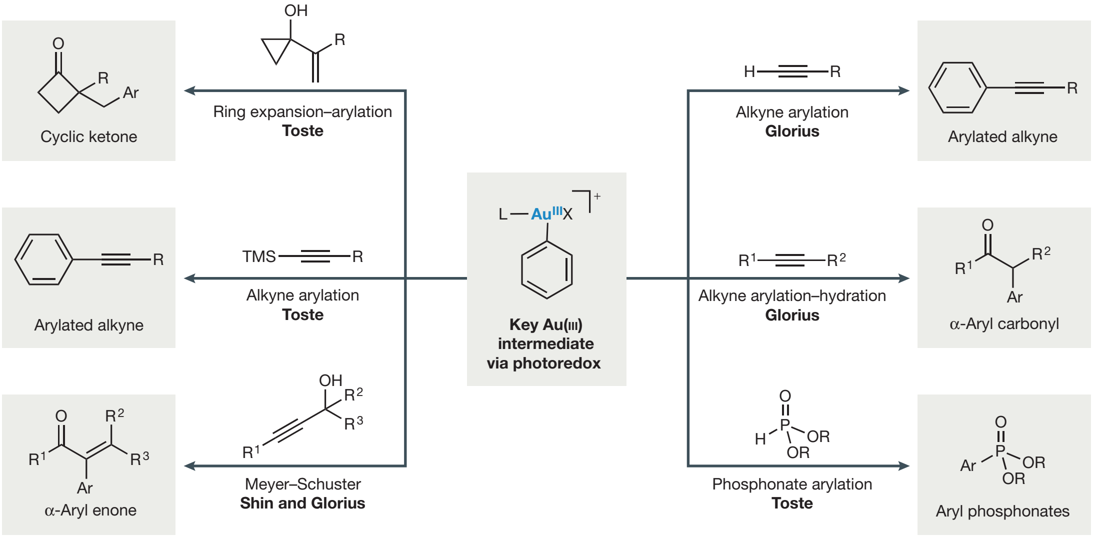


Figure 10 | **Arylative functionalization mediated by dual gold photoredox catalysis.** Photoredox-mediated access to cationic Au(III)–aryl complexes assists in a range of gold-mediated functionalizations of π-unsaturated substrates involving a terminal arylation event[155,160,162–164,166,169]. TMS, trimethylsilyl.

recent chemical actinometry studies from the Glorius group suggest that a radical chain mechanism could also be operative in other dual photoredox gold-catalysed processes[155]. In the context of alkyne functionalization, the groups of Glorius, Shin, and Alcaide have recently reported arylative Meyer–Schuster rearrangements for the efficient generation of α-aryl enones from propargyl alcohols[162–164]. Before these studies, the necessity of strong oxidants for generation of the requisite Au(III)–aryl species limited developments in the area. These metallaphotoredox protocols allow the synthesis of a variety of tri-substituted and tetra-substituted enones, and, in many cases, high *E* selectivity was observed. Expanding on this alkyne functionalization platform, an arylative alkyne hydration methodology has been developed by Glorius and co-workers for the synthesis of α-aryl ketones[164].

In a recent report from Hashmi and co-workers, it was demonstrated that arylative alkyne hydration[164] could be accomplished in the absence of a photosensitizer[165]. By optimizing the light source and ligand system on the gold catalyst, it is possible to effect this transformation by using only the gold catalyst. In this instance, it is likely that a gold complex that is generated *in situ* can function as the photoreductant in an analogous manner to the reactivity observed by Sanford[127] in the C–H arylation of 1-phenylpyrrolidin-2-one with electron-deficient aryl diazonium salts (photoactive cyclometallated palladium complexes facilitate reduction of the diazonium salts). It was proposed that, subsequent to PET, the Au(II) species and the aryl radical that are formed (following loss of dinitrogen) recombine to deliver an Au(III)–aryl complex, which can then engage an alkyne substrate as previously outlined. This mechanistic hypothesis is supported by stoichiometric studies in which, in the presence of a bidentate ligand, a Au(III)–aryl species could be isolated. The formation of this Au complex indicates that photoexcitation of a Au(I) species can induce stepwise SET oxidative addition into aryl diazonium salts, a reaction that does not occur without photoexcitation.

The diverse reactivity of Au(III) complexes can be exploited to establish a general platform for photoredox-promoted coupling of aryl radicals. In this regard, the Glorius and Toste groups concurrently reported alternative strategies for accomplishing C(*sp*)–C(*sp*^{2}) cross-coupling with aryl diazonium salts [155,166]. Toste and co-workers disclosed a catalyst system that promotes arylation of alkynyl trimethylsilanes and this transformation is proposed to proceed by transmetallation from the silane to the Au(III)–aryl species that is generated *in situ*. Terminal alkynes are used as the C(*sp*)-coupling fragment in the protocol reported by the Glorius laboratory, and a mechanistic pathway involving C(*sp*)–H activation by the Au(III)–aryl complex is proposed. Notably, in both cases, the mild, base-free conditions provide access to a wide variety of diaryl-alkynes and aryl, alkyl-alkynes. In addition, functional groups that are sensitive to traditional Sonogashira palladium catalysis conditions, such as aryl halides, are well tolerated. Hermange and Fouquet[167], and Lee[168] have subsequently reported the application of this metallaphotoredox strategy to the C(*sp*^{2})-C(*sp*^{2}) cross-coupling of aryl boronic acids and aryl diazonium salts. In addition to C–C bond-forming technologies, Toste and co-workers recently reported the dual photoredox gold-catalysed P–H arylation of alkyl phosphonates[169].

The methodologies discussed in this section demonstrate the benefits of merging photoredox catalysis with traditional transition metal catalysis platforms. In the context of gold catalysis, this combination enables the development of mild redox-neutral protocols and avoids the use of strong stoichiometric oxidants; reduces unproductive protodeauration and homodimerization pathways by promoting rapid generation of highly active cationic Au(III)–aryl complexes; and provides entry to valuable new gold-catalysed transformations.

