# Metal-Catalysed Radical Carbonylation Reactions

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# ARTICLE

## Metal-Catalysed Radical Carbonylation Reactions

Siling Zhao[a] and Neal P. Mankad*[a]

A review of metal-catalysed carbonylation reactions involving single-electron transfer mechanisms and organic radical intermediates is presented, emphasizing new avenues to carbonyl compounds that are enabled by this approach. Catalyst-induced, oxidant-induced, and photo-induced radical carbonylations are discussed, as are atom-transfer carbonylation chain processes. Collectively, this body of carbonylative coupling chemistry complements more traditional precious metal-based catalytic systems that engage in substrate carbonylation by two-electron pathways.

## Introduction

Carbon monoxide (CO) is one of the cheapest and most readily available C1 synthons, and thus it is used as a lynchpin during industrial syntheses of many important carbonyl compounds (e.g. aldehydes, ketones, esters, amides).[1] In light of this proven track record of being involved in industrially-relevant processes, there continues to be great interest in developing new catalytic methods for carbonylative formation of value-added products from simple starting materials.
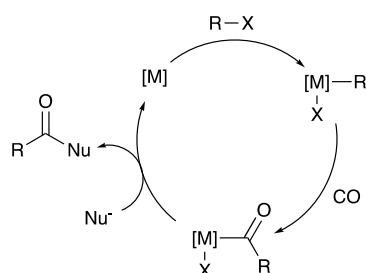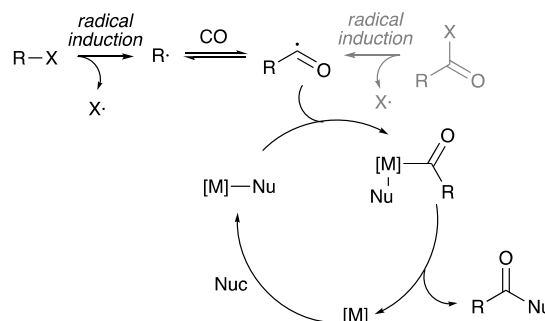


Scheme 1. General mechanism for precious metal-catalysed carbonylative coupling.

Established reaction classes in this area are typically catalysed by precious metal systems, including hydroformylation (Rh), carbonylative C-C coupling reactions such as the carbonylative Heck, Sonogashira, Suzuki, and related processes (Pd),[2] and formation of esters and amides from carbonylative C-X coupling of organohalides with alcohols and amines, respectively (Pd, Rh, Ir).[3] These precious metal-catalysed reactions operate by classical two-electron, oxidative addition/reductive elimination cycling mechanisms (e.g. Scheme 1). Such two-electron chemistry inherently favours coupling of C($sp^2$)-hybridized coupling partners, which undergo activation by oxidative addition quite readily. Activation of C($sp^3$)-hybridized coupling partners, on the other hand, tends

to be slow by oxidative addition pathways. More importantly, installation of C($sp^3$)-organyl ligands onto catalytic sites raises the possibility of β-hydride elimination side reactions competing with desired carbonylative coupling. These competitive elimination reactions are particularly problematic in carbonylation reactions, because both 1,1-migratory CO insertion and β-hydride elimination are accelerated by the presence of labile/open coordination sites. Indeed, most examples of Pd-catalysed carbonylative C-C and C-X coupling reactions involve either C($sp^2$)-hybridized partners or activated C($sp^3$)-hybridized species lacking β-hydrogens.

In direct, non-carbonylative C-C coupling chemistry, a renaissance of reaction development with C($sp^3$)-hybridized reactants has relied on the ability of 3$d$ metals (e.g. Ni) to favour single-electron transfer (SET) mechanisms over the two-electron chemistry of their 4$d$ and 5$d$ congeners (e.g. Pd and Pt).[4] The resulting reaction pathways involving net oxidative addition of electrophilic coupling partners to 3$d$ metals via radical intermediates favours C($sp^3$)-hybridized reactants and also raises the possibility of C($sp^3$)-H activation via H-atom abstraction. This behaviour of 3$d$ metal catalysts complements that of classical 4$d$ and 5$d$ systems and has opened a vast new reactivity landscape in cross-coupling catalysis.



Scheme 2. General mechanism for non-precious metal-catalysed SET carbonylation.

In comparison, SET approaches to carbonylative coupling catalysis are somewhat underdeveloped, possibly due to the

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propensity of the more labile 3$d$ metals to form inert polycarbonyl species (e.g. Ni(CO)$_4$) under CO atmosphere.[5] The successful examples that have emerged are the subject of this Mini-review. The prevailing paradigm (Scheme 2) for many of these transformations is for alkyl radical generation to occur by some method, such as metal-mediated SET, hydrogen or halogen atom abstraction, radical chain propagation, or photolysis. Under CO atmosphere, alkyl radicals are known to undergo carbonylation rapidly and reversibly to produce acyl radicals ($\Delta H° \sim$ -8 kcal/mol; $k_2 \sim 10^4$ M$^{-1}$s$^{-1}$)[6]. In some cases, the acyl radical is accessed by some other route to enter the same catalytic cycle (Scheme 2, grey pathway). When employing an appropriate metal, the resulting acyl radicals can then add to the catalytic site by SET oxidation, producing a high-valent metal-acyl intermediate poised for reductive elimination of a carbonylated product. The spectre of β-hydride elimination is circumvented because metal-alkyl intermediates are not necessarily involved in this mechanistic manifold. As summarized below, this paradigm has begun to enable new bond disconnections that lead to carbonyl compounds. The uncatalysed carbonylation chemistry of organic radicals has been reviewed thoroughly before[7] and will not be covered here. Similarly, the combination of SET carbonylation with Pd catalysis has been explored rigorously and reviewed thoroughly by Ryu,[8] and thus will largely be omitted from this Mini-review other than selected examples.

