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Recent Advances in the Transition Metal Catalyzed Carbonylation of Alkynes, Arenes and Aryl Halides Using CO Surrogates

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Transition metal catalyzed carbonylation reactions using carbon monoxide as the C-1 source have occupied an all important position in catalysis which is subsequently related to organic synthesis and industrial synthesis of molecules. However the use of carbon monoxide, an inflammable, toxic greenhouse gas acts as a deterrent in academic and industrial research. Hence it is imperative to develop a CO free protocol for promoting sustainable chemistry. The chemistry of CO surrogates has undergone a substantial progress with the development of newer reaction methodologies and newer surrogate molecules. Aldehydes, formate esters, formamides, metal carbonyls have been applied not only for the synthesis of industrial bulk chemicals, but also for the synthesis of specialty chemicals and molecules which are important pharmacological building blocks. Simultaneous development of the two-chamber reactor allows for the *ex situ* generation of CO and hence circumvents the compatibility issues associated with the substrate and the surrogate during *in situ* CO generation. Further, the development of specialized surrogate molecules allow for the incorporation of ^{13}C, ^{14}C labelled isotopes even at an advanced stage of the synthesis of the molecule. This review thus summarizes the progress in the last decade in the development of synthetic methodologies in which carbonylation reactions are carried out without the use of gaseous carbon monoxide or using carbon monoxide surrogates.

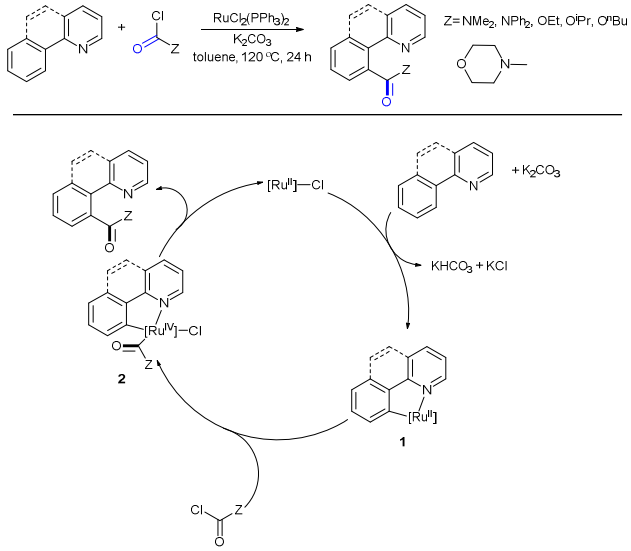
1. Introduction

The functionalization of substrates using carbon monoxide as the C1 source– carbonylation– comes in as one of the most important industrial process for the manufacture of bulk and fine chemicals.[1] The process typically uses gaseous CO and a transition metal catalyst for the synthesis of diverse set of products.[2] CO being an odourless, inflammable and toxic gas coupled with the need to use specialized high pressure reactors limits the use of the reaction on an industrial scale and also in academic research. The requirement to transport and store CO also poses a serious safety hazard. To address these problems, development of CO free carbonylation and homogeneous catalysis associated with it has gained importance recently. The use of CO surrogates serves as a convenient and safe approach for the synthesis of carbonyl derivatives circumventing the need to use gaseous CO. Such a process can also be extrapolated to industrial scale synthesis of diverse set of products.

In 2004, Morimoto and Kakiuchi documented the first review on CO surrogates[3] covering formic acid and its derivatives, metal carbonyls and aldehydes which can be applied to different substrates like alkenes, alkynes and aryl halides. There have been recent reviews published, focusing either on a particular surrogate or a substrate. In 2011, Odell *et al.* reviewed molybdenum hexacarbonyl as a solid surrogate.[4] In 2014, Konishi and Manabe covered formic acid and their derivatives for the carbonylation of alkenes and aryl halides.[5] Beller and co-workers recently reviewed carbonylation using CO surrogates focusing on alkenes as substrates.[6] There has been an advancement in the development of new surrogate molecules which have not been covered in the aforementioned reviews. Further, as far as substrates are concerned, only alkene has been focused upon specifically. In this review, we endeavour to cover carbonylation with specific emphasis on alkynes, arenes and aryl halides as substrates using different surrogate molecules. This review will cover the literature post Morimoto's review and is documented according to the molecules that can be used as surrogates.

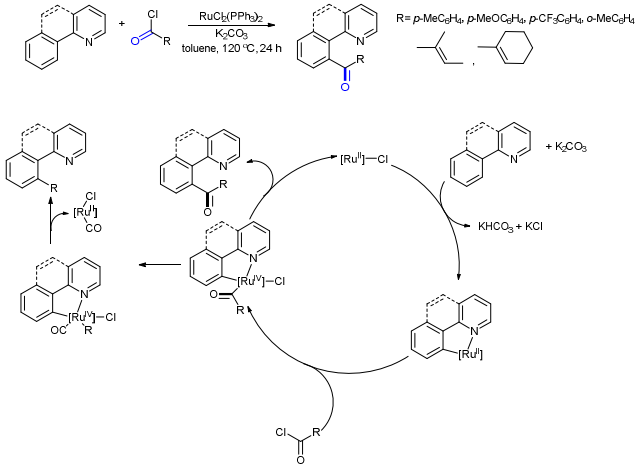
2. Acid chloride and carbamoyl chloride

In 2009, Kakiuchi and co-workers reported a ruthenium catalyzed amino- and alkoxycarbonylation of C-H bonds of aromatic compounds using carbamoyl chloride and alkyl chloroformates leading to the synthesis of amides and esters respectively.[7] The C-H functionalization was achieved using benzo[*h*]quinoline, 2-arylpyridine and imidazole as heterocyclic directing groups. A wide variety of *N,N*-disubstituted amides and esters were synthesized. Incidentally, the protocol was oxidant free and the mechanism proposed involved the formation of a ruthenacycle intermediate **1**. This underwent oxidative addition to give an intermediate **2** having ruthenium in +4 oxidation state. Subsequent reductive elimination gave the product (Scheme 1).



Scheme 1 Amino- and alkoxycarbonylation of aromatic C-H bonds using heterocyclic directing groups.

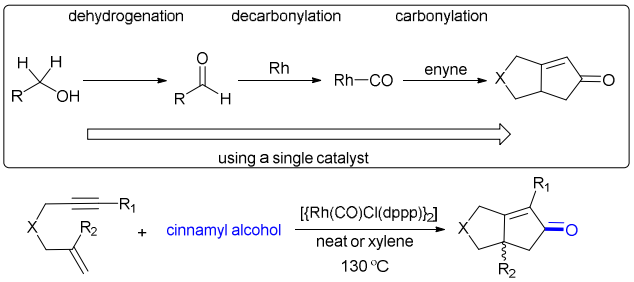
In 2011, Kakiuchi and co-workers extended their previous protocol involving the ortho C-H functionalization of arylpyridine and benzo[*h*]quinoline with carbamoyl chloride and alkyl chloroformate to the use of acyl chlorides as CO surrogates, thus leading to the synthesis of aromatic ketones.[8] The reaction conditions involving the catalyst, solvent and base remained the same. As far as the scope of acyl chlorides was concerned, aromatic acyl chlorides containing electron-releasing and –withdrawing groups and α,β-unsaturated acyl chlorides could be applied successfully to afford the corresponding ketones. A similar mechanism involving the formation of a ruthenacycle intermediate, followed by the oxidative addition of acyl chloride, decarbonylation and subsequent reductive elimination to give the desired product was proposed (Scheme 2).



Scheme 2 Ruthenium catalyzed acylation using acid chloride.

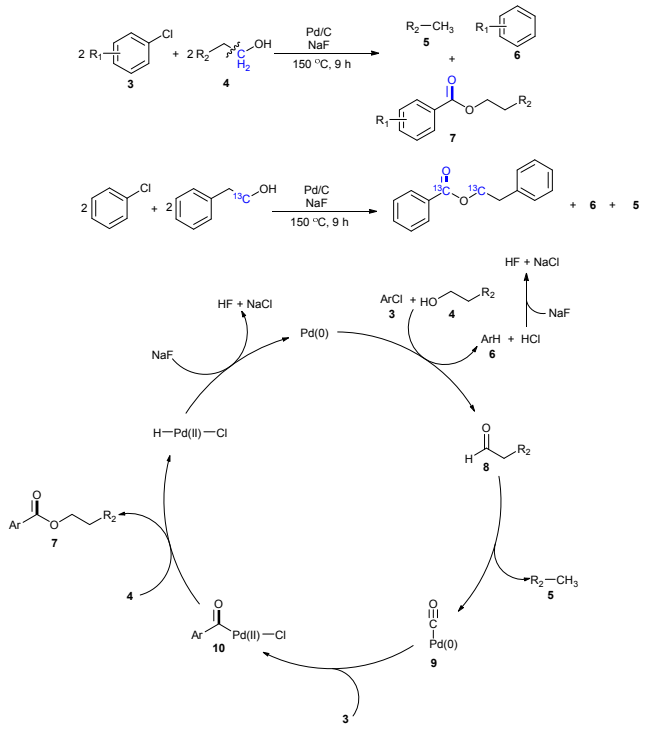
3. Alcohol

In 2010, Chung and co-workers reported alcohol as a CO source for the Pauson-Khand type reaction wherein alcohol was dehydrogenated to give aldehyde.[9] The aldehyde was subsequently decarbonylated in the presence of a rhodium catalyst and the CO generated was made to react with an enyne. Various rhodium catalysts and alcohols were screened and the combination of {Rh(CO)Cl(dppp)$_2$} and cinnamyl alcohol were found to be ideal for the reaction. All the three reactions took place in one pot and a single rhodium catalyst was used for all the reactions (Scheme 3).



Scheme 3 Pauson-Khand reaction of enyne using cinnamyl alcohol as a CO source.

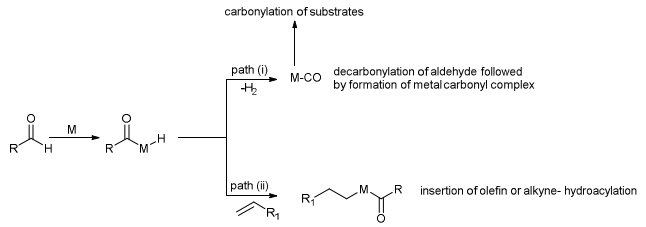
Recently, Jun and co-workers reported the alkoxycarbonylation of aryl chlorides with primary alcohols catalyzed by Pd/C involving a dehydroxymethylative C-C bond cleavage.[10] In the protocol, aryl chloride **3** and Pd(0) promote the dehydroxymethylation of the primary alcohol **4**. The Pd(0)CO produced carbonylatively couples with the aryl chloride and the alcohol to give the ester **7** along with **5** and **6**. The ^{13}C labelling studies showed that the carbonyl and the alkoxy carbon both are incorporated from the alcohol carbon. Hence, this comes in as an example where both the reactants serve a dual role, where in the aryl chloride acts as the oxidizing agent and the coupling partner and the alcohol as the CO source and the alkoxy part of the ester. The optimization studies revealed that the reaction can only be catalyzed by Pd/C and all other palladium catalysts are ineffective. Further, only NaF as the base is effective. The reaction tolerates various aryl chlorides but is limited to only primary alcohols. Even methanol was used for the synthesis of various methyl esters. The reaction mechanism proposed involves the formation of aldehyde **8** by the oxidation of alcohol **4** in presence of Pd(0) and aryl chloride to give **6** and HCl which is neutralized by NaF. Aldehyde **8** undergoes decarbonylation to give Pd(0)CO **9** and **5**. The aryl chloride **3** undergoes oxidative addition with **9** to give **10** which reacts with alcohol to give the ester product **7** (Scheme 4).



Scheme 4 Alkoxycarbonylation of aryl chlorides catalyzed by Pd/C through a dehydroxymethylative C-C bond cleavage.

4. Aldehyde

Aldehydes are important molecules which behave as a source of the carbonyl group. The reaction of aldehydes with transition metals takes place by insertion of metal into the formyl bond, thus forming a formyl ligated metal complex which can react in two mechanistic pathways- (i) decarbonylation to form a metal carbonyl complex and (ii) addition of alkenes and alkynes (hydroacylation) (Scheme 5). The hydroacylation reactions with aldehydes have been reviewed recently.[11]



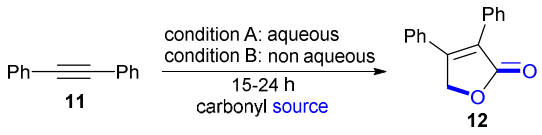
Scheme 5 Reaction pathway depicting the activation of aldehyde with transition metals.

4.1 Formaldehyde

4.1.1 Carbonylation Reactions

Morimoto and co-workers reported a rhodium(I) catalyzed cyclohydrocarbonylation of alkynes using formaldehyde as a CO substitute leading to the synthesis of α,β-butenolides.[12] The reaction involves double incorporation of the carbonyl moiety from formaldehyde, one as a carbonyl group and the other as a CH_2O unit of the butenolide ring. The reaction was performed in aqueous and non-aqueous conditions (Table 1).

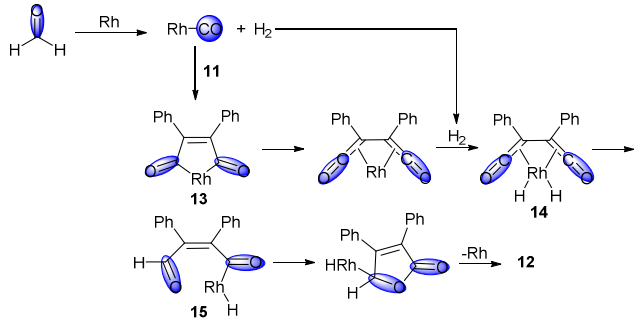
Table 1 Rh-catalyzed cyclohydrocarbonylation of 11 using various carbonyl source.



