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SYNERGISMS BETWEEN METAL AND PHOTOREDOX CATALYSIS: DECONVOLUTING COMPLEX SYSTEMS

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This review briefly describes the evolution of organometallic chemistry and photoredox catalysis as independent fields; followed by a more in-depth presentation and discussion of representative examples derived from their synergistic combination, which generally leads to powerful cross-coupling protocols. In this context, the rational deconvolution of these complex catalytic systems into their isolated, more simple components are evaluated in order to understand their properties and reactivities.

Keywords: photoredox catalysis; photochemistry; metal catalysis; homogeneous catalysis; organic synthesis.

INTRODUCTION

Organometallic Chemistry: brief overview of the field

The birth of organometallic chemistry can be attributed to the year of 1760, when in a military pharmacy in Paris, Cadet de Gassicourt was interested in preparing invisible inks from common ores containing cobalt, smaltite and cobaltite. However, these ores also typically contained arsenic. In the process, arsenic trioxide was generated as a by-product. The pyrolysis of this oxide, in the presence of potassium acetate produces cacodyl oxide and tetramethyldiarsine, among other products:[1] $As_2O_3 + AcOK \rightarrow [(AsMe_2)_2O] + [Me_2As\text{-}AsMe_2] + \ldots$ Bunsen also worked with this mixture (which was used to be known as "Cadet's fuming arsenical liquid") and he was the responsible for providing the definitive characterization of cacodyl oxide.[2]

In 1827, Zeise reported for the first time the preparation of a metal π complex $K[PtCl_3(\eta^2\text{-}C_2H_4)].H_2O$, that could be obtained from the treatment of $PtCl_2$ with boiling EtOH, followed by treatment with an aqueous solution of KCl.[3] The composition of this salt and the nature of the bond between the Pt center and the ethylene ligand was a matter of debate at the time,[4] which could be solved only years later, based on the studies of Birnbaum[5] and Dewar[6]/Chatt and Ducanson.[7] Birnbaum showed that the Zeise's salt could be directly prepared from the reaction of ethylene with H_2PtCl_6. Chatt and Ducanson explained that the surprisingly strong bond between Pt and the ethylene ligand can be understood as a consequence of the donation of π-electrons from the ethylene ligand to Pt, while the back-donation from *d* electrons of the Pt center to the ethylene π^* orbital creates a linkage stronger than what could be anticipated. (This concept can be also readily applied to metal carbonyls, and with slight modifications, to aromatic complexes.)

In 1850s, Edward Frankland (a former student of Bunsen) prepared a number of air-sensitive metal-alkyl complexes, including $ZnEt_2$,[8] $HgEt_2$[9], $SnEt_4$,[8,10] and EtLi,[11] with the zinc and mercury compounds being immediately employed for the synthesis of a variety of other main-group organometallic compounds. In this context, in 1863, Friedel and Crafts reacted ZnR_2 with $SiCl_4$ to prepare organochlorosilanes R_nSiCl_{4-n}.[12] Later, in 1868, Schützenberger reported the first metal-carbonyl complexes $[Pt(CO)_2Cl_2]$ and $[Pt(CO)Cl_2]_2$;[13] and in 1890, Mond was able to isolate the first binary metal-carbonyl compound, $Ni(CO)_4$;[14] then being followed in 1891 by the almost simultaneous reports of $[Fe(CO)_5]$, by Mond[15] and Berthelot.[16]

Earlier, in 1828, the serendipitous preparation of urea from ammonium cyanate reported by Wöhler[17] (a former student of Berzelius) attracted the attention of many chemists, thus representing a key historical event that triggered the rapid development of organic synthesis. In this context, important early examples referring to the use of metals or organometallic compounds in organic synthesis included the preparation of alkanes from alkyl halides and sodium, as reported by Wurtz in 1855,[18] and the Cu-promoted dimerization of terminal alkynes, as reported by Glaser in 1869.[19] At the end of the nineteenth century, in 1894, Phillips described the oxidation of ethylene to acetaldehyde, promoted by an aqueous solution containing stoichiometric amounts of a Pd salt.[20] In 1899, Barbier described part of his studies using organometallic reagents of type RMX that could be formed *in situ* from alkyl halides RX and a metal M (M = Mg, Zn) as nucleophiles in 1,2-additions to carbonyl compounds,[21,22] then being followed in 1900 by his student Victor Grignard, whose studies focused on the use of organomagnesium halides (RMgX) as strong bases and nucleophiles.[23,24] The french chemist Paul Sabatier (a former student of Berthelot) was the first to differentiate homogeneous from heterogeneous catalysis. He studied the hydrogenation of olefins to alkanes in the presence of heterogeneous Nickel catalysts.[25] As a consequence of these contributions, Grignard and Sabatier were awarded the Nobel Prize, approximately a decade later, in 1912.

Continuing on with the early advancements of the twentieth century, Ullman showed that Cu can promote the dimerization of arylbromides[26] and the coupling of amines with aryl halides.[27,28] In 1909, Wilhelm Ostwald was awarded the Nobel Prize for his contributions to the understanding of fundamental concepts related to catalysis, chemical equilibria and rates of reactions, which placed him as the founder of physical-chemistry.[29] Ostwald had several pulpils, among them, Van't Hoff (Nobel Prize in 1901), Arrhenius (Nobel Prize in 1903), and Nernst (Nobel Prize in 1920). In 1917, Schlenk reported the first isolation of organolithium compounds (e.g. MeLi, EtLi and PhLi) by reacting Li with the corresponding dialkyl- or diarylmercury compounds.[30] Later, in 1930, Ziegler would describe the ready preparation of such compounds, by reacting Li with the corresponding alkyl- or aryl halides.[31,32]

In 1918, Haber and Bosch were recognized with the Nobel Prize for the catalytic hydrogenation of N_2 to produce NH_3.[33] Since early developments, little has changed until today. A key event in the process development included the use of an α-Fe catalyst,[34] developed at BASF by Alwin Mittasch in the beginning of the 20th century.[35,36] The industrial process derived from this transformation paved the way for a revolution in the production of fertilizers. Indeed, *ca.* 80%

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of the ammonia produced in the world (>130 megatons)[37] is used in the production of fertilizers. Today, it is yet considered one of the greatest achievements of mankind in chemistry.

In 1938, as a consequence of his period in Mülheim (Ruhr area, Germany), when he was working with Franz Fischer and Hanz Tropsch, Roelen patented the first homogeneous hydroformylation reaction of olefins in the presence of synthesis gas (CO + H_2) and $HCo(CO)_4$ as catalyst.[38] In 1939, Meerwein reported a Cu-mediated arylation process of electron-poor olefins with diazonium salts,[39] and almost ten years later, in 1948, Reppe described the first Ni-catalyzed formal [2+2+2]-cycloaddition of alkynes leading to arenes.[40,41] Shortly after, Pauson[42] and Wilkinson[43] were involved in the first reports of Ferrocene,[44] while Gilman reported the generation of cuprates from the reaction of alkyl lithium compounds with copper halides.[45,46] In 1955, Ziegler and Natta independently described strategies to polymerize ethylene using a combination of Ti and Al complexes,[47] which would years later be recognized by the Nobel Prize.[48] In the following year, in 1956, Hodgkin reported the structure of vitamin B_{12}, the first biomolecule known at that time containing a metal-carbon bond.[49] In 1959, van der Kerk reported the reduction of alkylhalides using Bu_3SnH,[50,51] which was then demonstrated to involve a radical chain mechanism.[52] Later, this reactivity was further explored in other transformations, such as the Barton-McCombie deoxygenation[53] and the Barton decarboxylation.[54] Also in 1959, Smidt reported the Pd-catalyzed oxidation of olefins using O_2 and H_2O (Wacker oxidation);[55,56] and in 1965, Tsuji reported for the first time the use of Pd salts to promote the allylic alkylation of diethylmalonate.[57] In 1973[58] and in the following years, this strategy received several contributions from the Trost group, including numerous asymmetric catalytic protocols and elements of catalyst design. Among the contributions toward the development of Pd-catalyzed asymmetric allylic alkylation protocols (Pd-AAA), a powerful ligand, known today as the Trost ligand, would appear years later, in 1992.[59]

In 1966, Wilkinson described the preparation and use of $RhCl(PPh_3)_3$ as an efficient catalyst for hydrogenation reactions.[60] In the following year, Calderon reported early examples and coined the term "olefin cross metathesis",[61] then being followed by Penella in 1968, who reported that alkyne metathesis was also a feasible transformation, as it became evident from the conversion of 2-pentyne to a mixture of 2-butyne and 3-hexyne, in the presence of WO_3 on silica.[62] Also in 1968, Heck reported a Pd-promoted cross-coupling transformatin between olefins and organomercurials.[63] This Pd-based stoichiometric version would be improved in 1971 by the contribution of Mizoroki, who described that the same olefinic product could be accessed from a Pd-catalyzed cross-coupling reaction replacing organomercurials by aryl halides.[64] In 1969, Shilov reported a Pt-catalyzed transformation for a Pt-promoted oxidation of alkanes to the corresponding alcohols.[65] A year later, Chauvin would accurately describe the involvement of metallocyclobutanes as key intermediates in the mechanism of olefin metathesis.[66,67] After the seminal contribution of Heck and Mizoroki to the field of cross-coupling reactions, several other variants followed involving organic halides and an organometallic transmetallating species. In 1972, Corriu[68] and Kumada[69] reported the Ni-catalyzed cross-coupling of Grignard reagents; in 1975, Sonogashira reported on the Pd-catalyzed cross-coupling of terminal alkynes;[70] in 1976-77, Negishi reported the Pd- or Ni-catalyzed cross-coupling of alanes or organozinc reagents with alkenyl/aryl halides;[71] Migita[72] and Stille[73] reported on the Pd-catalyzed cross-coupling of stannanes; and in 1979, Suzuki reported the Pd-catalyzed cross-coupling of boronic acids.[74] During this period, other important achievements in organometallic chemistry also included the Nobel Prize in 1973 awarded to Fischer and Wilkinson, for their contributions to the chemistry of sandwich compounds;[75] the work of Mortreux and Blanchard involving the metathesis of alkynes employing a $Mo(CO)_6$/resorcinol catalytic system;[76] the work of Kagan in 1977 describing the use of SmI_2 as a SET reducing agent;[77,78] and the report of Crabtree in 1979 demonstrating that an Ir complex containing a cyclooctene ligand could lead to cyclooctadiene via a dehydrogenation process.[79]

While in 1981, Schrock reported the first well-defined catalyst for alkyne metathesis, a W(VI) alkylidyne complex;[80] in 1983, Sauvage described a new strategy to assemble interlocked molecules (catenanes) by means of Cu-based templates;[81] and in 1989, Kulinkovich reported a Ti-catalyzed preparation of cyclopropanol derivatives employing carboxylic acids.[82] During this period, asymmetric synthesis was gaining momentum; and a number of new transformations have appeared, including Noyori protocol for Rh- or Ru-BINAP catalyzed hydrogenation of olefins;[83] Narasaka[84] and Seebach[84] reports on the use of Ti-TADDOL complexes in Diels-Alder cycloadditions and 1,2-additions of Grignard or organolithium reagents to aldehydes; Sharpless dihydroxylation of olefins,[86] and Jacobsen[87] and Katsuki[88] protocols for the epoxidation of olefins.

In 1991, Arduengo reported the first stable, isolable NHC;[89] Larock introduced a convenient Pd-catalyzed indole synthesis starting from 2-iodoanilines and internal alkynes;[90] and Schrock reported a highly active Mo catalyst for ring-opening alkene metathesis polymerization.[91] In 1992, Shibasaki introduced the use of lanthanides-BINOL as powerful Lewis acid catalysts for a nitroaldol[92] and other transformations.[93] In 1993, Grubbs introduced a Ru catalyst for olefin metathesis (later called of first generation, it contained two tricyclohexylphosphine ligands).[94] In 1999, a second generation Ru catalyst was developed, in which one of the phosphine ligands of the first generation catalyst had been replaced by a NHC ligand.[95] Because these catalysts are not air sensitive, and generally exhibit a high functional group tolerance, they have allowed a significant extension of the scope of this transformation.[96] Due to the previous contributions of Schrock, Grubbs and Chauvin to the development of olefin metathesis, they were recognized with the Nobel Prize in 2005.[97]

In 1993, Keck also reported an asymmetric allylation method of aldehydes employing allyltributylstannane and a Ti-BINOL catalytic system;[98] in 1994, Hartwig[99] and Buchwald[100] reported simultaneously and independently Pd-catalyzed cross-coupling strategies between aryl halides and tin amides. Later, this Pd-catalyzed C-N cross-coupling strategy was further improved to become a powerful method employed in several domains, such as in the synthesis of heterocycles, ligands and catalysts, in medicinal chemistry, in process chemistry and in chemical biology applications.[101] In this context, some years later (1998), Buchwald and his group have also introduced a family of dialkylbiaryl phosphine ligands of superbe activity for Pd-catalyzed Suzuki cross-coupling reactions.[102,103] Nevertheless, these ligands got increased popularity over the years for being also competent in numerous other cross-coupling transformations.[104]

In 1995, Jacobsen reported on the stereoselective ring-opening of epoxides,[105] and Herrmann described the use of an NHC ligand in a Pd-catalyzed Heck reaction.[106] In 1996, Sharpless reported an extension of his previous work, this time describing a protocol for the enantioselective catalytic aminohydroxylation of olefins.[107]

Approaching the 21st century, C-H functionalization strategies received more attention. This synthetic interest can be highlighted by the reports of Periana in 1998, when his group described a Pt-based protocol to oxidize methane;[108] in 2005, Sames demonstrated a C-H functionalization process via a redox-neutral approach, consisting of Lewis acid-catalyzed 1,5-H shift/cyclization sequence for the preparation of spirocycles (Lewis acids employed: $Sc(OTf)_3$, $PtCl_4$, $BF_3.OEt_2$);[109,110] and in 2006, Bohle and Li described a CuBr-catalyzed cross-dehydrogenative coupling of amines with nucleophiles, such as nitroalkanes and malonates, among others.[111,112] These studies were accompanied by other impressive contributions in the following years, including: White selective oxidations using Fe(PDP) as catalyst (2007),[113] Yu protocol for the Pd-catalyzed directing-group guided meta-selective functionalization of arenes (2012)[114] and the highly seletive Rh-catalyzed protocols for the functionalization of linear alkanes using aryldiazoacetates, as reported by Davies (2016).[115,116]

Since the beginning of the 21st century, asymmetric catalysis has been also undergoing continuous developments. The importance of the field was further brought to the spotlight by the Nobel Prize in Chemistry of 2001, when Knowles, Noyori and Sharpless were recognized for their contributions.[117] In the following years, new developments included the use of a chiral counter-ion for enantioselective Au(I)-catalyzed intramolecular cyclization of allenes, as reported by Toste in 2007;[118] the synergistic combination of an aminocatalyst and a Ru photocatalyst to promote a highly stereoselective photochemical protocol for the α-alkylation of aldehydes, as reported by MacMillan in 2008;[119] TADDOL-derived phosphoramidite ligands for Au(I) asymmetric catalysis reported by Fürstner in 2010;[120] the use of a NHC ligand in a heterogeneous, enantioselective Pd-catalyzed α-arylation of ketones, as reported by Glorius in 2010;[121] the development of chiral Cp ligands for the Rh-catalyzed enantioselective synthesis of 3,4-dihydroisoquinolin-1(*2H*)-ones, as reported by Cramer in 2012;[122] the development of a pyrrolidine/pyridine bifunctional aminocatalyst/ligand for the Rh-catalyzed asymmetric α-alkylation of ketones using ethylene, as reported by Dong in 2014;[123] and the development of chiral-at-metal photoredox catalysts, as reported by Meggers, also in 2014.[124] During the past years, significant achievements have been made also involving other metal-promoted transformations. Representative examples include the Cu-catalyzed Huisguen [3+2] cycloaddition between terminal alkynes and azides,[125] reported independenly and simultaneously by Meldal[126] and by Fokin and Sharpless[127] (this transformation became a canonical representative of click chemistry);[128] the development of "Turbo Grignard" as highly reactive Grignard reagents, with practical handling and high functional group tolerance, as described by Knochel;[129,130] the Pd-catalyzed reductive carbonylation of arylbromides, as described by Beller (2006), which was the first example of such a reaction to be employed in industry;[131] the development of bench-stable alkyne metathesis precatalysts, as described by Fürstner;[132] C(sp^2)-C(sp^3) photochemically-promoted cross-coupling reactions, promoted by the synergistic combination of a Ni-catalyst and an Ir-photoredox catalyst, as described by Molander,[133] and Doyle and MacMillan;[134] a Ni-catalyzed carboxylation of alkyl bromides, as reported by Martin;[135] a Rh-catalyzed hydrogenation of perfluorinated arenes, as reported by Glorius;[136] the Ni-catalyzed decarboxylative cross-coupling reaction involving redox-active esters and alkenylzinc halides, as described by Baran,[137] and the Ni-catalyzed electrochemically promoted cross-coupling of aryl halides with amines, as described by Neurock, Minteer and Baran.[138] This brief presentation of selected achievements in the history of metal-promoted transformations has been chronologically ordered in Figure 1.