Metallaphotocatalysis with other metals

Although current research in the field of metallaphotocatalysis has primarily focused on nickel, palladium, copper and gold catalysis, the merger of ruthenium, rhodium and cobalt catalysis has also been reported. Photoredox catalysis can facilitate rhodium-catalysed and ruthenium-catalysed C–H oxidative Heck technologies by mediating regeneration of the requisite active catalysts. In the former case, Rueping and co-workers showed that traditional super-stoichiometric copper co-catalysts could be replaced with an iridium photocatalyst, molecular oxygen and visible light, to enable directed C–H olefination of aryl amides in good yields[170]. Following these encouraging results, this strategy was subsequently applied to the development of a photoredox ruthenium-catalysed protocol for the ortho-olefination of phenols[171]. These methodologies, in addition to the previously discussed palladium-catalysed oxidative Heck protocol (FIG. 6c), reveal the capability of photoredox catalysts to modulate the oxidation state of a diverse range of metals in the presence of molecular oxygen.

Finally, mild cross-coupling hydrogen evolution reactions were developed through the merger of cobalt and photoredox catalysis. In 2015, a collaborative publication from the Wu and Lei laboratories revealed that dehydrogenative C–S bond formation could be achieved through the dual action of a photocatalyst and a ‘proton-reducing’ cobaloxime catalyst[172]. Here, benzothiazoles were generated in high yields from thiobenzanilides, with hydrogen gas as the sole by-product. Notably, this dual catalytic strategy avoids the use of a stoichiometric terminal oxidant and has provided a general strategy for achieving ‘acceptorless’ dehydrogenative protocols. The Wu group has demonstrated that this dual catalysis strategy is useful for a variety of C–C bond-forming reactions, such as α-amino and α-oxy C–H functionalizations[173–177]. Lei and co-workers have exploited photoredox-mediated alkene radical cation generation[178–180] to accomplish both dehydrogenative cross-coupling of alkenes with alcohols and azoles[181] and anti-Markovnikov oxidation of styrenes[182]. More recently, the Li group have employed dual photoredox cobalt catalysis to achieve acceptorless dehydrogenation of saturated N-heterocycles[183]. Interestingly, extrusion of multiple equivalents of hydrogen could be accomplished and a range of heteroaromatic products could be accessed, including quinolines, quinoxalines, quinazolines, indoles and benzothiazoles.

Conclusion and future directions

Over the past decade, visible light photocatalysis has emerged as a powerful tool for accessing previously challenging reactivity in organic chemistry. Selective excitation of light-harvesting catalysts can promote oxidative or reductive generation of versatile reactive radical species under extremely mild conditions, and often from abundant, bench-stable precursors. The combination of photoredox catalysis with alternative catalytic platforms allows capture of these radical species with a diverse array of organic and organometallic coupling partners, and/or provides opportunities for radical generation that are impossible with typical photoredox catalysts alone. A dual catalytic platform that has recently attracted great interest from the synthetic community is the merger of photoredox and transition metal catalysis. Here, photoredox catalysis can offer exciting opportunities for the development of transition metal catalysis — a well-established, but constantly evolving, field of research. As mentioned above, photoredox catalysis offers access to a broad range of carbon-centred and heteroatom-centred radicals, and these species have been used as nucleophilic coupling partners in metallaphotocatalytic transformations. Importantly, this feature enables direct cross-coupling of abundant, native functional groups (for example, carboxylic acids, C–H bonds and alcohols) in place of typical organometallic coupling partners, which often require multistep synthesis and exhibit lower functional group tolerance. In addition, the development of organometallic processes that proceed via a radical capture mechanism can overcome inherently problematic two-electron oxidative addition (for example, aryl radical addition to Au(I) complexes) and transmetallation (for example, alkyl radical addition versus alkyl transfer from trifluoroborate salts) steps.

The advantages of combining photoredox and transition metal catalysis extend far beyond the singular aspect of radical generation. Photoredox catalysis provides a unique reaction environment, as the light-harvesting catalysts are simultaneously oxidizing and reducing in nature. By contrast, transition metal-catalysed protocols are typically oxidative, reductive or neutral, and, consequently, the addition of a photocatalyst and light allows the development of redox-neutral protocols that would be inaccessible under non-irradiative conditions. Furthermore, photoredox catalysis has been shown to mediate net oxidative processes without the requirement for harsh stoichiometric oxidants, using simply molecular oxygen as the terminal oxidant. Perhaps most importantly, photoredox catalysts can be of use in challenging mechanistic steps by either direct modification of the oxidation state of the transition metal via SET, or generation of excited-state metal complexes through energy transfer. For example, both of these activation modes have been used to assist challenging C–X bond-forming reactions by enhancing the capacity of metal complexes for reductive elimination.

Over the past 6 years, the merger of photoredox and transition metal catalysis has been demonstrated as a highly versatile platform for the development of new methodologies. By combining these individually powerful catalytic manifolds, synthetic chemists can strive to achieve transformations that are not currently possible using a single catalyst system. As such, we anticipate that the field of metallaphotocatalysis will continue to grow at a remarkable pace, providing the organic community with new synthetic tools for streamlined access to valuable chemical building blocks.

