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Palladium-Catalyzed Molybdenum Hexacarbonyl-Mediated Gas-Free Carbonylative Reactions

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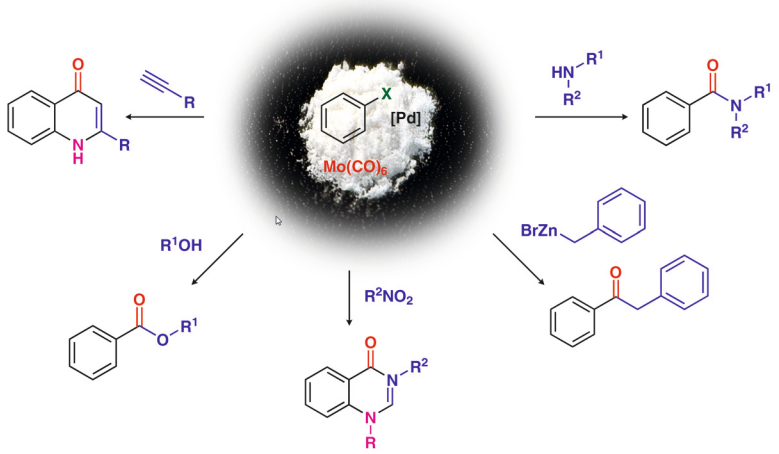

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Abstract This account summarizes Pd(0)-catalyzed $Mo(CO)_6$-mediated gas-free carbonylative reactions published in the period October 2011 to May 2018. Presented reactions include inter- and intramolecular carbonylations, carbonylative cross-couplings, and carbonylative multicomponent reactions using $Mo(CO)_6$ as a solid source of CO. The presented methodologies were developed mainly for small-scale applications, avoiding the problematic use of gaseous CO in a standard laboratory. In most cases, the reported $Mo(CO)_6$-mediated carbonylations were conducted in sealed vials or by using two-chamber solutions.

Key words carbonylation, molybdenum, multicomponent reactions, palladium, catalysis

1 Introduction

There has been considerable development in the carbonylation chemistry field since two of us authored the first Account on $Mo(CO)_6$-mediated CO gas-free carbonylative reactions.[1] The use of nongaseous CO sources has achieved general acceptance within the synthetic organic community and this update covers results from more than 50 new articles. As a consequence, this new Account, which covers the literature from October 2011 to May 2018, is substantially different from the first review. It contains more complex examples of carbonylative processes and new technologies such as the use of two-chamber systems for lab-scale synthesis and multicomponent reactions (MCRs). Highlighted methodologies were to a large extent selected from the authors' own laboratories.

In the late 1930s, hydroformylation with syngas (the Roelen reaction)[2] and hydrocarboxylation with carbon monoxide and water (the Reppe reaction)[3] were discovered. However, the finding by Heck and co-workers in 1974 that organohalides could be carbonylatively coupled with aliphatic alcohols and amines by employing catalytic amounts of Pd(0) represented a major step forward.[4–6]

The use of CO as a one-carbon building block has many advantages. The catalytic 1,1-insertion of the carbonyl moiety is highly atom-efficient and provides a valuable synthetic handle for further structural elaboration of the resulting carbonyl compound. Furthermore, carbonylations are in essence three-component reactions, and by varying the organohalide and nucleophile component, considerable product diversity can easily be achieved. Thus, Pd-catalyzed carbonylation reactions such as aminocarbonylation, alkoxycarbonylations, hydroformylations, and carbonylative cross-coupling reactions are now essential tools for radiochemists[7,8] as well as for synthetic and medicinal chemists.[6,9]

Despite the huge potential, the acute toxicity, flammable nature, and requirement for specialized lab equipment, such as metal reactors, in combination with the difficulty to detect leakages of the colorless and odorless gas have deterred synthetic chemists from fully applying the useful carbonylation methods despite their synthetic advantages. As a result, much recent effort has been invested in developing more convenient and safer methods for handling the toxic carbon monoxide gas.[6,10,11,12]

2 Recent Developments

2.1 New CO Sources

In order to avoid handling of gaseous CO, several methods employing a variety of CO precursors/sources have been developed (Figure 1). One approach has been to utilize molecules with carbonyl motifs, which by the exposure to transition metals, additives, base, or heat will release CO. Examples, include alkyl- and arylformates,[11,13–16] aldehydes,[17] formic acid,[18] formamides and *N*-formylsaccharin,[19–21] carbon dioxide,[22,23] and metal carbonyls,[24,25] such as the highly versatile $Mo(CO)_6$.[26,27,28] However, several of the mentioned CO sources require an additional transition metal, strong base, or high temperatures to release CO gas. Alternatively, the use of metal carbonyls will generate stoichiometric amounts of another transition metal as waste. Indeed, $Mo(CO)_6$ has been reported to possess catalytic activities[29,30] in addition to reducing aromatic nitro functionalities at elevated temperatures.[31]

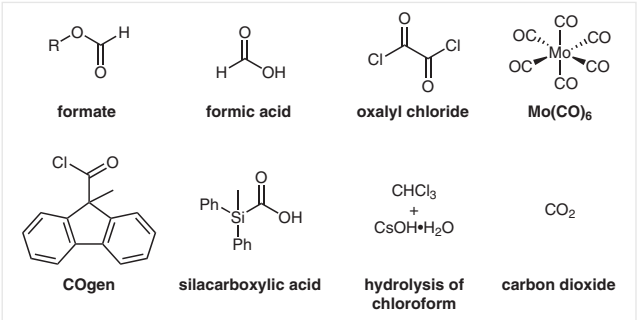


Figure 1 Representative selection of various CO sources reported in the literature

2.2 Two-Chamber System for ex Situ CO Generation

The issues with compatibility of the CO-generating reaction with the CO-consuming reaction may impose severe limitations on the scope of nongaseous carbonylation reactions. An elegant approach that circumvents these problems was developed by Skrydstrup et al., in which CO was liberated ex situ following Pd-catalyzed decomposition of

Biographical Sketches

Linda Åkerbladh graduated from the University of Gothenburg with an MSc in Organic and Medicinal Chemistry in 2010. She joined Professor Mats Larhed and Associate Professor Luke Odell at Uppsala University for her PhD studies focusing on the development of nongaseous carbonylative multicomponent reactions towards the synthesis of heterocycles for which she received her PhD in 2017.

Luke Odell was born in Tamworth, Australia in 1981. He graduated with an Honours BSc in Forensic Science from the University of Newcastle, Australia in 2002. He completed his PhD studies at the same university under the guidance of Professor Adam McCluskey in 2006 working on the synthesis of enzyme inhibitors. In 2006, he took up a postdoctoral position with Professor Mats Larhed at Uppsala University. Since 2009, he has been an Associate Professor at Uppsala University and his research interests include metal catalysis, heterocyclic chemistry, and medicinal chemistry.

Mats Larhed received his PhD in 1997 and became a full professor in 2007. Dr Larhed's main research focus has been towards the development of fast, selective, and robust synthetic methods for use in preparative medicinal chemistry. His work in metal catalysis covers different types of palladium-catalyzed coupling reactions, gas-free carbonylations, and the development of environmentally benign chemical transformations. During the last ten years he has been increasingly engaged in the development of PET radiotracers, angiotensin II ligands, and enzyme inhibitors for potential treatment of HIV, Malaria, Alzheimers disease, and TB.

9-methylfluorene-9-carbonyl chloride (COgen). A special two-chamber glassware system was developed to keep the carbonylation and the decarbonylation reaction mixtures separate, to avoid problems with incompatibility (Figure 2).[32] A similar approach was later described, in which a reaction of silacarboxylic acid with a fluoride source liberated CO.[33] Both these methods allow the use of stoichiometric or substoichiometric amounts of CO as well as a possibility to introduce an isotopically labeled carbonyl group.[32,33]

Figure 2 Two-Chamber vial after radical carbonylation reaction. Left-hand chamber (C_{CO}) contains DBU/$Mo(CO)_6$, right-hand chamber (C_{rxn}) contains reactants.[34]

Ex situ generation of carbon monoxide from solid CO sources, by using two-chamber glassware, has made it possible to use various carbonylation reactions for small-scale applications in a standard laboratory since lower pressures of CO can be used, which in turn eliminates the need for pressurized vessels. There are now several nongaseous CO sources reported, intended both for in situ and ex situ use, including the base-mediated decomposition of oxalyl chloride[35] and chloroform,[36,37] which have been reported as effective CO-generating strategies for carbonylation chemistry. Notably, the latter allow the preparation of ^{13}C- and ^{14}C-labeled carbonyl derivatives.

Finally, metal carbonyls such as $Mo(CO)_6$ offer a convenient solid CO source suitable for both in situ and ex situ gas release.[1,38] CO is readily released from $Mo(CO)_6$ either by ligand exchange with e.g. DBU[27,39] or MeCN,[40,41] or at elevated reaction temperatures.[26] However, because of the potential reduction of nitro groups[31] and precipitation of molybdenum complexes after the release of CO (complicating product purification)[42] ex situ protocols have been developed for the use of $Mo(CO)_6$-mediated carbonylations.[38,43] The carbonylative work presented in this review will fully focus on $Mo(CO)_6$ as the nongaseous CO source.