Entry	Conditions[a]	Carbonyl source	Yield[b]
1	A	Formalin (3 equiv.)	98
2	A	Benzaldehyde (5 equiv.)	0 (79)
3	A	CO (1 atm)	0 (84)
4	B	$(CH_2O)_n$ (5 equiv.)[c]	72
5	B	$CO-H_2$ = 1:1 (1 atm)	6 (68)

[a] Condition A: $[RhCl(cod)]_2$ (5 mol%), dppp (10 mol%), TPPTS (10 mol%) and SDS (2 equiv.) in H_2O at 100 °C; condition B: $[RhCl(cod)]_2$ (5 mol%) and dppp (10 mol%) in xylene at 100 °C [b] Isolated yields. Values in parentheses are the yields of **11**. [c] Paraformaldehyde was used.

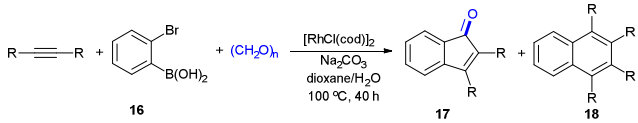
It was proposed that, the formation of butenolide under anhydrous conditions using paraformaldehyde is indicative of the fact that the γ-CH_2 unit comes from formaldehyde and not from water. Interestingly, when the reaction is performed under an atmosphere of CO, $CO-H_2$ or using benzaldehyde, the product is not formed indicating the uniqueness of using formaldehyde. As part of the substrate study, different alkynes bearing different groups on the termini were used. The formation of exclusive regioisomers depending on the condition of the reaction was also demonstrated. The mechanism involved decarbonylation of formaldehyde followed by formation of key intermediates like maleoylrhodium **13**, (η^4-bisketene)rhodium **14** and β-formyl-acylrhodium **15** to afford the product (Scheme 6).



Scheme 6 Proposed mechanistic pathway for the cyclohydrocarbonylation using formaldehyde.

In 2009, Morimoto *et al*. reported the carbonylative cyclization of alkynes with 2-halophenylboronic acids using paraformaldehyde as a CO surrogate leading to the efficient synthesis of indenone derivatives.[13] The catalytic system consisted of $[RhCl(cod)]_2$ and BINAP, where in the addition of BINAP lead to the partial formation of $[RhCl(BINAP)]_2$ (Table 2). Using these conditions, alkynes and 2-halophenylboronic acids with various substituents were cyclocarbonylated to give indenones in moderate to high yields. 2-chlorophenylboronic acids albeit gave lower yields.

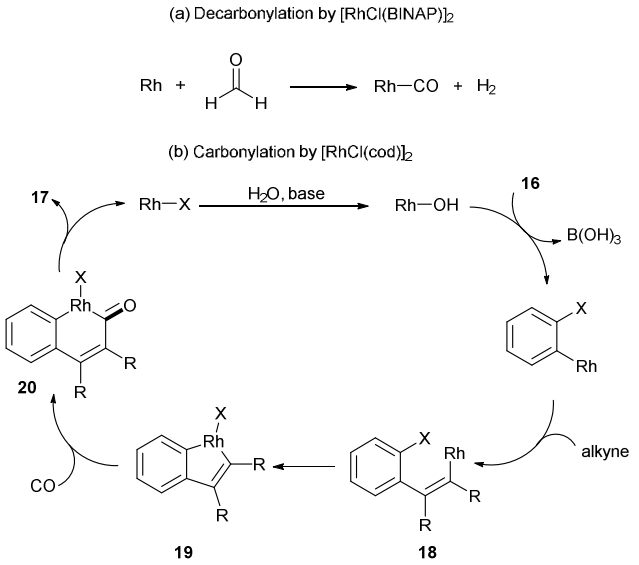
Table 2 Effect of BINAP ligand loading on the product yield.



Entry	BINAP (mol%)	Yield of **16**[b] (%)	Yield of **17**[b] (%)
1	-	41	9
2	1	75	4
3	2	47	3
4	5	32	Trace
5[c]	1	83	4

[a] Reactions conditions: 4-octyne (1 mmol), **16** (1.5 mmol), paraformaldehyde (5 mmol), $[RhCl(cod)]_2$ (0.025 mmol), Na_2CO_3 (2 mmol) in dioxane/H_2O (100/1, 2 mL) at 100 °C for 40 h. [b] Isolated yield. [c] 3 mmol of 1 was used for 30 h.

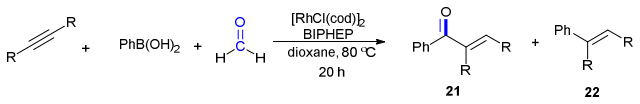
The decarbonylation-carbonylation pathway was proposed wherein $[RhCl(BINAP)]_2$ was involved in decarbonylation of formaldehyde leading to the evolution of CO and hydrogen and $[RhCl(cod)]_2$ was involved in catalyzing the main carbonylation process. The key steps involved are the formation of the vinylrhodium(I) complex **18** by the addition of the alkyne in a *cis*-manner which in turn undergoes an oxidative addition to produce a rhodacycle **19.** CO insertion gave **20** which is followed by reductive elimination to afford the indenone (Scheme 7).



Scheme 7 Mechanistic pathway for the formation of indenone from 2-halophenylboronic acid using formaldehyde.

In 2014, Morimoto's group reported a rhodium(I) catalyzed carbonylative arylation of alkynes with phenylboronic acid using formaldehyde leading to the synthesis of α,β-unsaturated ketones **21**, as an extension of their work using gaseous CO.[14] The carbonylation using CO gas was phosphine free, whereas the decarbonylation of formaldehyde required a rhodium(I)-phosphine complex. Hence the authors showed that a delicate balance of a phosphine-ligated and phosphine-free rhodium catalysis is required for the decarbonylation of formaldehyde and subsequent targeted carbonylation. The use of 5 mol% $[RhCl(cod)]_2$ and varying amounts of BIPHEP (0 to 10 mol%) was applied to check the yield of the enones. The best yields were obtained for 1 mol% of BIPHEP and at 10 mol% loading which accounted for all of the loaded rhodium, the yield was the lowest (Table 3), indicating that partially formed $[RhCl(BIPHEP)]_2$ was involved in catalysing the decarbonylation step and $[RhCl(cod)]_2$ in carbonylative arylation.

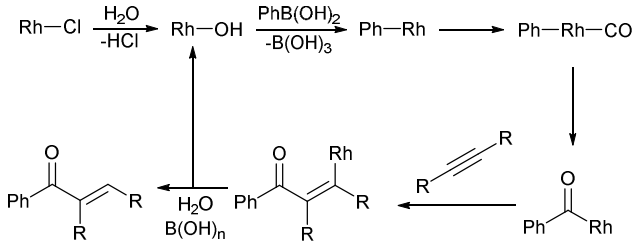
Table 3 Effect of BIPHEP ligand loading on the product yield.



Entry	BIPHEP (mol%)	Yield (%) of **21** (*E*/*Z*)	Yield (%) of **22**
1	0	32 (39/61)	56
2	1	62 (32/68)	7
3	2	46 (37/63)	9
4	5	27 (35/65)	4
5	10	4 (57/43)	1

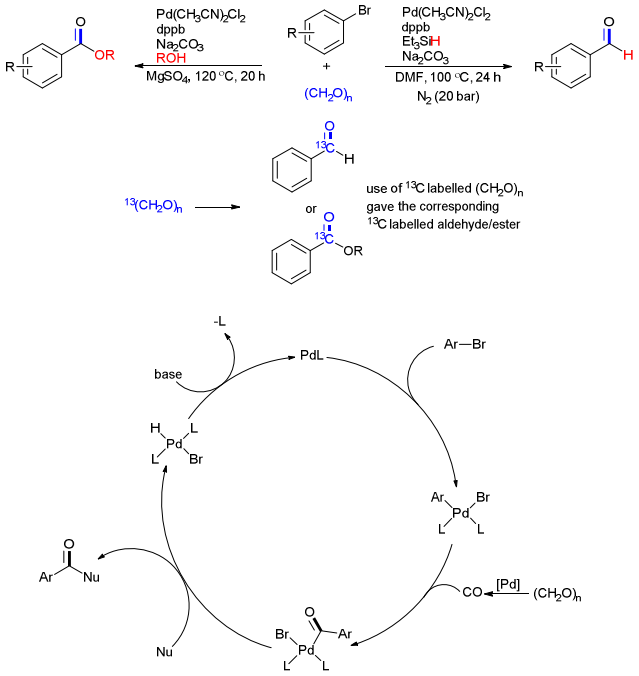
[a] Reaction conditions: alkyne (1 mmol), arylboronic acid (2 mmol), paraformaldehyde (5 mmol), $[RhCl(cod)]_2$ (5 mol%) in dioxane (1 mL) at 80 °C for 20 h. [b] Isolated yield. [c] Determined by 1H NMR.

Use of other phosphine ligands resulted in low yields. Based on the deuterium studies done to ascertain the origin of the β-hydrogen on the enone, a mechanism was proposed (Scheme 8).



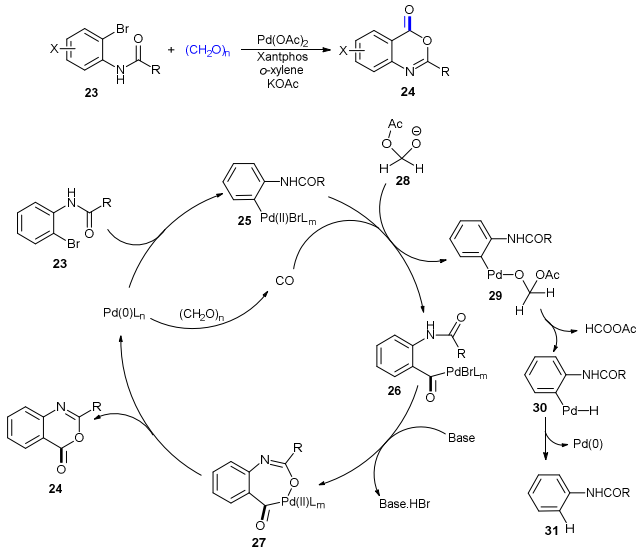
Scheme 8 Mechanistic pathway for the carbonylative arylation of alkynes using formaldehyde.

Beller and co-workers reported the use of paraformaldehyde for the alkoxycarbonylation and reductive carbonylation of aryl bromides leading to the synthesis of esters and aldehydes respectively.[15] The reductive carbonylation involved the use of triethylsilane as the hydride source. Screening of the active palladium catalyst and ligands showed that the combination of $[Pd(CH_3CN)_2Cl_2]$ and dppb gave the best yield of aldehydes and esters. A wide variety of aldehydes and esters were synthesized as part of the substrate study. ^{13}C-labelled experiments were carried out to get an insight and hence determine the mechanism (Scheme 9).



Scheme 9 Alkoxy- and reductive carbonylation of aryl bromides using paraformaldehyde.

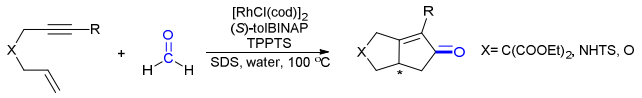
Recently Li and Wu reported the carbonylative synthesis of benzoxazinones **24** from *N*-(*o*-bromoaryl)amides **23** using paraformaldehyde.[16] Notably, this was the first example wherein paraformaldehyde was used as a CO source for the carbonylative synthesis of a heterocycle. The choice of the palladium catalyst, base, solvent and ligand were crucial for obtaining the product in high yield with $Pd(OAc)_2$, Xantphos as the ligand, KOAc as the base and *o*-xylene as the solvent forming part of the optimized conditions. Interestingly, formalin and trioxin gave lower yields of **24** thus emphasizing on the uniqueness of paraformaldehyde. The use of ^{13}C labelled paraformaldehyde allowed the synthesis of ^{13}C labelled benzoxazinone. The reaction mechanism proposed involves the oxidative addition of the aryl bromide **23** to give **25**. The decomposition of paraformaldehyde to CO in presence of palladium catalyst followed by its subsequent insertion to **25** gives **26**. Formation of **27** from **26** and its subsequent reductive elimination affords **24**. The formation of the side product was explained by the formation of the hemiacetal anion **28** from the aldehyde in presence of the acetate anion. This undergoes ligand exchange with **25** to give **29** which in turn undergoes a β-hydride elimination to give hydroaryl palladium complex **30** which being unstable gives the hydrodebromination product **31** (Scheme 10).



Scheme 10 Carbonylative synthesis of benzoxazinones using paraformaldehyde.