## Metal-induced radical generation

### Early metals (V, Mn)

Fujiwara and coworkers focused on carbonylation and carboxylation of small alkanes, mainly methane. Using a VO(acac)$_2$/K$_2$S$_2$O$_8$/CF$_3$COOH catalyst system, methane was quantitatively converted to acetic acid.[9] Although the detailed mechanism was not clear, a radical reaction pathway for the carbonylation was proposed, initiated by H-atom abstraction from methane by a high-valent vanadium(V) oxo species.[10]
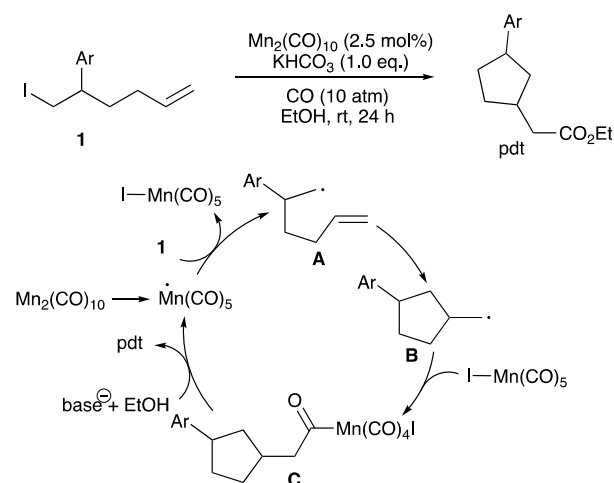


Scheme 3. Mn-catalysed carbonylative cyclization developed by Alexanian.

Based on seminal work by Heck and Breslow in 1963 on alkoxycarbonylation and aminocarbonylation of alkyl iodides catalysed by [Co(CO)$_4$]$^-$ and [Mn(CO)$_5$]$^-$,[11] several examples of carbonylative coupling reactions with alkyl halides catalysed by manganese carbonyls have been reported recently. The Alexanian group developed a practical manganese-catalysed carbonylation of alkenes to constitute diversified cyclic or bicyclic esters under very mild conditions (Scheme 3).[12] In the proposed mechanism, homolysis of Mn$_2$(CO)$_{10}$ produces the active [Mn(CO)$_5$]· catalyst.[13] Therefore, iodine atom abstraction then forms a carbon-centered radical **A**, which cyclizes to provide intermediate **B**. After a sequence of carbonylation and nucleophilic substitution via intermediate **C**, the carbonylated and cyclized product is delivered. Recently, another manganese-catalysed carbonylation of alkyl iodides or bromides was explored by Wu group.[14] To establish various imides from readily available amides, a Mn radical catalyst was similarly generated by thermolysis of Mn$_2$(CO)$_{10}$.
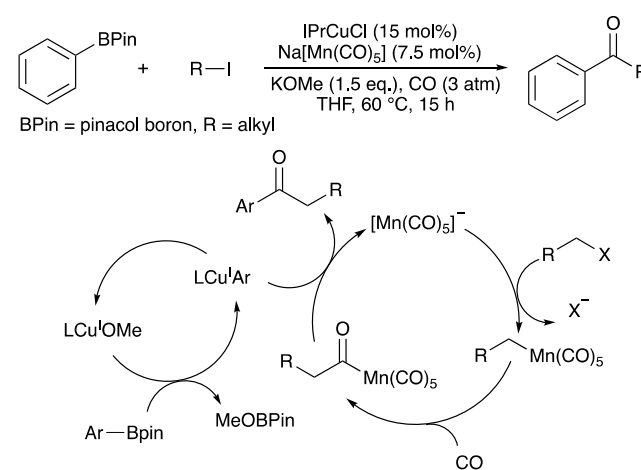


Scheme 4. Cu/Mn co-catalysed carbonylative Suzuki coupling developed by Pye et al. IPr = $N$,$N'$-bis(2,6-di-$iso$-propylphenyl)imidazol-2-ylidene.

Our group sought to replace the heteroatom nucleophiles in these Mn-catalysed carbonylation reactions with carbon nucleophiles. In 2017, we reported a carbonylative Suzuki coupling reaction of alkyl halides with arylboronic ester derivatives co-catalysed by (NHC)CuCl and Na[Mn(CO)$_5$] (NHC = $N$-heterocyclic carbene).[15] In the proposed mechanism (Scheme 4), alkylation of [Mn(CO)$_5$]$^-$ occurs by a radical rebound pathway. Subsequent carbonylation produces an electrophilic acylmanganese intermediate. Separately, transmetalation of the arylboronic ester nucleophile to the copper(I) catalyst produces a nucleophilic arylcopper(I) intermediate. A bimetallic C-C coupling step, whose plausibility was verified in a stoichiometric experiment, releases the ketone product and regenerates both co-catalysts. A key aspect of this process is the mild nucleophilicity of organocopper species, which prevent further addition to the carbonyl group in the ketone product. Primary and secondary alkyl iodides underwent coupling smoothly, and the reaction was found to be tolerant of several reactive and/or reducible functional groups.

## Late metals (Co, Ni, Cu, Pd)

de Bruin and coworkers developed a convenient [Co$^{II}$(Por)]-catalysed carbonylation of *N*-tosylhydrazones, occurring via cobalt carbene radical intermediates.[16] The ketene products can be converted to amides, esters, and $\beta$-lactams in one-pot tandem transformations. DFT calculations indicated the formation of a Co$^{III}$-carbene intermediate with carbon-based radical character after releasing N$_2$ from the diazo reagent. After CO addition and homolysis of Co-C bond, the released ketene is trapped by exogenous nucleophiles in the tandem transformations.
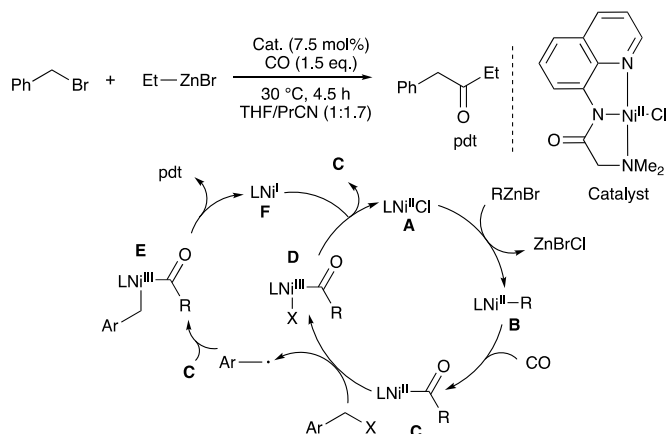
Scheme 5. Ni-catalysed carbonylative Negishi coupling developed by Skrydstrup.

Skrydstrup et al. reported a nickel-catalysed carbonylative coupling of benzyl bromides with alkylzinc reagents (Scheme 5).[17] To suppress the formation of inactive Ni poly(carbonyl) species, a *NN$_2$*-type pincer ligand was used to prevent coordination of multiple CO equivalents to Ni. Furthermore, controlled CO release was achieved using a solid CO precursor via a two-chamber reaction apparatus. Transmetallation between Ni(II) complex **A** and the alkylzinc reagent was proposed to produce intermediate **B**, followed by CO insertion to produce a acylnickel(II) intermediate **C**. Then a bimetallic oxidative addition occurs with **C** and benzyl bromide, resulting in Ni(III) complexes **D** and **E**. Reductive elimination from **E** delivers the ketone product and a Ni(I) species, which comproportionates with **D** to regenerate **A**.