2.3 Multicomponent Carbonylations

A multicomponent reaction is defined as a reaction with three or more reaction components that react to form a single product that contains essentially all of the atoms of the starting materials.[44,45] The components may be separate molecular entities or they may be different functional groups in bifunctional reagents.[44,46] As such, carbonylative coupling reactions, comprising the coupling of an electrophile, CO, and a nucleophile, constitute a three-component reaction. However, carbonylation reactions with less than four components are not usually categorized as MCRs, because the CO component is generally fixed, unless different carbon or oxygen isotopes are employed.[47]

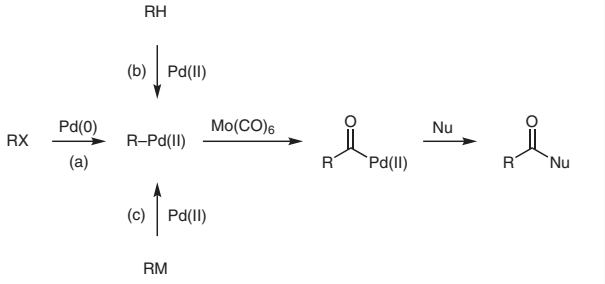
Many well-known noncarbonylative MCRs, such as the Mannich,[48] Strecker,[49] Biginelli,[50,51] Passerini,[52,53] and Ugi[54] reactions utilize carbonyl derivatives, for example in the form of aldehydes or ketones, to install additional carbons. The ability to incorporate one-carbon fragments by Pd(0)-catalyzed carbonylations from an additional source of organo(pseudo)halide starting materials is one of the reasons why carbonylation chemistry is such a powerful complement to the field of MCRs. The advance of carbonylation chemistry and the development of numerous new methods[6,10,55] has spurred an increased research interest in carbonylative MCRs.[47,56]

There are several advantages to carbonylative MCRs: (i) They are highly atom economical because nearly all atoms of the starting materials are incorporated into the product. (ii) The rapid assembly of simple starting materials to generate cyclic and acyclic scaffolds with increased molecular complexity is readily achieved. Furthermore, by secondary transformations, for example by using bifunctional reagents or secondary reactions, a wider chemical space can be reached. This strategy has been successful in the synthesis of various heterocycles.[57–59] (iii) Limiting the number of steps of a reaction and ideally the number of isolated intermediates, is both time- and cost-effective. (iv) The waste generated from a reaction, e.g. from unreacted starting materials and solvents used in purification processes, is kept to a minimum.

Considering the many benefits of carbonylative MCRs it is not surprising that the methodology has increased in popularity. However, the majority of carbonylative MCRs are performed by using gaseous CO[47] and only two examples of $Mo(CO)_6$-mediated MCRs were reported before October 2011.[60,61] In order to meet the demands of convenient and safe methods in the future it will be of importance to develop carbonylative MCRs that are compatible with nongaseous CO sources.

3 Carbonylations with N and O Nucleophiles

Most of the Pd(0)-catalyzed carbonylation reactions involve the coupling of a suitable carbon halide, or pseudo halide, (RX) starting material (e.g. aryl or vinyl) and a nucleophile (e.g. amine, amide, alcohol, water) in the presence of CO, although alternative organopalladium precursors can be used through C–H activation or transmetalation (Scheme 1).

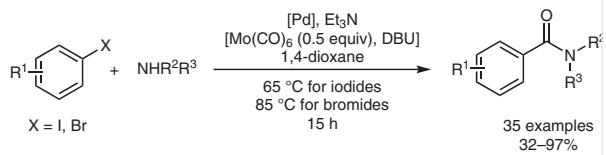


Scheme 1 General depiction of a palladium-catalyzed carbonylation reaction generating the essential R–Pd intermediate through (a) oxidative addition of RX (b) C–H activation of RH, or (c) transmetalation through an organometallic reactant RM

The three-component reaction between an organic (pseudo)halide, CO, and an amine to yield amides is known as an *aminocarbonylation* reaction. The corresponding reaction with an amide nucleophile is an *amidocarbonylation*. The reaction with an alcohol is an *alkoxycarbonylation*, and the process using water is a *hydroxycarbonylation*. A base is typically required to abstract a proton and usually a ligand is added to modulate the reactivity of the palladium complexes in the catalytic cycle. Most commonly, a phosphine ligand is used and several ligand properties may be considered when designing a catalytic system, such as electronic and steric properties. Moreover, various steps of the catalytic cycle will be facilitated by different ligand characteristics. For example, oxidative addition will be promoted by electron-rich phosphine ligands, whereas the CO 1,1-insertion will be favored by electron-deficient phosphine ligands.[10,62] Typically, Pd(II) salts are used as precatalysts, mainly because of their enhanced stability compared to available Pd(0) complexes. Therefore, as an initial step before entering the catalytic cycle, the Pd(II) precatalyst will be reduced by a solvent molecule, ligand, or CO to a 14-electron Pd(0) complex.[62] Once the active catalyst is formed, the first step in the catalytic cycle is the insertion of Pd(0) into the R–X bond, resulting in oxidation of the Pd(0) species to a square-planar organopalladium(II) complex (oxidative addition). The rate of oxidative addition is strongly dependent on the nature of the C–X bond, where strong C–X bonds will be less reactive. As a result, iodides react more readily than other halides or such as chlorides (I > OTf ≥ Br > Cl ~ Ts).[6] With this argument also follows that electron-deficient C–X substrates are more susceptible to oxidative addition, and electron-donating ligands that increase the electron density on Pd will promote oxidative addition.[10,63]

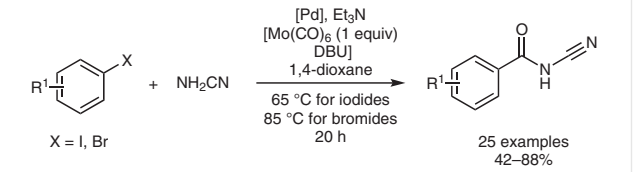
Next, coordination of CO to the Pd center accompanied by ligand displacement and 1,1-insertion generates the acylpalladium species. The introduction of the nucleophile can occur either directly on the acyl carbon and thereby releasing the carbonyl compound or the nucleophile can coordinate to the vacant site on palladium (nucleophilic attack). Abstraction of a proton from the nucleophile with base and subsequent reductive elimination then yields the carbonylated product and regenerates the catalytically active Pd(0) species.[62,64]

During our early work on $Mo(CO)_6$-mediated carbonylation reactions,[1] the use of aryl nitro-group-containing substrates was precluded because of their facile reduction by Mo species present in the reaction mixture.[31] To overcome this problem, we started using a variant of Skrydstrup's bridged two-chamber system, in which the carbon monoxide releasing $Mo(CO)_6$ was physically separated from the catalytic reaction mixture (Scheme 2).[12,38] The two-vial system was constructed by fusing two standard pyrex vials through a borosilicate cylinder and designed to fit DRYSYN™ system, making it both cheap and extremely convenient to use (Figure 2). The benefits of separating the catalytic and CO-releasing components were clearly demonstrated through the efficient and high-yielding transformation of various nitro-group-containing aryl and heteroaryl iodides and bromides into the corresponding benzamides. Notably, the same reactions conducted in a single-vial setting resulted in substantial competing nitro group reduction. This ex situ approach is today our preferred method for conducting $Mo(CO)_6$-mediated carbonylations and has been employed in the vast majority of reactions performed in our laboratory since 2012, the only exceptions being when high temperatures are required to enable the carbonylation of particularly unreactive substrates.



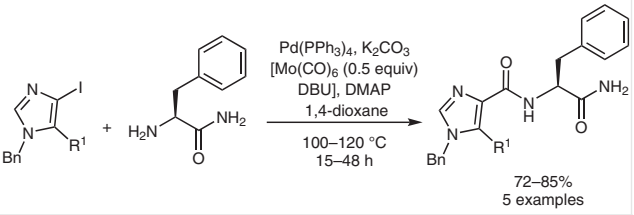
Scheme 2 Carbonylation of aryl halides with use of $Mo(CO)_6$ as an ex situ CO source

The aminocarbonylation of aryl halides with cyanamide by using CO generated ex situ from $Mo(CO)_6$ to produce *N*-cyanobenzamides has previously been described (Scheme 3).[65–67] The method was compatible with both aryl iodides at 65 °C and bromides at 85 °C in moderate to good yields. The mechanism is believed to follow a general aminocarbonylation reaction with cyanamide acting as a nucleophile through the terminal amine group.



Scheme 3 Carbonylation of aryl halides with cyanamide as nucleophile to yield *N*-cyanobenzamides

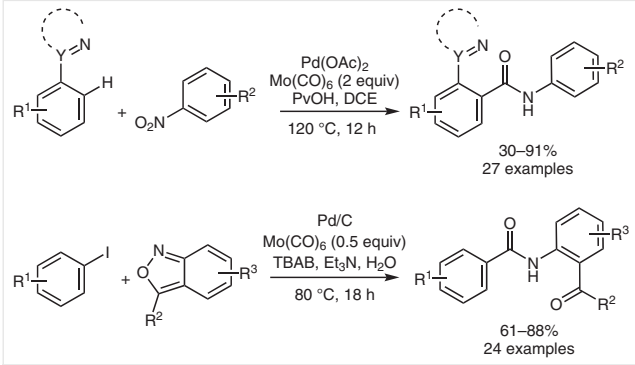
Amino acids are often considered to be challenging nucleophiles due to the inductive withdrawing nature of the carboxyl group and the additional steric bulk imparted by the α substituent. In 2013, the aminocarbonylation of 5-aryl-4-iodo-1*H*-indazoles with a phenylalanine amide nucleophile was reported (Scheme 4).[43] The ex situ generation of CO was again leveraged to prepare a number of constrained H–Phe–Phe–NH_2 analogues as part of a medicinal chemistry campaign. The aminocarbonylation reaction was particularly efficient (72–85%) given that the reaction took place at a hindered *ortho* position.



Scheme 4 Example of an amincarbonylation with use of a challenging phenylalanine amide nucleophile

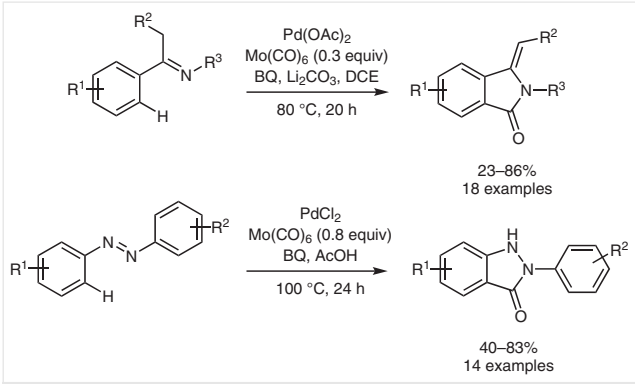
The reductive properties of $Mo(CO)_6$ can also be harnessed to enable the use of nitroarenes as nitrogen sources in aminocarbonylation reactions. Driver and co-workers have disclosed a dual C–H functionalization/aminocarbonylation process using 2-pyridyl substituted arenes as R–Pd precursors and nitroarenes as nitrogen donors (Scheme 5).[68] The reaction scope was broad with respect to both reaction components; however, the requirement for a 2-pyridyl substituent represents a practical limitation. In a conceptually related study, Wang et al. utilized the Mo-mediated reductive ring-opening of anthranils as an efficient strategy to generate 2-aminobenzaldehyde derivatives in situ (Scheme 5).[69] In the presence of an aryl iodide and Pd/C, the reactive intermediates were conveniently transformed into *N*-(2-carbonylaryl)benzamides in moderate to good yields. Notably, the reaction was conducted by using water as a green solvent, although the requirement for organic solvents in the aqueous work-up and silica gel chromatography limit the environmental benefits of the overall process.