Photoredox catalysis

Photocatalysis can be defined as the "change in the rate of a chemical reaction or its initiation under the action of ultraviolet, visible or infrared radiation in the presence of a substance - the photocatalyst - that absorbs light and is involved in the chemical transformation of the reacting partners."[139] The ability of Nature to transform the sun energy into chemical energy has inspired chemists for more than a century.[140] An example of an important photochemical transformation promoted by Nature is photosynthesis, which uses sunlight to convert carbon dioxide and water into glucose and oxygen.[141] Among the wavelenghts that can be harvested from the full electromagnetic spectrum, the visible region can be considered particularly strategic in organic synthesis. The reason for this is that the UV region is associated with photons of high energy, which can be generally absorbed by organic molecules, but often implicates in unselective, or unpredictable competitive reaction pathways. The IR region is associated to photons of quite low energy and have been only rarely employed in synthesis. In contrast, although most of the organic molecules cannot absorb in the visible region,[142,143] numerous metal photocatalysts and dyes can. As a consequence, general mechanisms of electron[144] or energy[145] transfers can be explored, thus allowing the development of new, mild and more sustainable synthetic methods.

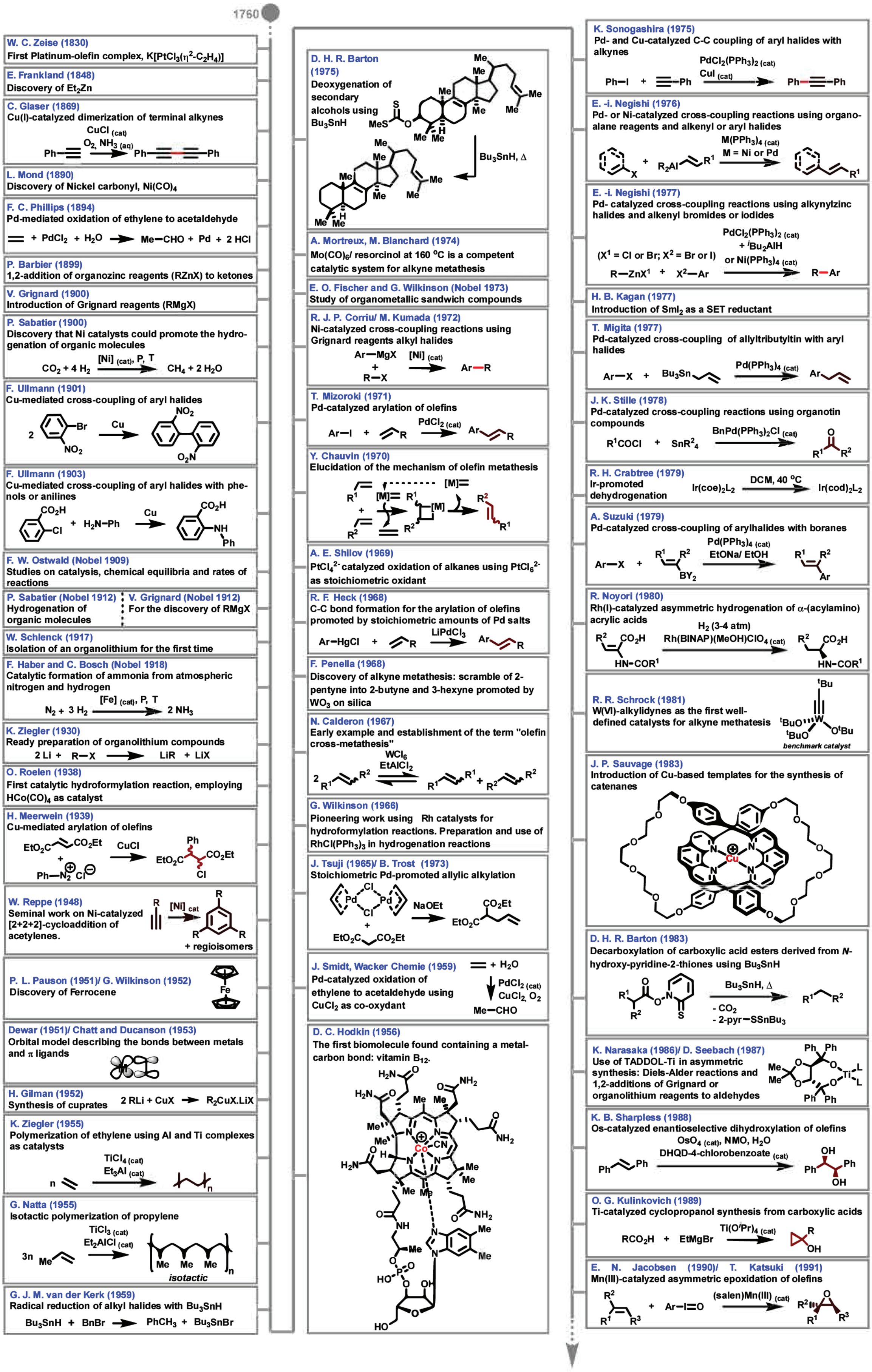
Photoredox catalysts and fundamental principles

Most common photoredox catalysts are represented by metal complexes of Ru or Ir carrying polyheteroaromatic rings as ligands[146] (although other metals complexes have been also reported)[147] or dyes,[148] which are highly conjugated organic molecules also absorbing in the visible region (Figure 2).

The polyunsaturated rings present in these catalysts are chromophores that absorb the low-energy radiation associated to the visible region and promote the excitation of an electron to a higher energy orbital, thus resulting in the formation of an excited state that is both a better reducing and oxidazing agent. In the case of the metal complexes, this electronic excitation typically takes part from the metal to an electron-poor ligand ($d\pi_{metal} \rightarrow \pi^*_{ligand}$), and it is called a metal to ligand charge transfer (MLCT). The singlet state of higher energy can undergo intersystem crossing (ISC) to create a triplet excited state, which has a longer lifetime, due to the spin-forbidden relaxation to the ground state.[146]

To a better understanding of how these electronic processes occur, the photocatalyst $Ru(bpy)_3^{2+}$ can be used to demonstrate these properties in greater detail. The metal species Ru^{2+} has 6 electrons in its *d* orbitals ($d\pi^6$) and the polypyridine ligands have low-lying π^* orbitals, thus becoming electron-acceptor orbitals. Upon absorption of a photon, an electron transfer has sufficient energy to occur from a $d\pi$ orbital of the metal to the π^* orbital of the ligand. This electron transfer event converts $[Ru^{II}(bpy)_3]^{2+}$ to $[Ru^{III}(bpy)_2(bpy)^{\bullet\ominus}]^{2+}$. As a consequence, the lower energy triplet state of $^*[Ru(bpy)_3]^{2+}$ can act either as an oxidant or a reductant, depending on the reacting partner present in the reaction mixture[146] (Scheme 1).

Electron transfer events might occur from a donor molecule (D) to the excited state of the photocatalyst via a reductive quenching cycle; or from the excited catalyst to an acceptor molecule (A), via an oxidative quenching cycle (Scheme 2). In the oxidative quenching cycle, the electron transfer event occurs from the π^* orbital of the complex (that is singly occupied after excitation, *cf.* Scheme 1) to A, thus forming $Ru(bpy)_3^{3+}$; while in the reductive quenching cycle, D gives an electron to the orbital $d\pi$ of the metal (that is singly occupied after excitation, *cf.* Scheme 1) to produce $Ru(bpy)_3^{+}$.[144,146] Because every oxidative or reductive quenching cycle needs a donor and an acceptor molecule to proceed, there are some important elements of design that must be present. Some protocols do contain both donor and acceptor partners directly implicated in the desired transformation. However, it is also possible to design a photoredox catalytic cycle employing one of these elements as sacrificial agents. For instance, sacrificial donors include amines, such as Et_3N, $E_{1/2}(Et_3N^{\bullet\oplus}/Et_3N)$ = +1.15 V; or thioethers, such as benzylmethylsulfide. $E_{1/2}(BnSMe^{\bullet\oplus}/BnSMe)$ = +1.25 V, or other electron-rich molecules, such as anisole $E_{1/2}(PhOMe^{\bullet\oplus}/PhOMe)$ = +1.76 V). Examples of sacrificial acceptors



W. C. Zeise (1830) First Platinum-olefin complex, $K[PtCl_3(\eta^2\text{-}C_2H_4)]$

E. Frankland (1848) Discovery of Et_2Zn

C. Glaser (1869) Cu(I)-catalyzed dimerization of terminal alkynes

L. Mond (1890) Discovery of Nickel carbonyl, $Ni(CO)_4$

F. C. Phillips (1894) Pd-mediated oxidation of ethylene to acetaldehyde

P. Barbier (1899) 1,2-addition of organozinc reagents (RZnX) to ketones

V. Grignard (1900) Introduction of Grignard reagents (RMgX)

P. Sabatier (1900) Discovery that Ni catalysts could promote the hydrogenation of organic molecules

F. Ullmann (1901) Cu-mediated cross-coupling of aryl halides

F. Ullmann (1903) Cu-mediated cross-coupling of aryl halides with phenols or anilines

F. W. Ostwald (Nobel 1909) Studies on catalysis, chemical equilibria and rates of reactions

P. Sabatier (Nobel 1912) Hydrogenation of organic molecules

V. Grignard (Nobel 1912) For the discovery of RMgX

W. Schlenck (1917) Isolation of an organolithium for the first time

F. Haber and C. Bosch (Nobel 1918) Catalytic formation of ammonia from atmospheric nitrogen and hydrogen

K. Ziegler (1930) Ready preparation of organolithium compounds

O. Roelen (1938) First catalytic hydroformylation reaction, employing $HCo(CO)_4$ as catalyst

H. Meerwein (1939) Cu-mediated arylation of olefins

W. Reppe (1948) Seminal work on Ni-catalyzed [2+2+2]-cycloaddition of acetylenes.

P. L. Pauson (1951)/ G. Wilkinson (1952) Discovery of Ferrocene

Dewar (1951)/ Chatt and Ducanson (1953) Orbital model describing the bonds between metals and π ligands

H. Gilman (1952) Synthesis of cuprates

K. Ziegler (1955) Polymerization of ethylene using Al and Ti complexes as catalysts

G. Natta (1955) Isotactic polymerization of propylene

G. J. M. van der Kerk (1959) Radical reduction of alkyl halides with Bu_3SnH

D. H. R. Barton (1975) Deoxygenation of secondary alcohols using Bu_3SnH

A. Mortreux, M. Blanchard (1974) $Mo(CO)_6$/ resorcinol at 160 °C is a competent catalytic system for alkyne metathesis

E. O. Fischer and G. Wilkinson (Nobel 1973) Study of organometallic sandwich compounds

R. J. P. Corriu/ M. Kumada (1972) Ni-catalyzed cross-coupling reactions using Grignard reagents alkyl halides

T. Mizoroki (1971) Pd-catalyzed arylation of olefins

Y. Chauvin (1970) Elucidation of the mechanism of olefin metathesis

A. E. Shilov (1969) $PtCl_4^{2-}$ catalyzed oxidation of alkanes using $PtCl_6^{2-}$ as stoichiometric oxidant

R. F. Heck (1968) C-C bond formation for the arylation of olefins promoted by stoichiometric amounts of Pd salts

F. Penella (1968) Discovery of alkyne metathesis: scramble of 2-pentyne into 2-butyne and 3-hexyne promoted by WO_3 on silica

N. Calderon (1967) Early example and establishment of the term "olefin cross-metathesis"

G. Wilkinson (1966) Pioneering work using Rh catalysts for hydroformylation reactions. Preparation and use of $RhCl(PPh_3)_3$ in hydrogenation reactions

J. Tsuji (1965)/ B. Trost (1973) Stoichiometric Pd-promoted allylic alkylation

J. Smidt, Wacker Chemie (1959) Pd-catalyzed oxidation of ethylene to acetaldehyde using $CuCl_2$ as co-oxydant

D. C. Hodkin (1956) The first biomolecule found containing a metal-carbon bond: vitamin B_{12}.

K. Sonogashira (1975) Pd- and Cu-catalyzed C-C coupling of aryl halides with alkynes

E. -i. Negishi (1976) Pd- or Ni-catalyzed cross-coupling reactions using organoalane reagents and alkenyl or aryl halides

E. -i. Negishi (1977) Pd- catalyzed cross-coupling reactions using alkynylzinc halides and alkenyl bromides or iodides

H. B. Kagan (1977) Introduction of SmI_2 as a SET reductant

T. Migita (1977) Pd-catalyzed cross-coupling of allyltributyltin with aryl halides

J. K. Stille (1978) Pd-catalyzed cross-coupling reactions using organotin compounds

R. H. Crabtree (1979) Ir-promoted dehydrogenation

A. Suzuki (1979) Pd-catalyzed cross-coupling of arylhalides with boranes

R. Noyori (1980) Rh(I)-catalyzed asymmetric hydrogenation of α-(acylamino) acrylic acids

R. R. Schrock (1981) W(VI)-alkylidynes as the first well-defined catalysts for alkyne methathesis

benchmark catalyst

J. P. Sauvage (1983) Introduction of Cu-based templates for the synthesis of catenanes

D. H. R. Barton (1983) Decarboxylation of carboxylic acid esters derived from *N*-hydroxy-pyridine-2-thiones using Bu_3SnH