4.1.2 Pauson-Khand Reaction (PKR)

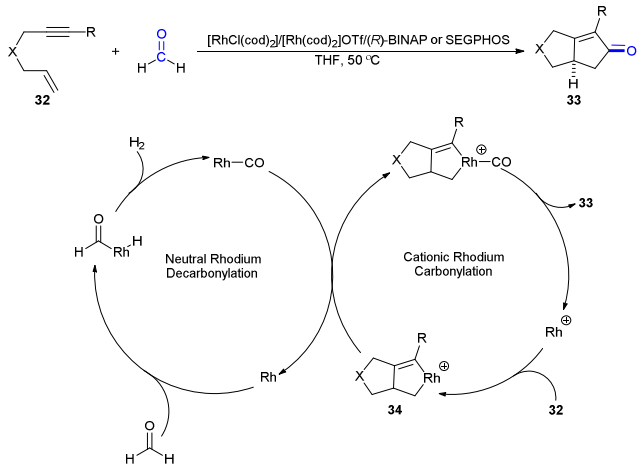
In 2004, Morimoto's group reported the first CO free, asymmetric, aqueous phase PKR reaction using formalin.[17] The combination of a hydrophilic phosphine (TPPTS) and a hydrophobic chiral phosphine ((*S*)-tolBINAP) in the presence of SDS surfactant allows for the synthesis of bicyclic cyclopentenones in high yields and with high enantiomeric excess. The combination of 5 mol% TPPTS and 10 mol% tolBINAP gives the best possible yield. Different enynes were smoothly coupled within 6 h although the reaction conditions depended on the type of substrate used (Scheme 11).



Scheme 11 The first asymmetric aqueous phase Pauson-Khand reaction using formalin.

Recently, Morimoto's group documented the effect of cooperative dual rhodium catalysis to carry out the asymmetric PKR of 1,6-enynes using formaldehyde at milder conditions.[18] A strategy involving the use of neutral and cationic rhodium complexes to carry out the two reversely oriented processes (decarbonylation and carbonylation) was formulated. It was shown that the use of neutral $[RhCl(cod)]_2$/*rac*-BINAP or cationic $[Rh(cod)_2]OTf$/*rac*-BINAP gave poor yields of **33** when **32** was reacted with formalin at 50 °C. However when both were used simultaneously, **33** was formed in 58% yield and on using *R*- and *S*-BINAP, the *R* and *S* enantiomers of **33** could be synthesized with high enantioselectivity. Further from a series of ^{31}P NMR experiments and reactions with gaseous CO, it was determined that the decarbonylation was effectively catalyzed by the neutral rhodium complex whereas the carbonylation was catalyzed by the cationic rhodium complex. It was also shown that the use of phosphine ligands with narrow dihedral angles gave the best enantioselectivity even though the product yields were comparatively less as compared to BINAP. A reaction mechanism involving the formation of a cationic rhodacycle **34** which subsequently undergoes carbonylation through the transfer

of the carbonyl unit from the neutral rhodium centre to afford the product was proposed (Scheme 12).

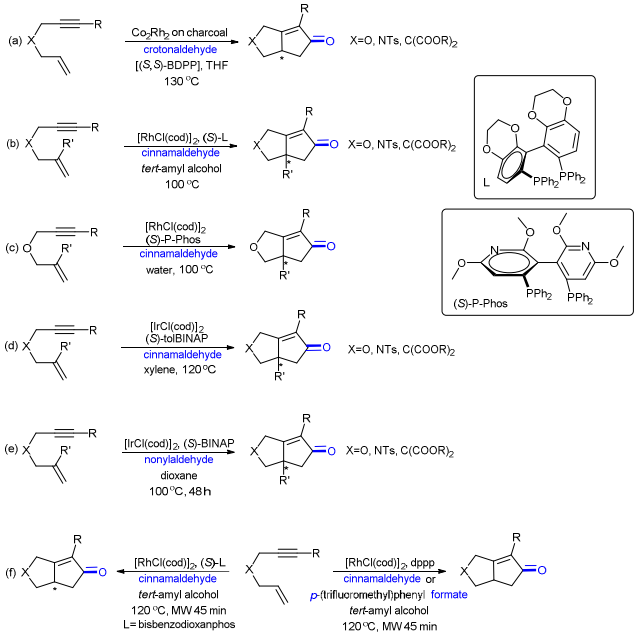


Scheme 12 Asymmetric Pauson-Khand reaction using formaldehyde by cooperative dual rhodium catalysis.

4.2 Miscellaneous Aldehydes

4.2.1 Pauson-Khand Reaction (PKR)

In 2005, Park and Chung reported Co/Rh heterobimetallic nanoparticle immobilized on charcoal for the PKR of 1,6 enynes using aldehydes.[19] Upon the introduction of chiral ligand in the system, an asymmetric version of the reaction could be realized. $Co_2Rh_2(CO)_{12}$ and $Co_3Rh(CO)_{12}$ were used as the precursors for the preparation of the nanoparticles with the HR-TEM analysis revealing the size of the nanoparticles to be 2 nm and the ICP-AES analysis showing the Co-Rh stoichiometry to be 2:2 and 3:1 (Co_2Rh_2 and Co_3Rh). The aldehydes when screened, showed that α,β-unsaturated aldehydes were better choices for carbonyl donation as compared to aliphatic and aromatic aldehydes with crotonaldehyde proving to be the best choice. The ligand screening study showed that (2*S*,4*S*)-(−)-2,4-bis(diphenylphosphino)pentane [(*S*,*S*)-BDPP] was the best choice as far as yield and enantiomeric excess of the product was concerned in the asymmetric reaction. Further the catalyst be recycled for 5 times in the racemic as well as the asymmetric versions and the Hg(0) poisoning study revealed that the nature of the catalyst was truly heterogeneous with its addition completely inhibiting further catalysis (a, Scheme 13). Later Kwong *et al*. showed that the use of chiral atropisomeric diphosphane, (*S*)-bisbenzodioxanphos allowed the asymmetric PKR of 1,6 enynes to be carried out in relatively less toxic alcoholic solvents using aldehydes.[20] *Tert*-amyl alcohol was found to be the best solvent and incidentally (*S*)-bisbenzodioxanphos has better solubility in alcoholic medium as compared to BINAP. The aldehyde screening study showed that cinnamaldehyde was the best choice for carbonyl donation. Various oxygen, nitrogen and carbon tethered enynes could be transformed in high yields and enenatioselectivity (b, Scheme 13). Almost at the same time when Morimoto's group reported the first asymmetric aqueous phase PKR using formaldehyde, Kwong *et al*. reported a similar aqueous phase asymmetric phase PKR.[21] After the reaction optimization study, it was shown that the combination of cinnamaldehyde as the CO source along with water as the solvent, neutral $[RhCl(cod)]_2$ as the catalyst and dipyridyldiphosphane ligand (*S*)-P-Phos gave the best results. Various oxygen tethered enynes were successfully transformed with high enantioselectivity (c, Scheme 13). Shibata and co-workers reported an iridium catalyzed asymmetric PKR using cinnamaldehyde and optically active (*S*)-tolBINAP.[22] Incidentally, when iridium was used as the catalyst, only 5 equivalent of the aldehyde was required, thereby generating an ee of 92%, whereas, using Rh required 20 equivalent of the aldehyde generating an ee of only 82% (d, Scheme 13). Almost at the same time Kwong *et al*. documented the iridium catalyzed asymmetric PKR using optically active (*S*)-BINAP.[23] Screening of aldehydes showed *n*-nonylaldehyde gave the best yield and ee in dioxane (e, Scheme 13). In 2008, Kwong and co-workers reported a microwave assisted, rhodium catalyzed achiral and enantioselective PKR using cinnamaldehyde.[24] The achiral version could be carried out using dppp as the phosphine ligand at 120 °C whereas for the chiral version, (*S*)-bisbenzodioxanphos was the best choice. The achiral reaction could also be carried out using *p*-(trifluoromethyl)phenyl formate as a CO source. Interestingly, the authors documented that the microwave versions of these reactions could be carried out in 45 min, whereas, when the reaction is carried out under conventional heating, it takes 36 h for completion of the reaction and in the case of formate, it takes 72 h (f, Scheme 13).

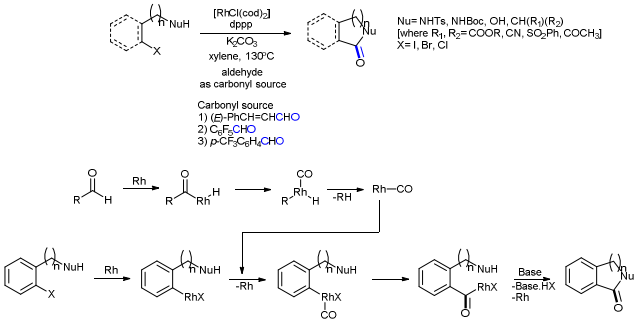


Scheme 13 Iridium and rhodium catalyzed asymmetric PKR using aldehyde.

4.2.2 Carbonylation Reactions

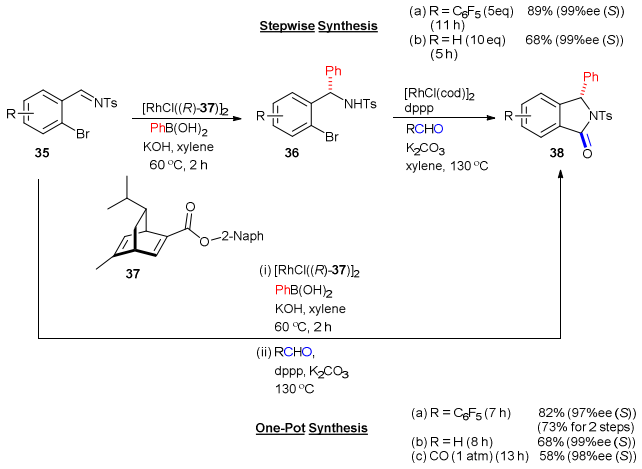
Morimoto and co-workers reported a carbonylative cyclization of aryl, alkyl and alkenyl halides with tethered nitrogen, oxygen and carbon nucleophiles using various aldehydes as a CO source.[25] The reaction was carried out under rhodium(I) catalysis. Different aldehydes were screened for their carbonyl donation and it was found out that, aldehydes with electron-withdrawing substituents, namely pentafluorobenzaldehyde, *trans*-cinnamaldehyde and *p*-trifluoromethylbenzaldehyde, smoothly underwent decarbonylation and subsequent carbonylation. In the case of nitrogen and oxygen nucleophiles, aryl as well as alkyl bromides

and chlorides reacted well. Carbon nucleophiles, which included active methylene groups (methylene group sandwiched between two strongly electron-withdrawing groups) also reacted with aryl and alkenyl iodides. Cyclization leading to the synthesis of five, six and seven membered rings was easily achieved. A possible reaction mechanism was proposed (Scheme 14).



Scheme 14 Carbonylative cyclization of organic halides with tethered nucleophiles using aldehydes.

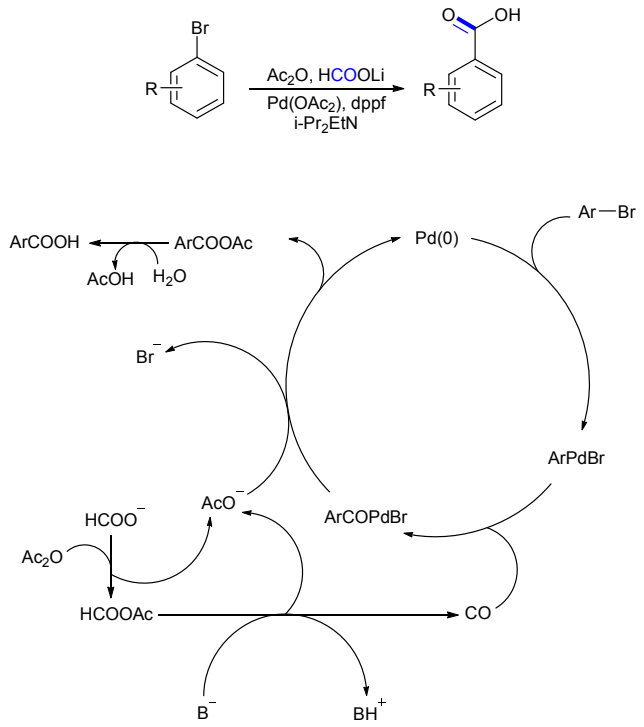
In 2012, Fujioka *et al.* reported the aminocarbonylation of enantiomerically pure *N*-tosyl-2-bromobenzylamine using $[RhCl(cod)]_2$ as the catalyst and an aldehyde to give optically pure 3-substituted isoindolinones.[26] The reaction was carried out independently in a two-step and a one-pot process. The two-step process involved the preparation of the enantiomerically pure benzylamine **36** from 2-bromobenzaldimine **35** by rhodium catalyzed arylation with phenylboronic acid in the presence of a chiral diene **37** and subsequent carbonylation to give **38**. Variation of substituents on the aromatic ring of phenylboronic acid and on the aromatic ring of 2-bromobenzaldimine formed part of the substrate study. Comparison between perfluorobenazaldehyde and paraformaldehyde as CO surrogates and gaseous CO was also done. Perfluorobenzaldehyde proved to be the best choice as far as product yield and preservation of enantiomeric excess is concerned. Although lower yields were obtained with gaseous CO and paraformaldehyde, high ee was still intact. The one pot process showed the conversion of 2-bromobenzaldimine to optically pure isoindolinones using the same catalytic system and optically active ligand without isolating the optically pure benzylamine. The one pot procedure proved to be more efficient than the two step procedure as far as product yield were concerned (Scheme 15).



Scheme 15 Asymmetric synthesis of 3-substituted isoindolinones using aldehyde under rhodium catalysis.