The Wu group has recently reported on two related nitrogen-directed C–H functionalization/aminocarbonylation strategies for the synthesis of 3-methyleneisoindolin-1-ones and 2-arylindazolones from acyl hydrazones[70] and



Scheme 5 Top: Directed aminocarbonylation of C(sp^2)–H bonds with use of nitroarenes as amine precursors. Bottom: Aminocarbonylation of aryl iodides with use of anthranils as amine precursors

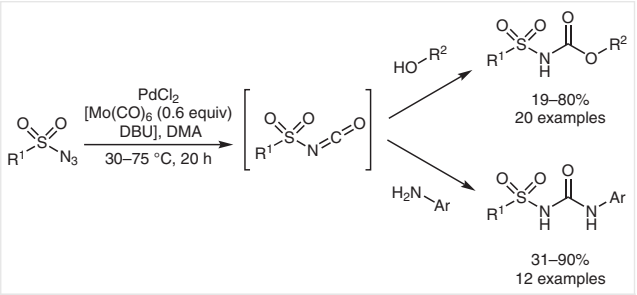
azoarenes,[71] respectively (Scheme 6). In both cases, coordination through a Lewis basic nitrogen atom followed by C–H insertion generated the key R–Pd precursors, which underwent subsequent CO insertion and intramolecular nucleophilic attack to afford the desired compounds. Interestingly, no Mo-mediated reductive cleavage of the potentially sensitive substrates was detected.



Scheme 6 Directed carbonylative synthesis of 3-methyleneisoindolin-1-ones (top) and 2-arylindazolones (bottom) by a C–H annulation strategy; BQ = benzoquinone

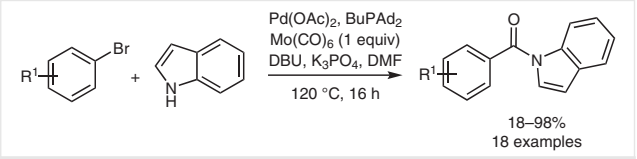
Sulfonyl isocyanates are versatile and valuable building blocks in synthetic chemistry; however, their utility is hampered by a lack of commercial availability, stability, and methods for their preparation. Recently, sulfonyl azides have been exploited as convenient precursors for the in situ generation and functionalization of sulfonyl isocyanates under carbonylative conditions.[72] The reaction was found to proceed under ligand-free conditions by using simple $PdCl_2$ and the use of aryl amine or alcohol nucleophiles afforded sulfonyl ureas or carbamates, respectively (Scheme 7). Mechanistically, the reaction was believed to occur in an analogous fashion to the general carbonylation mechanism, with oxidative addition on the sulfonyl azide group leading to a nitrene–palladium complex. Subsequent CO insertion and reductive elimination furnishes the key sulfonyl isocya-

nate intermediate, which can then be trapped by an appropriate nucleophile to afford the desired products. In the case of aliphatic amines, the carbonylative reaction pathway is disfavored and a competing direct S_N2 process leads to the exclusive formation of substituted sulfonamides, rather the expected sulfonyl ureas.



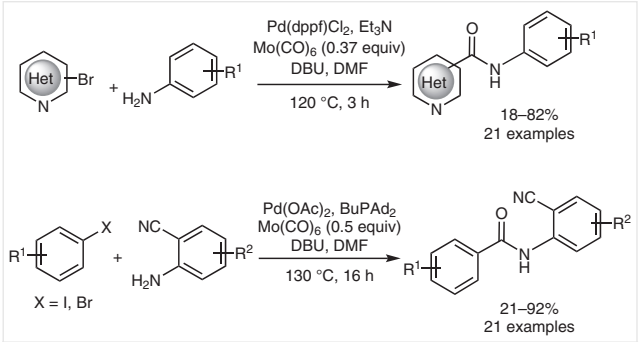
Scheme 7 Substrate-controlled carbonylative synthesis of sulfonyl carbamates or acyl sulfonyl ureas

The indole scaffold is one of the most important and pervasive structures in organic and medicinal chemistry[73] and new methods to access functionalized indoles are continually in demand. In 2015, the groups of Wu and Langer disclosed the carbonylative synthesis of *N*-benzoylindoles from indole and aryl iodides (Scheme 8).[74] The reaction scope was explored with a variety of aryl iodides and a significant preference for electron-rich substrates was noted.



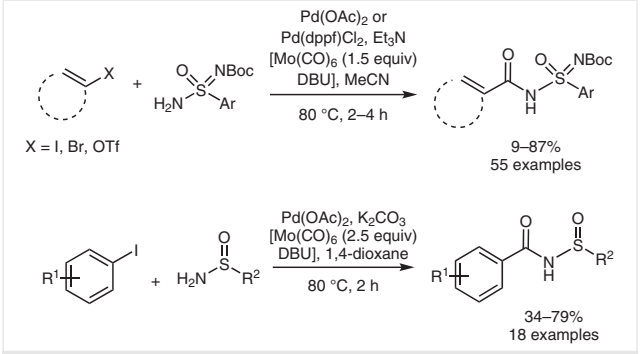
Scheme 8 Carbonylative synthesis of *N*-benzoylindoles with use of indole as a nucleophile

The use of aromatic amine nucleophiles in aminocarbonylation chemistry can often be problematic because of their inherent low nucleophilicity. Very recently, Piguel and co-workers reported an efficient procedure for the carbonylative coupling of various heteroaryl bromides with aryl and heteroaryl amine nucleophiles (Scheme 9).[75] The pre-catalyst $PdCl_2$(dppf) was found to be particularly effective in promoting the reaction, producing a diverse array of products in moderate to excellent yields. The reaction could even be extended to include the double functionalization of 2,6-diaminopyridine with 3-bromopyridine to produce an interesting 2,6-diamidopyridine product. The Wu and Langer groups have also utilized $Mo(CO)_6$ as a CO source in the aminocarbonylation of challenging 2-aminobenzonitrile nucleophiles using aryl bromides.[76] In this case, the use of $Pd(OAc)_2$ and cataCXium A [di(1-adamantyl)-*n*-butylphosphine, $BuPAd_2$] at elevated temperatures was optimal for the reaction (Scheme 9). The yields in many cases were only moderate; however, given the highly challenging nature of the nucleophile, these results are still rather impressive. In addition, the one-pot oxidative cyclization of a selected number of the *N*-(2-cyanoaryl)-benzamide products to give 2-aryl quinazolinone derivatives was also demonstrated.



Scheme 9 Top: Aminocarbonylation of N-heterocycles with arylamine nucleophiles. Bottom: Carbonylative synthesis of *N*-(2-cyanoaryl)-benzamides from aryl halides and 2-aminobenzonitriles

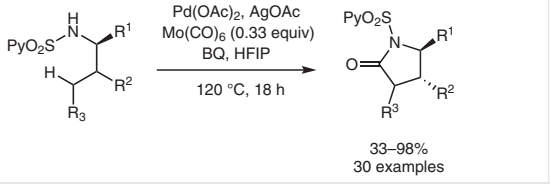
Similarly, the use of sulfonamide and related nucleophiles is often associated with lower reactivity because of the inductive effects from the neighboring oxygen atoms. The groups of Sandström and Arvidsson have described the carbonylative synthesis of interesting acyl sulfur-containing carboxylic acid bioisoteres using sulfonimidamide[77,78] and sulfonamide[79] nucleophiles, respectively. In the former case, (hetero)aryl and vinyl halides or triflates were suitable reaction partners and were successfully coupled with a selected number of aryl sulfonimidamide nucleophiles (Scheme 10). In general, the use of (hetero)aryl substrates led to higher yields of the target compounds and this was attributed to the lower stability of the vinyl acyl sulfonimidamide products. Interestingly, complete thermolytic removal of the Boc-protecting group was shown to occur at the same temperature (80 °C) as the carbonylation reaction suggesting that background Boc deprotection may be a con-



Scheme 10 Carbonylative synthesis of acyl sulfonimidamides and acyl sulfinimides from aryl or vinyl halides

tributing factor to the low reaction yields obtained with these substrates. The corresponding carbonylative synthesis of acyl sulfinimides was limited to (hetero)aryl iodide substrates and some erosion in *ee* was noted over the course of the reaction (Scheme 10).

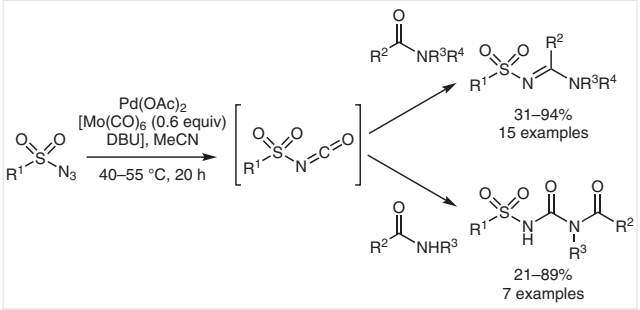
In 2016, the groups of Rodríguez, Arraýas, and Carretero published an impressive study detailing the carbonylative cyclization of (N-SO_2Py)-protected amines using a γ-C(sp^3)–H activation strategy.[80] The choice of protecting group and the use of substoichiometric amounts of $Mo(CO)_6$ were essential for obtaining high yields of the γ-lactam products (Scheme 11). The substrate compatibility was demonstrated on a wide variety of different amino acid and aliphatic amine derivatives containing suitably disposed γ-methyl or γ-methylene groups. The reaction could also be extended to C(sp^2)–H carbonylative cyclization, and in the case of substrates containing two potentially reactive C–H groups, carbonylation took place at the more acidic C(sp^2)–H bond. Importantly, the reaction was equally efficient on a gram scale and the sulfonamide directing group was readily removed by using Mg turnings in MeOH under sonication. Mechanistically, the reaction was suggested to occur through a Pd(II)-mediated C–H activation followed by CO insertion and reductive elimination with subsequent reoxidation of the Pd(0) species by benzoquinone and AgOAc closing the catalytic cycle.