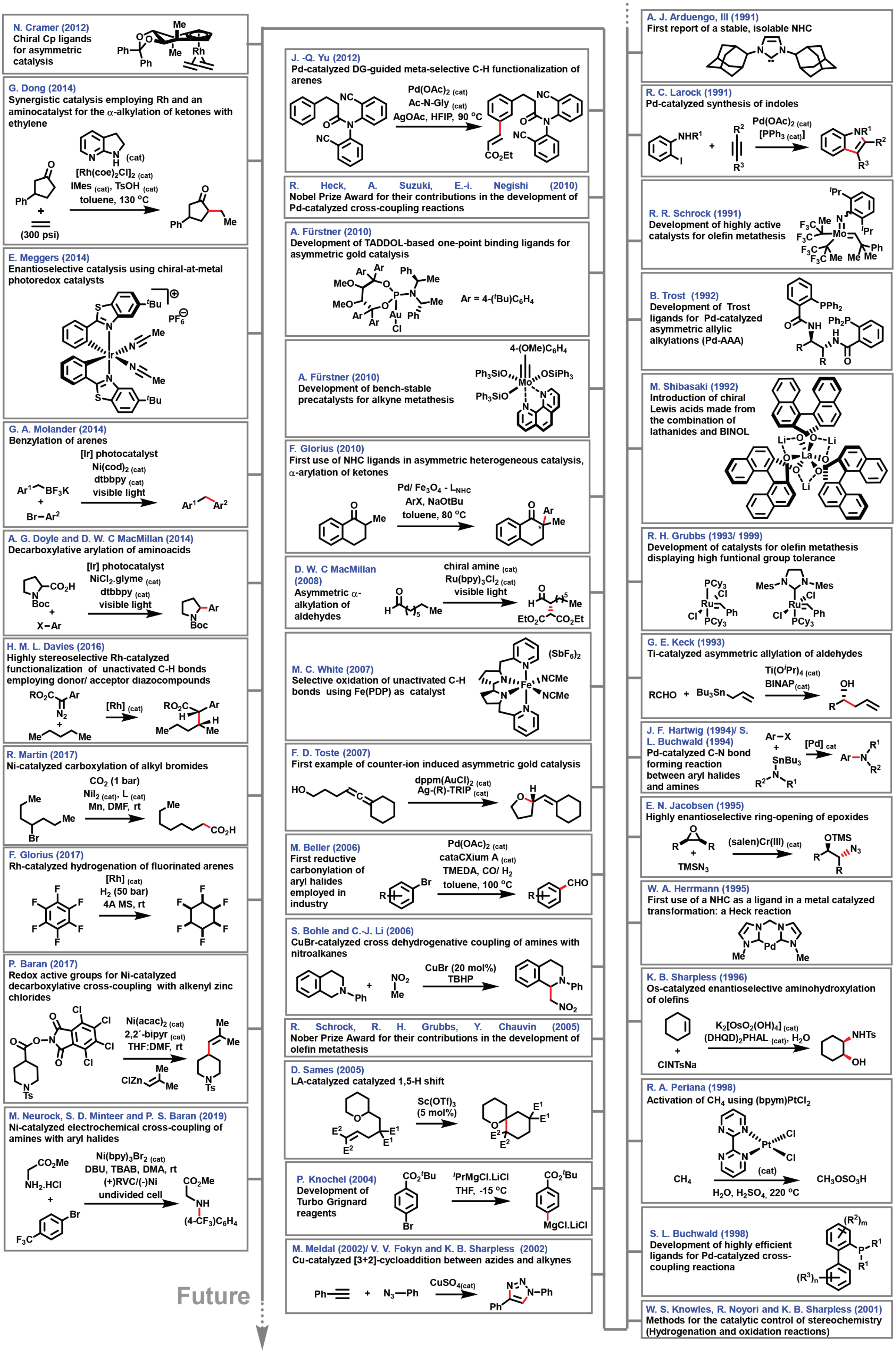
K. Narasaka (1986)/ D. Seebach (1987) Use of TADDOL-Ti in asymmetric synthesis: Diels-Alder reactions and 1,2-additions of Grignard or organolithium reagents to aldehydes

K. B. Sharpless (1988) Os-catalyzed enantioselective dihydroxylation of olefins

O. G. Kulinkovich (1989) Ti-catalyzed cyclopropanol synthesis from carboxylic acids

E. N. Jacobsen (1990)/ T. Katsuki (1991) Mn(III)-catalyzed asymmetric epoxidation of olefins

Figure 1. *A selection of important achievements in organometallic chemistry since 1760*



N. Cramer (2012)
Chiral Cp ligands for asymmetric catalysis

G. Dong (2014)
Synergistic catalysis employing Rh and an aminocatalyst for the α-alkylation of ketones with ethylene

E. Meggers (2014)
Enantioselective catalysis using chiral-at-metal photoredox catalysts

G. A. Molander (2014)
Benzylation of arenes

A. G. Doyle and D. W. C MacMillan (2014)
Decarboxylative arylation of aminoacids

H. M. L. Davies (2016)
Highly stereoselective Rh-catalyzed functionalization of unactivated C-H bonds employing donor/ acceptor diazocompounds

R. Martin (2017)
Ni-catalyzed carboxylation of alkyl bromides

F. Glorius (2017)
Rh-catalyzed hydrogenation of fluorinated arenes

P. Baran (2017)
Redox active groups for Ni-catalyzed decarboxylative cross-coupling with alkenyl zinc chlorides

M. Neurock, S. D. Minteer and P. S. Baran (2019)
Ni-catalyzed electrochemical cross-coupling of amines with aryl halides

J. -Q. Yu (2012)
Pd-catalyzed DG-guided meta-selective C-H functionalization of arenes

R. Heck, A. Suzuki, E.-i. Negishi (2010)
Nobel Prize Award for their contributions in the development of Pd-catalyzed cross-coupling reactions

A. Fürstner (2010)
Development of TADDOL-based one-point binding ligands for asymmetric gold asymmetric catalysis

A. Fürstner (2010)
Development of bench-stable precatalysts for alkyne metathesis

F. Glorius (2010)
First use of NHC ligands in asymmetric heterogeneous catalysis, α-arylation of ketones

D. W. C MacMillan (2008)
Asymmetric α-alkylation of aldehydes

M. C. White (2007)
Selective oxidation of unactivated C-H bonds using Fe(PDP) as catalyst

F. D. Toste (2007)
First example of counter-ion induced asymmetric gold catalysis

M. Beller (2006)
First reductive carbonylation of aryl halides employed in industry

S. Bohle and C.-J. Li (2006)
CuBr-catalyzed cross dehydrogenative coupling of amines with nitroalkanes

R. Schrock, R. H. Grubbs, Y. Chauvin (2005)
Nober Prize Award for their contributions in the development of olefin metathesis

D. Sames (2005)
LA-catalyzed catalyzed 1,5-H shift

P. Knochel (2004)
Development of Turbo Grignard reagents

M. Meldal (2002)/ V. V. Fokyn and K. B. Sharpless (2002)
Cu-catalyzed [3+2]-cycloaddition between azides and alkynes

A. J. Arduengo, III (1991)
First report of a stable, isolable NHC

R. C. Larock (1991)
Pd-catalyzed synthesis of indoles

R. R. Schrock (1991)
Development of highly active catalysts for olefin metathesis

B. Trost (1992)
Development of Trost ligands for Pd-catalyzed asymmetric allylic alkylations (Pd-AAA)

M. Shibasaki (1992)
Introduction of chiral Lewis acids made from the combination of lathanides and BINOL

R. H. Grubbs (1993/ 1999)
Development of catalysts for olefin metathesis displaying high funtional group tolerance

G. E. Keck (1993)
Ti-catalyzed asymmetric allylation of aldehydes

J. F. Hartwig (1994)/ S. L. Buchwald (1994)
Pd-catalyzed C-N bond forming reaction between aryl halides and amines

E. N. Jacobsen (1995)
Highly enantioselective ring-opening of epoxides

W. A. Herrmann (1995)
First use of a NHC as a ligand in a metal catalyzed transformation: a Heck reaction

K. B. Sharpless (1996)
Os-catalyzed enantioselective aminohydroxylation of olefins

R. A. Periana (1998)
Activation of CH$_4$ using (bpym)PtCl$_2$

S. L. Buchwald (1998)
Development of highly efficient ligands for Pd-catalyzed cross-coupling reactiona

W. S. Knowles, R. Noyori and K. B. Sharpless (2001)
Methods for the catalytic control of stereochemistry (Hydrogenation and oxidation reactions)

Figure 1. *A selection of important achievements in organometallic chemistry since 1760 (cont.)*

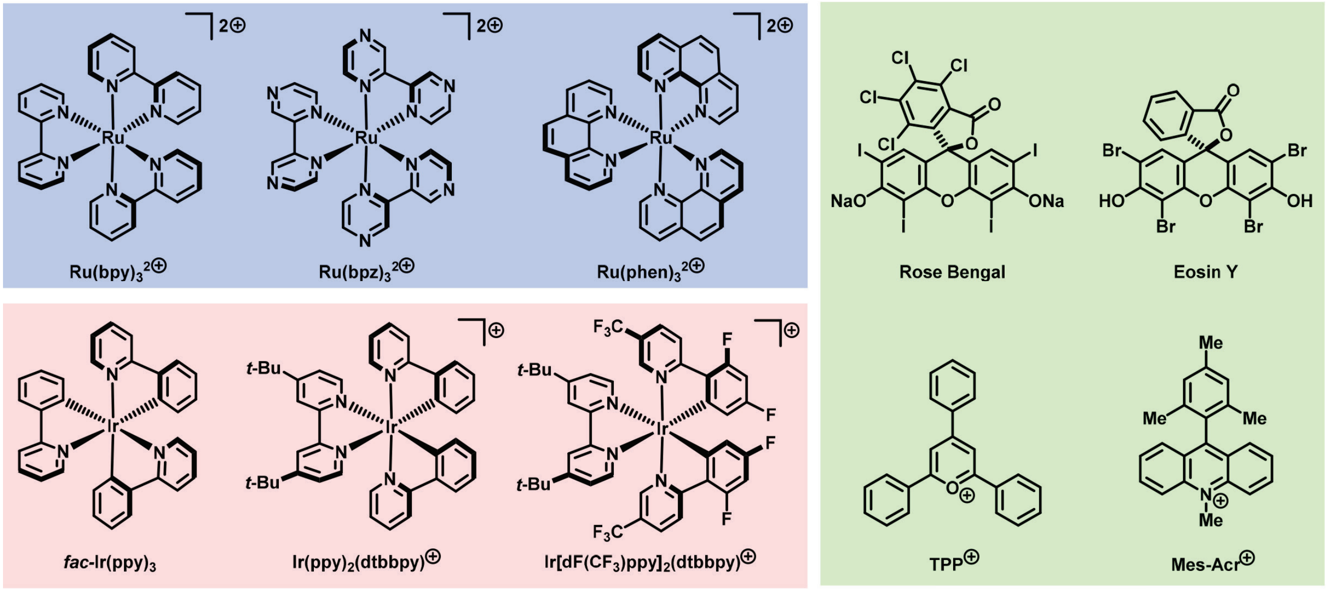
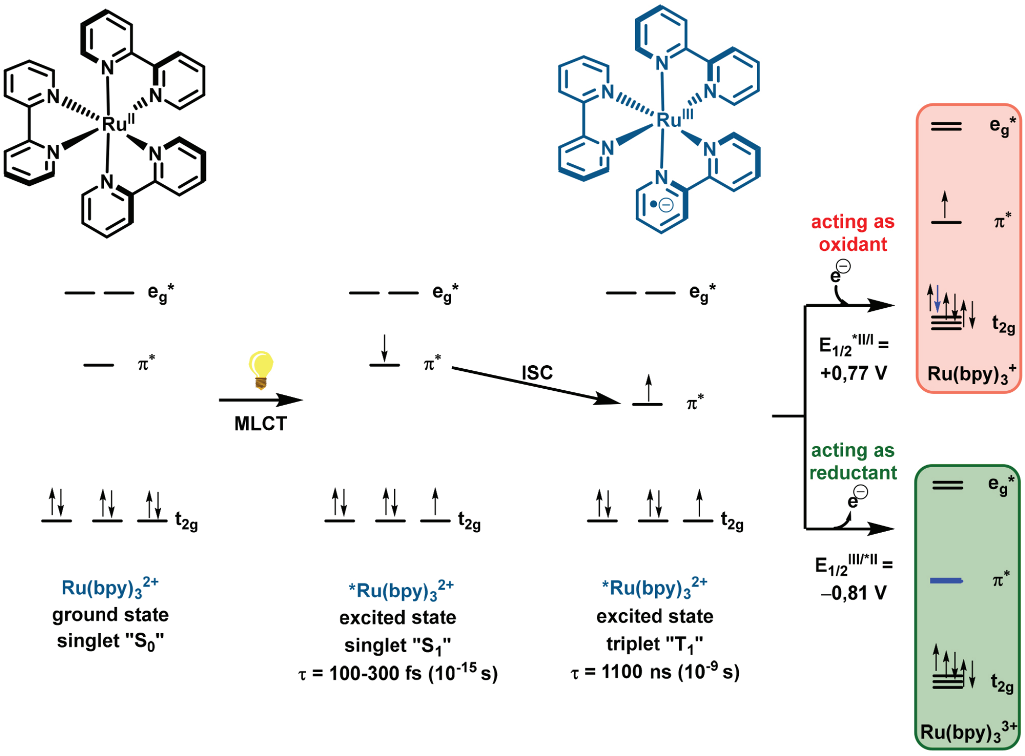


Figure 2. *Examples of common photoredox catalysts (bpy = 2,2'-bipyridine; bpz = 2,2'-bipyrazine; phen = 1,10-phenanthroline; ppy = 2-phenylpyridine; dtbbpy = 4,4'-di-terc-butyl-2,2'-bipyridyne; dF(CF_3)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; TPP = 2,4,6-triphenylpyrylium; Mes-Acr = 9-mesityl-10-methylacridium)*



Scheme 1. *Simplified molecular orbital diagram of Ru(bpy)$_3^{2+}$*

include dicyanobenzenes, *e.g.* $E_{1/2}(1,4\text{-}C_6H_4(CN)_2/1,4\text{-}C_6H_4(CN)_2^{\bullet\ominus})$ = -1.64 V,[149] aryldiazonium salts, *e.g.* $E_{1/2}(PhN_2BF_4/Ph\bullet)$ = -0.16 V[150] or molecular oxygen $E_{1/2}(O_2/O_2^{\bullet\ominus})$ = -1.25 V.[151]

The knowledge of the redox potentials of all involved molecules in either of these catalytic cycles is important to establish whether the envisioned overall transformation is thermodynamically favored. This is a necessary condition but is not sufficient, as kinetics also play a role. Concerning thermodynamics, in the case of $[Ru(bpy)_3]^{2+}$, the excited photocatalyst, having $E_{1/2}(Ru^{*II}/Ru^{I})$ = +0.77 V, is a better oxidant than its ground state, having $E_{1/2}(Ru^{II}/Ru^{I})$ = -1.33 V. In the same manner, its excited state $*Ru(bpy)_3^{2+}$ is a better reducing agent, *cf.* $E_{1/2}(Ru^{III}/Ru^{*II})$ = -0.81 V than its ground state $[Ru(bpy)_3]^{2+}$, *cf.* $E_{1/2}(Ru^{III}/Ru^{II})$ = +1.29 V. The redox potential and some photophysical properties of some common photocatalysts are presented in Table 1.[146]

The different metals and ligands employed when synthesizing photocatalysts produce distinctive redox potentials.[146,152] The presence of electron donating heteroarenes typically afford more strongly reducing species, while the presence of electron withdrawing heteroarenes typically produce stronger oxidants. For instance, considering the redox potential of Ru^{III}/Ru^{II}, it is possible to note that when two pyrazole ligands are present, they make the oxidative power of the corresponding complex $Ru(bpy)_2(pz)_2^+$ to be lower, *cf.* $E_{1/2}(Ru^{III}/Ru^{II})$ = +0.30 V than the one of $Ru(bpy)_3Cl_2$, *cf.* $E_{1/2}(Ru^{III}/Ru^{II})$ = +1.26 V. Following the same trend, the use of strongly π-acceptor ligands, such as 2,2'-bipyrazine, makes the oxidizing power of $Ru(bpz)_3^{3+}$ to be even more elevated, *cf.* $E_{1/2}(Ru^{III}/Ru^{II})$ = +1.86 V. These effects are a consequence of the reactivity of the Ru center upon MLCT events: more the Ru center is deficient in electrons, the stronger it is as an oxidizing agent. Extending this analysis to different substitutents on pyridine ligands; donor groups will destabilize the radical anion generated upon MLCT; while electronwithdrawing groups will stabilize them. Therefore, EDG on pyridine ligands will render the corresponding photocatalysts stronger reducing agents, while EWG groups will promote the opposite effect, that is, to generate weaker reducing agents[146,152,153] (Figure 3).