1. Ault, A. The Nobel prize in chemistry for 2001. *J. Chem. Educ.* **79**, 572–577 (2002).
2. Casey, C. P. 2005 Nobel prize in chemistry. Development of the *E*-olefin metathesis method in organic synthesis. *J. Chem. Educ.* **83**, 192–195 (2006).
3. 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.* **51**, 5062–5085 (2012).
4. Hegedus, L. S. & Söderberg, B. C. G. *Transition Metals in the Synthesis of Complex Organic Molecules* 3rd edn (Univ. Science Books, 2010).
5. Ruiz-Castillo, P. & Buchwald, S. L. Application of palladium-catalyzed C–N cross-coupling reactions. *Chem. Rev.* **116**, 12564–12649 (2016).
6. Matsunaga, P. T., Hillhouse, G. L. & Rheingold, A. L. Oxygen-atom transfer from nitrous oxide to a nickelmetallacycle. Synthesis, structure, and reactions of [cyclic] (2,2′-bipyridine)Ni($OCH_2CH_2CH_2CH_2$). *J. Am. Chem. Soc.* **115**, 2075–2077 (1993).
7. Matsunaga, P. T., Mavropoulos, J. C. & Hillhouse, G. L. Oxygen-atom transfer from nitrous oxide (N = N = O) to nickel alkyls. Syntheses and reactions of nickel(II) alkoxides. *Polyhedron* **14**, 175–185 (1995).
8. Han, R. & Hillhouse, G. L. Carbon–oxygen reductive-elimination from nickel(II) oxametallacycles and factors that control formation of ether, aldehyde, alcohol, or ester products. *J. Am. Chem. Soc.* **119**, 8135–8136 (1997).
9. Camasso, N. M. & Sanford, M. S. Design, synthesis, and carbon-heteroatom coupling reactions of organometallic nickel(IV) complexes. *Science* **347**, 1218–1220 (2013).
10. Chan, D., Monaco, K., Wang, R. & Winter, M. New N- and O-arylations with phenylboronic acids and cupric acetate. *Tetrahedron Lett.* **39**, 2933–2936 (1998).
11. Evans, D., Katz, J. & West, T. Synthesis of diaryl ethers through the copper-promoted arylation of phenols with arylboronic acids. An expedient synthesis of thyroxine. *Tetrahedron Lett.* **39**, 2937–2942 (1998).
12. Lam, P. *et al.* New aryl/heteroaryl C–N bond cross-coupling reactions via arylboronic acid/cupric acetate arylation. *Tetrahedron Lett.* **39**, 2941–2944 (1998).
13. Ye, Y., Schimler, S. D., Hanley, P. S. & Sanford, M. S. Cu(OTf)$_2$-mediated fluorination of aryltrifluoroborates with potassium fluoride. *J. Am. Chem. Soc.* **135**, 16292–16295 (2013).
14. 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.* **132**, 12203–12205 (2010).
15. Mei, T.-S., Wang, X. & Yu, J.-Q. Pd(II)-catalyzed amination of C–H bonds using single-electron or two-electron oxidants. *J. Am. Chem. Soc.* **131**, 10806–10807 (2009).
16. Engle, K. M., Mei, T.-S., Wang, X. & Yu, J.-Q. Bystanding F$^+$ oxidants enable selective reductive elimination from high-valent metal centers in catalysis. *Angew. Chem. Int. Ed.* **50**, 1478–1491 (2011).
17. Hickman, A. J. & Sanford, M. S. High-valent organometallic copper and palladium in catalysis. *Nature* **484**, 177–185 (2012).
18. Hickman, A. J. & Sanford, M. S. Catalyst control of site selectivity in the Pd$^{II/IV}$-catalyzed direct arylation of naphthalene. *ACS Catal.* **1**, 170–174 (2011).
19. Bitterwolf, T. E. Organometallic photochemistry at the end of its first century. *J. Organometal. Chem.* **689**, 3939–3952 (2004).
20. Grätzel, M. Artificial photosynthesis: water cleavage into hydrogen and oxygen by visible light. *Acc. Chem. Res.* **14**, 376–384 (1981).
21. Meyer, T. J. Chemical approaches to artificial photosynthesis. *Acc. Chem. Res.* **22**, 163–170 (1989).
22. Lowry, M. S. & Bernhard, S. Synthetically tailored excited states: phosphorescent, cyclometalated iridium(III) complexes and their applications. *Chem. Eur. J.* **12**, 7970–7977 (2006).
23. Kalyanasundaram, K. & Grätzel, M. Applications of functionalized transition metal complexes in photonic and optoelectronic devices. *Coord. Chem. Rev.* **177**, 347–414 (1998).
24. Shaw, M. H., Twilton, J. & MacMillan, D. W. C. Photoredox catalysis in organic chemistry. *J. Org. Chem.* **81**, 6898–6926 (2016).
25. Burk, M. J. & Crabtree, R. H. Selective catalytic dehydrogenation of alkanes to alkenes. *J. Am. Chem. Soc.* **109**, 8025–8032 (1987).
26. Maguire, J. A., Boese, W. T. & Goldman, A. S. Photochemical dehydrogenation of alkanes catalyzed by *trans*-carbonylchlorobis(trimethylphosphine) rhodium: aspects of selectivity and mechanism. *J. Am. Chem. Soc.* **111**, 7088–7093 (1989).
27. Sakakura, T., Sodeyama, T., Sasaki, K., Wada, K. & Tanaka, M. Carbonylation of hydrocarbons via carbon-hydrogen activation catalyzed by RhCl(CO)(PMe$_3$)$_2$ under irradiation. *J. Am. Chem. Soc.* **112**, 7221–7229 (1990).
28. Ishiyama, T., Miyaura, N. & Suzuki, A. Palladium-catalyzed carbonylative cross-coupling reaction of iodoalkanes with 9-alkyl-9-BBN derivatives. A direct and selective synthesis of ketones. *Tetrahedron Lett.* **47**, 6923–6926 (1991).
29. 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* **338**, 647–651 (2012).
   A light-mediated Ullmann coupling that proceeds under exceptionally mild conditions, demonstrating the capacity for metallaphotocatalysis to enable challenging transformations.
30. Lindsey, J. Copper assisted nucleophilic substitution of aryl halogen. *Tetrahedron* **40**, 1433–1456 (1984).
31. Sumino, S., Ui, T. & Ryu, I. Synthesis of alkyl aryl ketones by Pd/light induced carbonylative cross-coupling of alkyl iodides and arylboronic acids. *Org. Lett.* **15**, 3142–3145 (2013).
32. Kainz, Q. M. *et al.* Asymmetric copper-catalyzed C–N cross-couplings induced by visible light. *Science* **351**, 681–684 (2016).
33. Kärkäs, M. D., Porco, J. A. Jr & Stephenson, C. R. J. Photochemical approaches to complex chemotypes: applications in natural product synthesis. *Chem. Rev.* **116**, 9638–9747 (2016).
34. Bach, T. & Hehn, J. P. Photochemical reactions as key steps in natural product synthesis. *Angew. Chem. Int. Ed.* **50**, 1000–1045 (2011).
35. Hoffmann, N. Photochemical reactions as key steps in organic synthesis. *Chem. Rev.* **108**, 1052–1103 (2008).
36. Roth, H. D. The beginnings of organic photochemistry. *Angew. Chem. Int. Ed. Engl.* **28**, 1193–1207 (1989).