Scheme 11 Directed carbonylative cyclization of amines and amino acids through C(sp^3)–H functionalization; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, BQ = benzoquinone

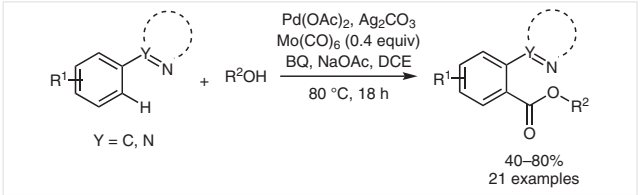
The in situ formation of sulfonyl isocyanates has also been exploited in the carbonylation of sulfonyl azides with amide nucleophiles.[81] The reaction pathway was shown to be dependent on the amide nucleophile with tertiary amides reacting through a [2+2] cycloaddition/decarboxylation cascade to afford substituted sulfonyl amidine products (Scheme 12). In contrast, primary and secondary amides proceeded through a more conventional pathway and nucleophilic attack at the amine nitrogen led to the formation of various acyl sulfonyl ureas (Scheme 12).

The alkoxylcarbonylation reaction, which is typically defined by the use of oxygen-centered nucleophiles, is one of the most useful methods for transforming R–Pd precursors into carboxylic acid and ester derivatives. In 2016, the Wu group reported the Pd(II)-catalyzed alkoxycarbonylation of C(sp^2)–H bonds using an array of aliphatic alcohol



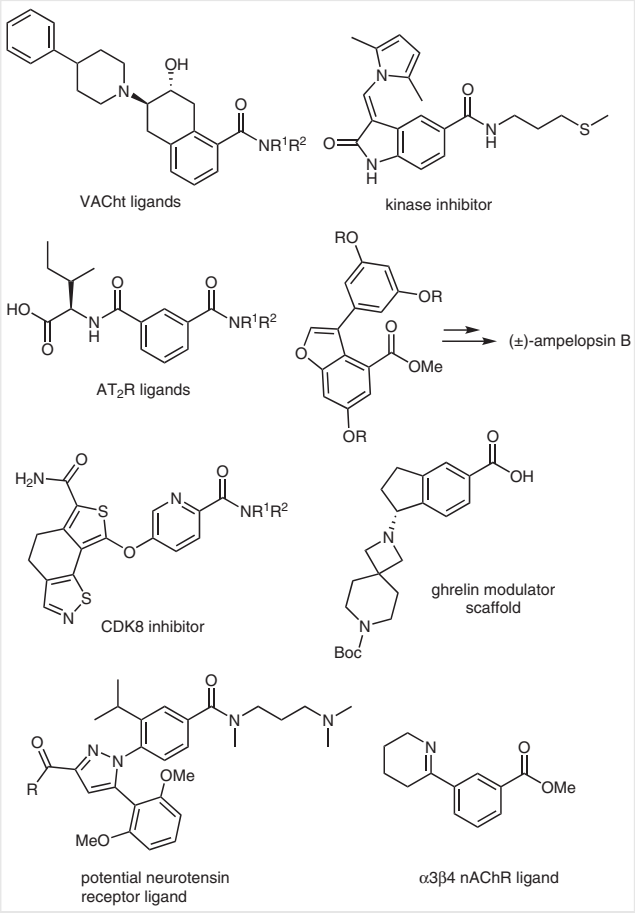
Scheme 12 Substrate-controlled carbonylative synthesis of sulfonyl amidines or acyl sulfonyl ureas

nucleophiles (Scheme 13).[82] The use of pendant nitrogen-containing heterocycles (2-pyridine, pyrazole, and pyrimidine) as directing groups and benzoquinone as a co-oxidant and a Pd ligand was crucial for reactivity. Under the optimized conditions a range of ester products were obtained in moderate yields, and good selectivity towards Pd(0)-labile functional groups (bromide and chloride) was observed. Taszarek and Ressig have recently demonstrated that alkenyl triflates and nonaflates are also competent substrates for alkoxycarbonylations using water or methanol as the nucleophile.[83] However, only a limited number of substrates were examined and the scope and limitations of the process are yet to be determined.



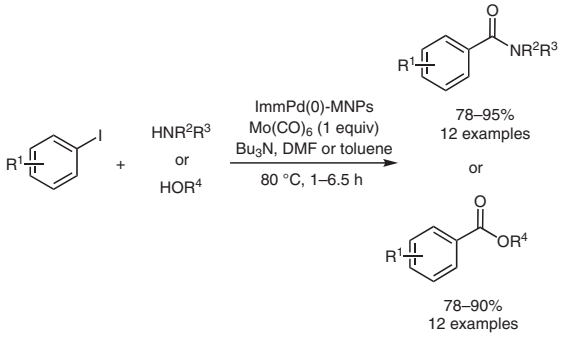
Scheme 13 Directed alkoxycarbonylation of C(sp^2)–H bonds; BQ = benzoquinone

One of the most important factors in determining the practical utility of synthetic methodology is its applicability to real world substrates that fall outside the limited chemical space usually covered in screening tables. Pleasingly, the $Mo(CO)_6$-mediated carbonylation reaction has been applied in a wide range of target-molecule-based studies, primarily medicinal chemistry campaigns aimed at the discovery of new compounds against multiple different indications. Although a detailed description of the design, synthesis, and evaluation of these compounds is outside the scope of this account, some representative examples of target compounds synthesized by using this approach are given in Scheme 14.[84,85] It is clearly evident from the chemotypes represented in Scheme 14 that this reaction is not just an academic curiosity and can be effectively utilized to access a wide range of structurally complex and biologically relevant molecules.



Scheme 14 Selected examples of biologically relevant target compounds synthesized by $Mo(CO)_6$-mediated alkoxy- or aminocarbonylation. References: VACht,[86] kinase,[87] AT_2R,[88] ghrelin,[89] (±)-ampelopsin B,[90] CDK8,[91] neurotensin,[92] α3β4 nAChR ligand[93]

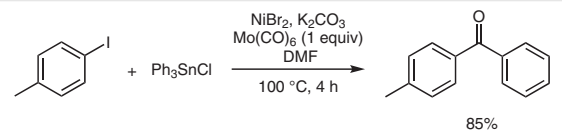
All of the examples described in the preceding pages have been conducted under a homogenous catalysis regime. Despite its immense popularity and utility, homogeneous catalysis suffers from two major drawbacks. Firstly, the expensive transition-metal catalyst is often discarded following the reaction because of problems associated with catalyst recovery. Secondly, contamination of the final product with traces of transition metals can be troublesome, especially in a good manufacturing practice (GMP) production setting. These issues have led to the development of numerous immobilized-palladium catalysts that can be used to catalyze a wide range of cross-coupling reactions, under heterogeneous conditions.[94] In 2015, Hajipour and coworkers reported the synthesis and application of immobilized palladium containing magnetic nanoparticles [ImmPd(0)-MNPs] in the amino- and alkoxycarbonylation of aryl iodides (Scheme 15).[95] In both cases the substrate scope was wide and good to excellent yields of the carbonylated products were obtained by using a catalyst loading of 0.14 mol%. Catalyst reusability was also assessed and a slight decrease in conversion was noted after four consecutive runs. A control experiment by using a hot-filtration test was conducted to determine whether the catalytic activity was due to Pd leaching from the solid support, and no catalytic activity was detected in the filtrate, consistent with the operation of a heterogeneous catalytic reaction.



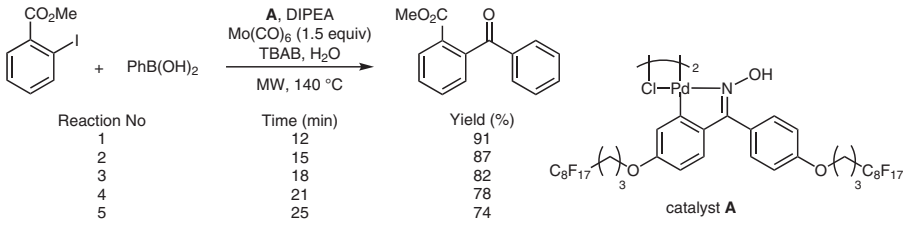
Scheme 15 Amino- and alkoxylcarbonylation of aryl iodides by using immobilized palladium-containing magnetic nanoparticles [ImmPd(0)-MNPs]

4 Carbonylative Cross-Coupling Reactions with Organometallics

The typical cross-coupling reactions with an organometallic reactant (or more correctly a transmetalation substrate) are available in a carbonylative version, with one exception, namely the Kumada cross-coupling. The first reports of the Pd-catalyzed carbonylative Stille coupling of aryl diazonium salts with organotin reagents appeared in 1982 and 1987.[96] Shortly thereafter, Echavarren and Stille presented a similar carbonylative coupling of aryl triflates with organostannanes.[97] Further developments expanded the scope of this reaction and reactions of various electrophiles with different stannanes have been performed in the presence of CO gas.[45] More recently, Nilsson and coworkers presented in situ $Mo(CO)_6$-assisted cross-coupling of arylstannanes with aryl triflates and aryl bromides using Pd catalysis.[98,99] In 2015, the CO-free methodology was expanded by the research group of Iranpoor, using nickel catalysis and predominantly chromium hexacarbonyl as the CO source but also $Mo(CO)_6$ (Scheme 16).[100]



Scheme 16 A nickel-catalyzed carbonylative Stille cross-coupling reaction



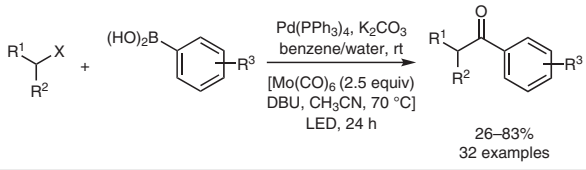
Scheme 17 Aqueous carbonylative Suzuki–Miyaura cross-coupling reactions

Horváth and Rábai introduced the term "fluorous" as an analog to aqueous because of the special properties of highly fluorinated compounds.[101] The poor solubility of fluorous systems in different organic solvents and water is due to low surface tension, low intermolecular interactions, high density, and low dielectric constants. The main field of application for fluorous chemistry is in the fluorous biphasic catalysis method, since the often complex and expensive catalyst can be recycled. Originally the fluorous-tagged catalyst was dissolved in the fluorous solvent and the substrate and reagents were added to the organic phase, which is immiscible with the perfluorocarbons at room temperature. On heating, the reaction medium becomes homogeneous and the reaction occurs. By utilizing fluorous extractions or fluorous chromatography the perfluoro-tagged catalyst can be separated and reused.[102] In 2014, Lo and Lam published an article in which they presented expedient $Mo(CO)_6$-mediated carbonylative Suzuki cross-couplings using a fluorous oxime-based palladacycle as catalyst (**A**) under aqueous or neat conditions.[103] By employing microwave heating (MW) with in situ release of carbon monoxide followed by fluorous silica gel column chromatography, unsymmetric aryl ketones were obtained in high yields (Scheme 17). The fluorous Pd catalyst was recycled five times and a number of biologically relevant molecules were synthesized.