A. Reductive coupling of alkyl halides with different electrophiles by Gong
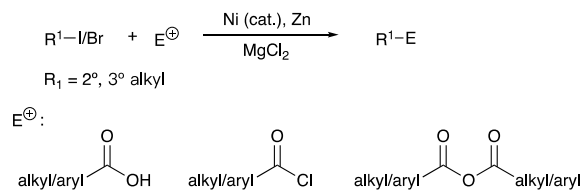
B. asymmetric reductive acyl cross-coupling by Reisman
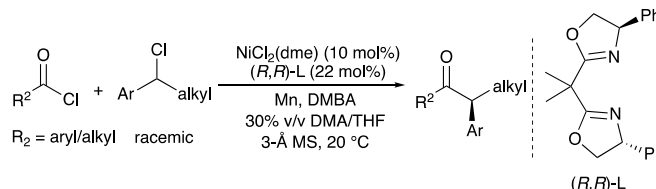
Scheme 6. Alkylketone syntheses using Ni-catalysed alkyl halide activation.

Gong and coworkers have reported a series of nickel-catalysed reductive couplings of secondary or tertiary alkyl halides with different carboxylate derivatives, such as free carboxylic acids,[18] acid chlorides,[19] and acid anhydrides,[20] to generate alkyl ketone products (Scheme 6A). Reisman reported an asymmetric variant using a nickel(II) catalyst and a chiral bis(oxazoline) ligand, allowing for coupling of acid chlorides with racemic benzyl chlorides to provide enantioenriched $\alpha,\alpha$-disubstituted ketones (Scheme 6B).[21] In another Ni-catalysed example, the Weix group established a cross-electrophile carbonylation between aryl bromides and alkyl bromides via nickel catalysis to deliver cross-ketones products.[22] While the mechanism was not established definitively, it is likely that alkyl bromide activation involves radical chemistry as is seen in Ni-catalysed, non-carbonylative cross-electrophile coupling also developed by Weix.[23]
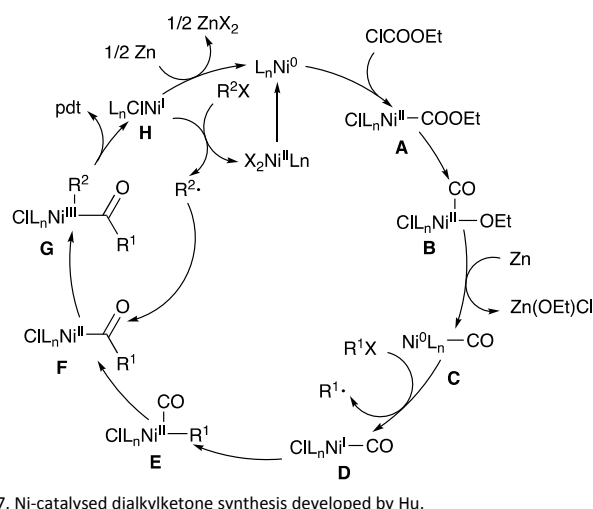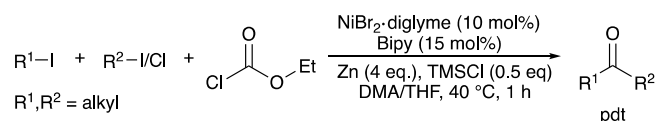
Scheme 7. Ni-catalysed dialkylketone synthesis developed by Hu.

Most recently, Hu and coworkers revealed a modular synthesis of dialkyl ketones from alkyl halides catalysed by nickel.[24] A safer and more convenient carbonyl source than CO gas, ethyl chloroformate, was used in this transformation. Both symmetric and unsymmetrical dialkyl ketones with variable functional groups were easily accessed under very mild conditions and within 1-2 h reaction time. According to the results from radical clock experiments, a radical pathway was proposed (Scheme 7). Alkyl halide activation by Ni(0)-carbonyl intermediate **C** occurs by a radical-rebound pathway, ultimately producing acylnickel species **F** after carbonylation. Simultaneously, a different alkyl halide is activated by nickel(I) species **H**, also through a radical pathway. This second radical is trapped by **F** to generate intermediate **G**, which releases the dialkyl ketone product by reductive elimination.
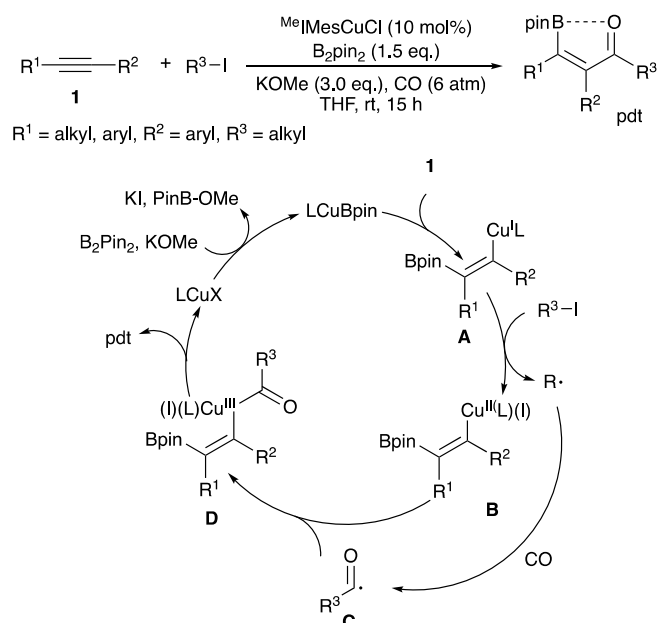


Scheme 8. Borocarbonylative coupling reaction of alkynes with alkyl iodides developed by Cheng & Mankad. $^{Me}$IMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dimethylimidazol-2-ylidene.