5. Anhydride

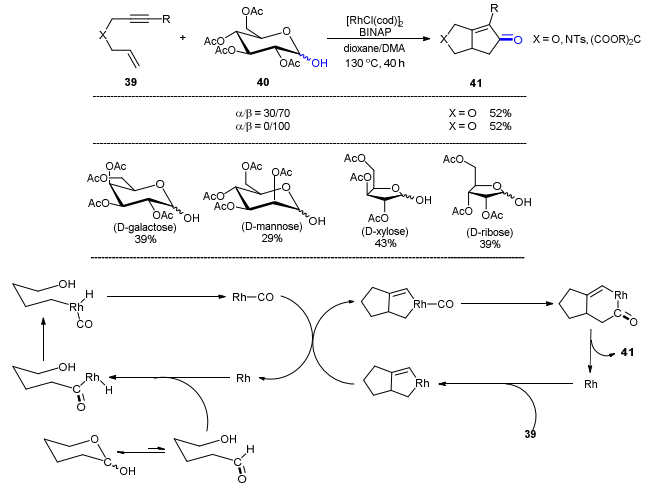
In 2003, Cacchi and co-workers demonstrated that carboxylic acids can be synthesized through hydroxycarbonylation of aryl and vinyl halides or triflates using a formate anion and acetic anhydride as a mixed system for the generation of *in situ* CO.[27] It was proposed and experimentally established that the formate anion reacted with acetic anhydride to generate a mixed anhydride, namely, formic acetic anhydride which serves as the condensed CO source. However their system was predominantly restricted to iodides with bromides and triflates reacting sluggishly. In 2006, Berger *et al.* reported the hydroxycarbonylation of aryl bromides using an efficient catalytic system comprising of $Pd(OAc)_2$ and dppf as ligand.[28] Just like Cacchi's protocol, the use of lithium formate proved to be beneficial in achieving high yield although the addition of LiCl did not have any effect on the yield. A variety of aryl bromides were successfully converted to aryl carboxylic acids (Scheme 16).



Scheme 16 Hydroxycarbonylation of aryl and vinyl bromides by mixed acetic formic anhydride.

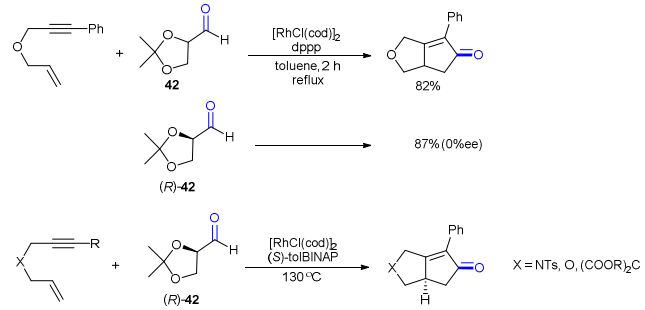
6. Carbohydrates

In 2010, Ikeda *et al*. documented the use of aldoses as CO surrogates for the Pauson Khand reaction of enynes leading to the synthesis of bicyclic cyclopentenones.[29] The reaction was initially carried out using D-glucose as the CO surrogate in presence of rhodium catalyst only to give poor yield of the desired product. This was attributed to the fact that D-glucose has very poor solubility in organic solvents. On changing to tetracetyl D-glucose **40**, which is easily obtained from D-glucose, the yield improved to 55 %. ^{13}C labelled studies showed that the anomeric carbon of the masked glucose gets incorporated in the product as the carbonyl carbon. Further, when a mixture of α- and β-anomers or the β-anomer was exclusively used, **41** was obtained in 52% yield in both the cases. This was attributed to the fact that the mixture of α/β-anomers or the β-anomer is quantitatively converted into a mixture of α- and β-anomers in an α/β ratio of 77/23. The effect of different aldoses and electronic nature of substituents in the enyne on product yield formed part of the substrate study. An asymmetric version of the reaction using optically active (*R*)- or (*S*)-BINAP was also done, wherein moderate to high enantiomeric excess was obtained. The mechanism proposed (Scheme 17) involved decarbonylation of the acyclic aldehyde, which is in equilibrium with the cyclic counterpart, by the rhodium catalyst and subsequent carbonylation to give the desired product.



Scheme 17 Cyclocarbonylation of enynes using aldoses as a CO source.

In 2012, the same group reported glyceraldehyde acetonide as an efficient CO substitute for the Pauson Khand reaction of enynes.[30] Racemic glyceraldehyde acetonide **42** and chiral glyceraldehyde acetonide (*R*)-**42** can be easily prepared from glycerol and D-mannitol. The use of both **42** and (*R*)-**42** in combination with rhodium catalyst and dppp as a ligand lead to the synthesis of bicyclic cyclopentenones, although (*R*)-**42** gave a higher yield of the product. Further the chirality in (*R*)-**42** had no effect on the enantioselectivity of the product. Various 1,6- and 1,7-enynes were coupled smoothly to give the desired products. In order to carry out the asymmetric version, dppp as a ligand was replaced by optically active tolBINAP, resulting in decent enantioselectivity (Scheme 18).

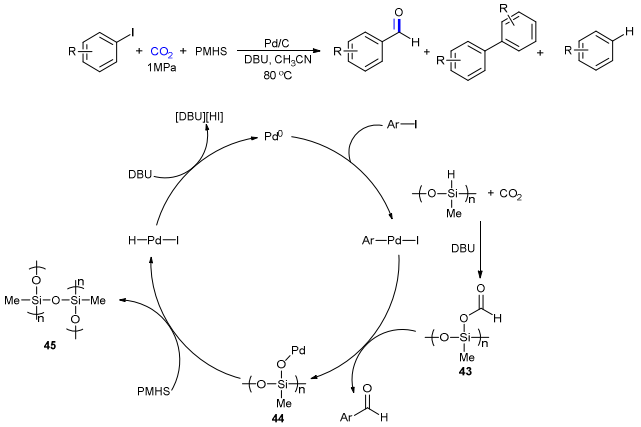


Scheme 18 Cyclocarbonylation of enynes using glyceraldehyde acetonide.

8. Carbon dioxide

Liu and co-workers demonstrated the formylation of aryl iodides using carbon dioxide as the C1 source to synthesize aromatic aldehydes.[31] The reaction was catalyzed by commercial Pd/C. The use of PMHS (polymethylhydrosiloxane) and DBU were essential for the success of the reaction and PMHS showed the best performance vis-à-vis other phenyl silanes. The mechanism involves formation of silyl formate **43** from CO_2 and PMHS in presence of DBU. The silyl formate serves as the CO surrogate which reacts with the aryl palladium species formed from the oxidative addition of the aryl iodide to give the aromatic aldehyde product and silyloxylpalladium halide **44**. This is followed by the reaction with PMHS to generate polysiloxane **45** and HPdI after which DBU helps in the regeneration of Pd(0). Hence in this

protocol, DBU had dual roles: catalysing the formation of silyl formate **43** and neutralizing HI produced in the reaction. A wide variety of substituted aryl iodides were tolerated to give aldehydes in good yields and hence proved as an economical and safe alternative to the CO catalyzed formylation (Scheme 19).

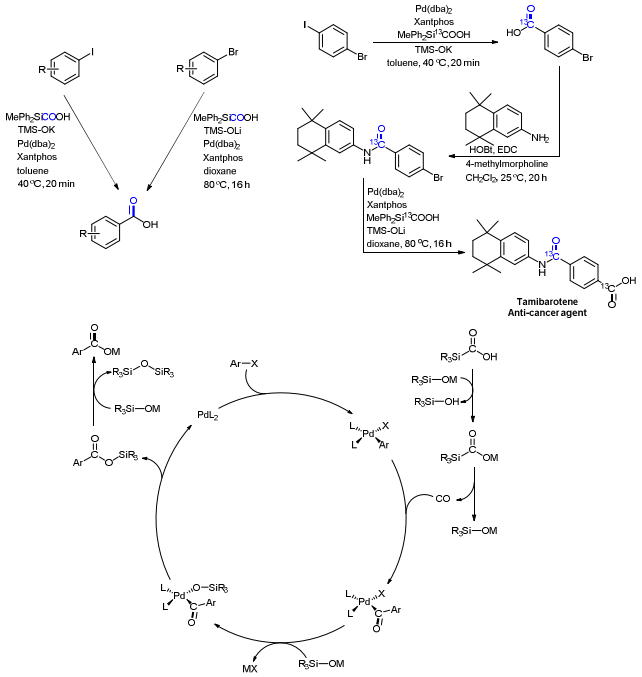


Scheme 19 Formylation of aryl iodides using carbon dioxide as the C1 source.

9. Carboxylic acid

9.1 Silacarboxylic acid

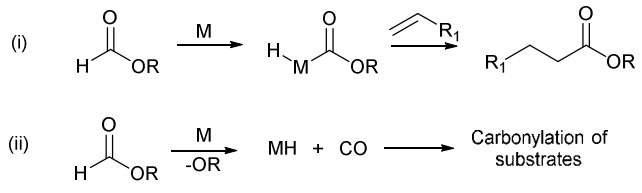
Skrydstrup and co-workers reported the synthesis of aromatic carboxylic acids from aryl iodides and bromides using silacarboxylic acid as a CO releasing molecule.[32] In the case of aryl iodides, $Pd(dba)_2$ as the catalyst of choice with Xantphos as the ligand and alkaline potassium trimethylsilanoate afforded the carboxylic acids in high yield. The catalytic system was so efficient, that the reaction reached completion in 15 mins at 50 °C. On increasing the reaction time, the reaction could even be performed at a temperature as low as 30 °C. However, aryl bromides were successfully converted to carboxylic acids in presence of lithium trimethylsilanoate as the activator and dioxane as the solvent at 80 °C in 16 h. The authors also reported the synthesis of the double ^{13}C-labelled potent anti-cancer agent tamibarotene. In the mechanism proposed, it was postulated that the release of CO could occur via two pathways- (i) deprotonation, followed by 1,2-Brook rearrangement results in CO generation and (ii) decarbonylation through a $S_N2(Si)$ pathway with TMS-OM leads to the generation of CO and formation of hydroxide. Insertion of CO in the aryl palladium complex formed by oxidative addition of the aryl halide, followed by halide-silanoate exchange at Pd and subsequent reductive elimination affords the silylated benzoic acid. The carboxylate is released through a silanoate substitution and siloxane formation (Scheme 20).



Scheme 20 Synthesis of aromatic carboxylic acids using silacarboxylic acids under palladium catalysis.

10. Ester

Esters have traditionally found a place as CO surrogates in carbonylation reactions. Alkyl and aryl formates have been widely used as C1 building blocks in combination with transition metals as catalysts. Formates function as carbonyl group donors typically in two ways: (i) activation of the formyl bond and subsequent oxidative addition to the metal followed by reactions with alkenes (hydroesterification) and (ii) decomposition into CO and alcohol, typically in the presence of base followed by carbonylative coupling with electrophiles and nucleophiles (Scheme 21). Reports of esters, other than formates, as surrogates are few and will also be covered in this section.

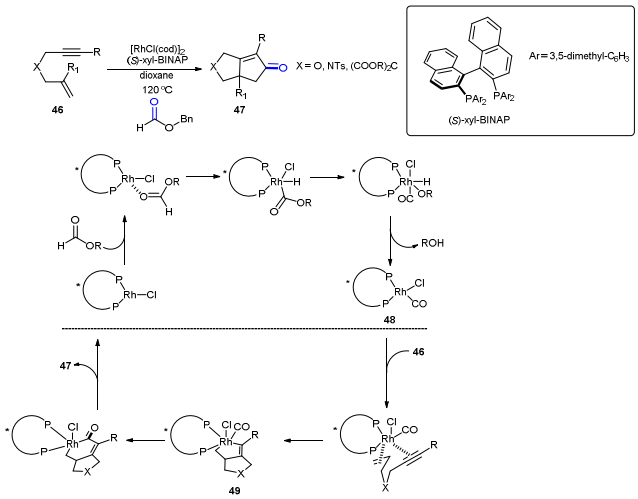


Scheme 21 Reaction pathway depicting the reactivity of formates as CO surrogates in presence of transition metals.

10.1 Formate

In 2007, Kwong and co-workers reported the first asymmetric carbonylation using formate as a CO surrogate.[33] The protocol involved a rhodium catalyzed decarbonylation of a formate ester followed by a carbonylative cyclization of an enyne (Pauson-Khand reaction) leading to the synthesis of cyclopentenones. Amongst the various formates screened, benzyl and substituted benzyl formates provided the best yields. $[Rh(COD)Cl]_2$ as the catalyst, dioxane as the solvent and BINAP as the ligand were the optimized conditions. For the asymmetric cyclization, (*S*)-xyl-

BINAP provided the best ee. The use of ^{13}C labelled formate showed the incorporation of the carbonyl group from the formate in the cyclopentenone moiety. The mechanism (Scheme 22) involves decarbonylation of the formate generating the rhodium-carbonyl species **48**, followed by coordination of the enyne and formation of the stereo-determined rhodacycle **49**. CO insertion and reductive-elimination gives the desired cyclopentenone.



Scheme 22 Rhodium catalyzed asymmetric PKR using formate ester.