Alkyl halides have been elusive substrates in transition-metal-mediated cross-coupling reactions because of their slow oxidative addition and the risk of beta elimination.[104] During the last decade, the use of alkyl halides as coupling agents has increased with the application of radical chemistry to the traditional cross-coupling protocols.[105] By creating a single-electron transfer (SET) event, in which an alkyl radical is generated, the challenges related to the oxidative addition step can be circumvented. By employing visible-light photocatalysis, unactivated alkyl halides have been used as substrates in cross-coupling reactions and functionalized under mild conditions, and displayed great functional group tolerance. The alkyl radical can thus be generated in catalytic amounts with the aid of an organometallic- or organic dye-based photocatalyst. Upon irradiation with visible light, the photocatalyst forms an excited-state species capable of transferring an electron to generate the alkyl radical.

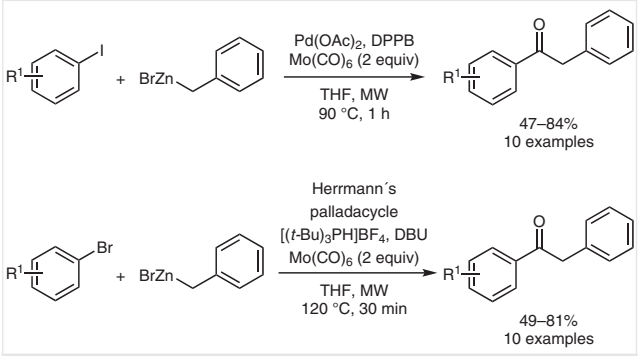
For carbonylative cross-couplings with alkyl halides as substrates, SET methodology has been employed but the generation of the alkyl radical has varied. Notably, whereas visible-light photocatalysis has been utilized in an aminocarbonylation,[34] the methods have generally applied a combination of intense light or UV irradiation, elevated carbon monoxide pressures, or elevated temperatures.[106–112]

In 2017, Odell et al reported that the use of visible-light irradiation together with Pd(0) catalysis enabled the carbonylative Suzuki cross-coupling of unactivated alkyl iodides and alkyl bromides (Scheme 18).[113] The reaction was performed under ambient temperature and pressure whilst utilizing $Mo(CO)_6$ as an ex situ solid source of carbon monoxide. The methodology represents a very convenient and accessible reaction procedure, which allowed the preparation of a range of functionalized aryl alkyl ketones including the antipsychotic drug, melperone. For a recent example of biaryl ketone synthesis by metal-carbonyl-mediated Suzuki cross-coupling methodology, see also the published work by Jung et al.[114]

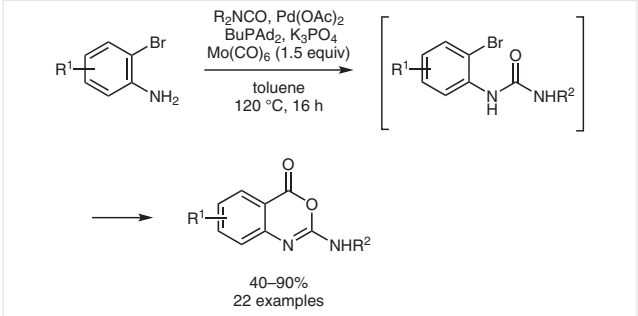


Scheme 18 Visible-light-mediated carbonylative Suzuki–Miyaura cross-coupling reactions

Examples of palladium-catalyzed carbonylative Negishi couplings reported in the literature use CO gas to carry out the carbonylation, and the reaction time is several hours (ca. 20–30 h).[115–119] Two new $Mo(CO)_6$-promoted in situ protocols for carbonylative Negishi cross-couplings were developed for aryl iodides and aryl bromides (Scheme 19).[120] The carbonylative cross-coupling reactions were carried out by using commercially available benzylzinc bromide in closed vials at 90–120 °C for 0.5–1 hours, providing a set of diarylated ethanones, a common pharmacophore among several pharmaceuticals, in moderate to high isolated yields (47–84%).

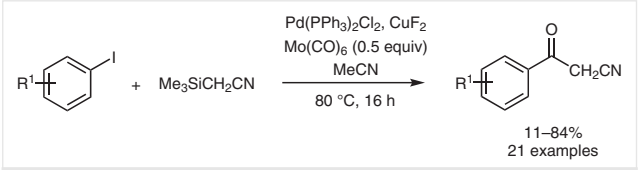


Scheme 19 Carbonylative Negishi cross-coupling reactions



Scheme 21 Synthesis of 2-aminobenzoxazinones from 2-bromoanilines and isocyanates by carbonylation/cyclization

Benzoylacetonitriles are highly useful building blocks in pharmaceutical and material chemistry fields.[121] A straightforward in situ method for the synthesis of benzoylacetonitriles through CO-free palladium(0)-catalyzed Hiyama-type carbonylative cross-coupling employing $Mo(CO)_6$ was published in 2012 (Scheme 20).[122] The key reactant, trimethylsilyl acetonitrile, was activated by CuF_2 and reacted smoothly at 80 °C. The reaction showed good tolerance toward functional groups such as alkoxy, bromo, chloro, ester, ketone, and nitrile moieties.

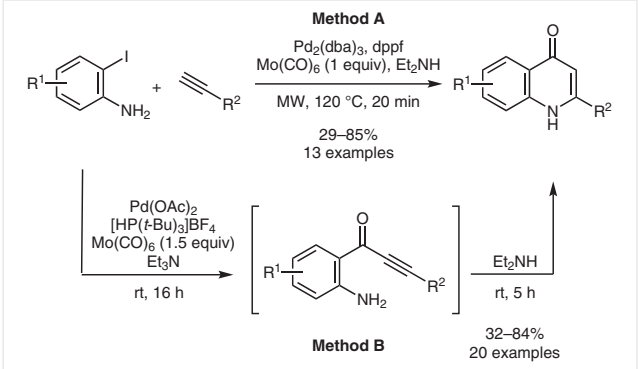


Scheme 20 Carbonylative Hiyama-type cross-coupling reaction

5 Carbonylative Cascade Reactions

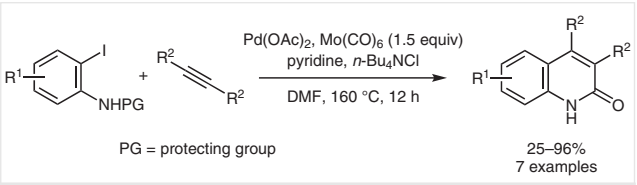
In 2013, Wu and co-workers presented a synthesis of 2-aminobenzoxazinones from 2-bromoanilines and isocyanates employing $Mo(CO)_6$ as the CO source (Scheme 21).[123] The authors proposed that the corresponding urea is formed in an initial step from 2-bromoaniline and phenylisocyanate. Following oxidative addition of the C–Br bond, CO insertion, and reductive elimination furnished 2-aminobenzoxazinones in good yields. Remarkably, the alternative 3-phenylquinazoline-2,4-(1*H*,3*H*)dione was not detected and it was suggested that $Mo(CO)_6$ might act as a Lewis acid and aid in chemoselectivity. With the developed method, 22 examples were prepared in 40–90% isolated yield for a diverse set of reagents. The scope of the reaction was also expanded to 2-bromophenylisocyanate and aniline, potentially increasing the scope of the reaction.

The quinolone scaffold is one of the most frequently occurring heterocyclic fragments in small-molecule drugs.[124] The interest in the quinolone scaffold largely explains the constant development of new synthetic strategies for the synthesis of that heterocyclic core. In 2015, we disclosed a nongaseous synthesis of 4-quinolones from *ortho*-iodoanilines and terminal acetylenes, in which CO is released in situ from $Mo(CO)_6$.[41] Two methods were developed allowing for either rapid assembly of the quinolone scaffold or introduction of potentially labile substituents such as nitro or bromide groups (Scheme 22). In method A, $Pd_2(dba)_3$ and dppf were used to efficiently catalyze the reaction under MW irradiation at 120 °C for 20 minutes. With the presence of a secondary amine in the reaction mixture, the cyclization was completed in situ, providing 13 examples of 4-quinolones in one step in 29–85% isolated yield. As expected, the high reaction temperature in combination with the presence of $Mo(CO)_6$ in the reaction mixture significantly reduced the yield of the nitro-substituted quinolone. To circumvent this problem a second method was developed to allow the introduction of chemically labile groups. Method B employed acetonitrile as solvent which has been used to generate CO from $Mo(CO)_6$ at room temperature (Scheme 22).[40,60] In addition, electron-rich precatalyst $[(t\text{-Bu})_3PH]BF_4$ was used as a ligand. As a result, the reaction could be performed at room temperature providing 20 examples of quinolones in 32–84% isolated yield. Notably, both nitro and bromide groups were successfully introduced in good yields.