Our group developed a four-component carbonylative coupling using NHC-copper catalysis. With commercially available alkynes, alkyl iodides or bromides, $B_2pin_2$ and CO gas, a largely unknown class of tetrasubstituted, $\beta$-borylated $\alpha,\beta$-unsaturated ketones were readily acquired under mild conditions (Scheme 8).[25] Moreover, the $\beta$-borylated enones obtained from this method were further transformed to other valuable organic substances through reduction, oxidation, halogenation and protodeboronation. The catalytic cycle starts with the addition of the *in situ* generated (NHC)CuBpin catalyst to an alkyne, producing $\beta$-borylated alkenylcopper(I) intermediate **A**. Alkyl iodide activation by SET forms a Cu(II) complex **B**. Meanwhile, alkyl radical carbonylation occurs to afford an acyl radical **C**. Subsequently, radical **C** rebounds to intermediate **B** to yield Cu(III) complex **D**. Reductive elimination then expels the $\beta$-borylated $\alpha,\beta$-unsaturated ketone. When a silane reagent (PHMS) was using under similar

conditions in place of $B_2pin_2$, unsymmetrical dialkyl ketone were easily constructed from terminal alkynes and primary or secondary alkyl iodides via a tandem sequence of hydrocarbonylative coupling followed by in-situ 1,4-reduction.[26]
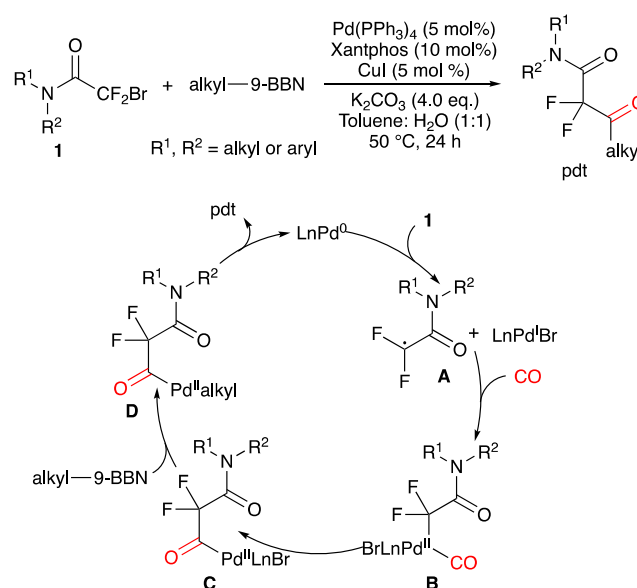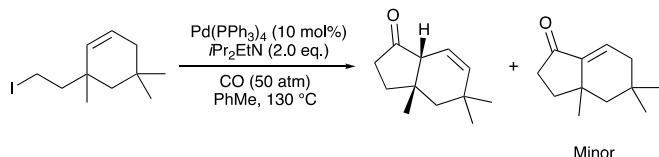


Scheme 9. Pd-catalysed carbonylative C–C coupling developed by Skrydstrup.

Apart from the Pd-catalysed, light-induced radical carbonylation reactions of Ryu referenced in the Introduction above,[8] a couple of thermal radical processes catalysed by Pd merit mentioning. Skrydstrup reported the carbonylative coupling of alkylboron reagents and bromodifluoroacetamides (Scheme 9).[27] This reaction goes through a radical pathway initiated by Pd(0) interacting with the bromoacetamide reactant. The resulting carbon-centered radical adds to Pd(I) species **B**, and CO insertion then takes place to yield acylpalladium(II) intermediate **C**. Stepwise transmetallation and reductive elimination expels the final product from **D**. Through this methodology, different $\alpha,$-difluoro-$\beta$-ketoamides were constituted in moderate to good yields. In addition, this manipulation is also useful for isotope labeling applications. Using the same CO-controlled technique mentioned above, the same group also realized a four-component carbonylative coupling.[28] A variety of perfluoroalkyl-substituted enones and indolin-2-ones were assembled from simple alkynes, aryl boronic acid derivatives, CO, and alkyl iodides. Closely related examples were reported contemporaneously by Liang and coworkers.[29]

Another set of thermal Pd-catalysed carbonylation reactions were developed by Alexanian and coworkers.[30] In 2010, they disclosed the Pd-catalysed carbonylative Heck reaction of alkyl iodides, focusing on intramolecular variants that provide valuable carbocycle products (Scheme 10A). A related alkoxycarbonylation of unactivated secondary alkyl bromides was developed by the same group in 2016 (Scheme 10B). A hybrid organometallic-radical pathway was supported by mechanistic investigations. Upon the treatment of Pd(0) with

an alkyl bromide, bromine-atom abstraction results in a carbon-centered radical and a Pd(I) intermediate. These two species then undergo either migratory CO insertion or radical addition to a bound CO ligand to afford an acylpalladium(II) intermediate. Finally, a nucleophilic displacement by alcohol releases the ester product.
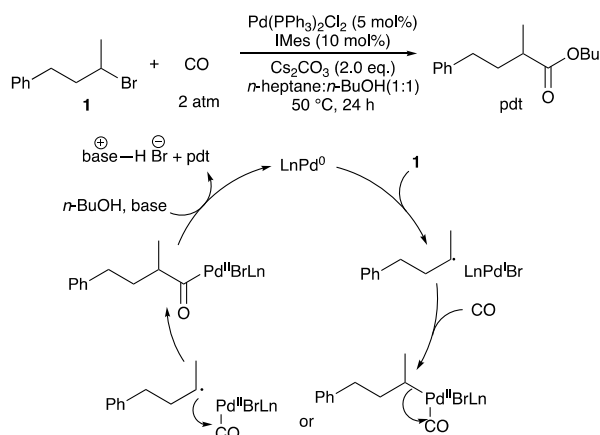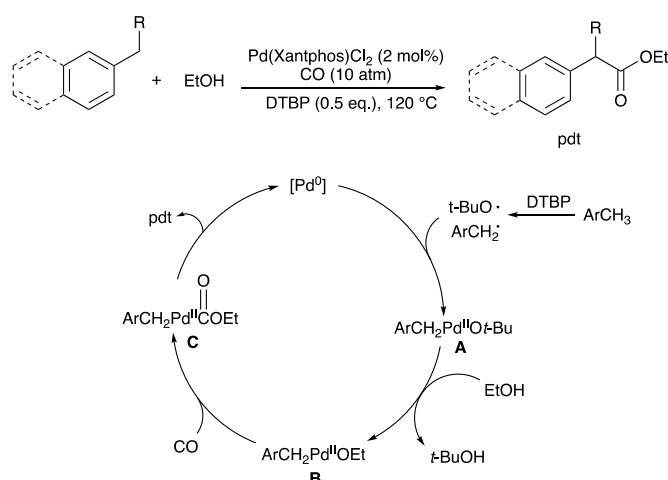