37. Trommsdorff, H. Über Santonin [German]. *Ann. Chem. Pharm.* **11**, 190–207 (1834).
38. Ciamician, G. & Silber, P. Chemische Lichtwirkungen [German]. *Ber. Dtsch. Chem. Ges.* **41**, 1928–1935 (1908).
39. Narayanam, J. M. R. & Stephenson, C. R. J. Visible light photoredox catalysis: applications in organic synthesis. *Chem. Soc. Rev.* **40**, 102–113 (2011).
40. Xuan, J. & Xiao, W.-J. Visible-light photoredox catalysis. *Angew. Chem. Int. Ed.* **51**, 6828–6838 (2012).
41. Reckenthäler, M. & Griesbeck, A. G. Photoredox catalysis for organic syntheses. *Adv. Synth. Catal.* **355**, 2727–2744 (2013).
42. Prier, C. K., Rankic, D. A. & MacMillan, D. W. C. Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. *Chem. Rev.* **113**, 5322–5363 (2013).
43. Schultz, D. M. & Yoon, T. P. Solar synthesis: prospects in visible light photocatalysis. *Science* **343**, 1239176 (2014).
44. Romero, N. A. & Nicewicz, D. A. Organic photoredox catalysis. *Chem. Rev.* **116**, 10075–10116 (2016).
45. Takeda, H. & Ishitani, O. Development of efficient photocatalytic systems for CO$_2$ reduction using mononuclear and multinuclear metal complexes based on mechanistic studies. *Coord. Chem. Rev.* **254**, 346–354 (2010).
46. van Bergen, T. J., Hedstrand, D. M., Kruizinga, W. H. & Kellogg, R. M. Chemistry of dihydropyridine. 9. Hydride transfer from 1,4-dihydropyridine to *sp*^{3}-hybridized carbon in sulfonium salts and activated halides. Studies with NAD(P)H models. *J. Org. Chem.* **44**, 4953–4962 (1979).
47. Pac, C., Ihama, M., Yasuda, M., Miyauchi, Y. & Sakurai, H. Tris(2,2′-bipyridine)ruthenium^{2+}-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.* **103**, 6495–6497 (1983).
48. Fukuzumi, S., Koumitsu, S., Hironaka, K. & Tanaka, T. Energetic comparison between photoinduced electron-transfer reactions from NADH model compounds to organic and inorganic oxidants and hydride-transfer reactions for NADH model compounds to *p*-benzoquinone derivatives. *J. Am. Chem. Soc.* **109**, 305–316 (1987).
49. Cano-Yelo, H. & Deronzier, A. Photo-oxidation of some carbinols by the Ru(II) polypyridyl complex-aryl diazonium salt system. *Tetrahedron Lett.* **25**, 5517–5520 (1984).
50. Okada, K., Okamoto, K., Morita, N., Okubo, K. & Oda, M. Photosensitized decarboxylative Michael addition through *N*-(acyloxy)phthalimides via an electron-transfer mechanism. *J. Am. Chem. Soc.* **113**, 9401–9402 (1991).
51. Nicewicz, D. A. & MacMillan, D. W. C. Merging photoredox catalysis with organocatalysis: the direct asymmetric alkylation of aldehydes. *Science* **322**, 77–80 (2008).
52. Ischay, M. A., Anzovino, M. E., Du, J. & Yoon, T. P. Efficient visible light photocatalysis of [2 + 2] enone cycloadditions. *J. Am. Chem. Soc.* **130**, 12886–12887 (2008).
53. Narayanam, J. M. R., Tucker, J. W. & Stephenson, C. R. J. Electron-transfer phtotoredox catalysis: development of a tin-free reductive dehalogenation reaction. *J. Am. Chem. Soc.* **131**, 8756–8757 (2009).
54. Arias-Rotondo, D. M. & McCusker, J. M. The photophysics of photoredox catalysis: a roadmap for catalyst design. *Chem. Soc. Rev.* **45**, 5803–5820 (2016).
55. Cismesia, M. A. & Yoon, T. P. Characterizing chain processes in visible light photoredox catalysis. *Chem. Sci.* **6**, 5426–5434 (2015).
56. Skubi, K. L., Blum, T. R. & Yoon, T. P. Dual catalysis strategies in photochemical synthesis. *Chem. Rev.* **116**, 10035–10074 (2016).
57. Hopkinson, M. N., Sahoo, B., Li, J.-L. & Glorius, F. Dual catalysis see the light: combining photoredox with organo-, acid, and transition-metal catalysis. *Chem. Eur. J.* **20**, 3874–3886 (2014).
58. Vila, C. Merging visible-light-photoredox and nickel catalysis. *ChemCatChem* **7**, 1790–1793 (2015).
59. Levin, M. D., Kim, S. & Toste, F. D. Photoredox catalysis unlocks single-electron elementary steps in transition metal catalyzed cross-coupling. *ACS Cent. Sci.* **2**, 293–301 (2016).
60. de Meigere, A. & Diederich, F. (eds) *Metal-Catalyzed Cross-Coupling Reactions* 2nd edn (Wiley, 2004).
61. Tasker, S. Z., Standley, E. A. & Jamison, T. F. Recent advances in homogeneous nickel catalysis. *Nature* **509**, 299–309 (2014).
62. Hu, X. Nickel-catalyzed cross coupling of non-activated alkyl halides: a mechanistic perspective. *Chem. Sci.* **2**, 1867–1886 (2011).
63. Zuo, Z. & MacMillan, D. W. C. Decarboxylative arylation of α-amino acids via photoredox catalysis: a one-step conversion of biomass to drug pharmacophore. *J. Am. Chem. Soc.* **136**, 5257–5260 (2014).
64. Chu, L., Ohta, C., Zuo, Z. & MacMillan, D. W. C. Carboxylic acids as a traceless activation group for conjugate additions: a three-step synthesis of (±)-Lyrica. *J. Am. Chem. Soc.* **136**, 10886–10889 (2014).
65. Noble, A. & MacMillan, D. W. C. Photoredox α-vinylation of α-amino acids and *N*-aryl amines. *J. Am. Chem. Soc.* **136**, 11602–11605 (2014).
66. Zuo, Z., Ahneman, D. T., Chu, L., Terrett, J. A. & MacMillan, D. W. C. Merging photoredox with nickel catalysis: coupling of α-carboxyl *sp*^{3}-carbons with aryl halides. *Science* **345**, 437–440 (2014).
   An early report on nickel metallaphotoredox catalysis, allowing direct cross-coupling of carboxylic acids via a radical decarboxylative activation mode.
67. Zuo, Z. *et al.* Enantioselective decarboxylative arylation of α-amino acids via the merger of photoredox and nickel catalysis. *J. Am. Chem. Soc.* **138**, 1832–1835 (2015).
68. 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.* **137**, 624–627 (2015).
69. 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* **536**, 322–325 (2016).
70. 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.* **111**, 1417–1492 (2011).
71. Chu, L., Lipshultz, J. M. & MacMillan, D. W. C. Merging photoredox and nickel catalysis: the direct synthesis of ketones by the decarboxylative arylation of α-oxo acids. *Angew. Chem. Int. Ed.* **54**, 7929–7933 (2015).
72. Le, C. C. & MacMillan, D. W. C. Fragment couplings via CO$_2$ extrusion–recombination: expansion of a classic bond-forming strategy via metallaphotoredox. *J. Am. Chem. Soc.* **137**, 11938–11941 (2015).