The energy distance (Δ_0) between t_{2g} and e_g increases with the increase of the period (of the periodic table) of the metal employed, as well as the ion charge. Therefore, Ir^{3+} catalysts are generally more stable than Ru^{2+} catalysts and can hold numerous ligands of type LX, thus rendering more efficient charge transfers between the metal and the ligand (Figure 4).[146]

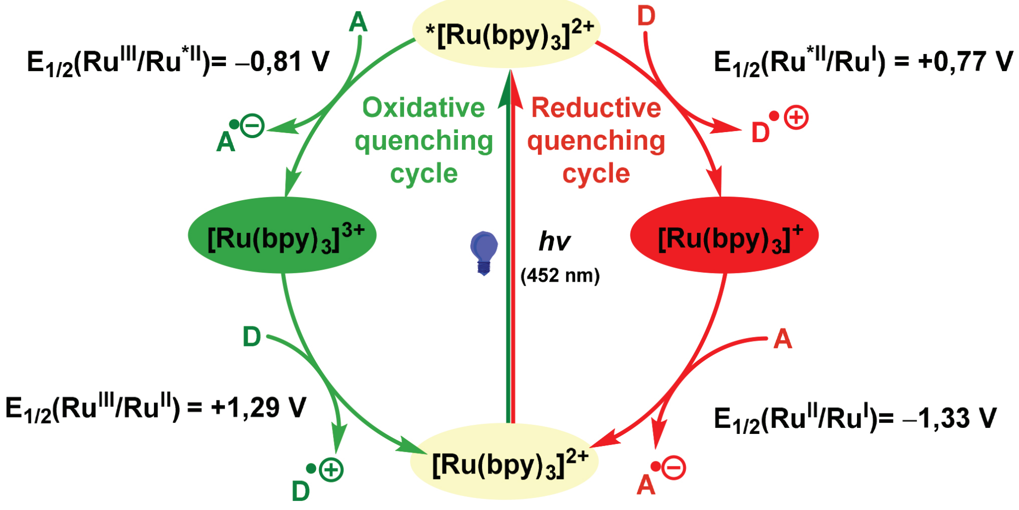
Early examples

An initial example in this field can be dated back to as early as 1978, when Kellogg and co-workers reported the $RuCl_2(bpy)_3$-photomediated reduction of sulfonium ion **1**, in the presence of 1,4-dihydropyridine **2**, to afford the corresponding reduced compound **3** and dimethylsulfide **4**[154] (Scheme 3a). Then, other reports from the groups of Fukuzumi and Tanaka,[155] and Pac[156] described similar catalytic systems, which allowed the reduction of electron-poor olefins, aromatic ketones and benzyl halides. Some years later, in 1984, Cano-Yelo and Deronzier described the first photoredox catalyzed reaction using aryldiazonium salts as terminal oxidants for the conversion of benzyl alcohols to the corresponding aldehydes.[157] They have also reported a photocatalyzed Pschorr reaction using $Ru(bpy)_3Cl_2$ for the conversion of (*Z*)-2-styrylbenzenediazonium salt **6** to the corresponding phenanthrene **7** in quantitative yield (Scheme 3b).[158]

In 1991, Okada and co-workers demonstrated that *N*-(acyloxy) phthalimides **8** could serve as a convenient source for alkyl radicals R^1-CH_2• (Scheme 3c). This radical can participate in Michael additions with electron-poor olefins leading to ketones **9**,[159] chlorinated products **10**,[160] phenylselenated compounds **11**[161] or reduced compounds **12**.[162,163]

Despite these initial efforts, examples in this field remained relatively scarce until the beginning of the 21st century. It was only in 2008, with the landmak work of Nicewicz and MacMillan,[119] that catalytic photoredox transformations started to attract the attention of the synthetic organic chemistry community (Figure 5).[164]

Among the most important developments made so far in the field of photoredox catalysis, its merger with metal catalysis has often allowed the development of new powerful protocols, which take advantage of the best of the two worlds: allow the access to highly reactive radical intermediates, as well as generate metal intermediates that can be more easily interconverted between different oxidation states. This review aims to present the most representative developments in this intersection, while critically presenting their reactivity profiles, scope and limitations.



Scheme 2. *Possible photoredox cycles accessible from* $[Ru(bpy)_3]^{2+}$

Table 1. Redox potentials and photophysical properties of photocatalysts in the presence of visible light[a]

entry	photocatalyst	$E_{1/2}$ (M^+/M^*)	$E_{1/2}$ (M^*/M^-)	$E_{1/2}$ (M^+/M)	$E_{1/2}$ (M/M^-)	life time of the excited state τ (ns)	excitation λ_{max} (nm)	emission λ_{max} (nm)
1	$Ru(bpz)_3^{2+}$	– 0.26	+1.45	+ 1.86	– 0.80	740	443	591
2	$Ru(bpy)_3^{2+}$	– 0.81	+ 0.77	+ 1.29	– 1.33	1100	452	615
3	$Ru(phen)_3^{2+}$	– 0.87	+ 0.82	+ 1.26	– 1.36	500	422	610[b]
4	$Ir[dF(CF_3)ppy]_2(dtbbpy)^+$	– 0.89	+ 1.21	+ 1.69	– 1.37	2300	380	470
5	$Ir(ppy)_2(dtbbpy)^+$	– 0.96	+ 0.66	+ 1.21	– 1.51	557	410	581
6	*fac*-$Ir(ppy)_3$	– 1.73	+ 0.31	+ 0.77	– 2.19	1900	375	494[c]

[a]Potentials are in V, in relation to SCE in MeCN, at r.t. [b]In water. [c]In 1:1 EtOH:MeOH at 77 K.

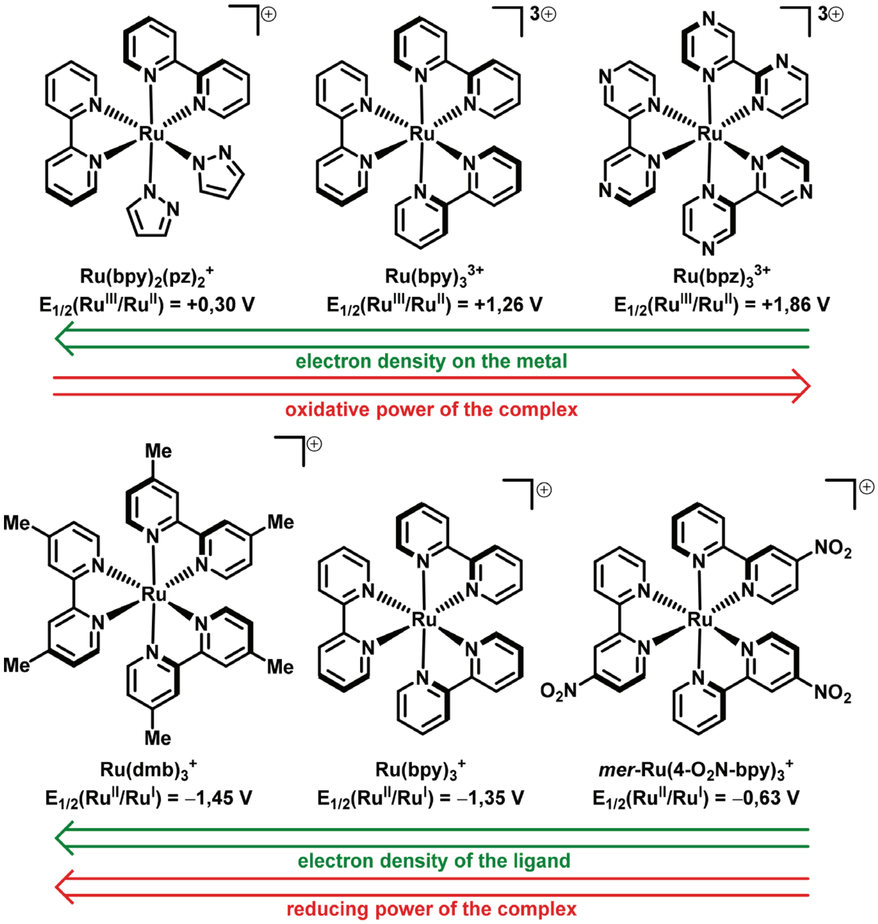


Figure 3. *Effect of the ligands on the redox properties of catalyst in the ground state*

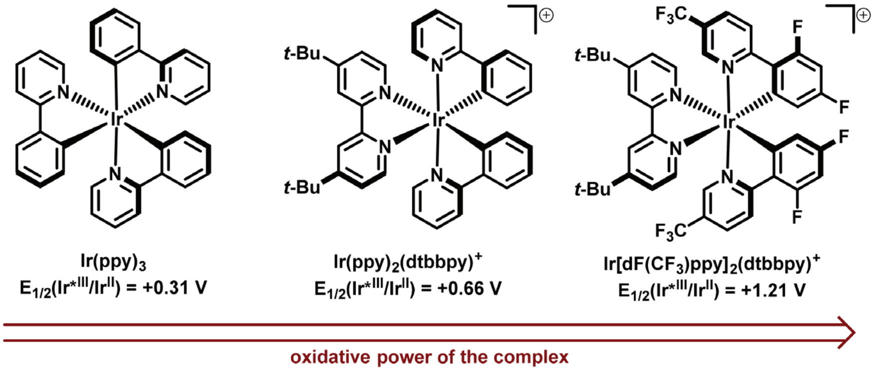


Figure 4. *Ir-based photoredox catalysts*

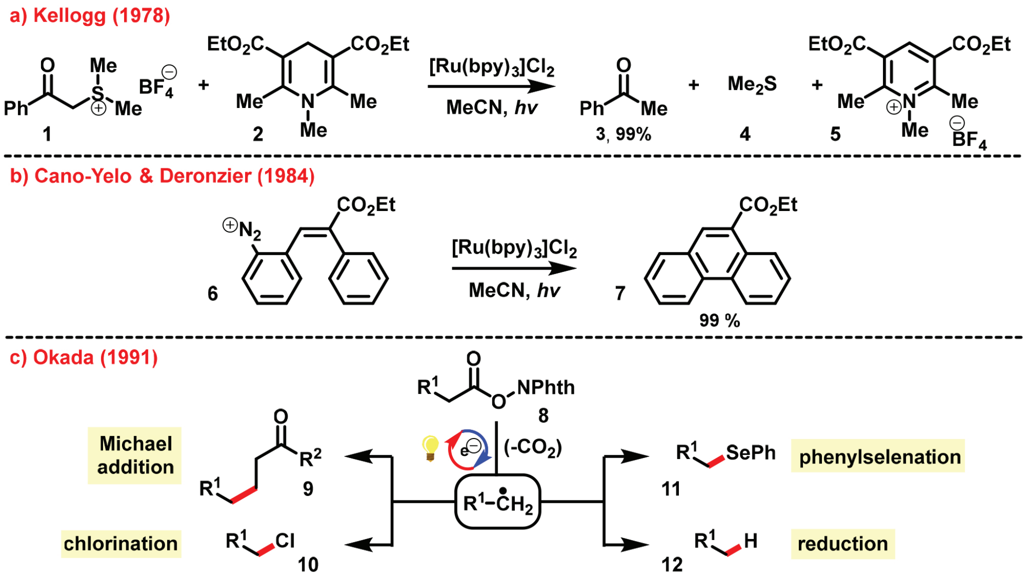
Merging photoredox catalysis and metal catalysis

The synergistic combination of photoredox catalysis with metal catalysis has appeared as a versatile strategy for the development of new synthetic methods. The use of photoredox catalysts allows the mild generation of radical species, which in the presence of metal catalysts, can afford the coupling with non-traditional partners. Overall, photoredox catalysis can modulate oxidation states of the organometallic complexes employed, thus facilitating individual steps of a number of catalytic cycles.[165]

Applications employing Pd

The combination of photoredox catalysis and metal catalysis has been accomplished for the first time in 2007, by Osawa and co-workers.[166] The use of Ru(bpy)$_3$$^{2+}$ and visible light has been observed to accelerate the Sonogashira cross-coupling between aryl halides **13** and terminal alkynes **14**, in the presence of Pd(MeCN)$_2$Cl$_2$ as catalyst, to afford the corresponding internal alkynes **15**. The authors remarked that the excited photoredox catalyst has facilitated the oxidative addition step, but more details of the mechanism were not provided (Scheme 4).