Scheme 22 Palladium-catalyzed carbonylative Sonogashira/cyclization sequence for the synthesis of 4-quinolones

Jafarpour developed a versatile $Mo(CO)_6$-promoted route to 3,4-disubstituted 2(1*H*)-quinolones using mono-protected 2-iodoanilines, which involved palladium(0)-catalyzed carbonylative annulation of internal alkynes (Scheme 23).[125] In addition to the successful application with disubstituted alkynes, the use of norbornene furnished the corresponding (dihydro)quinolin-2(1*H*)-ones in good yields. With both annulation substrates free 2-iodoaniline afforded lower yields than *N*-protected 2-iodoanilines.

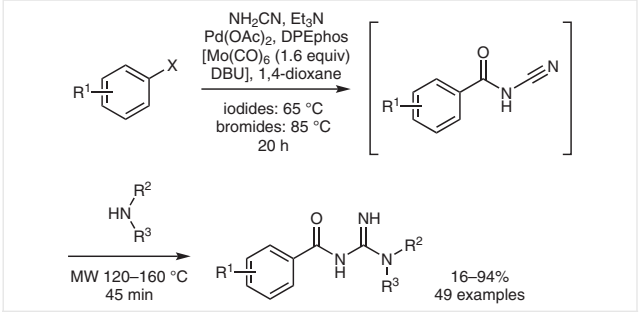


Scheme 23 Palladium-catalyzed carbonylative annulation reaction for the synthesis of 2(1*H*)-quinolones

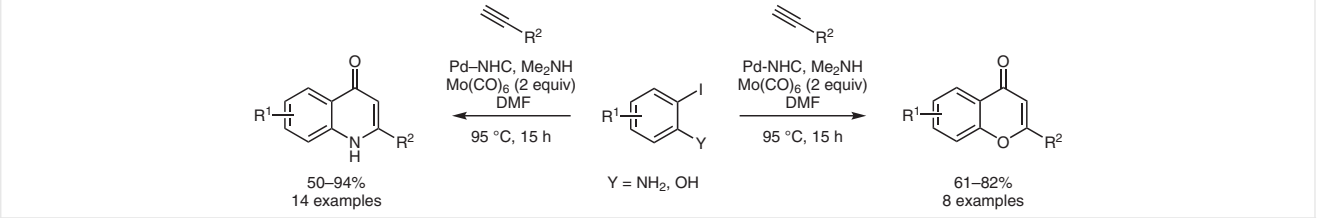
Adding to the available strategies for the synthesis of quinolones and chromones (flavones), Ghosh and co-workers recently reported a carbonylative Sonogashira annulation sequence (Scheme 24). The heterocycles were prepared from 2-iodoanilines or 2-iodophenols in the presence of a benzimidazole-based Pd–N-heterocyclic carbene catalyst (Pd–NHC) in moderate to excellent yields and good functional group tolerance.[126]

Further adding to the carbonylation/cyclization strategy, a method was developed for the synthesis of functionalized 2-aminoquinazolinones (Scheme 25).[127] It was envisioned that by changing the nucleophilic coupling partner different heterocyclic structures could readily be assembled. Accordingly, 2-iodoanilines were carbonylatively coupled with cyanamide to yield an *N*-cyanobenzamide intermediate,[65] which following a heating step could undergo cyclization. Both unsubstituted and *N*1-substituted quinazolinones were readily obtained by precipitation in moderate to excellent yields with broad substrate scope. Recently, this approach has been extended to the synthesis of 4*H*-benzo[*e*][1,3]oxazin-4-ones from 2-iodophenols or 2-bromophenols by using either $Mo(CO)_6$ or a range of non-gaseous CO-sources.[128]

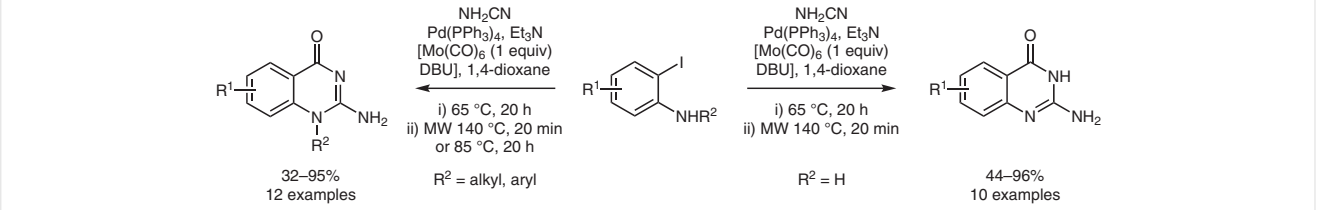
In 2017, we developed a four-component carbonylation/amination two-step one-pot protocol for the synthesis of *N*-acylguanidines (Scheme 26).[129] The reaction was initiated by the formation of an *N*-cyanobenzamide intermediate from the carbonylative coupling of aryl iodides and bromides with cyanamide. A sequential amination step provided access to a large variety of *N*-acylguanidines in moderate to excellent yields. During the optimization studies an impurity was detected which gave rise to ^{31}P–^{13}C couplings in ^{13}C NMR spectra when $Pd(PPh_3)_4$ was used as the catalyst. It was suspected that monodentate phosphine ligands might attack the *N*-cyanobenzamide intermediate and therefore a ligand screening was performed, which revealed DPEphos as the optimal ligand for this reaction. In addition, the acylguanidine moiety was utilized as a precursor in the preparation of three different heterocycles.



Scheme 26 Carbonylation/amination two-step one-pot synthesis of *N*-acylguanidines

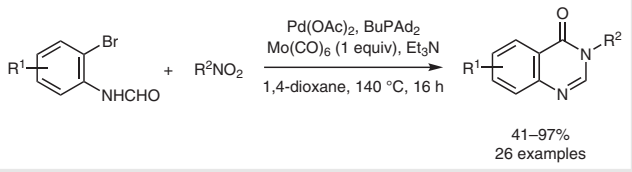


Scheme 24 Palladium-catalyzed carbonylative Sonogashira/cyclization sequence for the synthesis of 4-quinolones and 4*H*-chromen-4-ones



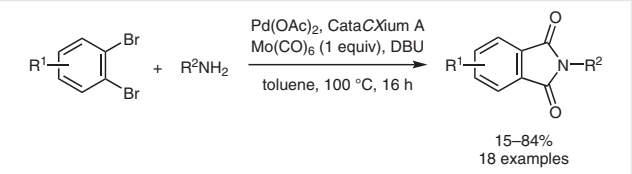
Scheme 25 Synthesis of 2-aminoquinazolinones by carbonylation/cyclization from *ortho*-iodoanilines and cyanamide

Nitrocompounds are inexpensive and readily available precursors to many *N*-containing compounds. However, the limitations of the reduction of the nitro group impose considerable constraints for the use of such precursors in e.g. Pd-catalyzed aminocarbonylations. In 2014, Wu and co-workers reported the synthesis of 4(3*H*)-quinazolinones from 2-bromoformanilides and organonitro compounds in which $Mo(CO)_6$ served as a CO source as well as a reducing agent of the nitro group and a cyclization promoter (Scheme 27).[130] Under the given conditions aromatic and aliphatic nitro compounds as well as electron-rich and electron-deficient substituents were successfully used to produce 4(3*H*)-quinazolinones in 26 examples in moderate to excellent yields.



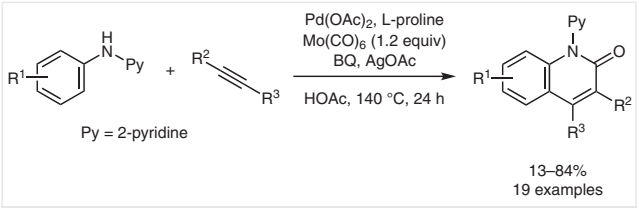
Scheme 27 Carbonylative synthesis of 4(3*H*)-quinazolinones from 2-bromoformanilides and organonitro substrates

N-Substituted phthalimide derivatives have been explored for their biological activities. In 2013, Langer and co-workers described a Pd-catalyzed double carbonylation of 1,2-dibromoarenes with amines (Scheme 28). The reaction was used to prepare *N*-substituted phthalimides from a wide range of aliphatic and aromatic amines and 1,2-dibromoarenes in moderate to good yields.[131] A somewhat related $Mo(CO)_6$-mediated but Pd-free method to generate benzimidazoles and benzoxazoles was published by Vidavalur in 2015.[132]



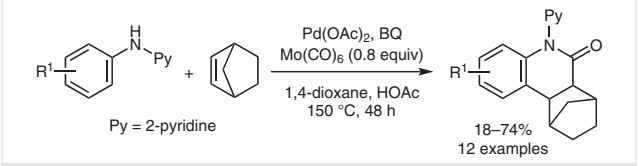
Scheme 28 Carbonylative synthesis of phthalimides from 1,2-dibromoarenes

The combination of C–H activation and carbonylation in heterocyclic synthesis is a particularly desirable approach in the development of new and sustainable synthetic strategies. Wu and co-workers have developed a carbonylative cyclization of *N*-aryl-pyridine-2-amines and internal alkynes by C–H activation with which 2-quinolinone derivatives were prepared in moderate to good yields (Scheme 29).[133] The developed strategy was used with electron-rich and electron-poor substituents with good yields and non-symmetric alkynes were incorporated with good regioselectivity. Partly on the basis of a kinetic isotope effect experiment the reaction was suggested to proceed through C–H activation with the pyridyl acting as the directing group. Next, alkyne insertion followed by CO insertion produces an acyl palladium intermediate. The desired product was obtained after reductive elimination and finally reoxidation of Pd(0) by benzoquinone and AgOAc led to regeneration of the active Pd(II) catalytic species.