73. Shimizu, I., Yamada, T. & Tsuji, J. Palladium-catalyzed rearrangement of allylic esters of acetoacetic acid to give γ, δ-unsaturated methyl ketones. *Tetrahedron Lett.* **21**, 3199–3202 (1980).
74. 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) β-ketocarboxylate and its utilization in allylic acylation. *J. Am. Chem. Soc.* **102**, 6381–6384 (1980).
75. 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.* **137**, 11270–11273 (2015).
76. 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.* **138**, 13862–13865 (2016).
77. Tellis, J. C., Primer, D. N. & Molander, G. A. Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. *Science* **345**, 433–436 (2014).
A nickel metallaphotoredox catalysis procedure for C(sp^2)–C(sp^3) cross-coupling, providing a solution for the long-standing challenge of alkyl transmetallation from boron by invoking a radical pathway.
78. El Khatib, M., Serafim, R. A. M. & Molander, G. A. α-Arylation/heteroarylation of chiral α-aminomethyltrifluoroborates by synergistic iridium photoredox/nickel cross-coupling catalysis. *Angew. Chem. Int. Ed.* **55**, 254–258 (2016).
79. Karakaya, I., Primer, D. N. & Molander, G. A. Photoredox cross-coupling: Ir/Ni dual catalysis for the synthesis of benzylic ethers. *Org. Lett.* **17**, 3294–3297 (2015).
80. Primer, D. N., Karakaya, I., Tellis, J. C. & Molander, G. A. Single-electron transmetalation: an enabling technology for secondary alkylboron cross-coupling. *J. Am. Chem. Soc.* **137**, 2195–2198 (2015).
81. Amani, J., Sodagar, E. & Molander, G. A. Visible light photoredox cross-coupling of acyl chlorides with potassium alkoxymethyltrifluoroborates: synthesis of α-alkoxyketones. *Org. Lett.* **18**, 732–735 (2016).
82. Luo, J. & Zhang, J. Donor–acceptor fluorophores for visible-light-promoted organic synthesis: photoredox/Ni dual catalytic C(sp^3)–C(sp^2) cross-coupling. *ACS Catal.* **6**, 873–877 (2016).
83. Uoyama, H., Goushi, K., Shizu, K., Nomura, H. & Adachi, C. Highly efficient organic light-emitting diodes from delayed fluorescence. *Nature* **492**, 234–238 (2012).
84. Corcé, V. *et al.* Silicates as latent alkyl radical precursors: visible-light photocatalytic oxidation of hypervalent bis-catecholato silicon compounds. *Angew. Chem. Int. Ed.* **54**, 11414–11418 (2015).
85. Jouffroy, M., Primer, D. N. & Molander, G. A. Base-free photoredox/nickel dual-catalytic cross-coupling of ammonium alkylsilicates. *J. Am. Chem. Soc.* **138**, 475–478 (2016).
86. Patel, N. R., Kelly, C. B., Jouffroy, M. & Molander, G. A. Engaging alkenyl halides with alkylsilicates via photoredox dual catalysis. *Org. Lett.* **18**, 764–767 (2016).
87. 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* **8**, 1028–1032 (2016).
88. Zheng, C. & You, S.-L. Transfer hydrogenation with Hantzch esters and related organic hydride donors. *Chem. Soc. Rev.* **41**, 2498–2518 (2012).
89. 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.* **55**, 14106–14110 (2016).
90. Gutiérrez-Bonet, Á., 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.* **6**, 8004–8008 (2016).
91. 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.* **137**, 4896–4899 (2015).
92. Ahneman, D. T. & Doyle, A. G. C–H functionalization of amines with aryl halides by nickel-photoredox catalysis. *Chem. Sci.* **7**, 7002–7006 (2016).
93. Jeffrey, J. L., Terrett, J. A. & MacMillan, D. W. C. O–H hydrogen bonding promotes H-atom transfer from α-C–H bonds for C-alkylation of alcohols. *Science* **349**, 1532–1536 (2015).
94. Shaw, M. H., Shurtleff, V. W., Terrett, J. A., Cuthbertson, J. D. & MacMillan, D. W. C. Native functionality in triple catalytic cross-coupling: sp^3 C–H bonds as latent nucleophiles. *Science* **352**, 1304–1308 (2016).
95. Roberts, B. P. Polarity-reversal catalysis of hydrogen-atom abstraction reactions: concepts and applications in organic chemistry. *Chem. Soc. Rev.* **28**, 25–35 (1999).
96. Shields, B. J. & Doyle, A. G. Direct C(sp^3)–H cross coupling enabled by catalytic generation of chlorine radicals. *J. Am. Chem. Soc.* **138**, 12719–12722 (2016).
97. Hwang, S. J. *et al.* Halogen photoelimination from monomeric nickel(III) complexes enabled by the secondary coordination sphere. *Organometallics* **34**, 4766–4774 (2015).
98. Hwang, S. J., Powers, D. C., Maher, A. G. & Nocera, D. G. Tandem redox mediator/Ni(II) trihalide complex photocycle for hydrogen evolution from HCl. *Chem. Sci.* **6**, 917–922 (2015).
99. Hwang, S.-J. *et al.* Trap-free halogen photoelimination from mononuclear Ni(III) complexes. *J. Am. Chem. Soc.* **137**, 6472–6475 (2015).
100. Heitz, D. R., Tellis, J. C. & Molander, G. A. Photochemical nickel-catalyzed C–H arylation: synthetic scope and mechanistic investigations. *J. Am. Chem. Soc.* **138**, 12715–12718 (2016).
101. 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.* **138**, 8084–8087 (2016).
102. Torraca, K. E., Huang, X., Parrish, C. A. & Buchwald, S. L. An efficient intermolecular palladium-catalyzed synthesis of aryl ethers. *J. Am. Chem. Soc.* **123**, 10770–10771 (2001).
103. Kataoka, N., Shelby, Q., Stambuli, J. P. & Hartwig, J. F. Air stable, sterically hindered ferrocenyl dialkylphosphines for palladium-catalyzed C–C, C–N, and C–O bond forming cross-couplings. *J. Org. Chem.* **67**, 5553–5566 (2002).
104. Wolter, M., Nordmann, G., Job, G. E. & Buchwald, S. L. Copper-catalyzed coupling of aryl iodides with aliphatic alcohols. *Org. Lett.* **4**, 973–976 (2002).