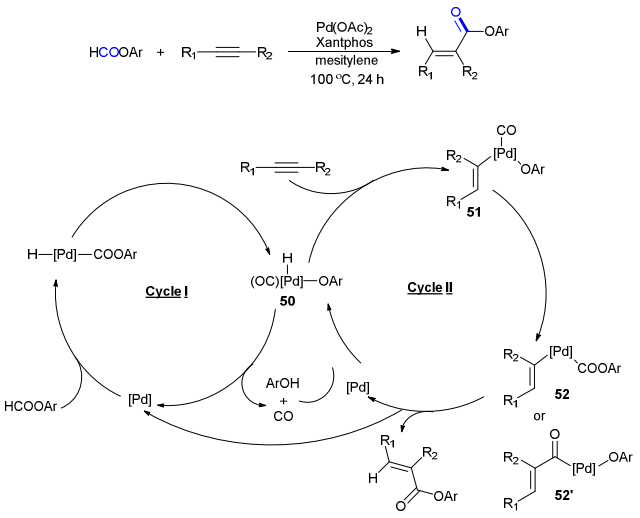
In 2011, Tsuji and co-workers reported the hydroesterification of alkynes using various aryl formates as CO substitutes under palladium catalysis leading to the synthesis of α,β-unsaturated esters.[34] It was shown that Xantphos as a ligand was essential for the synthesis of esters in high yields and with high stereoselectivity. (Table 4).

Table 4 Effect of phosphine ligands on the hydroesterification of diphenylacetylene with phenyl formate.

Entry	Ligand	Yield [%][b]	*E*/*Z*[c]
1	PPh_3	1	-
2	PCy_3	27	100/0
3	dppf	54	100/0
4	dppe	75	100/0
5	dppb	99	84/16
6	*rac*-BINAP	99	83/17
7	Xantphos	99	100/0
8	Xantphos[d]	99 (97)[e]	100/0

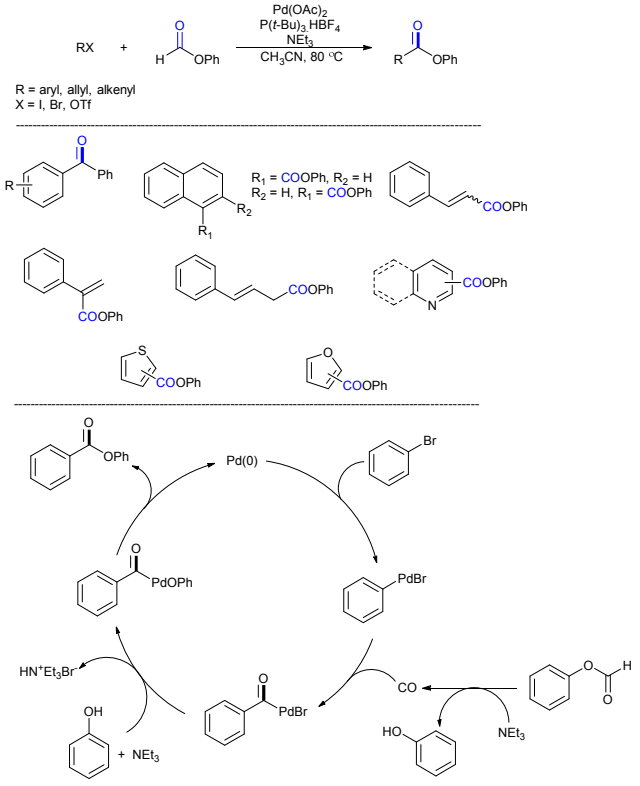
[a] Diphenylacetylene (2a, 0.50 mmol), phenyl formate (1a, 2.0 mmol), $[Pd(OAc)_2]$ (0.025 mmol, 5.0 mol%), phosphane (0.050 mmol or 0.10 mmol, P/Pd=4), mesitylene (0.50 mL) at 100 °C for 20 h. [b] GC Yield. [c] Determined by GC analysis. [d] 0.0375 mmol (P/Pd=3). [e] Isolated yield.

Moderate to high regioselectivities were obtained in the case of unsymmetrical and terminal alkynes. The protocol was also extended for the esterification of alkenes. Control experiments and kinetics showed that the reaction was zero-order and proceeded with the generation of CO and phenol and a mechanism elucidating the same was proposed (Scheme 23). In cycle I, aryl formate gets transformed to phenol and carbon monoxide. It was further postulated that the conversion of aryl formate in cycle I is faster than the hydroesterification in cycle II, mainly due to the fact that phenol and CO were accumulated in the reaction system. The generated phenol reacts with Pd species to form **50**. Alkyne insertion gives the alkynyl intermediate **51** followed by CO insertion to give **52** or **52′**. Reductive elimination affords the product and the active Pd species is regenerated.



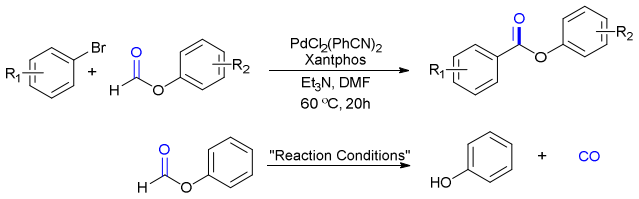
Scheme 23 Hydroesterification of alkynes using aryl formates.

Ueda *et al*. reported carbonylation of aryl, alkenyl and allyl halides using phenyl formate under palladium catalysis.[35] The reaction yield depended on the choice of ligand, base and temperature. A wide variety of substrates including heterocyclic bromides were successfully converted into phenyl esters. The mechanism involved decarbonylation of phenyl formate in the presence of base and subsequent carbonylation in presence of palladium (Scheme 24).



Scheme 24 Palladium catalyzed carbonylation of aryl, alkenyl and allyl halides using phenyl formate.

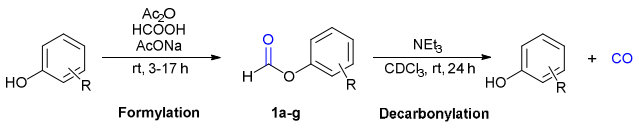
In 2012, Tsuji and co-workers reported the palladium catalyzed esterification of aryl bromides and triflate using phenyl formate.[36] The use of alkyl formates did not lead to formation of esters and phenyl formate exclusively worked as the CO substitute. Optimization of the reaction conditions involved choosing the ideal palladium catalyst, ligand and base and subsequently the optimized reaction conditions were $PdCl_2(PhCN)_2$ as the Pd source, Xantphos as the ligand and Et_3N as the base. The protocol was successfully applied to a variety of substituted aromatic bromides. The control experiments showed that under the given conditions, phenyl formate decomposed into phenol and CO. The *in situ* generated CO took part in the carbonylation (Scheme 25).



Scheme 25 Hydroesterification of aryl bromides using aryl formates under palladium catalysis.

Manabe and co-workers reported the use of 2,4,6-trichlorophenyl formate as a stable and crystalline CO producing molecule.[37] A range of phenyl formates were synthesized with electron-withdrawing groups at the *ortho* and *para* position and their decarbonylative conversion in presence of NEt_3 was studied (Table 5).

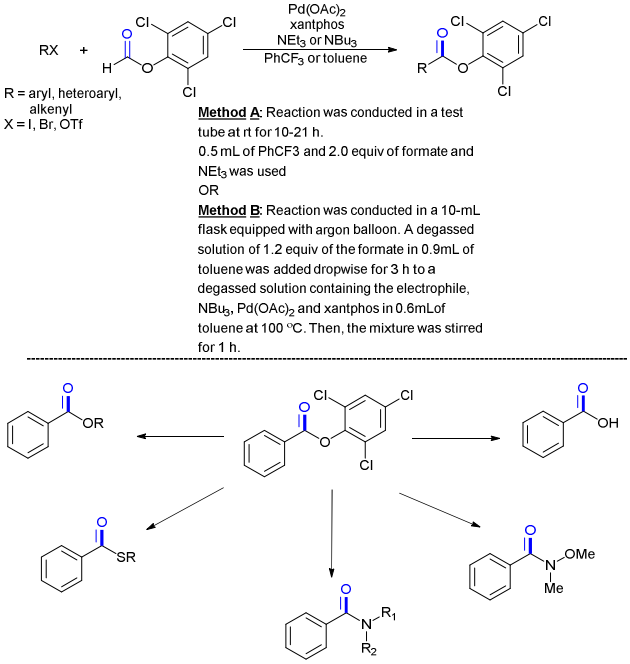
Table 5 Decarbonylative conversion of phenyl formate and substituted phenyl formates in presence of Et_3N.



Entry	Formate (R)	Yield (%)	Appearance	Decarbonylative Conversion (%)[b]
1	**1a** (H)	71	oil	16
2	**1b** (4-Ph)	96	crystal	11
3	**1c** (4-F)	66	oil	11
4	**1d** (4-Cl)	95	oil	24
5	**1e** (4-CF_3)	91	oil	69
6	**1f** (2,4,6-Cl_3)	98	crystal	92 (10 min) 98 (30 min) 100 (24 h)
7	**1g** (2,6-F_2)	53	oil	46 (30 min) 100 (24 h)

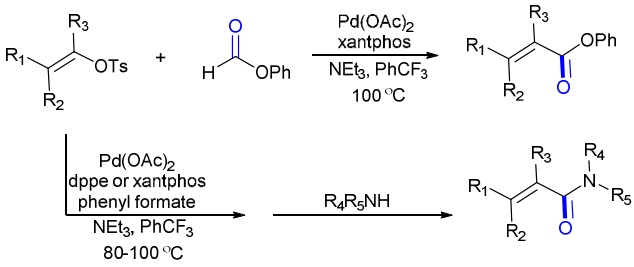
[a] Concentration: 0.5 M. [b] Determined by 1H NMR.

The high activity of 2,4,6-trichlorophenyl formate to undergo decarbonylation was applied for the carbonylation of aryl, heteroaryl, alkenyl iodides, bromides and triflates. High product yields were obtained at room temperature, albeit aryl bromides as electrophiles needed a method variation to get good product yields. The 2,4,6-trichlorophenyl esters can easily be converted into various carboxylic acid derivatives through the action of nucleophiles (Scheme 26).



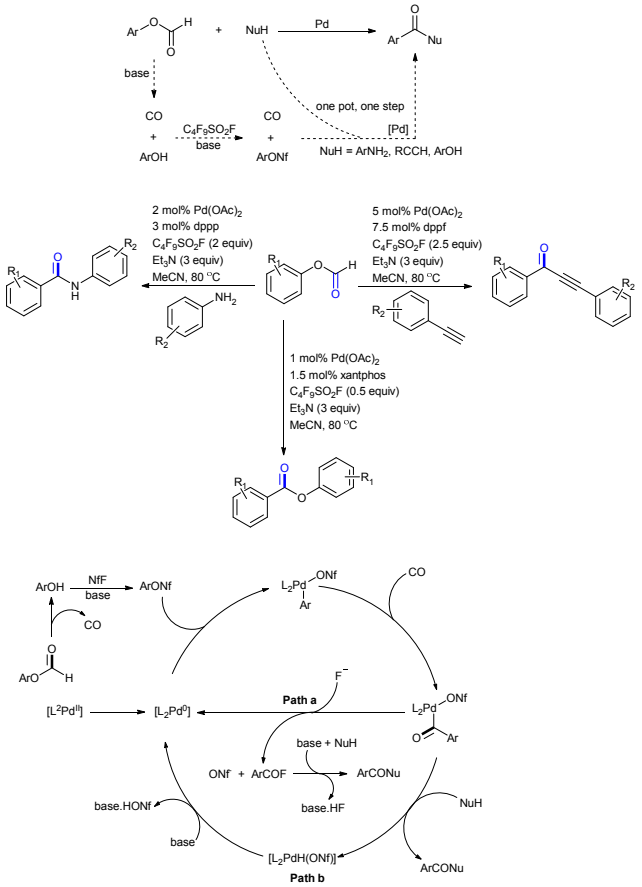
Scheme 26 Palladium catalyzed carbonylation of aryl, alkenyl halides and triflates using 2,4,6-trichlorophenyl formate.

Further, the carbonylation of alkenyl tosylates, leading to the synthesis of α,β-unsaturated phenyl esters and amides using phenyl formate[38] was reported by Manabe's group. The phenyl esters were successfully converted into amides in one pot by adding the appropriate amine after carbonylation (Scheme 27).



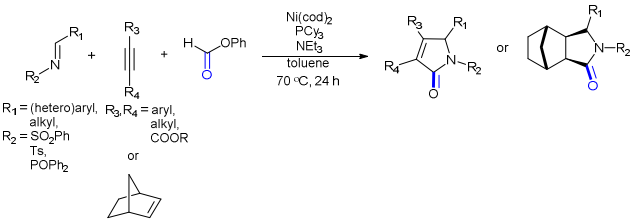
Scheme 27 Palladium catalyzed carbonylation of alkenyl tosylates using phenyl formate.

Li *et al.* reported the use of aryl formate as a bifunctional reagent[39] for carbonylative coupling reactions under palladium catalysis leading to the synthesis of amides, alkynones, furanones and phenyl benzoates. The protocol involved generation of CO and phenol from the formate in the presence of base. The phenol was converted into the corresponding nonaflate *in situ* by treating with nonafluorobutanesulfonyl fluoride ($C_4F_9SO_2F$). The nonaflate, acting as a pseudohalide (electrophile) carbonylatively coupled in the presence of the *in situ* generated CO with added nucleophiles to give the desired products. Reaction with each nucleophile was optimized with respect to the $Pd(OAc)_2$ loading, ligand choice and amount of $C_4F_9SO_2F$. The proposed mechanism involves generation of products by the attack of nucleophile on benzoyl fluoride formed from the acyl palladium intermediate (**Path b**) or by the direct attack of nucleophile on the acyl palladium (**Path a**) intermediate (Scheme 28).