In 2011, Sanford and co-workers have investigated the arylation of C(sp^2)-H of 2-arylpyridines **16** and aryldiazonium salts **17**, in the presence of Pd(OAc)$_2$ and Ru(bpy)$_3$Cl$_2$.6H$_2$O as catalysts, under blue light irradiation.[167] In contrast to previous arylation protocols employing strong oxidants and/or high temperatures,[168] here, the use of a photoredox catalyst allowed the same transformation in the absence of any oxidant and at rt.[167]



Scheme 3. *Initial studies involving photoredox catalysis in organic synthesis*

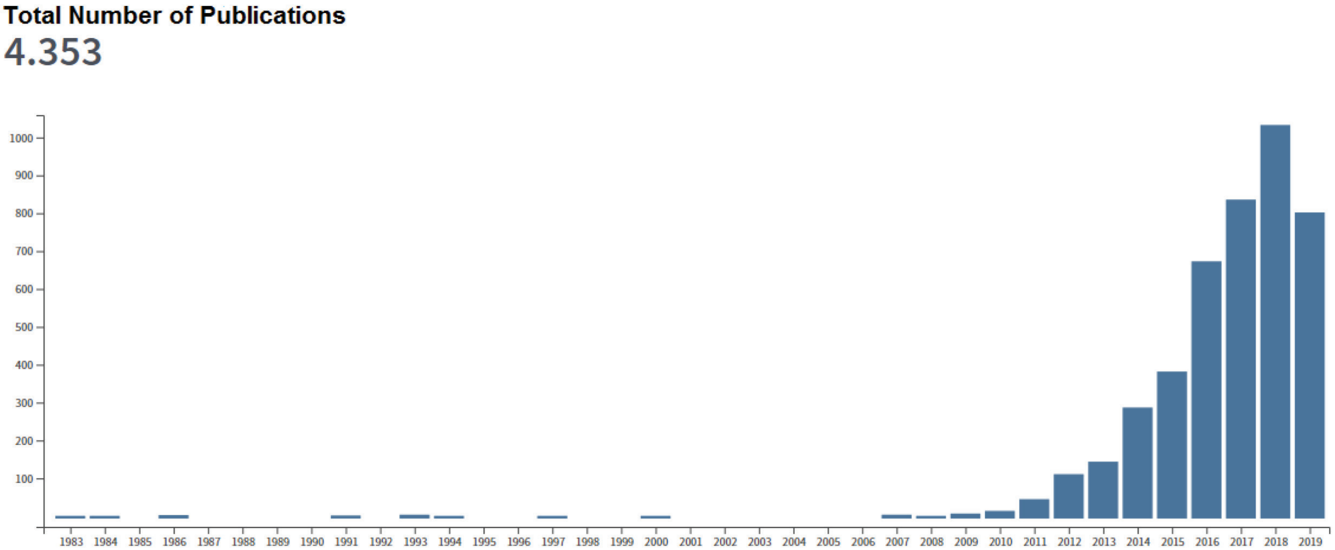


Figure 5. *Recent advances observed in the number of publications on photoredox catalysis. This evolution shows the hits for the term "photoredox catalysis"*[164]

In the proposed mechanism, a paladacycle **20** is formed upon a metallation-deprotonation step involving starting substrate **16** and the Pd catalyst. Simultaneously, the excited photoredox catalyst *Ru reduces the aryldiazonium salt **17** (via a SET process) to afford the aryl radical **19**. The aryl radical **19** inserts into the palladium intermediate **20** to form Pd(III) species **21**. Subsequent Ru(III)-promoted oxidation of this intermediate leads to Pd(IV) **22**, which then undergoes reductive elimination to produce the observed arylated products **18**, while regenerating a Pd(II) species[167] (Scheme 5).

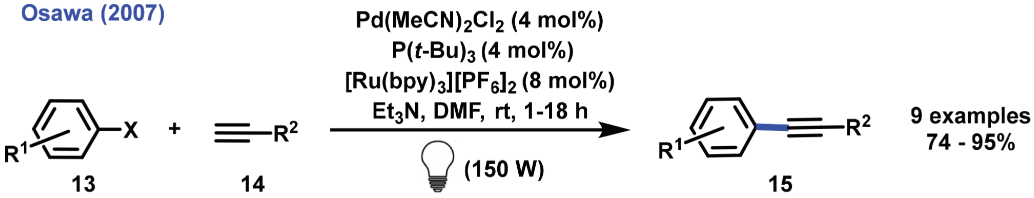
Years later, Rueping and co-workers reported a photoredox-catalyzed C-H functionalization protocol starting from aromatic enamines **23** in the presence of a Pd catalyst to produce indoles **24**, while employing molecular oxygen as the terminal oxidant.[169] The reported scope for this transformation included 15 examples, with yields varying from 57 to 95% (Scheme 6a).

In 2015, Wang and co-workers have demonstrated that it was possible to perform a decarboxylative C-H acylation of phenylamides **25** using α-ketocarboxylic acids **26** in the presence of eosin Y and $Pd(OAc)_2$ as catalysts to afford the desired compounds **27** (Scheme 6b).[170] In this same context, Tunge and co-workers reported a photoredox co-catalyzed decarboxylative Tsuji-Trost reaction converting allyl esters **28** to allylic compounds **29** (Scheme 6c).[171]

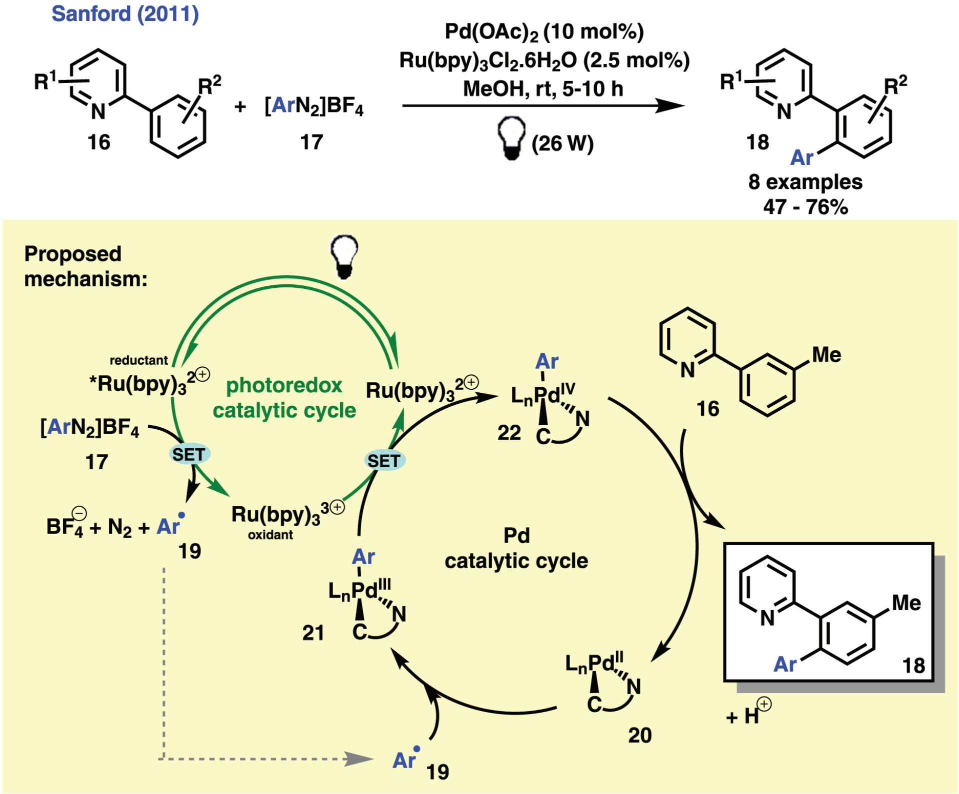
Applications employing Cu

Trifluoromethylation strategies are important because the CF_3 group can increase the metabolic stability of drugs, improve its permeability into membranes and favor protein-ligands interactions.[172] In this context, Sanford and co-workers reported a protocol employing photoredox catalysis and Cu catalysis for the reaction of boronic acids **30** with CF_3I **31** to afford the corresponding trifluoromethyl arenes **32**.[173] In the proposed mechanism, the trifluoromethyl radical **33** is generated from the Ru(I)-promoted reduction of CF_3I, followed by addition of the resulting radical **33** to the $Cu(II)X_2$ complex to generate Cu(III) intermediate **34**. Then, this new Cu(III) species **34** undergoes transmetallation with the boronic acid **30** to afford a new Cu(III) species **35**. Finally, reductive elimination of **35** produces the corresponding trifluoromethylated arene **32**. An electron transfer between the oxidant, excited $^*Ru^{2+}$, and the Cu(I)X allows the turnover of both catalytic cycles (Scheme 7).

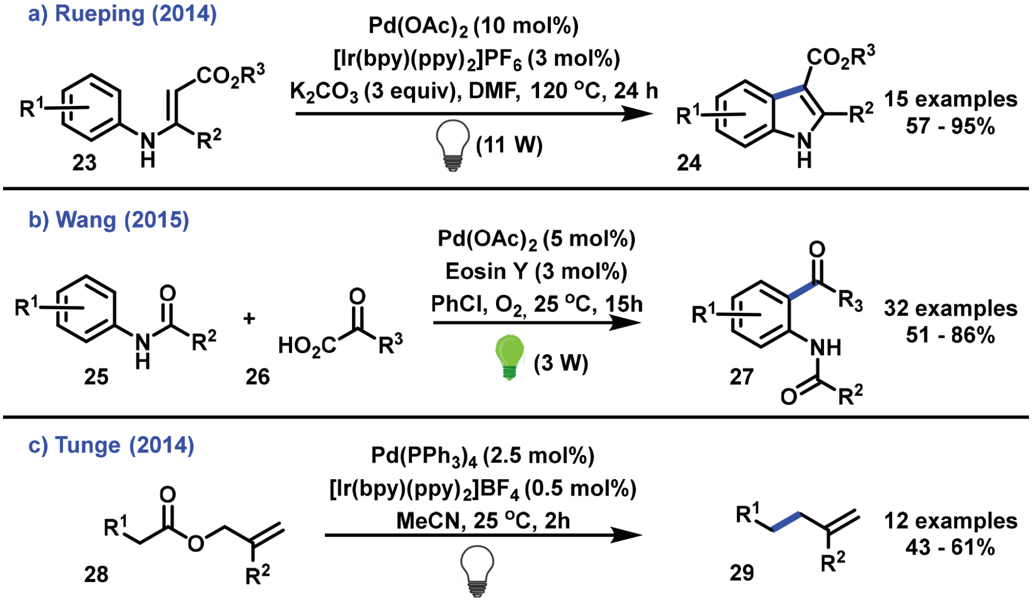
In 2015, Kobayashi and co-workers presented a photoredox catalyzed Cham-Lam coupling strategy between anilines **36** and boronic acids **30** to afford the corresponding diarylamines **37**.[174,175] In this context, boronic acids **30** carrying electronwithdrawing groups could be used and the authors proposed that the role of the photoredox



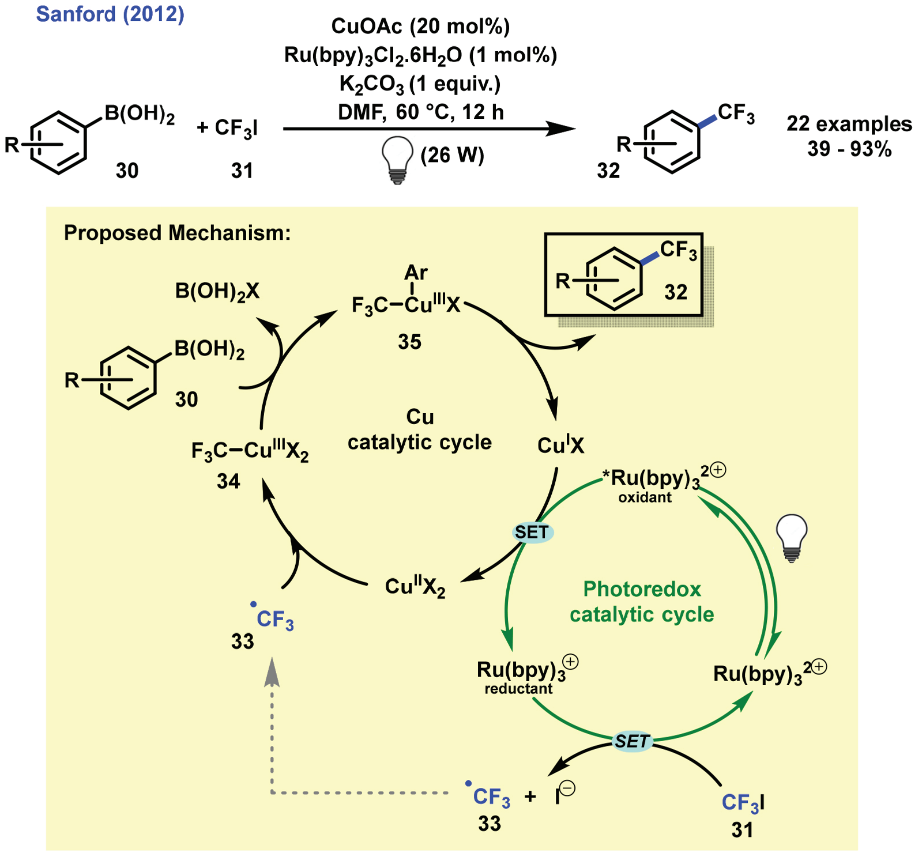
Scheme 4. Sonogashira cross-coupling using a Pd catalyst and a Ru photocatalyst



Scheme 5. Photoredox catalysis merged with Pd-catalysis for the arylation of C-H bonds



Scheme 6. Examples of cross-coupling reactions merging photoredox catalysis and Pd-catalysis



Scheme 7. An example of synergistic protocol for the trifluoromethylation of boronic acids

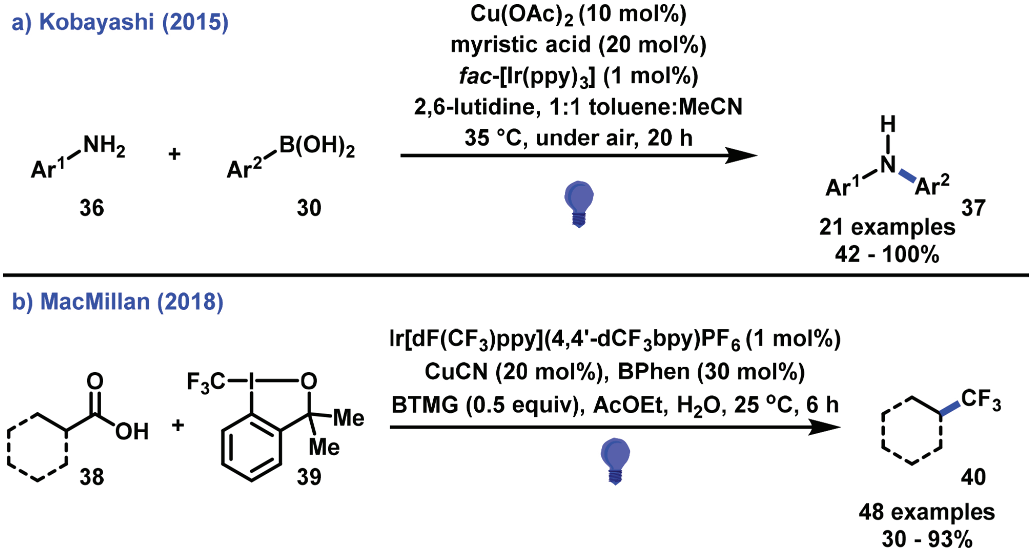
catalyst was to promote the efficient oxidation of Cu(II) to Cu(III) species, which could then undergo reductive elimination to produce the N-C coupling leading to amines **37**, while also generating Cu(I) intermediates. Finally, oxidation of Cu(I) intermediates by air is proposed to regenerate the Cu(II) species (Scheme 8a).

Another method that uses a Cu-catalyst in the presence of a photoredox catalyst has been established by MacMillan and co-workers.[176] A decarboxylative trifluoromethylation of aliphatic carboxylic acids **38** in the presence of Togni reagent **39** allowed the formation of C(sp^3)-CF_3 bonds for the corresponding trifluoromethyl compounds **40**. Several examples were reported, including the use of natural products and pharmaceutical drugs (Scheme 8b).