Scheme 29 Carbonylative annulation of *N*-aryl-pyridine-2-amines with internal alkynes by C–H activation providing 2-quinolinones

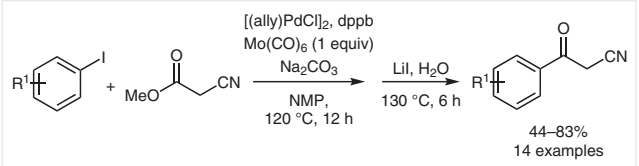
In 2016, the same strategy was applied to norbornene by Wu and co-workers. The Pd-catalyzed carbonylative C–H bond annulation of arenes with norbornene as the coupling partner was reported for the synthesis of 5-(pyridine-2-yl)hexahydro-7,10-methanophenanthridin-6(5*H*)-one scaffold (Scheme 30). With this more challenging alkene coupling partner, the desired heterocycle was obtained in low to moderate yields.[134]



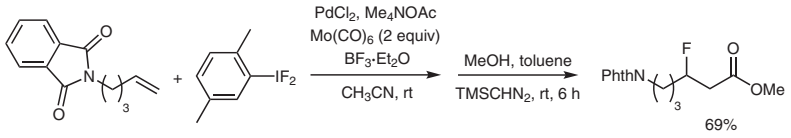
Scheme 30 Carbonylative annulation of *N*-aryl-pyridine-2-amines with norbornene by C–H activation

6 Carbonylative Cascade, Multistep Reactions

In 2016, Lee reported a one-pot synthesis of benzoylacetonitriles through sequential carbonylation and decarboxylation.[135] A reaction of methyl cyanoacetate, an acetonitrile equivalent, with an aryl iodide in the presence of a palladium(0) catalyst and $Mo(CO)_6$ provided a beta-keto cyanoester, which was treated with LiI in water at 130 °C to afford the benzoylacetonitrile in good yields (Scheme 31).



Scheme 31 One-pot two-step carbonylation–decarboxylation process to provide benzoylacetonitriles



Scheme 32 Two-step fluoriniation alkoycarbonylation synthesis of β-fluoro esters

An impressive two-step palladium-catalyzed and iodine(III)-mediated β-fluorocarboxylation of alkenes was presented by Liu et al. in 2017 (Scheme 32).[136] The cooperative electrophilic alkene activation–carbonylation process smoothly gave the β-fluoro ester with high regioselectivity by using $Mo(CO)_6$ as the solid CO source.

7 Summary and Outlook

A broad array of new, convenient, and efficient Pd-catalyzed carbonylative $Mo(CO)_6$-mediated reactions have been developed and reported in the last six years. The use of non-gaseous CO sources has gained general acceptance resulting in a larger overall usage in modern organic synthesis, and especially in natural product synthesis, bioorganic chemistry, and medicinal chemistry. Furthermore, the increased use of two-chamber systems for ex situ CO generation and the development of carbonylative cascade reactions have further increased the interest in CO-free protocols. We anticipate that the methods reported in this account will further stimulate the development within the field.

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We are indebted to all our co-workers and in particular to those involved in this research program for their invaluable intellectual and experimental contributions. Their names are seen in the references cited.

References

(1) Odell, L. R.; Russo, F.; Larhed, M. *Synlett* **2012**, *5*, 685.
(2) GDCh-Ortsverband-Braunschweig; *Angew. Chem.* **1948**, *60*, 211.
(3) Reppe, W.; Vetter, H. *Justus Liebigs Ann. Chem.* **1953**, *582*, 133.
(4) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318.
(5) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.
(6) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114.
(7) Rahman, O. *J. Label. Compd. Radiopharm.* **2015**, *58*, 86.
(8) Rotstein, B. H.; Liang, S. H.; Placzek, M. S.; Hooker, J. M.; Gee, A. D.; Dollé, F.; Wilson, A. A.; Vasdev, N. *Chem. Soc. Rev.* **2016**, *45*, 4708.
(9) Wu, X.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986.
(10) Grigg, R.; Mutton, S. P. *Tetrahedron* **2010**, *66*, 5515.
(11) Morimoto, T.; Kakiuchi, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 5580.
(12) (a) Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. *Acc. Chem. Res.* **2016**, *49*, 594. (b) Gautam, P.; Bhanage, B. M. *Catal. Sci. Technol.* **2015**, *5*, 4663. (c) Peng, J.-P.; Qi, X.; Wu, X.-F. *Synlett* **2017**, *28*, 175. (d) Wang, L.; Sun, W.; Liu, C. *Chin. J. Chem.* **2018**, *36*, 353.
(13) Schareina, T.; Zapf, A.; Cotté, A.; Gotta, M.; Beller, M. *Adv. Synth. Catal.* **2010**, *352*, 1205.
(14) Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2012**, *14*, 3100.
(15) Wang, Y.; Ren, W.; Li, J.; Wang, H.; Shi, Y. *Org. Lett.* **2014**, *16*, 5960.
(16) Konishi, H.; Manabe, K. *Synlett* **2014**, *25*, 1971.
(17) (a) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (b) Cao, J.; Zheng, Z.-J.; Xu, Z.; Xu, L.-X. *Coord. Chem. Rev.* **2017**, *336*, 43. (c) Kuan, S. H. C.; Sun, W.; Wang, L.; Xia, C.; Tay, M. G.; Liu, C. *Adv. Synth. Catal.* **2017**, *359*, 3484.
(18) Brancour, C.; Fukuyama, T.; Mukai, Y.; Skrydstrup, T.; Ryu, I. *Org. Lett.* **2013**, *15*, 2794.
(19) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232.
(20) Ueda, T.; Konishi, H.; Manabe, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 8611.
(21) Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2013**, *15*, 5370.
(22) Yu, B.; Zhao, Y.; Zhang, H.; Xu, J.; Hao, L.; Gao, X.; Liu, Z. *Chem. Commun.* **2014**, *50*, 2330.
(23) Yu, B.; Yang, Z.; Zhao, Y.; Hao, L.; Zhang, H.; Gao, X.; Han, B.; Liu, Z. *Chem. Eur. J.* **2016**, *22*, 1097.
(24) Lin, W.-H.; Wu, W.-C.; Selvaraju, M.; Sun, C.-M. *Org. Chem. Front.* **2017**, *4*, 392.
(25) Suresh, A. S.; Baburajan, P.; Ahmed, M. *Tetrahedron Lett.* **2014**, *55*, 3482.
(26) Kaiser, N. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109.
(27) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750.
(28) Letavic, M. A.; Ly, K. S. *Tetrahedron Lett.* **2007**, *48*, 2339.
(29) Roberts, B.; Liptrot, D.; Alcaraz, L.; Luker, T.; Stocks, M. J. *Org. Lett.* **2010**, *12*, 4280.
(30) Roberts, B.; Liptrot, D.; Luker, T.; Stocks, M. J.; Barber, C.; Webb, N.; Dods, R.; Martin, B. *Tetrahedron Lett.* **2011**, *52*, 3793.
(31) Spencer, J.; Anjum, N.; Patel, H.; Rathnam, R. P.; Verma, J. *Synlett* **2007**, *16*, 2557.
(32) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061.
(33) Friis, S. D.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 18114.
(34) Chow, S. Y.; Stevens, M. Y.; Åkerbladh, L.; Bergman, S.; Odell, L. R. *Chem. Eur. J.* **2016**, *22*, 9037.
(35) Hansen, S. V. F.; Ulven, T. *Org. Lett.* **2015**, *17*, 2832.
(36) Gockel, S. N.; Hull, K. L. *Org. Lett.* **2015**, *17*, 3236.