105. Macgregor, S. A., Neave, G. W. & Smith, C. Theoretical studies on C–heteroatom bond formation via reductive elimination from group 10 $M(PH_3)_2(CH_3)(X)$ species ($X = CH_3$, NH_2, OH, SH) and the determination of metal–X bond strengths using density functional theory. *Faraday Discuss.* **124**, 111–127 (2003).
106. 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.* **137**, 7604–7607 (2015).
107. Terrett, J. A., Cuthbertson, J. D., Shurtleff, V. W. & MacMillan, D. W. C. Switching on elusive organometallic mechanisms with photoredox catalysis. *Nature* **524**, 330–334 (2015).
108. Klein, A. *et al.* Halide ligands — more than just σ-donors? A structural and spectroscopic study of homologous organonickel complexes. *Inorg. Chem.* **47**, 11324–11333 (2008).
109. 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* **355**, 380–385 (2017).
110. Osawa, M., Nagai, H. & Akita, M. Photo-activation of Pd-catalyzed Sonogashira coupling using a Ru/bipyridine complex as energy transfer agent. *Dalton Trans.* **8**, 827–829 (2007).
111. Yoo, W.-J., Tsukamoto, T. & Kobayashi, S. Visible light-mediated Ullmann-type C–N coupling reactions of carbazole derivatives and aryl iodides. *Org. Lett.* **17**, 3640–3642 (2015).
112. Corcoran, E. B. *et al.* Aryl amination using ligand-free Ni(II) salts and photoredox catalysis. *Science* **353**, 279–283 (2016).
113. Wolfe, J. P. & Buchwald, S. L. Nickel-catalyzed amination of aryl chlorides. *J. Am. Chem. Soc.* **119**, 6054–6058 (1997).
114. Gao, C.-Y. & Yang, L.-M. Nickel-catalyzed amination of aryl tosylates. *J. Org. Chem.* **73**, 1624–1627 (2008).
115. Park, N. H., Teverovskiy, G. & Buchwald, S. L. Development of an air-stable nickel precatalyst for the amination of aryl chlorides, sulfamates, mesylates, and triflates. *Org. Lett.* **16**, 220–223 (2014).
116. Ge, S., Green, R. A. & Hartwig, J. F. Controlling first-row catalysts: amination of aryl and heteroaryl chlorides and bromides with primary aliphatic amines catalyzed by a BINAP-ligated single-component Ni(0) complex. *J. Am. Chem. Soc.* **136**, 1617–1627 (2014).
117. Shimasahi, T., Tobisu, M. & Chatani, N. Nickel-catalyzed amination of aryl pivalates by the cleavage of aryl C–O bonds. *Angew. Chem. Int. Ed.* **49**, 2929–2932 (2010).
118. Lavoie, C. M. *et al.* Challenging nickel-catalyzed amine arylations enabled by tailored ancillary ligand design. *Nat. Commun.* **7**, 11073 (2016).
119. Surry, D. S. & Buchwald, S. L. Biaryl phosphane ligands in palladium-catalyzed amination. *Angew. Chem. Int. Ed.* **47**, 6338–6361 (2008).
120. Kutchukian, P. S. *et al.* Chemistry informer libraries: a cheminformatics enabled approach to evaluate and advance synthetic methods. *Chem. Sci.* **7**, 2604–2613 (2016).
121. Tasker, S. Z. & Jamison, T. F. Highly regioselective indoline synthesis under nickel/photoredox dual catalysis *J. Am. Chem. Soc.* **137**, 9531–9534 (2015).
122. Oderinde, M. S. *et al.* Highly chemoselective iridium photoredox and nickel catalysis for the cross-coupling of primary aryl amines with aryl halides. *Angew. Chem. Int. Ed.* **55**, 13219–13223 (2016).
123. Oderinde, M. S., Frenette, M., Robbins, D. W., Aquila, B. & Johannes, J. M. Photoredox mediated nickel catalyzed cross-coupling of thiols with aryl and heteroaryl iodides via thiyl radicals. *J. Am. Chem. Soc.* **138**, 1760–1763 (2016).
124. Jouffroy, M., Kelly, C. B. & Molander, G. A. Thioetherification via photoredox/nickel dual catalysis. *Org. Lett.* **18**, 876–879 (2016).
125. 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.* **21**, 4962–4965 (2015).
126. Negishi, E.-I. & Anastasia, L. Palladium-catalyzed alkynylation. *Chem. Rev.* **103**, 1979–2017 (2003).
127. 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.* **133**, 18566–18569 (2011).
The first example of palladium metallaphotoredox catalysis in which a distinct role for the photocatalyst was proposed.
128. 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.* **127**, 7330–7331 (2005).
129. 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.* **131**, 11234–11241 (2009).
130. Yu, W.-Y., Sit, W., Zhou, Z. & Chan, A. S. C. Palladium-catalyzed decarboxylative arylation of C–H bonds by aryl acylperoxides. *Org. Lett.* **11**, 3174–3177 (2009).
131. Maestri, G., Malacria, M. & Derat, E. Radical Pd(III)/Pd(I) reductive elimination in palladium sequences. *Chem. Commun.* **49**, 10424–10426 (2013).
132. Powers, D. C., Benitez, D., Tkatchouk, E., Goddard, W. A. & Ritter, T. Bimetallic reductive elimination from dinuclear Pd(III) complexes. *J. Am. Chem. Soc.* **132**, 14092–14103 (2010).
133. Chow, P.-K. *et al.* Highly luminescent palladium(II) complexes with sub-millisecond blue to green phosphorescent excited states. Photocatalysis and highly efficient PSF-OLEDs. *Chem. Sci.* **7**, 6083–6098 (2016).
134. 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.* **53**, 13264–13268 (2014).
135. Rodriguez, N. & Gooβen, L. J. Decarboxylative coupling reactions: a modern strategy for C–C bond formation. *Chem. Soc. Rev.* **40**, 5030–5048 (2011).
136. Zhou, C., Li, P., Zhu, X. & Wang, L. Merging photoredox with palladium catalysis: decarboxylative ortho-acylation of acetanilides with α-oxocarboxylic acids under mild reaction conditions. *Org. Lett.* **17**, 6198–6201 (2015).
137. Xu, N., Li, P., Xie, Z. & Wang, L. Merging visible-light photocatalysis with palladium catalysis for C–H acylation of azo- and azoxybenzenes with α-keto acids. *Chem. Eur. J.* **22**, 2236–2242 (2016).