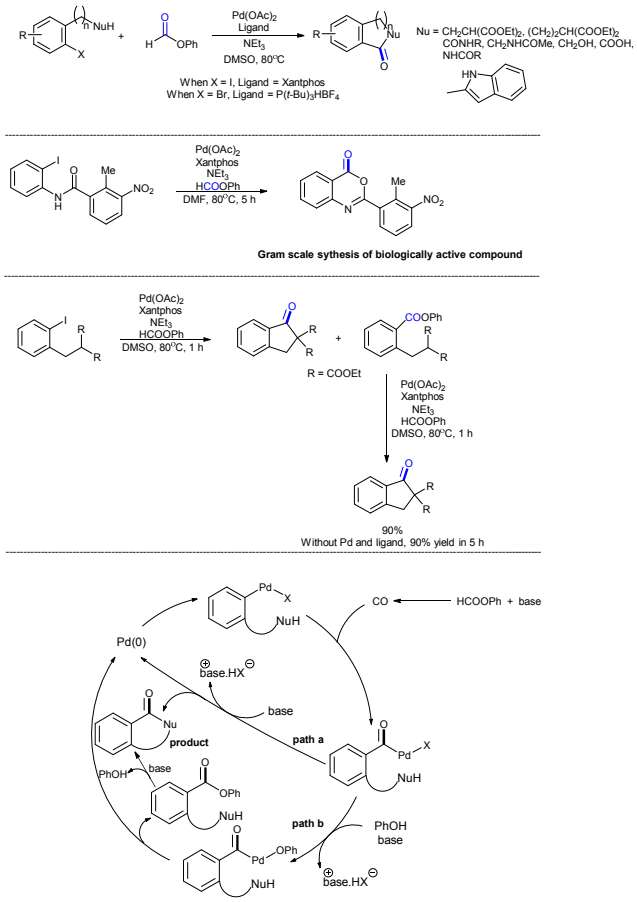
Scheme 28 Palladium catalyzed carbonylative coupling using aryl formate as a bifunctional reagent.

Ogoshi and co-workers reported the synthesis of *N*-substituted γ-lactams and bicyclic γ-lactams through the nickel catalyzed [2+2+1] carbonylative cycloaddition of imines with alkynes and norbornene.[40] Such cycloaddition (aza-Pauson-Khand) reactions leading to the synthesis of α,β-unsaturated-γ-lactones typically are catalyzed by transition metals and proceed through a heterometalacycle intermediate. Heteronickelacycles are promising candidates for such transformations but react with gaseous CO to form catalytically unreactive nickel carbonyl complexes. This was solved by using phenyl formate as a CO surrogate. The concentration of the formate was also adjusted in such a way so as to react with the nickelacycle without forming unreactive complexes. Incidentally, the phenol produced after the decarbonylation of phenyl formate did not react with the heteronickelacycle intermediate and was not incorporated in the product as was reported in other reports making using of phenyl formate. A wide range of *N*-benzenesulfonyl, tosyl and phosphoryl substituted γ-lactams were synthesized. Norbornene was employed instead of alkynes to generate bicyclic γ-lactams (Scheme 29).



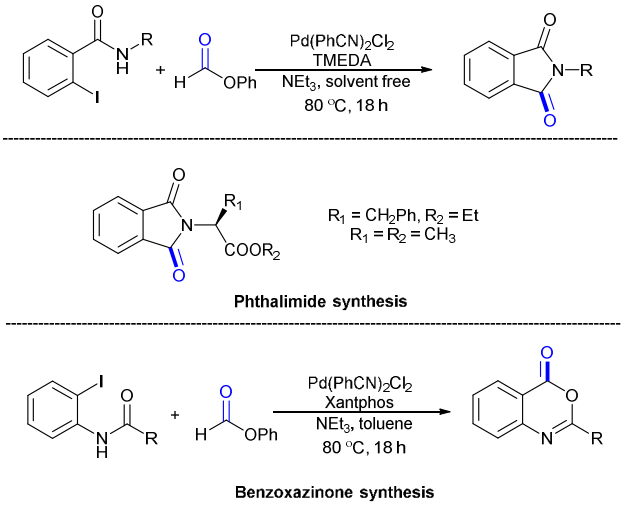
Scheme 29 Nickel catalyzed carbonylative cycloaddition of imines with alkynes or norbornene using phenyl formate.

Recently, Manabe's group reported the synthesis of cyclic carbonyl compounds through the palladium catalyzed carbonylative cyclization of haloarenes with tethered nuclepohiles using phenyl formate.[41] After optimizing the reaction conditions using iodo- and bromoarene with a tethered malonate, it was found out that, the reaction proceeded well in the presence of a polar solvent like DMSO and the iodoarene gave high product yield in the presence of Xantphos ligand, whereas the bromoarene gave in the presence of $P(t\text{-}Bu)_3HBF_4$. The optimized conditions were applied for the synthesis of tetralone, phthalimide, indolone, lactone, anhydride and benzoxazinone derivatives. The synthesis of a biologically active compound used for the inhibition of prostate cancer cell lines was carried out on a large scale. One of the by-products formed in the reaction is the phenoxycarbonylated product which is formed by the attack of the phenoxide ion generated after the decomposition of phenyl formate. When this byproduct is isolated and is either subjected to the same reaction conditions or without the catalyst and ligand, the desired product is formed. This shows the presence of alternate pathways in the reaction mechanism. One proceeds via an intramolecular attack of the tethered nucleophilic moiety on the acylpalladium intermediate (**path a**) while the other proceeds via the formation of the phenoxycarbonylated byproduct followed by intramolecular attack of the tethered nucleophile on the carbonyl group of the phenoxycarbonylated byproduct (**path b**) (Scheme 30).



Scheme 30 Palladium catalyzed carbonylative cyclization of haloarenes with tethered nucleophiles using phenyl formate.

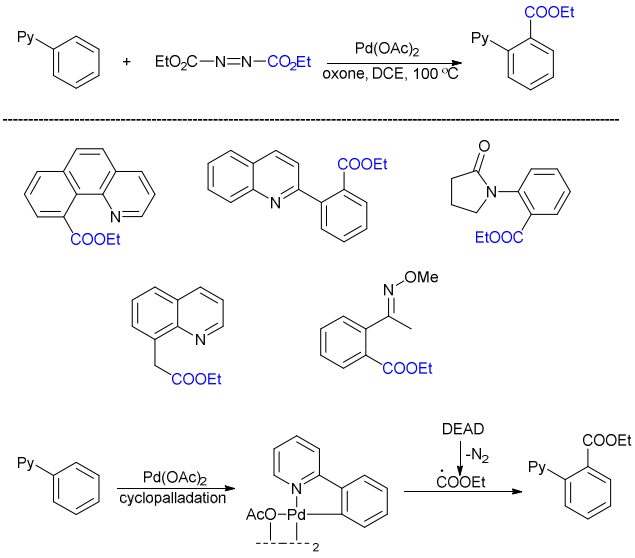
Very recently and almost at the same time, Chavan and Bhanage reported the carbonylative cyclization of *N*-substituted 2-iodobenzamides and 2-iodoanilides for the synthesis of phthalimides and benzoxazinones respectively using phenyl formate.[42] Interestingly, after the optimization studies and as compared to Manabe's protocol described above, it was found out that the synthesis of phthalimide proceeds under phosphine and solvent free condition. $Pd(PhCN)_2Cl_2$ as the palladium source and TMEDA (*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine) as the ligand gave the best product yields. However, in the case of benzoxazinone, Xantphos ligand in toluene as the solvent was need for high product yields. A wide range of 2-iodobenzamides, including chiral amino acid derived iodobenzamides and 2-iodoanilides could be successfully cyclized (Scheme 31).



Scheme 31 Palladium catalyzed carbonylative synthesis of phthalimide and benzoxazinone using phenyl formate.

10.2 Miscellaneous ester

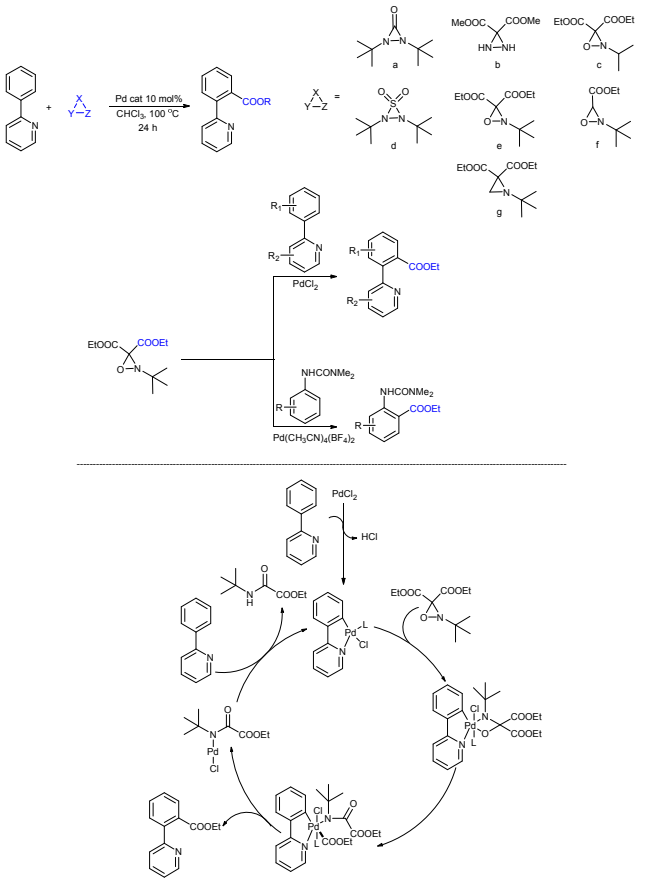
In 2008, Yu *et al*. carried out palladium catalyzed ethoxycarbonylation of the ortho C-H bond of arenes using diethyl azodicarboxylate[43] as the carbonylating agent. Various directing groups were used to carry out the C-H functionalization. The reaction required the use of an oxidizing agent and oxone was the preferred choice. 2-arylpyridine, pyrrolidinone, acetylindoline, aldimines and ketimines were efficiently converted into the ethyl esters. Interestingly the C(sp3)-H bond of 8-methylquinoline was also converted into the corresponding ethyl ester. The ethoxycarbonylation was proposed to take place through a radical mechanism (Scheme 32).



Scheme 32 Palladium catalyzed oxidative ethoxycarbonylation of aromatic C-H bonds using diethyl azodicarboxylate.

Shi and co-workers reported the C-H ethoxycarbonylation of 2-phenylpyridine under palladium catalysis using oxaziridine.[44] Various three-membered heterocyclic moieties were screened and their reactivity evaluated. It was found that oxaziridine **e** (Scheme 33) gave the best yield in combination with $PdCl_2$. Substituted 2-phenylpyridines and benzo[*h*]quinoline could be successfully

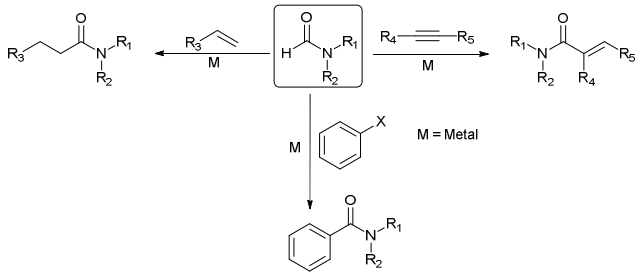
ethoxycarbonylated. Aryl urea derivatives could also be carbonylated to give anthranilates, however, required the use of $Pd(CH_3CN)_4(BF_4)_2$ as the catalyst. The reaction mechanism involves the formation of a palladacycle intermediate from the reaction between 2-phenylpyridine and $PdCl_2$ via C-H activation. The Pd(II) subsequently inserts into the N–O bond of oxaziridine to generate a Pd(IV) intermediate. This undergoes a rearrangement involving a shift of CO_2Et from the carbon to the Pd via a C–C bond cleavage. The reductive elimination affords the ethoxycarbonylated product and Pd(II) species (Scheme 33).



Scheme 33 Palladium catalyzed ethoxycarbonylation of 2-phenylpyridine using oxaziridine.

11. Formamide

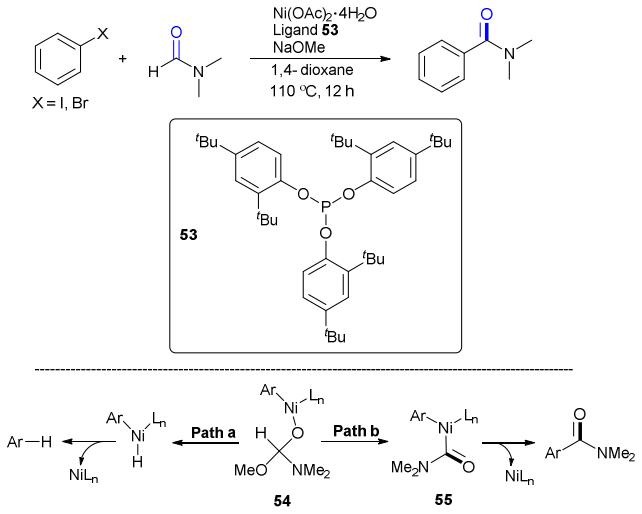
The activation of the C(sp2)-H formyl bond of formamides with transition metals makes them donate the amide group to substrates. Hence formamides can be considered surrogates for aminocarbonylation reactions. Depending on the type of substrates employed, formamides can be made to react in different ways using different catalytic systems (Scheme 34). These will be summarized in this section.



Scheme 34 Reaction pathway depicting the reactivity of amide as a CO source.