Applications employing Ni

Metal catalysis employing Ni has presented solutions to some challenging cross-coupling reactions involving C(sp^3). Their success is owned to the ability of promoting oxidative additions with alkyl halides, rather than undergoing β-hydride eliminations, which are fairly common to other metals, such as Pd.[177]

The first photoredox catalyzed transformations merged with



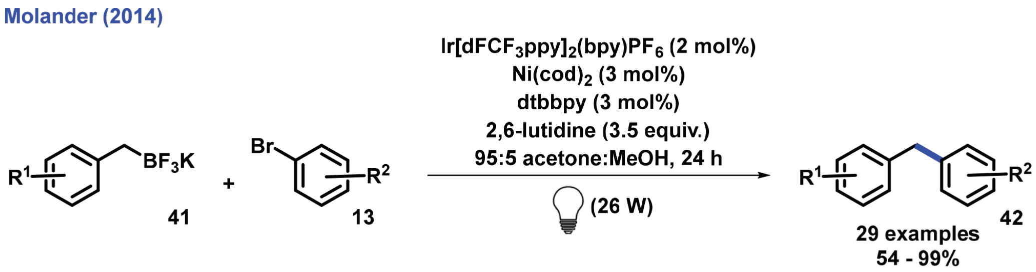
Scheme 8. Examples of catalytic processes merging Cu-catalysis and Ir-photoredox catalysis. (BPhen = bathophenanthroline; BTMG = 2-tert-butyl-1,1,3,3-tetramethylguanididine)

Ni catalysis have been reported by Molander and co-workers;[178] and Doyle, MacMillan and co-workers,[179] simultaneously and independently in 2014. The work of the Molander group described a C(sp^2)-C(sp^3) coupling between aryl radicals generated from a SET process involving potassium organotrifluoroborates **41**, aryl bromides **13** and an excited photoredox catalyst *Ir(III), in the presence of Ni(cod)$_2$ catalyst[178] (Scheme 9).

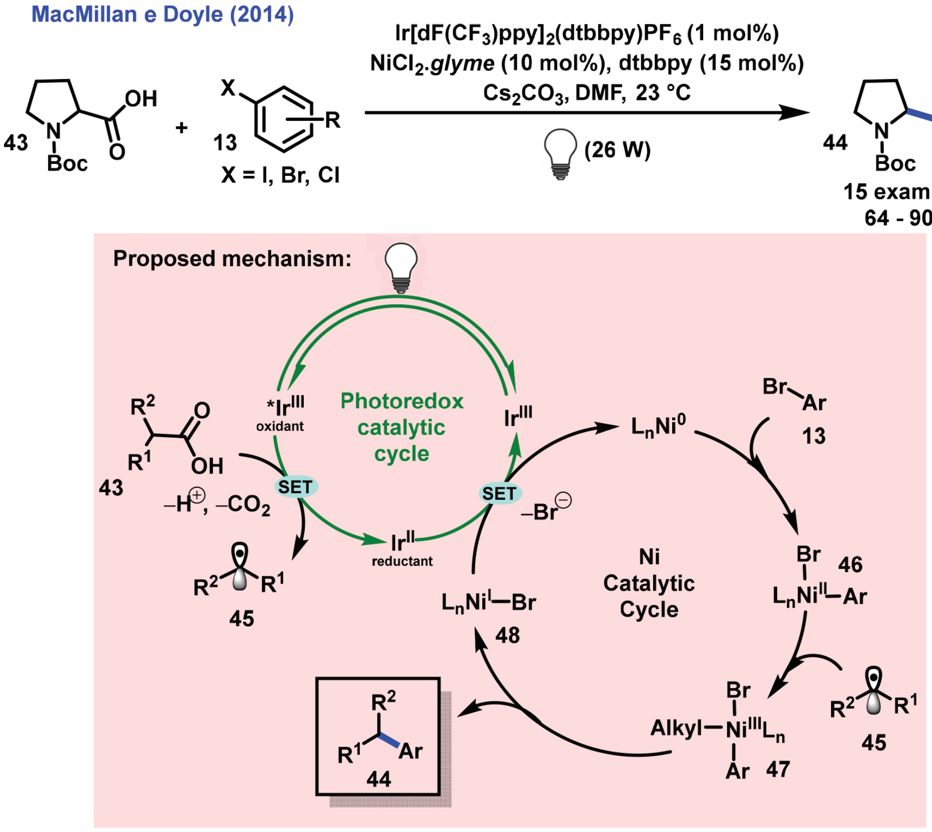
MacMillan and Doyle reported a decarboxylative coupling between carboxylic acids, such as **43**, and aryl halides **13** for the formation of the corresponding arylated amines **44**. In the proposed mechanism, the Ir(III) photoredox catalyst is excited by visible light to generate *Ir(III), which is a good oxidant. After the deprotonation of the α-aminoacid by the base, the oxidation of the substrate is promoted by *Ir(III) to afford an alkyl radical **45**. Simultaneously, the initial catalyst NiL$_n$ undergoes oxidative addition with the aryl halide **13** to produce Ni(II)-intermediate **46**, which rapidly intercepts the alkyl radical **45** to form organometallic complex Ni(III) **47**. Finally, reductive elimination from **47** generates the C-C bond of the final arylated compound **44** and the Ni(I) intermediate **48**, which undergoes a SET promoted by the Ir(II)-photocatalyst species, thus regenerating both starting catalysts, NiL$_n$ and Ir(III)[179] (Scheme 10).

In 2016, MacMillan, Fu and co-workers reported an efficient method for the decarboxylative enantioselective arylation of aminoacids employing aryl halides, by means of photoredox catalysis merged with Ni-catalysis. The corresponding arylated amines have been obtained in good yields and > 82% ee.[181] In addition, extension of this work to the use of vinyl halides,[181] and alkyl halides was also demonstrated (Scheme 11).[182]

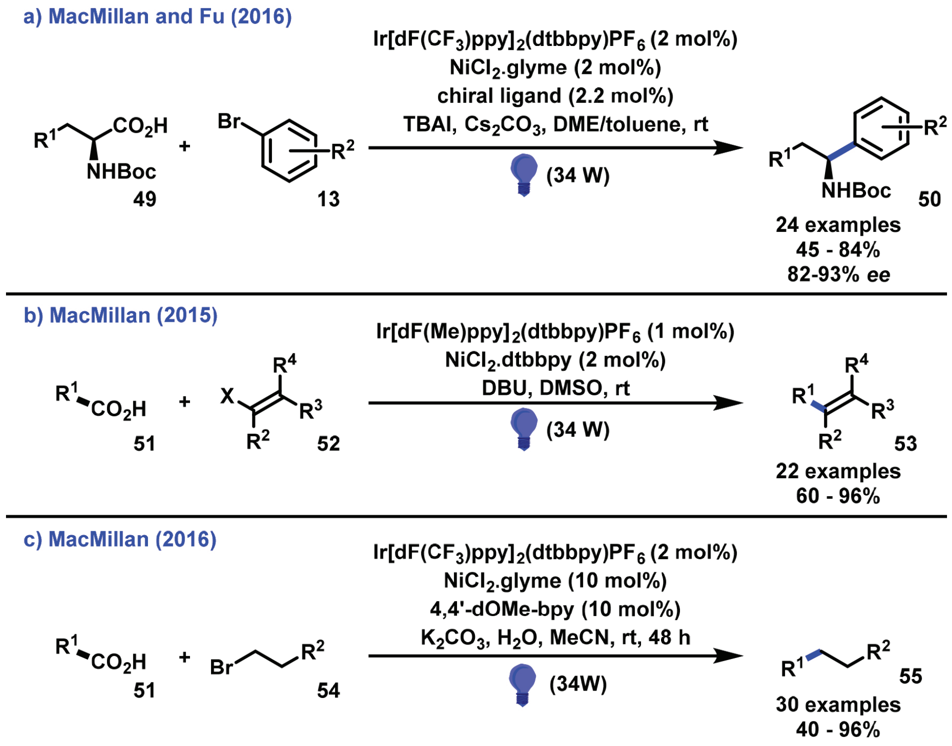
In the same context, MacMillan and co-workers have also described asynergistic combination of Ir(III)/Ni(0) catalysts, acting in the presence of (Me$_3$Si)$_3$SiH (TTMSS), for the C(sp^2)-C(sp^3) coupling between aryl halides **13** and alkyl bromides **56** to produce the corresponding arylated compounds **57**.[183] The mechanism of this transformation is believed to proceed via the generation of bromine radical **58** from a SET between the excited photocatalyst *Ir(III) and a bromide anion, followed by hydrogen abstraction from (Me$_3$Si)$_3$SiH to produce the corresponding silicon radical **59**. Then,



Scheme 9. Combination of Ir(III)/Ni(0) catalysts for the Csp^2-Csp^3 coupling between aryl bromides and potassium organotrifluoroborates (cod = 1,5-cyclooctadieene)



Scheme 10. Transformation merging an Ir(III)-photoredox catalyst and a Ni(0)-metal catalyst (glyme = 1,2-dimethoxyethane)



***Scheme 11.** Decarboxylative protocols employing Ni-catalysis and Ir-photoredox catalysis (TBAI = tetrabutylammonium iodide; DME = 1,2-dimethoxyethane; dF(Me)ppy = 2-(2,4)-difluorophenyl-5-methylpyridine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; 4,4'-dOMe-bpy = 4,4'-dimethoxy-2,2'-bipyridine)*

the silicon radical **59** reacts with the alkyl bromide **56** to generate an alkyl radical **60**, which adds to the Ni(II) species **61** (derived from the oxidative addition of aryl bromide **13** and Ni(0)L_n) to afford the Ni(III) intermediate **62**. Finally, reductive elimination leads to Ni(I) species **63**, which undergoes a single electron reduction from Ir(II)-photocatalyst to simultaneously regenerate Ir(III) and Ni(0) catalysts, as discussed in some of the previous protocols (Scheme 12).

In 2017, another protocol reported by the MacMillan group involved the combination of three types of catalysis: metallic, photoredox and organocatalyis. Using this approach, aldehydes **64** could be arylated with aryl halides **13** to the corresponding ketones **65** (Scheme 13).[184] Because the excited complex *Ir(III) is a strong oxidant, $E_{1/2}(\mathrm{Ir}^{*\mathrm{III}}/\mathrm{Ir}^{\mathrm{II}}) = +1.21$ V, it can remove one electron from quinuclidine to generate the corresponding radical cation **66**. In the presence of the aldehyde **64**, the radical cation of quinuclidine **66** abstracts a hydrogen atom to form the corresponding acyl radical **67**. Upon oxidative addition of the catalyst $NiBr_2$ with aryl halide **13**, which produces intermediate **69**, it undergoes addition of the radical **67** to generate the Ni(III) species **70**. Then, reductive elimination and single electron reduction of the resulting Ni(I) catalyst **71** produces the observed ketones **65** and regenerates both catalytic species Ni(0) and Ir(III). This reactivity has been demonstrated for several aryl bromides and some vinyl and alkyl bromides. In this context, aromatic, linear, branched and cyclic aldehydes can be also employed (Scheme 13).

Coupling reactions involving C-X (X = heteroatom) have been also investigated by means of the merger of Ni catalysis with photoredox catalysis. The formation of C-N bonds has been reported by the groups of Jamison,[185] Oderinde and Johannes,[186] Buchwald and MacMillan[187] and Molander[188] (Scheme 14). The work of Jamison involves the conversion of iodoacetanilides **72** and alkenes **73** to indolines **74**. Stoichiometric studies and cyclic voltammetry of the Ni complexes indicate that the oxidation of Ni(II) to Ni(III), which is promoted by the photoredox catalyst, is necessary for the C-N coupling, thus avoiding the formation of Heck-type products via a competitive β-elimination event[185] (Scheme 14a).

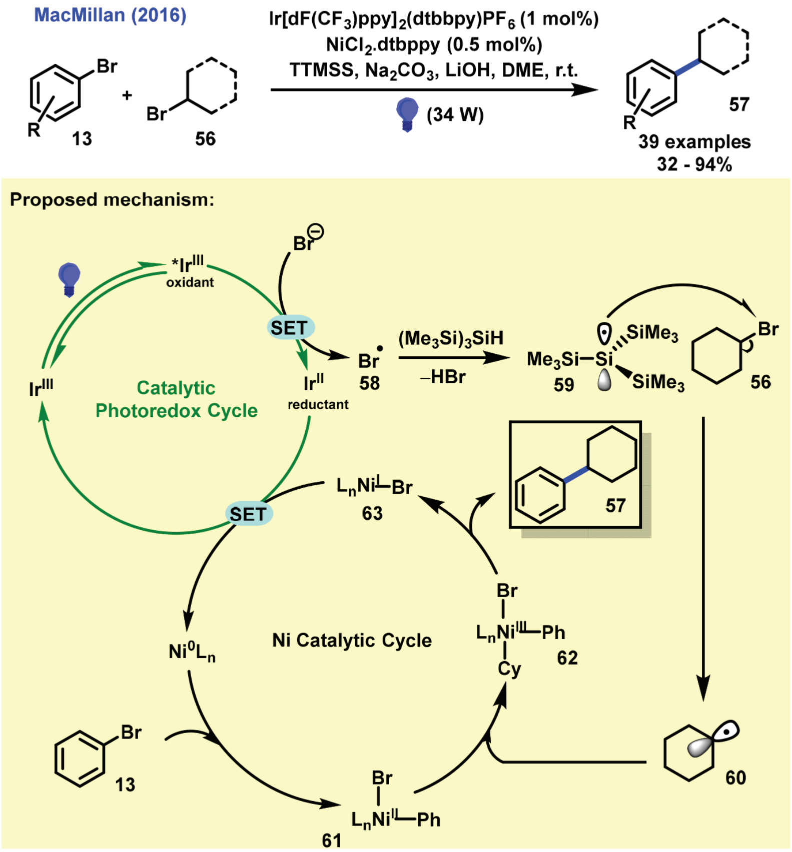
In 2016, Oderinde, Johannes and co-workers reported the formation of C-N bonds by the coupling of anilines **36** with aryl iodides **13** to afford diarylamines **37**. The Ir(III) photoredox catalyst is responsible for oxidizing the employed amine, and then to reduce the Ni(II) catalyst to Ni(I). This methodology is efficient and can tolerate several functional groups, such as alcohols, fluorides, chlorides, aldehydes, ketones, carbamates, eters, cyanides, ethers, thioethers, alkynes, among others[186] (Scheme 14b).

The formation of a C-N bond has been also described by Buchwald and MacMillan for the preparation of heteroaromatic amines **77** starting from aryl bromides **75** and amines **76** in the presence of a Ni(II) catalyst and an Ir(III) photoredox catalyst. In collaboration with Merck, the coupling between 18 drug candidates containing halides and piperidine derivatives has been tested. Among these tests, most of them (78%) presented the coupled product, therefore demonstrating the power of this strategy[187] (Scheme 14c).