Scheme 10. Pd-catalysed carbonylative coupling reactions developed by Alexanian. IMes = *N,N'*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.
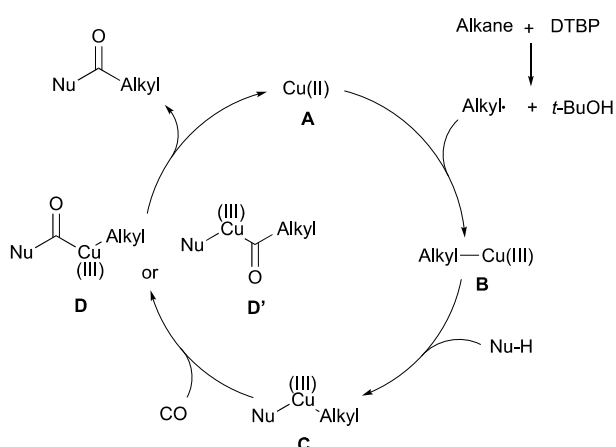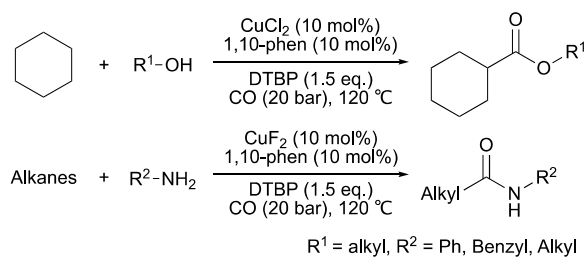
# Oxidant-induced radical generation

### Peroxide oxidants

In 2012, Huang and coworkers reported a Pd-catalysed oxidative alkoxycarbonylation of C($sp^3$)-H bonds (Scheme 11).[31] Di-*tert*-butyl peroxide (DTBP) was employed as the stoichiometric oxidant at 120°C and 10 atm, and a variety of functionalized alkylarenes underwent alkoxycarbonylation without assistance of coordinating directing groups. The proposed mechanism for this transformation involves the reaction of DTBP and alkylarene to produce *tert*-butoxy and benzyl radicals, both of which add to the palladium(0) catalyst to provide benzylpalladium(II) intermediate **A**. Carbonylation of **A** was reported to be slow due to steric hindrance, and so first alkoxide exchange with the ethanol nucleophile provides intermediate **B**, which then readily undergoes carbonylation, ultimately producing the product via reductive elimination of **C**.



Scheme 11. Oxidative alkoxycarbonylation of benzylic C-H bonds developed by Huang.

The Wu group reported remarkable radical carbonylation reactions coupling alkanes with nucleophiles under copper-catalysed conditions with di-*tert*-butyl peroxide (DTBP) as the stoichiometric oxidant (Scheme 12).[32] The authors proposed that reactions initiate with homolytic cleavage of DTBP, followed by hydrogen atom abstraction from a substrate such as cyclohexane by the *tert*-butoxy radical. The resulting alkyl radical adds to the copper(II) catalyst **A** to yield a copper(III) complex **B**. This complex **B** then undergoes ligand exchange with the nucleophilic partner (alcohol or amine) to produce intermediate **C**. Subsequently, CO insertion affords intermediate **D** or **D'**, followed by a reductive elimination to release the carbonylated product (ester or amide). Paraformaldehyde could be directly applied to this transformation to yield corresponding esters from the *in-situ* generated alcohol. A limitation of this noteworthy methodology is that site selectivity for C-H carbonylation was not well controlled for substrates such as *n*-pentane or *n*-hexane.

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carbonyl epoxides in one pot. Here it was proposed that TBHP reacts directly with the Fe catalyst, releasing alkoxy and alkylperoxy radicals.[37] The alkoxy radical then abstracts the aldehyde hydrogen to form an acyl radical, which adds to the alkene. Finally, addition of alkylperoxy radical terminates the reaction. The authors also observed a competing decarbonylation reaction when a pivaldehyde was subjected to these conditions, indicating that the aldehyde substituent provides kinetic control in this reaction.



Scheme 14. Carbonylation/peroxidation developed by Li.



Scheme 12. Oxidative C-H carbonylation developed by Wu.

In 2016, this methodology was extended to include the use of amides as nucleophiles.[33] A variety of acyclic secondary amides and lactams were reacted with cyclohexane to construct imides, excepting that *N*-phenylacetamide and *N*-phenylformamide only provided corresponding amides. The authors postulated that the desired imides decomposed under the high-temperature conditions.
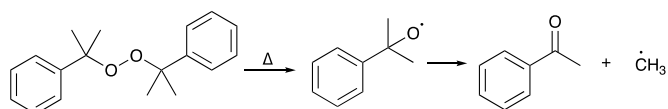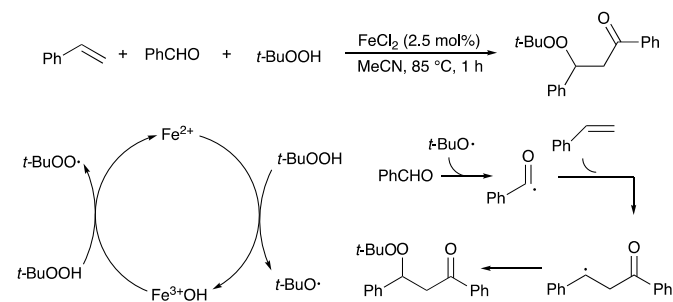


Scheme 13. Methyl radical generation from DCP.

In conducting the above reactions, Wu et al. observed formation of acetylated byproducts when using the TBHP oxidant. Motivated by this observation, they subsequently developed a method for acetylation of amines using dicumyl peroxide (DCP) as the oxidant as well as carbon source.[34] The reaction initiates by thermal homolytic cleavage of DCP, followed by methyl radical generation via a $\beta$-scission of the alkoxyl radical (Scheme 13).[35] The methyl radical intermediate then enters the same catalytic cycle shown in Scheme 12.