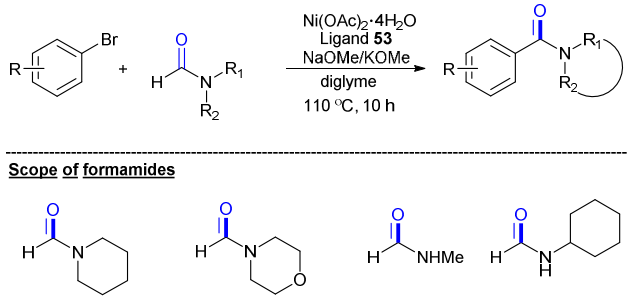
11.1 *N,N*-Dimethyl Formamide

In 2007, Lee and co-workers reported a nickel catalyzed aminocarbonylation using *N,N*-DMF.[45] The catalytic system was a nickel-phosphite complex and optimization studies were done to identify the best nickel source, phosphite ligand, solvent and base. These optimized conditions were applied for the carbonylation of a wide variety of aryl iodides and bromides. In some cases dehalogenated products were obtained and a reaction mechanism showing the formation of arenes and carbonylated product was proposed. The key intermediate is the nickel-coordinated alkoxide-DMF adduct **54** which undergoes an unwanted β-hydrogen elimination with electron deficient aryl halides to give the dehalogenated arene (**Path a**) or forms a nickel amido intermediate **55** (**Path b**) which gives the amide product after reductive elimination (Scheme 35).



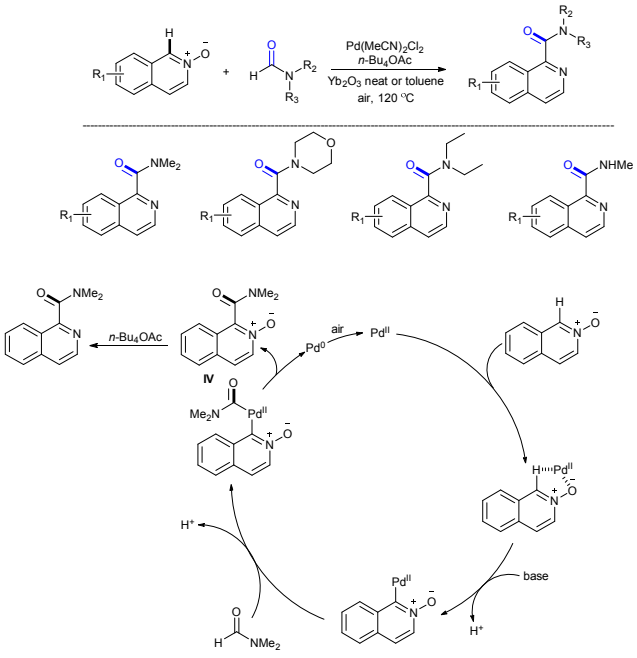
Scheme 35 Aminocarbonylation of aryl halides using *N,N*-DMF catalyzed by a nickel-phosphite system.

Later in 2009, Lee's group applied the nickel-phosphite system to the aminocarbonylation of aryl bromides expanding the scope of formamide substrates[46] which could be used. Optimization studies were carried out to determine the minimum amount of formamide, catalyst loading and base loading required to effect maximum product yield. It was found out that less hindered formamides required lower catalyst and base loading as compared to the hindered formamides (Scheme 36).



Scheme 36 Aminocarbonylation of aryl bromides using formamide derivatives catalyzed by a nickel phosphite system.

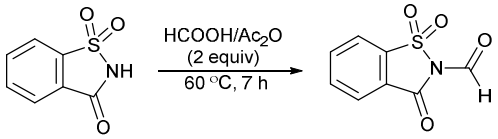
Very recently, Yao *et al*. reported the first example of a dual C-H activation of isoquinoline and quinoline *N*-oxides with formamides leading to the synthesis of isoquinoline-1-carboxamides and quinoline-2-carboxamides.[47] Formamide was used as the CO substitute and the reaction could be carried out under palladium catalysis using air as a benign oxidant. $Pd(MeCN)_2Cl_2$ as the palladium source in conjunction with Yb_2O_3 as the base and *n*-Bu_4NOAc as a phase transfer catalyst, which also might play the role of a reductant formed part of the optimized reaction parameters. Incidentally, the arylamides were obtained in higher yields when the formamide was taken in toluene as the solvent as compared to neat conditions. The substrate study revealed that a range of isoquinoline *N*-oxides and *N,N*-dialkylformamides other than *N,N*-DMF could be coupled. Even *N*-monosubstituted formamides were coupled in moderate to decent yields. Control experiments indicated that isoquinoline failed to couple and hence the presence of the N-O bond of the oxide plays a crucial role in the reaction mechanism. The key steps of the reaction mechanism involve insertion of palladium into the ortho C-H bond followed by formamide coordination and reductive elimination to give the carbonylated *N*-oxide. This finally undergoes reduction in presence of *n*-Bu_4NOAc to give the product (Scheme 37).



Scheme 37 Palladium catalyzed oxidative aminocarbonylation of isoquinoline *N*-oxides with formamides.

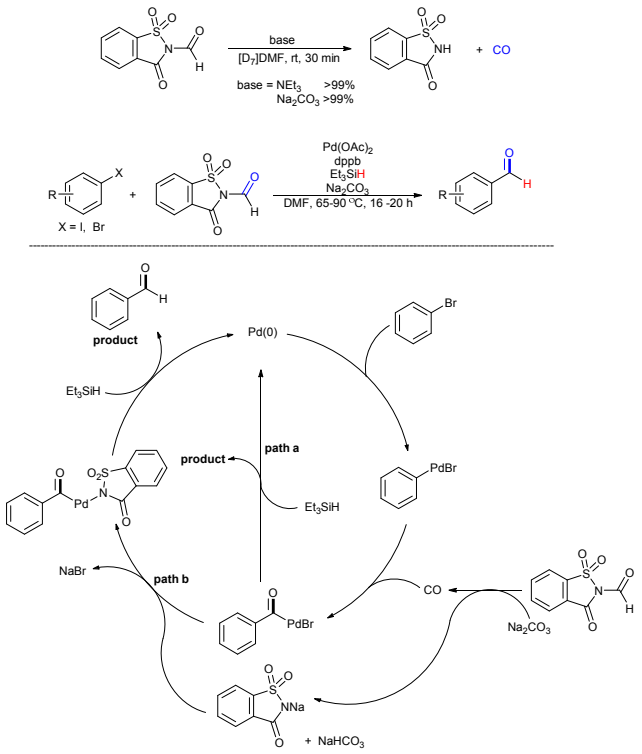
11.2 *N*-formylsaccharin (NFS)

In 2011, Cossy and co-workers reported the synthesis of *N*-formylsaccharin and its role as a chemoselective formylating agent for the formylation of amines (Scheme 38).[48] Even though the protocol was mild and efficient, it was not catalytic.



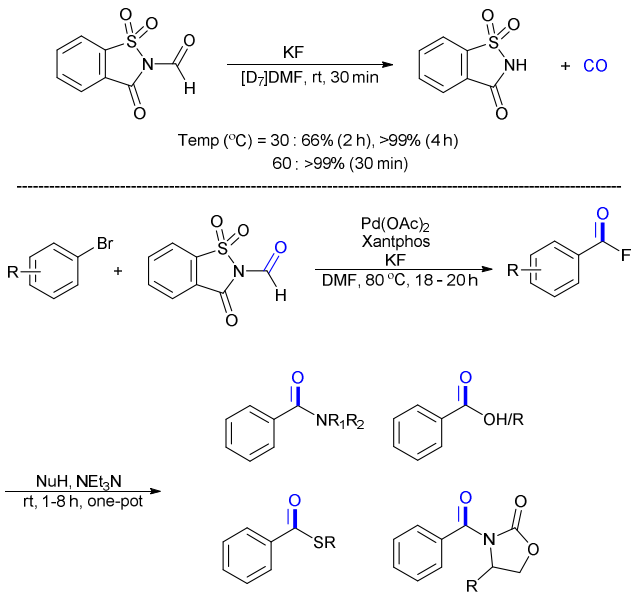
Scheme 38 Synthesis of *N*-formylsaccharin.

However, in 2011, Manabe's group reported the palladium catalyzed reductive carbonylation of aryl halides using NFS as a CO source.[49] The authors initially wanted to carry out the reductive carbonylation of aryl bromide using formate esters and triethylsilane as the hydride source, but ended up mainly with the alkoxycarbonylated products. The authors hypothesized that, phenol, which is generated after the decomposition of phenyl formate has higher nucleophilicity for the Pd-centre as compared to silane, thus preventing the acyl-Pd intermediate from getting converted to the aldehyde. However, saccharin (pK_a = 1.6) which is generated after the release of CO from NFS has lower nucleophilicity than phenols (pK_a = 6-10). Further it was also observed that NFS undergoes rapid and complete decarbonylation in the presence of a weak base like Na_2CO_3. After the conditions of the reaction were optimized, $Pd(OAc)_2$ in combination with dppb as the ligand, Na_2CO_3 as the base and triethylsilane as the hydride source in DMF gave the best product yield. Based on the control experiments carried out, two pathways were proposed for the reductive carbonylation. One involves the formation of the acyl-Pd intermediate and subsequent reaction with Et_3SiH to give the aldehyde (**path a**). The other involves the interception of the acyl-Pd intermediate by sodium saccharin, which is generated after the release of CO from NFS to give an acylsaccharin intermediate which then reacts with Et_3SiH to give the aldehyde and active Pd species (**path b**) (Scheme 39).



Scheme 39 Palladium catalyzed reductive carbonylation of aryl halides using *N*-formylsaccharin.

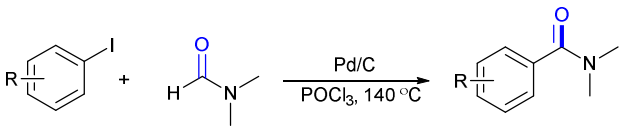
In continuation of their work on NFS, the palladium catalyzed fluorocarbonylation and the subsequent conversion of the acyl fluoride to various carboxylic acid derivatives was documented by the same group.[50] The dual role of potassium fluoride, as the activator for generation of CO from NFS, as well as the nucleophile was identified. Advantageously, NFS could be completely decarbonylated to give CO at 30 °C in 4 h and at 60 °C within 30 min. After identifying the catalytic system comprising of $Pd(OAc)_2$ and Xantphos in polar DMF, starting from (hetero)aryl and alkenyl bromides, the protocol was used for the synthesis and isolation of acyl fluorides and the one pot synthesis of acyl fluoride, followed by its subsequent conversion to a range of carbonyl compounds by reacting with the appropriate nucleophiles. Thus amides, carboxylic acids, thioesters, Weinreb amides and *N*-acyloxazolidinones could be easily synthesized (Scheme 40).



Scheme 40 Palladium catalyzed fluorocarbonylation and subsequent synthesis of carboxylic acid derivatives.

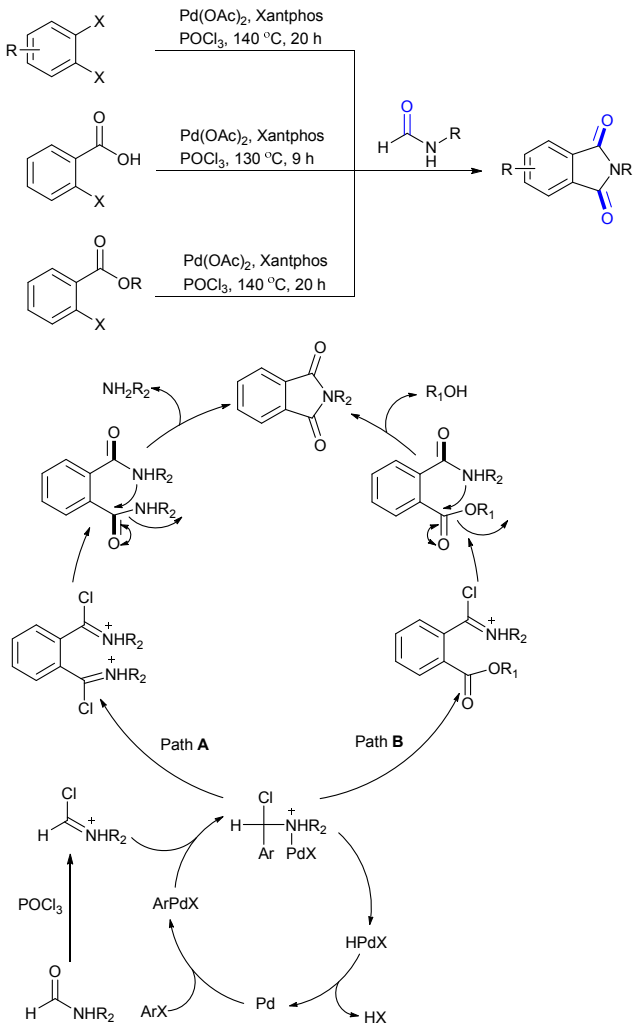
11.3 Vilsmeier system

After the pioneering work of Hiyama and co-workers in which they carried out aminocarbonylation of aryl and alkenyl iodides using DMF as the CO surrogate[51] in presence of $POCl_3$ (Vilsmeier system), the reaction has undergone progress as far as catalyst development and expanding the scope of substrates are concerned. In 2008, Bhanage and co-workers reported Pd/C as a heterogeneous catalyst for the aminocarbonylation of aryl iodides using DMF-$POCl_3$.[52] As far as the catalytic activity was concerned, the heterogeneous catalyst was as active as the homogeneous counterpart and a wide variety of aryl iodides were successfully converted into amides. Leaching of palladium was observed during the course of the reaction. Thermal redeposition and subsequent activation of the catalyst allowed it to be recycled successfully (Scheme 41).