138. Cheng, W.-M., Shang, R., Yu, H.-Z. & Fu, Y. Room-temperature decarboxylative couplings of α-oxocarboxylates with aryl halides by merging photoredox with palladium catalysis. *Chem. Eur. J.* **21**, 13191–13195 (2015).
139. 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.* **136**, 13606–13609 (2014).
140. Lang, S. B., O'Nele, K. M. & Tunge, J. A. Dual catalytic decarboxylative allylations of α-amino acids and their divergent mechanisms. *Chem. Eur. J.* **21**, 18589–18593 (2015).
141. Xuan, J. *et al.* Redox-neutral α-allylation of amines by combining palladium catalysis and visible-light photoredox catalysis. *Angew. Chem. Int. Ed.* **54**, 1625–1628 (2015).
142. Ye, Y. & Sanford, M. S. Merging visible-light photocatalysis and transition-metal catalysis in the copper-catalyzed trifluoromethylation of boronic acids with CF$_3$I. *J. Am. Chem. Soc.* **134**, 9034–9037 (2012).
A practical, mild protocol for the synthesis of trifluoromethylated arenes; moreover, this is the first example of copper metallaphotoredox catalysis.
143. Purser, S., Moore, P. R., Swallow, S. & Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **37**, 320–330 (2008).
144. Nagib, D. A., Scott, M. E. & MacMillan, D. W. C. Enantioselective α-trifluoromethylation of aldehydes via photoredox organocatalysis. *J. Am. Chem. Soc.* **131**, 10875–10877 (2009).
145. 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.* **54**, 6587–6590 (2015).
146. Antilla, J. C. & Buchwald, S. L. Copper-catalyzed coupling of arylboronic acids and amines. *Org. Lett.* **3**, 2077–2079 (2001).
147. Zhang, G., Cui, L., Wang, Y. & Zhang, L. Homogeneous gold-catalyzed oxidative carboheterofunctionalization of alkenes. *J. Am. Chem. Soc.* **132**, 1474–1475 (2010).
148. Hopkinson, M. N., Ross, J. E., Giuffredi, G. T., Gee, A. D. & Gouverneur, V. Gold-catalyzed cascade cyclization–oxidative alkynylation of allenoates. *Org. Lett.* **12**, 4904–4907 (2010).
149. Melhado, A. D., Brenzovich, W. E. Jr, Lackner, A. D. & Toste, F. D. Gold-catalyzed three-component coupling: oxidative oxyarylation of alkenes. *J. Am. Chem. Soc.* **132**, 8885–8887 (2010).
150. Ball, L. T., Lloyd-Jones, G. C. & Russell, C. A. Gold-catalyzed oxyarylation of styrenes and mono- and *gem*-disubstituted olefins facilitated by an iodine (III) oxidant. *Chem. Eur. J.* **18**, 2931–2937 (2012).
151. Joost, M. *et al.* Facile oxidative addition of aryl iodides to gold(I) by ligand design: bending turns on reactivity. *J. Am. Chem. Soc.* **136**, 14654–14657 (2014).
152. Joost, M., Estévez, L., Miqueu, K., Amgoune, A. & Bourissou, D. Oxidative addition of carbon–carbon bonds to gold. *Angew. Chem. Int. Ed.* **54**, 5236–5240 (2015).
153. Wu, C.-Y., Horibe, T., Jacobsen, C. B. & Toste, F. D. Stable gold(III) catalysts by oxidative addition of a carbon–carbon bond. *Nature* **517**, 449–454 (2015).
154. Hopkinson, M. N., Tlahuext-Aca, A. & Glorius, F. Merging visible light photoredox and gold catalysis. *Acc. Chem. Res.* **49**, 2261–2272 (2016).
155. 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.* **7**, 89–93 (2016).
156. 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.* **22**, 11587–11592 (2016).
157. Sahoo, B., Hopkinson, M. N. & Glorius, F. Combining gold and photoredox catalysis: visible light-mediated oxy- and aminoarylation of alkenes. *J. Am. Chem. Soc.* **135**, 5505–5508 (2013).
A leading report in the field of gold metallaphotoredox catalysis, providing a new strategy for achieving gold-mediated difunctionalization of alkenes.
158. Zhang, Q., Zhang, Z.-Q., Fu, Y. & Yu, H.-Z. Mechanism of the visible light-mediated gold-catalyzed oxyarylation reaction of alkenes. *ACS Catal.* **6**, 798–808 (2016).
159. Hopkinson, M. N., Sahoo, B. & Glorius, F. Dual photoredox and gold catalysis: intermolecular multicomponent oxyarylation of alkenes. *Adv. Synth. Catal.* **356**, 2794–2800 (2014).
160. 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.* **136**, 5844–5847 (2014).
161. Patil, D. V., Yun, H. & Shin, S. Catalytic cross-coupling of vinyl golds with diazonium salts under photoredox and thermal conditions. *Adv. Synth. Catal.* **357**, 2622–2628 (2015).
162. Um, J., Yun, H. & Shin, S. Cross-coupling of Meyer–Schuster intermediates under dual gold-photoredox catalysis. *Org. Lett.* **18**, 484–487 (2016).
163. 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.* **358**, 1526–1533 (2016).
164. Tlahuext-Aca, A., Hopkinson, M. N., Garza-Sanchez, R. A. & Glorius, F. Alkyne difunctionalization by dual gold/photoredox catalysis. *Chem. Eur. J.* **22**, 5909–5913 (2016).
165. 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.* **55**, 4808–4813 (2016).