In 2011, Li group disclosed an iron-catalysed sequential carbonylation/peroxidation of terminal alkenes using TBHP as initiator and oxidant (Scheme 14).[36] By combining styrene, aliphatic or aryl aldehydes, and TBHP in acetonitrile, $\beta$-peroxy ketones were produced under mild reaction conditions. Subsequent treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was found to mediate further transformation to $\alpha$-
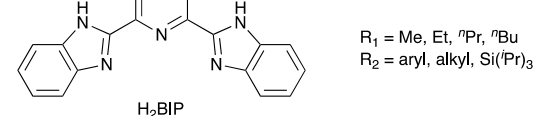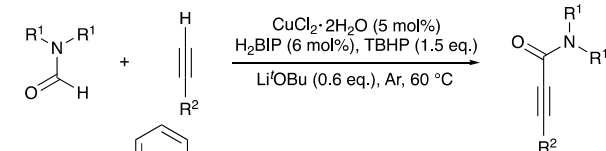
The groups of Reddy and Ye each reported copper-catalysed, TBHP-initiated carbamoylations. Reddy accessed various carbamates from benzoylacetates or *ortho*-substituted phenolic derivatives (Scheme 15A).[38] They proposed the formation of formamide radical[39] under the oxidative conditions,[40] since the radical scavenger TEMPO inhibited the reaction. Ye and coworkers published a cross-dehydrogenative coupling between terminal alkynes and formamides.[41] A tridentate ligand, 2,6-bis(benzimidazol-2'-yl)pyridine, was used to enhance the reactivity of the metal center by modulating the coordination capacity through responsive protonation/deprotonation at the imidazole moieties (Scheme 15B). However, this reaction was found to be highly sensitive to the steric environment of the formamide. Only *N,N*-diethylformamide (DEF) worked smoothly whereas DMF, *N,N*-di-*n*-propylformamide, and *N,N*-di-*n*-butylformamide were less effective.
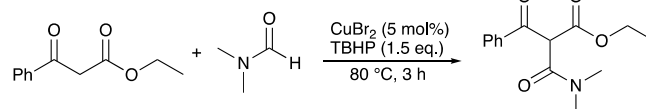


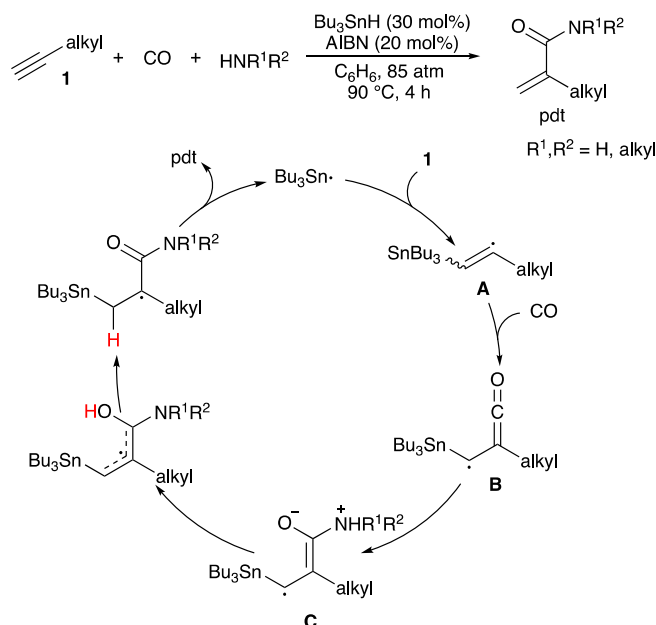Scheme 15. Cu-catalysed carbamoylation reactions.

## Azocarboxylate oxidants

Azo compounds can act as both initiators and CO sources in carbonylation of C($sp^2$)-H bonds. In 2016, Zhang et al. reported a cobalt-catalysed and 8-aminoquinoline group-assisted carbonylation to construct phthalimides (Scheme 16).[42] Based on mechanistic observations, they hypothesized that an esteric radical was generated through thermal decomposition of diisopropyl azodicarboxylate (DIAD). This radical then either attacked the Co intermediate **B** to furnish a Co(IV) intermediate **C** or underwent further decomposition to release CO, which subsequently inserted into complex **B**. Koley and coworkers investigated the same reaction but with a copper catalyst and 2,2'-azobisisobutyronitrile (AIBN) as initiator,[43] and Daugulis and coworkers reported a related strategy for cobalt-catalysed aminoquinoline-directed carbonylation of sulfonamide C($sp^2$)-H bonds using DIAD as the oxidant.[44] Here, a CN radical is generated from AIBN and oxygen.[45] Then a C-H cyanation is followed by hydrolysis to afford carbonylated product. However, electron-deficient benzamides were not applicable under these conditions. Zhong group also conducted a similar cobalt-catalysed, traceless directing group assisted, and regioselective C($sp^2$)-H carbonylation with diethyl azodicarboxylate (DEAD).[46]
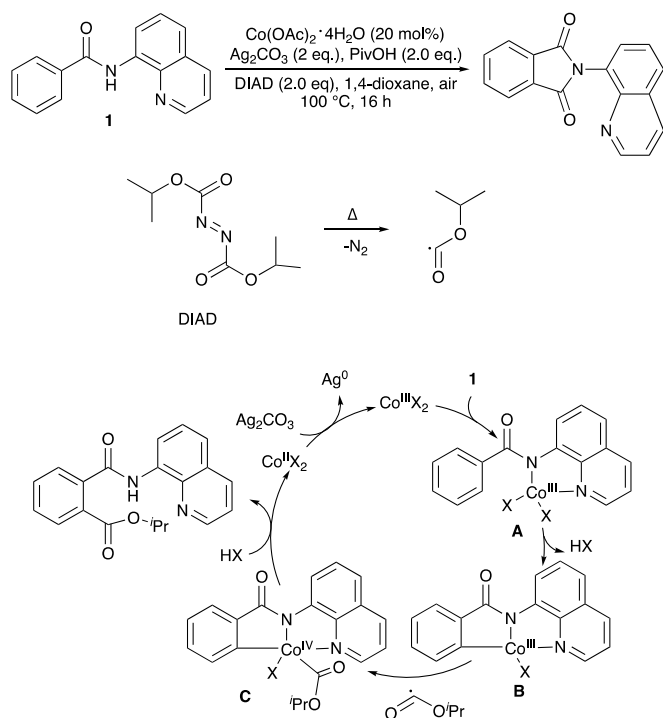


Scheme 16. Cobalt-catalysed C($sp^2$)-H carbonylation developed by Zhang.

Ryu employed a tin catalyst and AIBN to synthesize 2-substituted acrylamides from terminal alkynes, CO gas, and amines (Scheme 17).[47] A hybrid radical/ionic mechanism was proposed, starting with addition of the tributyltin radical to the alkyne substrate to form a vinyl radical **A**. Carbonylation of **A** generates α-ketenyl radical **B**, which is then attacked by amine to produce allyl radical **C**. After a sequence of 1,4-H shift and β-fission, the methylene amide product was delivered. The

plausibility of the 1,4-H shift was supported by DFT calculations, which predicted that the migration was favored by 80.0 kJ/mol.



Scheme 17. Sn-catalysed carbonylation developed by Ryu.