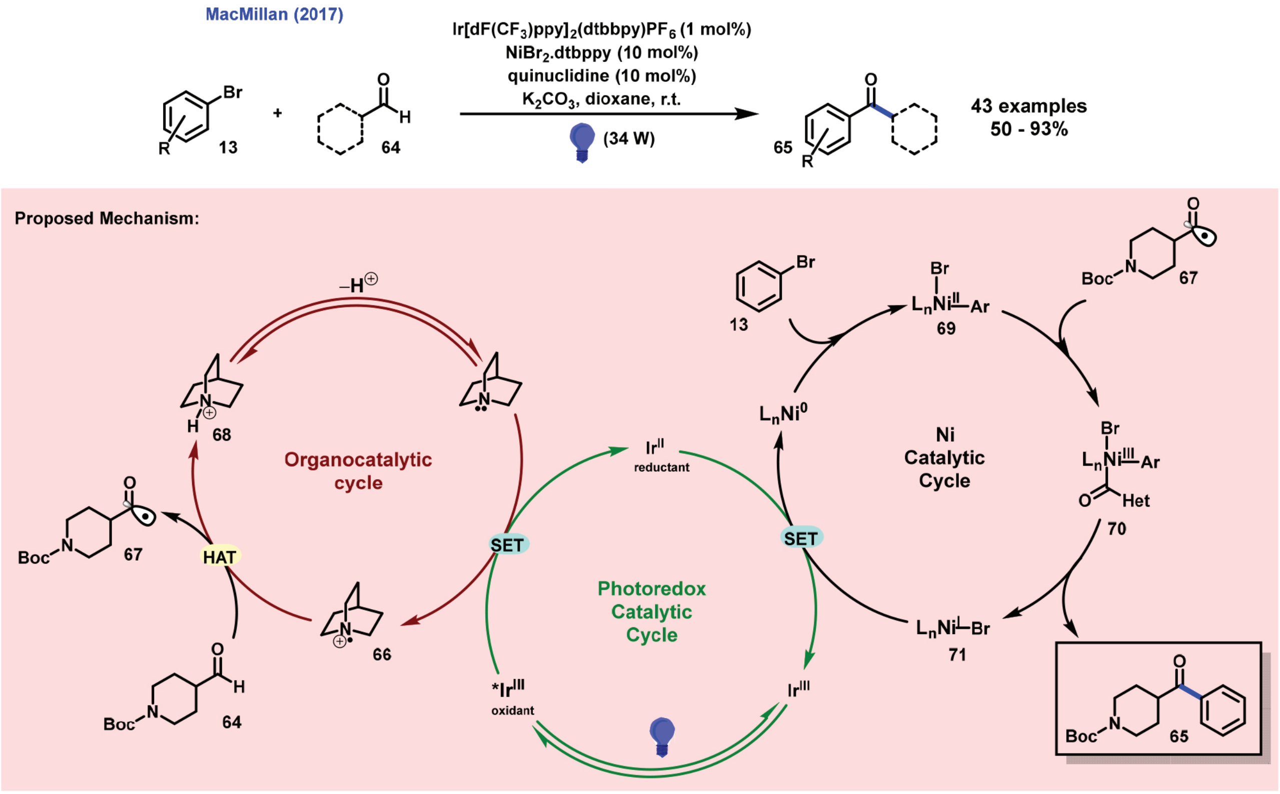
Recently, Molander reported a strategy of aminomethylation employing arylbromides **75** and a silylmethylamines **78** to produce the corresponding products **79** via a synergistic combination of Ni catalysis/photoredox catalysis. The relatively low redox potential of silylated methylamines allows the formation of α-amino radicals that can be engaged in cross-coupling transformations with numerous aryl halides[188] (Scheme 14d).

In 2015, MacMillan and co-workers reported the coupling between alcohols **80** and aryl bromides **13** for the formation of C-O bonds in ethers **81**. The *Ir(III) species oxidizes the Ni(II) catalyst **83** to Ni(III) intermediate **84**. Then, reductive elimination leads to the Ni(I) species **85**, while generating cross-coupled product **81**. Then, intermediate **85** is reduced by an Ir(II) species to to afford L_nNi(0), thus turning over both catalytic cycles[189] (Scheme 15).

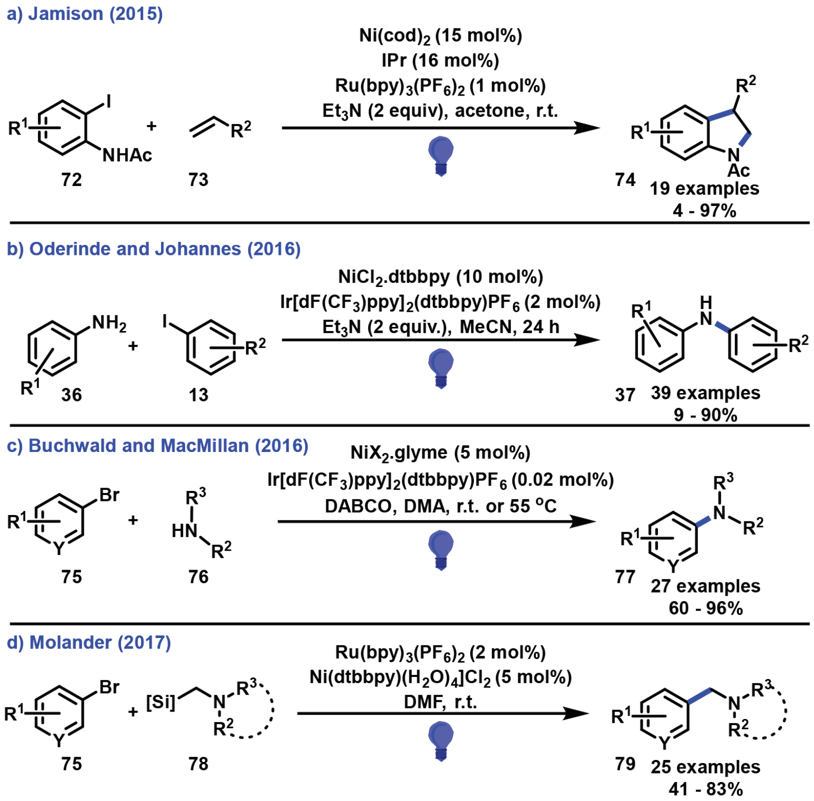
Aiming at the formation of C-S bonds, Oderinde, Johannes and co-workers reported in 2016 a thioetherification of aryl iodides **13** involving a sulfur radical formed from the oxidation of thiols **86** using an Ir(III) photoredox catalyst. The generated Ir(II) reduced the Ni(II)



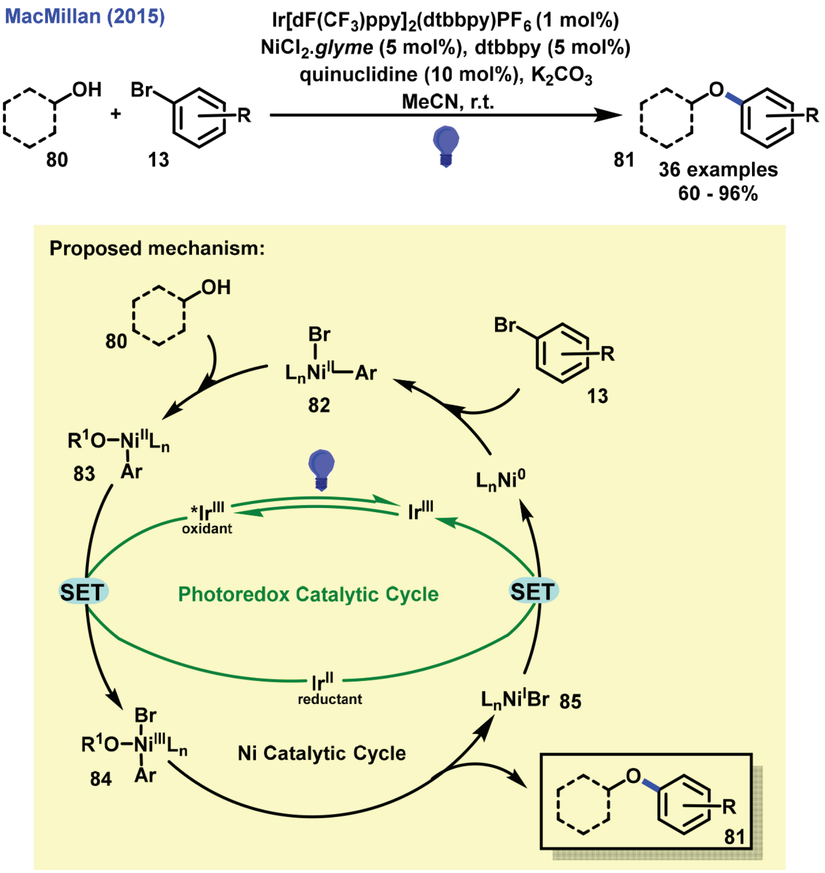
Scheme 12. Synergistic combination of Ir(III)/Ni(0) catalysts for the C(sp^2)-C(sp^3) coupling between aryl bromides and alkyl bromides (DME = 1,2-dimethoxyethane)



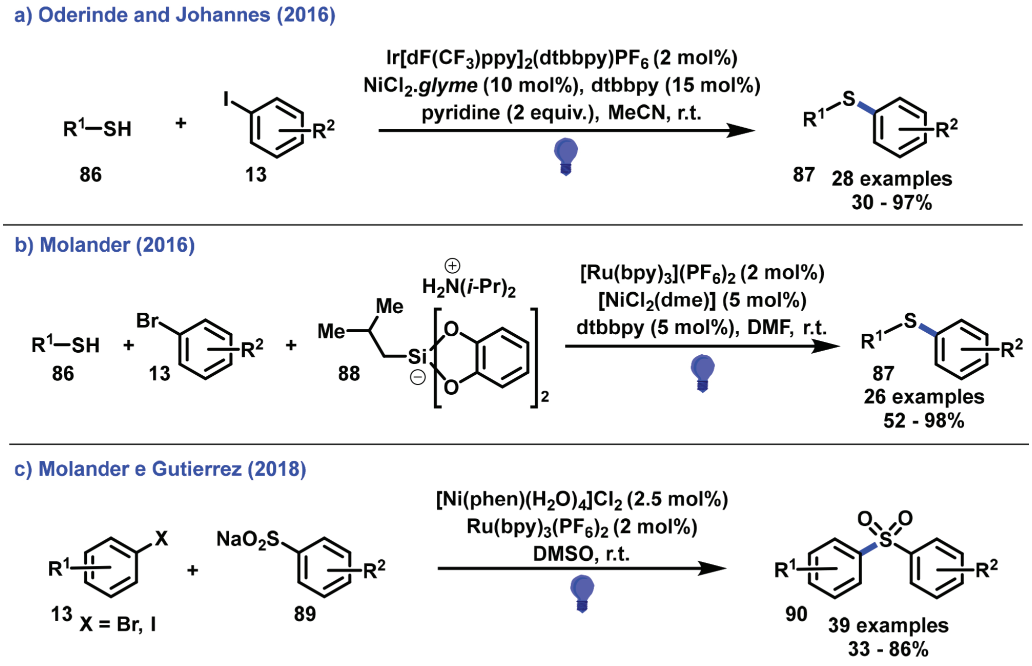
Scheme 13. C-H bond arylation of aldehydes via Ni catalysis, photoredox and organocatalysis



Scheme 14. Representative examples of protocols merging Ni catalysis and photoredox catalysis aiming at the preparation of more elaborated amines (IPr = 1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene; DABCO = 1,4-diazabicyclo[2.2.2]octane; DMA = N,N-dimethylacetamide)



Scheme 15. Formation of a C-O bond in ethers by means of the merger between Ni-catalysis and Ir-photoredox catalysis


a) Oderinde and Johannes (2016)

b) Molander (2016)

c) Molander e Gutierrez (2018)

Scheme 16. *Synergistic combination of Ni-catalysis and metal photocatalyst for the formation of C-S bonds (dme = dimethoxyetane; phen = 9,10-phenanthroline)*

species to Ni(I) and cyclic voltammetry experiments supported the porposed mechanism (Scheme 16).[190]

In the same year, Molander also reported a thietherification process of aryl bromides **13**. Following this strategy, a sulfur radical is generated from a hydrogen atom transfer from the alkyl radical resulting from the oxidation of isobutyl bis(catecolate)silicate **88** by the excited species *Ru(II) and a thiol **86**. This sulfur radical reacts with the Ni catalyst and the aryl bromide **13** to afford the corresponding arylthioether **87** (Scheme 16b).[191] It was possible to use primary, secondary or tertiary thiols in this transformation; and high selectivity was observed for the C-S coupling in the presence of a variety of functional groups.

Recently, Gutierrez, Molander and co-workers reported a method involving Ni catalysis and a Ru photoredox catalyst for the construction of aryl and heteroaryl sulfones **90**, starting from aryl halides **13** and sulfinate salts **89** (Scheme 16c).[192] A sulfonyl radical is formed from the oxidation promoted by the *Ru(II) species (thus generating a Ru(I) species) and adds to the Ni(0) species, thus generating a Ni(I) complex, that undergoes an oxidative addition in the presence of the aryl halide **13**. Finally, the resulting Ni(III) species undergoes reductive elimination to afford the sulfone **90** and generates a Ni(I) catalyst, that is finally reduced by the previously formed Ru(I) species to regenerate both Ni(0) and Ru(II) catalysts.

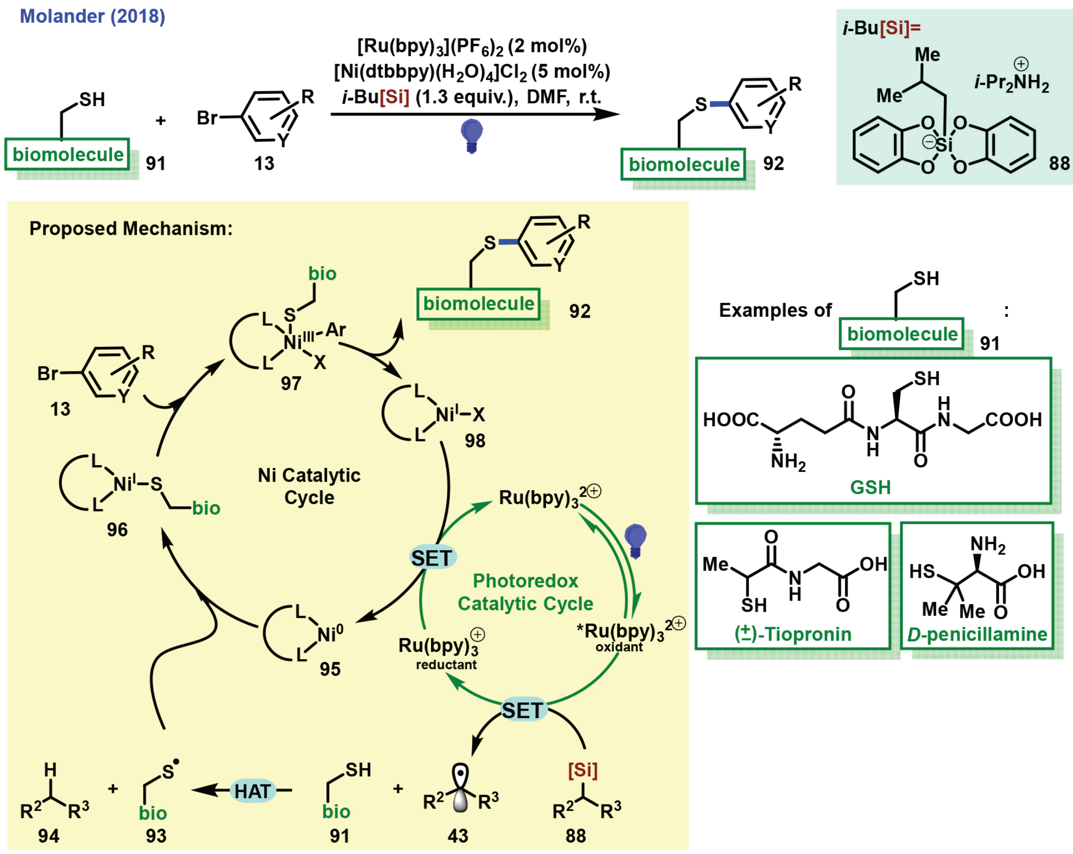
In addition, other similar photochemically-promoted cross-coupling reactions leading to the preparation of other sulfones have been also reported by Rueping[193] and Manolikakes.[194]

Molander and co-workers explored the interplay between Ni catalysis and photoredox catalysis to react aryl bromides **13** with SH-containing biomolecules **91** to afford the corresponding cross-coupled products **92**, in the absence of any protecting groups. The mechanism of this transformation is proposed to proceed by the generation of a sulfur radical **93** from a hydrogen atom transfer event between the biomolecule **91** and the alkyl radical **43**, which in turn is derived from the *Ru(II)-promoted oxidation of the silicon reagent **88**. Then, the thioradical **93** adds to the Ni(0) catalyst **95** to form the Ni(I) species **96**. This intermediate undergoes oxidative addition with the starting aryl halide **13** to produce the Ni(III) intermediate **97**. Finally, reductive elimination leads to the formation of the cross-coupled product **92**, while producing Ni(I) catalyst **98**. This catalytic species is reduced by the Ru(I) photoredox catalyst to regenerate both the Ni(0) catalyst **95** and the Ru(II) photoredox catalyst (Scheme 17).[195] This method can be performed in gram-scale and the scope of this transformation has been demonstrated to the use of L-glutathione, Tiopronin, D-penicillamine, biological probes, and pharmaceuticals.