166. Kim, S., Rojas-Martin, J. & Toste, F. D. Visible light-mediated gold-catalysed carbon(sp^2)–carbon(sp) coupling. *Chem. Sci.* **7**, 85–88 (2016).
167. Cornilleau, T., Hermange, P. & Fouquet, E. Gold-catalysed cross-coupling between aryldiazonium salts and arylboronic acids: probing the usefulness of photoredox conditions. *Chem. Commun.* **52**, 10040–10043 (2016).
168. Gauchot, V. & Lee, A.-L. Dual gold photoredox C(sp^2)–C(sp^2) cross couplings — development and mechanistic studies. *Chem. Commun.* **52**, 10163–10166 (2016).
169. He, Y., Wu, H. & Toste, F. D. A dual catalytic strategy for carbon–phosphorous cross-coupling via gold and photoredox catalysis. *Chem. Sci.* **6**, 1194–1198 (2015).
170. Fabry, D. C., Zoller, J., Raja, S. & Rueping, M. Combining rhodium and photoredox catalysis for C–H bond functionalization of arenes: oxidative Heck reactions with visible light. *Angew. Chem. Int. Ed.* **53**, 10228–10231 (2014).
171. Fabry, D. C., Ronge, M. A., Zoller, J. & Rueping, M. C–H functionalization of phenols using combined ruthenium and photoredox catalysis: in situ generation of the oxidant. *Angew. Chem. Int. Ed.* **54**, 2801–2805 (2015).
172. Zhang, G. *et al.* External oxidant-free oxidative cross-coupling: a photoredox cobalt-catalyzed aromatic C–H thiolation for constructing C–S bonds. *J. Am. Chem. Soc.* **137**, 9273–9280 (2015).
173. Zhong, J.-J. *et al.* Cross-coupling hydrogen evolution reaction in homogenous solution without noble metals. *Org. Lett.* **16**, 1988–1991 (2014).
174. Gao, X.-W. *et al.* Visible light catalysis assisted site-specific functionalization of amino acid derivatives by C–H bond activation with oxidant: cross-coupling hydrogen evolution reaction. *ACS Catal.* **5**, 2391–2396 (2015).
175. Zhong, J.-J. *et al.* A cascade cross-coupling and *in situ* hydrogenation reaction by visible light catalysis. *Adv. Synth. Catal.* **356**, 2846–2852 (2014).
176. Xiang, M. *et al.* Activation of C–H bonds through oxidant-free photoredox catasis: cross-coupling hydrogen-evolution transformation of isochromans and β-keto esters. *Chem. Eur. J.* **21**, 18080–18084 (2015).
177. Wu, C.-J. *et al.* An oxidant-free strategy for indole synthesis via intramolecular C–C bond construction under visible light irradiation: cross-coupling hydrogen evolution reaction. *ACS Catal.* **6**, 4635–4639 (2016).
178. Ischay, M. A., Lu, Z. & Yoon, T. P. [2 + 2] cycloadditions by oxidative visible light photocatalysis. *J. Am. Chem. Soc.* **132**, 8572–8574 (2010).
179. Lin, S., Ischay, M. A., Fry, C. G. & Yoon, T. Radical cation Diels–Alder cycloadditions by visible light photocatalysis. *J. Am. Chem. Soc.* **133**, 19350–19353 (2011).
180. Margrey, K. A. & Nicewicz, D. A. A general approach to catalytic alkene anti-Markovnikov hydrofunctionalization reactions via acridinium photoredox catalysis. *Acc. Chem. Res.* **49**, 1997–2006 (2016).
181. Yi, H. *et al.* Photocatalytic dehydrogenative cross-coupling of alkenes with alcohols or azoles without external oxidant. *Angew. Chem. Int. Ed.* **56**, 1120–1124 (2017).
182. Zhang, G. *et al.* Anti-Markovnikov oxidation of β-alkyl styrenes with H_2O as the terminal oxidant. *J. Am. Chem. Soc.* **138**, 12037–12040 (2016).
183. He, K.-H. *et al.* Acceptorless dehydrogenation of N-heterocycles by merging visible-light photoredox catalysis and cobalt catalysis. *Angew. Chem. Int. Ed.* **56**, 3080–3084 (2017).

Acknowledgements

Support was provided by the US National Institutes of Health, National Institute of General Medical Sciences (R01 GM103558-06) and gifts from Merck, AbbVie and Bristol-Myers Squibb.

Competing interests statement

The authors declare no competing interests.

Publisher's note

How to cite this article

Twilton, J., Le, C. Zhang, P., Shaw, M. H., Evans, R. W. & MacMillan, D. W. C. The merger of transition metal and photocatalysis. *Nat. Rev. Chem.* **1**, 0052 (2017).

Subject categories
Physical sciences / Chemistry / Organic chemistry / Synthetic chemistry methodology
[URI /639/638/403/933]
Physical sciences / Chemistry / Photochemistry / Photocatalysis
[URI /639/638/439/890]

ToC blurb

000

The merger of transition metal and photocatalysis

Jack Twilton, Chi (Chip) Le, Patricia Zhang, Megan H. Shaw, Ryan W. Evans and David W. C. MacMillan

Transition metal catalysis is well established as an enabling tool in synthetic organic chemistry. Photoredox catalysis has recently emerged as a method to effect reactions that occur through single-electron-transfer pathways. Here we review the combination of the two to show how this provides access to highly reactive oxidation states of transition metals and distinct activation modes that further enable the synthetic chemist.