# Radical chain reactions and photochemistry

## Atom-transfer carbonylation

In attempting to expand the scope of the Cu-catalysed multicomponent coupling reactions described above (see Scheme 8), our group found that hydrocarbonylative coupling of alkynes with tertiary alkyl halides (or internal alkynes with any alkyl electrophiles) provided highly-substituted allylic alcohol derivatives (Scheme 18),[48] presumably via in-situ 1,2-reduction of the α,β-unsaturated ketone formed from the coupling reaction. The selectivity for 1,2-reduction of tertiary alkyl derivatives over 1,4-reduction observed with primary and secondary alkyl derivatives was rationalized on the basis of a computational model showing that the trajectory of (NHC)Cu-H approach towards the α,β-unsaturated ketone is highly sensitive to steric interactions. Crucially, a radical chain mechanism was proposed for tertiary alkyl electrophiles, contrasting the Cu-mediated radical generation proposed earlier for less substituted alkyl electrophiles (see Scheme 8). This mechanistic divergence was indicated by stoichiometric reactivity studies, which showed that alkenylcopper(I) intermediates resulting from alkyne hydrocupration are not sufficiently reducing to activate tertiary alkyl halides. Instead, a radical chain process initiated by the silane/base combination was proposed (Scheme 18).[49] In this atom transfer carbonylation chain, the tertiary alkyl halide is carbonylated without metal mediation, producing an acyl iodide intermediate. The acyl iodide then adds to the copper catalyst, ultimately expelling the coupled product by reductive

elimination. Mechanistic experiments confirmed the competency of acyl iodides as reaction intermediates for tertiary alkyl derivatives but not for primary or secondary derivatives.
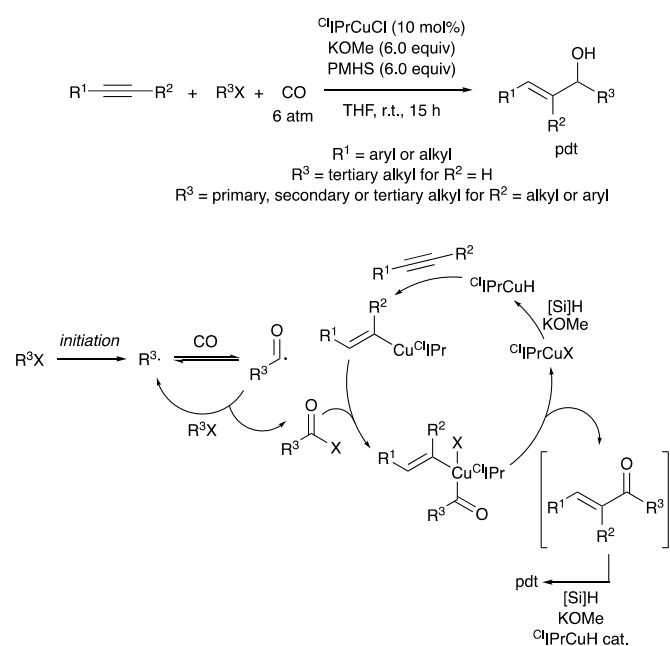
Scheme 18. Hydrocarbonylative coupling of alkynes with alkyl halides developed by Cheng et al. $^{Cl}$IPr = 1,3-bis(2,6-di-*iso*-propylphenyl)-4,5-dichloroimidazol-2-ylidene. PMHS = polymethylhydrosiloxane.

In the absence of the alkyne coupling partner, we also showed that the acyl iodide resulting from atom transfer carbonylation of alkyl iodides undergoes direct reduction by copper-hydride catalysis, first generating an aldehyde that is further reduced in situ.[50] The overall transformation, then, is a reductive hydroxymethylation of primary, secondary, and tertiary alkyl iodides to provide one carbon-extended alcohols (Scheme 19). Mechanistic experiments conclusively showed that a radical mechanism was operative, akin to the alkyne coupling reactions discussed above.
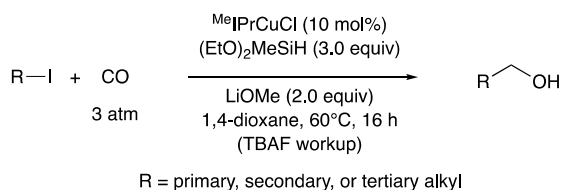
Scheme 19. Reductive hydroxymethylation of alkyl iodides developed by Zhao & Mankad. $^{Me}$IPr = 1,3-bis(2,6-di-*iso*-propylphenyl)-4,5-dimethylimidazol-2-ylidene

Recently, Wu and coworkers published an iron-catalysed carbonylation of tertiary carbon substrate involving 1,5-hydrogen atom transfer (Scheme 20).[51] First, radical generation is initiated by reduction of the *O*-benzyl oxime substrate by a low-valent species generated *in situ* from the precatalyst under CO. The resulting iminyl radical **A** goes through 1,5-hydrogen atom transfer to form a new carbon radical **B**. After CO addition to **B**, the Fe$^{(n+1)}$ is reduced by acyl

radical **C** to regenerate the Fe$^{(n)}$ catalyst and release an acyl carbocation **D**. Subsequently, intramolecular ring-closing followed by base-mediated double bond isomerization provides the final lactam. The same group reported a related alkyl acylation of heteroarenes using cyclobutanone oximes as the source of alkyl radicals,[52] as well as a Mn-catalysed variant on radical ring opening carbonylation.[53]
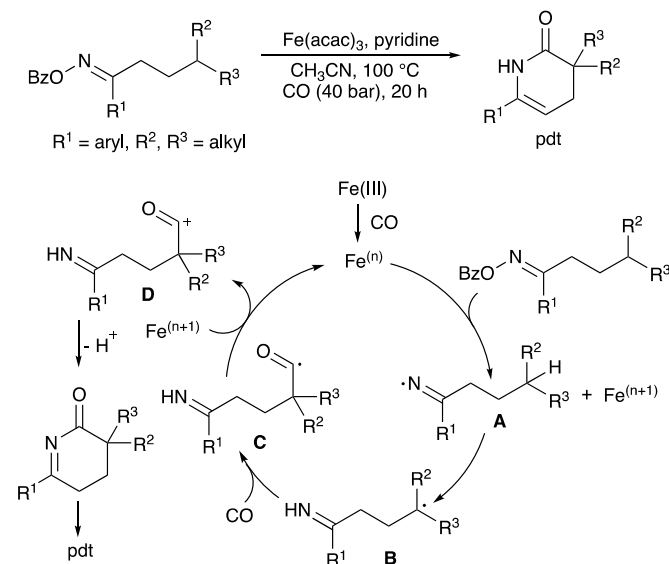
Scheme 20. 1,5-hydrogen atom transfer carbonylation developed by Wu.