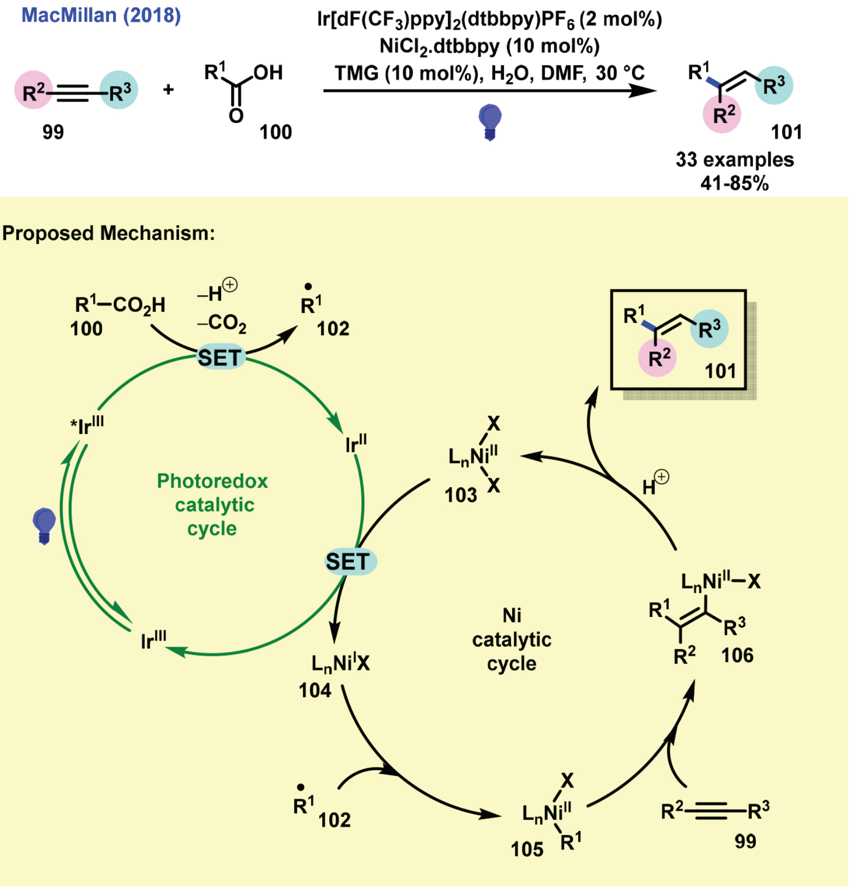
In 2018, MacMillan and co-workers reported a protocol for a decarboxylative hydroalkylation of internal alkynes **99** using carboxylic acids **100**, in order to produce the corresponding trisubstituted alkenes **101**. Accordingly, this transformation involves the *Ir(III)-promoted oxidation of carboxylic acids **100**, followed by a decarboxylation event to generate the corresponding alkyl radical **102**. Upon generation of the alkyl radical **102**, *Ir(III) is reduced to Ir(II), which is then oxidized back to Ir(III) by transferring one electron to Ni(II) species **103**, thus forming a Ni(I) intermediate **104**. The generated alkyl radical **102** adds onto the Ni(I) intermediate **104** to afford the corresponding Ni(II) species **105**. Subsequently, 1,2-insertion onto the internal alkyne **99** leads to Ni(II) intermediate **106**, which undergoes protodemetallation to produce the desired trisubstituted alkene **101** and Ni(II) catalyst **103**. Finally, a SET involving Ir(II) photocatalyst and Ni(II) intermediate **103** regenerates Ni(I) starting catalyst species **104** (Scheme 18). Control experiments have shown that the observed regioselectivity of the 1,2-migration involving Ni intermediate **105** and alkyne **99** depends on the size of the groups envolved.[196]

Applications employing Au

Oxidative additions between Au(I) and aryl halides are challenging[197] and the redox pair Au(I)/Au(III) is generally not easily interconverted.[198] Among some of the catalytic cycles reported for cross-coupling reactions involving gold, this challenging redox interconversion can be performed in the presence of an oxidizing agent or a photoredox catalyst. The merger of Au catalysis with photoredox catalysis has been reported by the first time by Glorius and co-workers in 2013.[199] They employed aryldiazonium salts **17** as the source of aryl radicals **19**, that were generated for the intramolecular oxy/aminoarylation of alkenes. The excited photoredox catalyst *Ru(II) reduces the aryldiazonium salt **17** to produce aryl radicals **19**, while Au(I) catalyst **109** promotes an intramolecular cyclization



Scheme 17. *Thioarylation of peptides and biomolecules by means of Ni catalysis and photoredox catalysis*



Scheme 18. *Decarboxylative hydroalkylation of carboxylic acids onto internal alkynes employing a synergistic combination of Ni-catalysis and photoredox catalysis (TMG = 1,1,3,3-tetramethylguanidine)*

event of starting substrate **107**, leading to organogold intermediate **110**. The Au(I) intermediate **110** reacts with aryl radical **19** to afford Au(II) intermediate **111**, which upon an electron transfer event converting Ru(III) into starting Ru(II), generates Au(III) intermediate **112**. Finally, reductive elimination of **112** leads to the cross coupled product **108** and regenerates the Au(I) catalyst **109** (Scheme 19). Remarkably, the formation of Au(III)-Ar complexes, such as **112**, typically produces a fast reductive elimination, thus avoiding protodeauration compounds and a potentially competing homodimerization pathway.

In contrast to the use of strong oxidizing agents employed in stoichiometric amounts for other gold-catalyzed cross-coupling protocols,[200] the merger with photocatalysis allows the use of mild conditions, based on an overall neutral redox conditions.

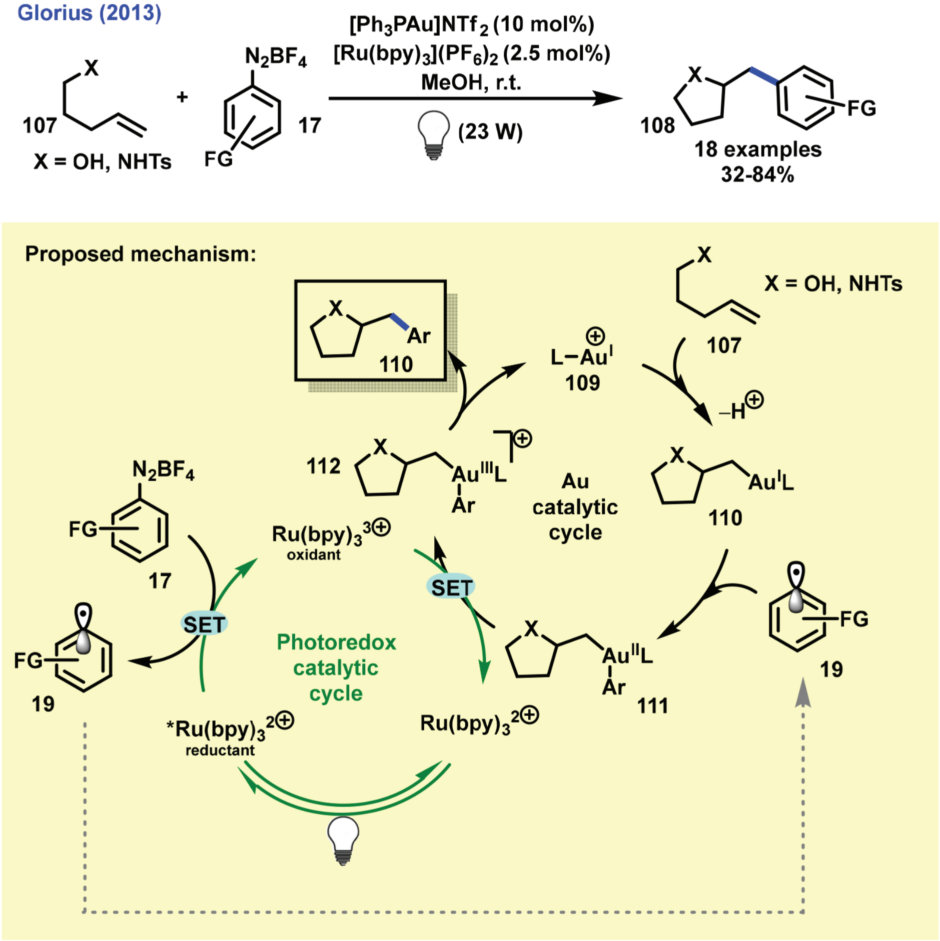
Inspired by the early work of Sanford,[167] Glorius and Toste have demonstrated that aryl radicals **19** generated by photoredox catalysis from aryldiazonium salts **17** could be employed in gold-catalyzed reactions in a variety of transformations, such as arylation of alkynes **113** or **119**;[201,202] *H*-phosphonates **115**;[203] in arylative-ring-expansions using substrates **117**;[204] arylation-hydration sequences usig alkynes **99** and α-arylation within Meyer-Shuster rearrangements of propargyl alcohols **121**[205] (Scheme 20).

Although the synergistic combination of metal catalysis and photoredox catalysis has been mainly composed of contributions employing Cu, Pd, Ni and Au as metal catalysts, other protocols involving Co,[206] Ru,[207] and Rh[208] have been also reported for C-H functionalization processes, C-C and C-O couplings and oxidation reactions.

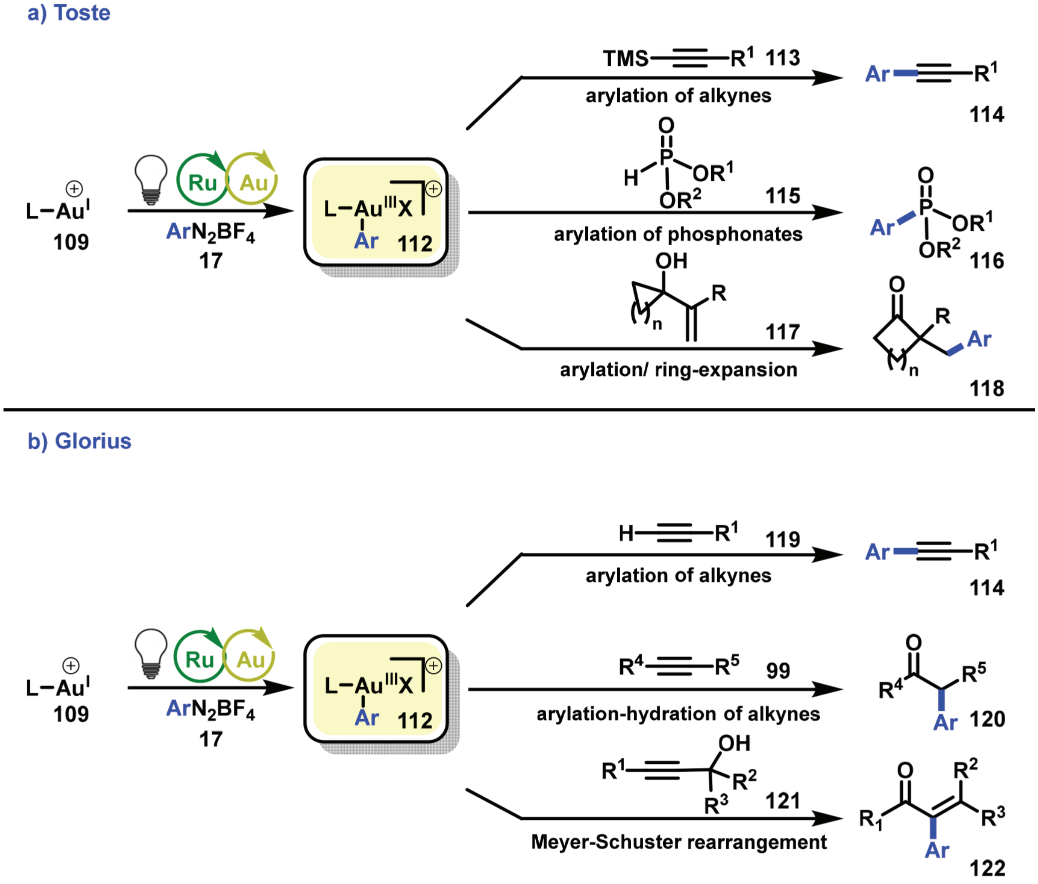
CONCLUSIONS

Since 2011, the synergism involving photoredox catalysis and metal catalysis has been used as a powerful strategy for the development of new synthetic technologies. In this context, advantages and disadvantages generally involve low catalyst loadings and potential toxicity issues associated to the use of metals, or sustainability aspects when rare metals are employed, respectively. Metal catalysis is a well-established field, which did not cease to evolve over the years. Nevertheless, the involvement of SET processes has allowed the development of new cross coupling protocols, most remarkably due to the involvement of new oxidation states of key catalytic intermediates (which are not as easily generated by other strategies). It is likely that the merger of both catalytic strategies will become increasingly important in the next years. It is possible to anticipate that new reactivity profiles will continue to be unlocked, proceeding via mild reaction conditions and significantly contributing to the broad advancement of organic synthesis.

Although economic aspects are always important to be taken into account, looking at the great number of publications appearing every year in the field of photoredox catalysis and metal catalysis in general; and the price of most common promoters, such as classical photoredox catalysts or Ni catalysts, their values do not seem to be a dominant barrier here for the advancement of this chemistry. Creativity and understanding the reactivity aspects underpinning these fields are far more important ingredients for the development of useful new protocols.



Scheme 19. *Oxi/amino-arylation of alkenes through the merger of gold catalysis and photoredox catalysis*



Scheme 20. Transformations performed by the groups of Toste and Glorius via the synergistic combination of gold catalysis and photoredox catalysis

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