(37) Grushin, V. V.; Alper, H. *Organometallics* **1993**, *12*, 3846.
(38) Nordeman, P.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2012**, *77*, 11393.
(39) Begouin, A.; Queiroz, M. R. P. *Eur. J. Org. Chem.* **2009**, 2820.
(40) Yamazaki, K.; Kondo, Y. *J. Comb. Chem.* **2004**, *6*, 121.
(41) Åkerbladh, L.; Nordeman, P.; Wejdemar, M.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2015**, *80*, 1464.
(42) Herrero, M. A.; Wannberg, J.; Larhed, M. *Synlett* **2004**, 2335.
(43) Skogh, A.; Fransson, R.; Sköld, C.; Larhed, M.; Sandström, A. *J. Org. Chem.* **2013**, *78*, 12251.
(44) Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 115.
(45) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6234.
(46) Wang, W.; Dömling, A. *J. Comb. Chem.* **2009**, *11*, 403.
(47) Shen, C.; Wu, X. F. *Chem. Eur. J.* **2017**, *23*, 2973.
(48) Mannich, C.; Krösche, W. *Arch. Pharm.* **1912**, *250*, 647.
(49) Strecker, A. *Justus Liebigs Ann. Chem.* **1850**, *75*, 27.
(50) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
(51) Kappe, O. C. *Tetrahedron* **1993**, *49*, 6937.
(52) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126.
(53) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181.
(54) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.
(55) Wu, X.-F. *RSC Adv.* **2016**, *6*, 83831.
(56) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1.
(57) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083.
(58) Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15*, 1300.
(59) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
(60) Iizuka, M.; Kondo, Y. *Eur. J. Org. Chem.* **2007**, 5180.
(61) Stonehouse, J. P.; Chekmarev, D. S.; Ivanova, N. V.; Lang, S.; Pairaudeau, G.; Smith, N.; Stocks, M. J.; Sviridov, S. I.; Utkina, L. M. *Synlett* **2008**, 100.
(62) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402.
(63) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449.
(64) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons: New York, **2002**.
(65) Mane, R. S.; Nordeman, P.; Odell, L. R.; Larhed, M. *Tetrahedron Lett.* **2013**, *54*, 6912.
(66) Lian, Z.; Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. *Synlett* **2014**, *25*, 1241.
(67) Nordeman, P.; Chow, S. Y.; Odell, A.; Antoni, G.; Odell, L. R. *Org. Biomol. Chem.* **2017**, *15*, 4875.
(68) Zhou, F.; Wang, D.-S.; Guan, X.; Driver, T. G. *Angew. Chem. Int. Ed.* **2017**, *56*, 4530.
(69) Wang, Z.; Yin, Z.; Wu, X.-F. *Chem. Eur. J.* **2017**, *23*, 15026.
(70) Wang, Z.; Zhu, F.; Li, Y.; Wu, X.-F. *ChemCatChem* **2017**, *9*, 94.
(71) Wang, Z.; Yin, Z.; Zhu, F.; Li, Y.; Wu, X.-F. *ChemCatChem* **2017**, *9*, 3637.
(72) Chow, S. Y.; Stevens, M. Y.; Odell, L. R. *J. Org. Chem.* **2016**, *81*, 2681.
(73) Chadha, N.; Silakari, O. *Eur. J. Med. Chem.* **2017**, *134*, 159.
(74) Wu, X.-F.; Oschatz, S.; Sharif, M.; Langer, P. *Synthesis* **2015**, *47*, 2641.
(75) Mamone, M.; Aziz, J.; Le Bescont, J.; Piguel, S. *Synthesis* **2018**, *50*, 1521.
(76) Wu, X.-F.; Oschatz, S.; Sharif, M.; Beller, M.; Langer, P. *Tetrahedron* **2014**, *70*, 23.
(77) Borhade, S. R.; Sandström, A.; Arvidsson, P. I. *Org. Lett.* **2013**, *15*, 1056.
(78) Wakchaure, P. B.; Borhade, S. R.; Sandström, A.; Arvidsson, P. I. *Eur. J. Org. Chem.* **2015**, 213.
(79) Belfrage, A. K.; Wakchaure, P.; Larhed, M.; Sandström, A. *Eur. J. Org. Chem.* **2015**, 7069.
(80) Hernando, E.; Villalva, J.; Martínez, Á. M.; Alonso, I.; Rodríguez, N.; Gómez Arrayás, R.; Carretero, J. C. *ACS Catal.* **2016**, *6*, 6868.
(81) Chow, S. Y.; Odell, L. R. *J. Org. Chem.* **2017**, *82*, 2515.
(82) Wang, Z.; Li, Y.; Zhu, F.; Wu, X.-F. *Adv. Synth. Catal.* **2016**, *358*, 2855.
(83) Taszarek, M.; Reissig, H.-U. *ChemistrySelect* **2016**, *1*, 5712.
(84) Lotesta, S. D.; Marcus, A. P.; Zheng, Y.; Leftheris, K.; Noto, P. B.; Meng, S.; Kandpal, G.; Chen, G.; Zhou, J.; McKeever, B.; Bukhtiyarov, Y.; Zhao, Y.; Lala, D. S.; Singh, S. B.; McGeehan, G. M. *Bioorg. Med. Chem.* **2016**, *24*, 1384.
(85) Jones, D.; Tellam, J.; Bresciani, S.; Wojno-Picon, J.; Cooper, A.; Tomkinson, N. *Synlett* **2016**, *28*, 577.
(86) Roslin, S.; De Rosa, M.; Deuther-Conrad, W.; Eriksson, J.; Odell, L. R.; Antoni, G.; Brust, P.; Larhed, M. *Bioorg. Med. Chem.* **2017**, *25*, 5095.
(87) Patel, H.; Chuckowree, I.; Coxhead, P.; Guille, M.; Wang, M.; Zuckermann, A.; Williams, R. S. B.; Librizzi, M.; Paranal, R. M.; Bradner, J. E.; Spencer, J. *MedChemComm* **2014**, *5*, 1829.
(88) Behrends, M.; Wallinder, C.; Wieckowska, A.; Guimond, M.-O.; Hallberg, A.; Gallo-Payet, N.; Larhed, M. *ChemistryOpen* **2014**, *3*, 65.
(89) Fernando, D. P.; Jiao, W.; Polivkova, J.; Xiao, J.; Coffey, S. B.; Rose, C.; Londregan, A.; Saenz, J.; Beveridge, R.; Zhang, Y.; Storer, G. E.; Vrieze, D.; Erasga, N.; Jones, R.; Khot, V.; Cameron, K. O.; McClure, K. F.; Bhattacharya, S. K.; Orr, S. T. M. *Tetrahedron Lett.* **2012**, *53*, 6351.
(90) Lindgren, A. E. G.; Öberg, C. T.; Hillgren, J. M.; Elofsson, M. *Eur. J. Org. Chem.* **2016**, 426.
(91) Ono, K.; Banno, H.; Okaniwa, M.; Hirayama, T.; Iwamura, N.; Hikichi, Y.; Murai, S.; Hasegawa, M.; Hasegawa, Y.; Yonemori, K.; Hata, A.; Aoyama, K.; Cary, D. R. *Bioorg. Med. Chem.* **2017**, *25*, 2336.
(92) Lang, C.; Gmeiner, P. *Synthesis* **2013**, *45*, 2474.
(93) Matera, C.; Quadri, M.; Sciaccaluga, M.; Pomè, D. Y.; Fasoli, F.; De Amici, M.; Fucile, S.; Gotti, C.; Dallanoce, C.; Grazioso, G. *Eur. J. Med. Chem.* **2016**, *108*, 392.
(94) Pagliaro, M.; Pandarus, V.; Ciriminna, R.; Béland, F.; Demma Carà, P. *ChemCatChem* **2012**, *4*, 432.
(95) Hajipour, A.-R.; Tavangar-Rizi, Z.; Iranpoor, N. *RSC Adv.* **2016**, *6*, 78468.
(96) Kikukawa, K.; Kono, K.; Wada, F. T. M. *Chem. Lett.* **1982**, 35.
(97) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557.
(98) Lindh, J.; Fardost, A.; Almeida, M.; Nilsson, P. *Tetrahedron Lett.* **2010**, *51*, 2470.
(99) Sävmarker, J.; Lindh, J.; Nilsson, P. *Tetrahedron Lett.* **2010**, *51*, 6886.
(100) Iranpoor, N.; Firouzabadi, H.; Etemadi-Davan, E. *J. Organomet. Chem.* **2015**, *794*, 282.
(101) Horvath, I. T.; Rabai, J. *Science* **1994**, *266*, 72.
(102) Barthel-Rosa, L. P.; Gladysz, J. A. *Coord. Chem. Rev.* **1999**, 190-192, 587.
(103) Ang, W. J.; Lo, L. C.; Lam, Y. *Tetrahedron* **2014**, *70*, 8545.
(104) Wu, L.; Fang, X.; Liu, Q.; Jackstell, R.; Beller, M.; Wu, X.-F. *ACS Catal.* **2014**, *4*, 2977.
(105) Roslin, S.; Odell, L. R. *Eur. J. Org. Chem.* **2017**, 1993.
(106) Ishiyama, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1991**, *32*, 6923.
(107) Ishiyama, T.; Murata, M.; Suzuki, A.; Norio, M. *J. Chem. Soc., Chem. Commun.* **1995**, *9*, 295.
(108) Ryu, I.; Kreimerman, S.; Araki, F.; Nishitani, S.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2002**, *124*, 3812.

(109) Fusano, A.; Fukuyama, T.; Nishitani, S.; Inouye, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 2410.
(110) Fusano, A.; Sumino, S.; Nishitani, S.; Inouye, T.; Morimoto, K.; Fukuyama, T.; Ryu, I. *Chem. Eur. J.* **2012**, *18*, 9415.
(111) Sumino, S.; Ui, T.; Ryu, I. *Org. Lett.* **2013**, *15*, 3142.
(112) Pye, D. R.; Cheng, L.-J.; Mankad, N. P. *Chem. Sci.* **2017**, *8*, 4750.
(113) Roslin, S.; Odell, L. R. *Chem. Commun.* **2017**, *53*, 6895.
(114) Cho, S. K.; Song, J. H.; Hahn, J. T.; il Jung, D. *Bull. Korean Chem. Soc.* **2016**, *37*, 1567.
(115) Wu, X. F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Asian J.* **2012**, *7*, 40.
(116) Tamaru, Y.; Ochiai, H.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1983**, *24*, 3869.
(117) Yasui, K.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1995**, *60*, 1365.
(118) O'Keefe, B. M.; Simmons, N.; Martin, S. F. *Org. Lett.* **2008**, *10*, 5301.
(119) Jackson, R. F. W.; Turner, D.; Block, M. H. *J. Chem. Soc., Perkin Trans. 1* **1997**, *4*, 865.
(120) Motwani, H. V.; Larhed, M. *Eur. J. Org. Chem.* **2013**, 4729.
(121) Park, A.; Lee, S. *Org. Lett.* **2012**, *14*, 1118.
(122) Pyo, A.; Park, A.; Jung, H.; Lee, S. *Synthesis* **2012**, *44*, 2885.
(123) Wu, X. F.; Sharif, M.; Shoaib, K.; Neumann, H.; Pews-Davtyan, A.; Langer, P.; Beller, M. *Chem. Eur. J.* **2013**, *19*, 6230.
(124) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.
(125) Jafarpour, F.; Otaredi-Kashani, A. *ARKIVOC* **2014**, *(iv)*, 193.
(126) Ghosh, P.; Nandi, A. K.; Das, S. *Tetrahedron Lett.* **2018**, *59*, 2025.
(127) Åkerbladh, L.; Odell, L. R. *J. Org. Chem.* **2016**, *81*, 2966.
(128) Åkerbladh, L.; Chow, S. Y.; Odell, L. R.; Larhed, M. *ChemistryOpen* **2017**, *6*, 620.
(129) Åkerbladh, L.; Schembri, L. S.; Larhed, M.; Odell, L. R. *J. Org. Chem.* **2017**, *82*, 12520.
(130) He, L.; Sharif, M.; Neumann, H.; Beller, M.; Wu, X.-F. A. *Green Chem.* **2014**, *16*, 3763.
(131) Wu, X.-F.; Oschatz, S.; Sharif, M.; Flader, A.; Krey, L.; Beller, M.; Langer, P. *Adv. Synth. Catal.* **2013**, *355*, 3581.
(132) Kebede, E.; Tadikonda, R.; Nakka, M.; Inkollu, B.; Vidavalur, S. *Eur. J. Org. Chem.* **2015**, 5929.
(133) Chen, J.; Natte, K.; Spannenberg, A.; Neumann, H.; Beller, M.; Wu, X.-F. *Chem. Eur. J.* **2014**, *20*, 14189.
(134) Chen, J.; Natte, K.; Wu, X.-F. *J. Organomet. Chem.* **2016**, *803*, 9.
(135) Lee, S.; Kim, H.-S.; Min, H.; Pyo, A. *Tetrahedron Lett.* **2016**, *57*, 239.
(136) Qi, X.; Yu, F.; Chen, P.; Liu, G. *Angew. Chem. Int. Ed.* **2017**, *56*, 12692.