## Photocatalysis

In 1991, Crabtree and coworkers used metallic Hg as a photocatalyst under 254-nm irradiation to carbonylate cyclohexane under mild conditions.[54] However, relatively poor selectivity (<60%) for the cyclohexyl aldehyde was observed under all conditions examined, with the main byproducts being cyclohexyl dimer from radical homocoupling and dicyclohexyl ketone. In a separate experiment, the researchers showed that exposure of aldehydes to the reaction conditions also produced the alkyl homodimers and dialkyl ketone products, indicating that the poor selectivity results in C-H carbonylation derive from reactivity of the photocatalyst towards the C-H bonds of both the cyclohexane reactant and the cyclohexyl aldehyde product.
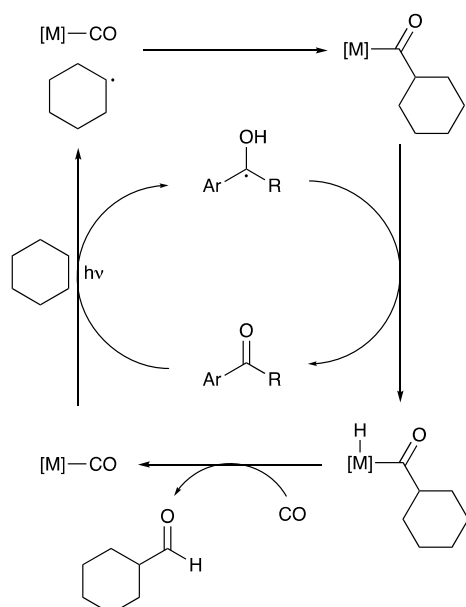
Scheme 21. Photocatalytic carbonylation of cyclohexane elucidated by Goldman.

Contemporaneously, it had been reported by both Eisenberg[55] and Tanaka[56] that more promising selectivity for photochemical C-H carbonylation could be attained by using metal-carbonyls such as Rh(PMe₃)₂(CO)Cl as photocatalysts under mild conditions (1 atm). However, several aspects of the reaction were poorly understood, including the curious observation that addition of benzene accelerated the reaction 10-fold. In 1992, Goldman studied the reaction mechanism in detail,[57] allowing for the discovery of optimal reaction conditions that call for a transition metal carbonyl catalyst (e.g. Rh(PPh₃)₂(CO)Cl, Rh(P$^i$Pr₃)₂(CO)Cl, Ir(PMe₃)₂(CO)₂Cl, Ru(CO)₃(dmpe) along with an aromatic carbonyl co-catalyst (e.g. benzaldehyde, benzophenone, acetophenone, *p*-(trifluoromethyl)acetophenone) under visible light irradiation ($\lambda > 340$ nm). Presumably, in previous studies the benzene additive was undergoing carbonylation to generate the aromatic carbonyl compound in situ. In the mechanism elucidated in this study (Scheme 21), the role of the aromatic carbonyl co-catalyst is to act as a H-atom shuttle, first abstracting hydrogen from cyclohexane and then delivering it to the metal-acyl intermediate formed subsequently. High selectivity for cyclohexyl aldehyde was obtained under these conditions, although with relatively low efficiency (TON < 10 with respect to the aromatic carbonyl co-catalyst).

Higher efficiency (TON > 50) while maintaining high selectivity (>90%) for C-H carbonylation of cyclohexane was achieved in 1995 by Hill, using the polyoxotungstate [$^n$Bu₄N]₄[W₁₀O₃₂] as the photocatalyst.[58] Here the polyoxotungstate plays a mechanistic role akin to the aromatic carbonyl co-catalyst in the Goldman system, abstracting a hydrogen atom from the alkane and then delivering it to the acyl radical resulting from free alkyl radical carbonylation to produce aldehyde. Less promising efficiency and selectivity results were obtained from other alkane substrates (cyclooctane, *n*-hexane, toluene).
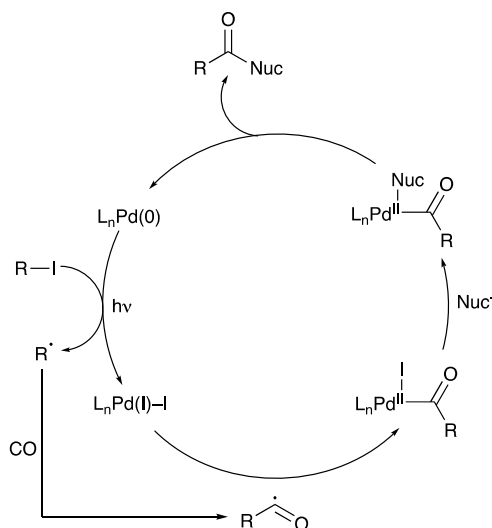


Scheme 22. General mechanism for Pd-catalysed photochemical carbonylative coupling reactions developed by Ryu.

Beyond these examples, the most promising examples of photocatalytic carbonylative coupling are the Pd-catalysed processes reported by Ryu. A general mechanism for these reactions is presented in Scheme 22, and we refer the reader to Ryu's excellent account on this topic.[8]

## Conclusions

In conclusion, several new bond disconnections have emerged in recent years which allow readily available C(*sp*³)-hybridized coupling partners such as alkanes and alkyl halides to be carbonylated under industrially relevant conditions, producing value-added carbonyl compounds that are useful synthetic building blocks for downstream processes. These reactions rely on the generation of acyl radicals either by carbonylation of free alkyl radicals or by activation of acyl electrophiles themselves. The key radical generation step requires either a transition metal catalyst, a stoichiometric oxidant, or a photoexcited species capable of mediating SET to the C(*sp*³)-hybridized partner. In analogy to direct C-C cross-coupling,[4] we expect the area of SET carbonylative coupling to grow as the reactivity landscapes reviewed here undergo further development.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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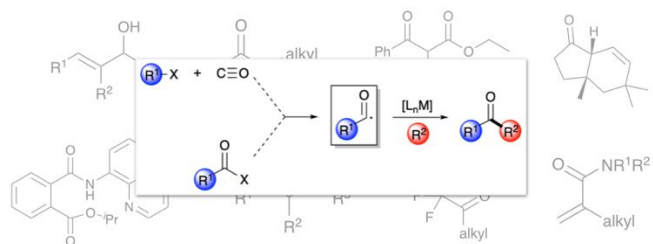
A review of metal-catalysed radical carbonylation reactions is presented.