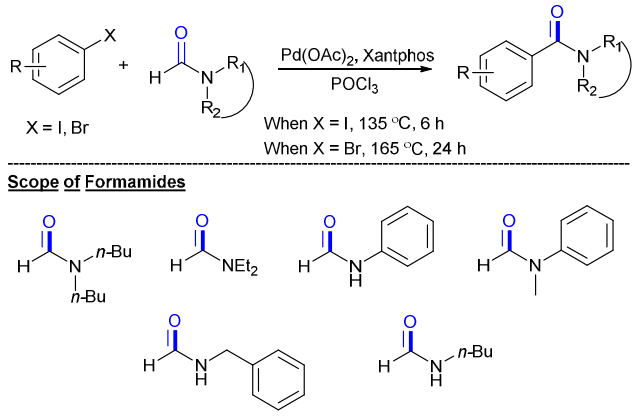
Scheme 41 Aminocarbonylation of aryl iodides using *N,N*-DMF catalyzed by Pd/C.

In 2011, Bhanage and co-workers reported the synthesis of isoindole-1,3-diones from various *o*-haloarene substrates through a cyclocarbonylation reaction using the formamide-$POCl_3$ system.[53] The palladium-Xantphos combination was found to be ideal and isoindole-1,3-diones were synthesized in moderate to high yields from o-diiodobenezene, o-dibromobenzene, o-iodobenzoic acid and o-iodobenzoate esters. Product yields from o-iodobenzoic acid were the highest. Mechanism involving the formation of iminium salt and its subsequent nucleophilic attack on the aryl palladium halide intermediate was proposed (Scheme 42).



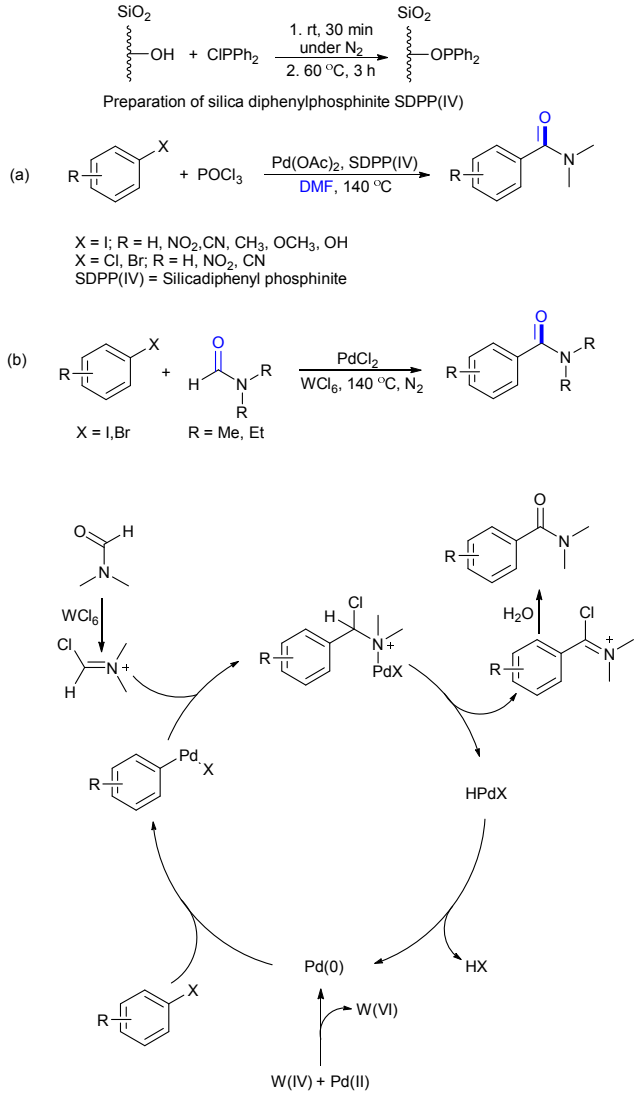
Scheme 42 Palladium catalyzed cycloaminocarbonylation of *o*-haloarenes using formamides.

A drastic improvement in the previously reported protocols for aminocarbonylation using the formamide-$POCl_3$ system was reported by Bhanage's group.[54] Not only a wide range of aryl iodides and bromides with different functional groups, but also various formamides, including sterically hindered ones could be smoothly coupled. The palladium-Xantphos catalytic system was found to be highly active and the reaction could be completed in 6 hours in the case of aryl iodides and in 24 h in the case of aryl bromides even with bulky and hindered formamides (Scheme 43).



Scheme 43 Palladium catalyzed aminocarbonylation of aryl halides using bulky and hindered N-substituted formamides.

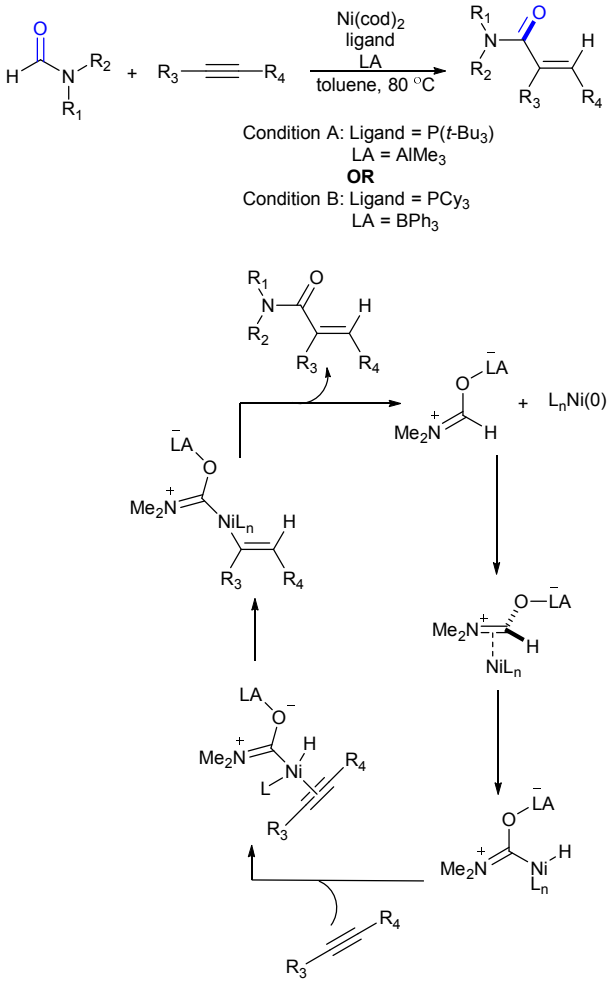
In 2012, Iranpoor *et al*. reported silicadiphenyl phosphinite (SDDP)/Pd(0) as a nanocatalyst for the aminocarbonylation of aryl halides using the formamide-$POCl_3$ system.[55] The catalytic system allowed carbonylation of activated aryl bromides and chlorides and also took less time to reach completion in the case of aryl iodides. However, the reaction was limited only to *N,N*-DMF as the amide source and the recyclability of the ligand was not shown (a, Scheme 40) . In 2014, Iranpoor *et al*. documented a WCl_6-formamide system under palladium catalysis replacing the formamide-$POCl_3$ system for aminocarbonylation of aryl halides.[56] On screening different metal halides, WCl_6 was found to be the best choice. Mechanistically, it was shown that, WCl_6 got reduced to W(IV) with DMF which in turn reduced Pd(II) to Pd(0) which took part in the catalytic cycle as reported in the earlier version. WCl_6 also plays part in the generation of the chloroiminium salt with DMF (b, Scheme 44)



Scheme 44 (a) Aminocarbonylation of aryl halides catalyzed by silica diphenylphosphinite (SDDP)/Pd(0).[55] (b) Palladium catalyzed aminocarbonylation of aryl halides using a WCl6/formamide system.[56]

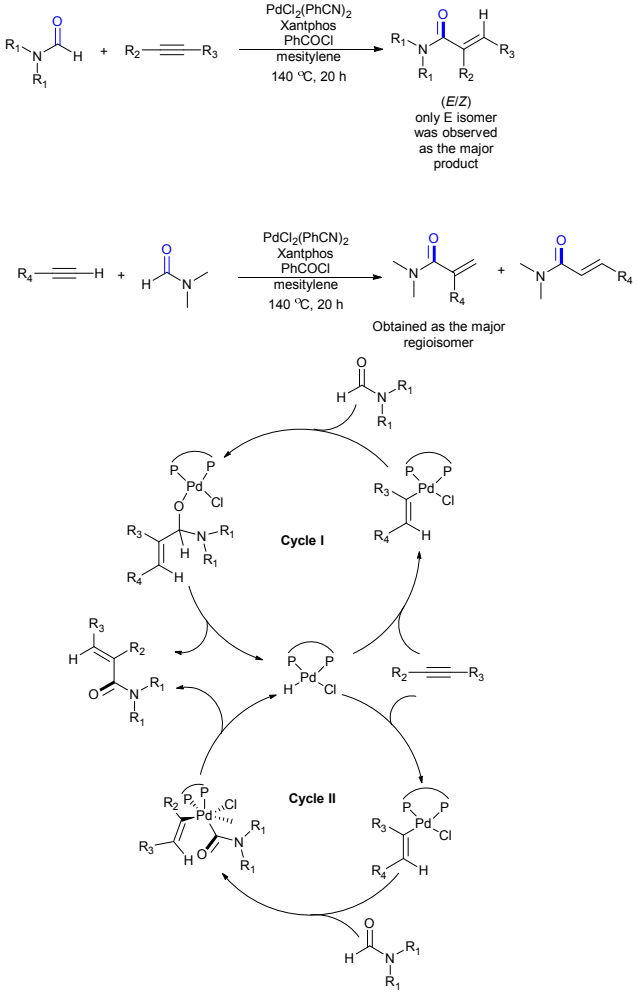
11.4 Hydrocarbamoylation of Alkynes

In 2009, Hiyama and co-workers reported the hydrocarbamoylation of alkynes with various formamides under nickel catalysis using aluminium and boron compounds as Lewis acid co-catalysts.[57] It was proposed that the co-ordination of formamide to a Lewis acid would result in the activation of the formyl (sp2 C-H) bond and subsequently its oxidative addition to nickel. Unlike the previous reports (which were restricted to the use of only DMF), various formamides could be used and the resulting unsaturated amides were obtained with good regio- and stereoselectivity. A mechanism involving the oxidative addition of the formyl bond to nickel followed by coordination of the alkyne, formation of a π-allylnickel intermediate and reductive elimination was proposed in the mechanism (Scheme 45).



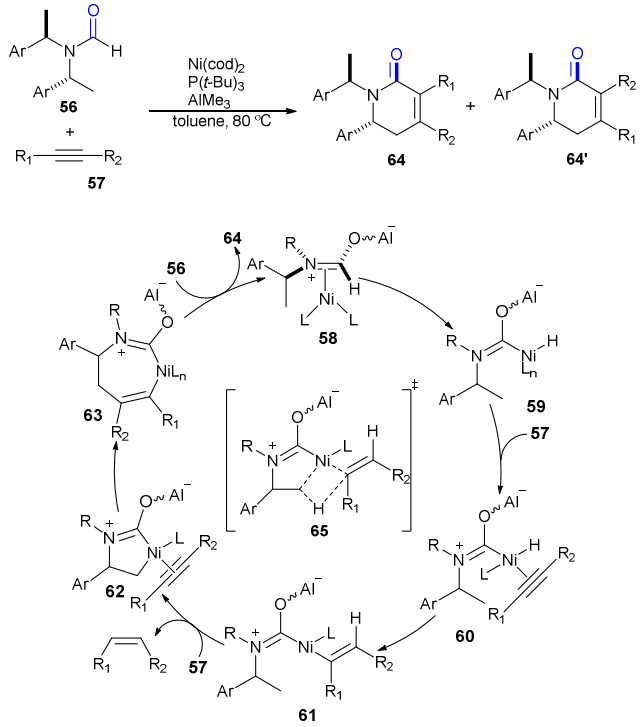
Scheme 45 Hydrocarbamoylation of alkynes using nickel/Lewis acid catalysis.

Tsuji and co-workers reported a variation of Hiyama's system for the addition of formamides to alkynes.[58] The reaction was catalyzed by the palladium-Xantphos system and the use of acid chloride as an additive was essential for the success of the reaction. In the present protocol, terminal alkynes were carbonylated, functionalities susceptible to Lewis acids were tolerated, no E/Z isomerization was observed and the products were obtained with excellent regio- and stereoselectivity (only *E* isomer was observed as major product). Control experiments and deuterium labelling studies showed that CO was not formed *in situ* and the addition of the formamide occurred directly. The mechanism proposed involved formation of Pd-H species in presence of which the alkyne underwent hydropalladation. Two pathways- one leading to the formation of alkoxypalladium intermediate (Cycle I) and the other involving the oxidative addition of the formyl C-H bond were postulated (Cycle II) (Scheme 46).



Scheme 46 Intermolecular addition of formamides to alkynes catalyzed by palladium.

In continuation of their previous work, Hiyama's group reported a [4+2] cycloaddition of *N,N*-bis(1-arylalkyl)formamides with alkynes.[59] In this protocol, the formyl C(sp2)-H bond and the C(sp3)-H bond of the alkyl group undergo simultaneous functionalization with alkynes under nickel-Lewis acid cooperative catalysis leading to the synthesis of dihydropyridones with good regioselectivity. Optically active substrates gave the cycloadduct products having high ee indicating no loss in stereochemical information. Interestingly meso substrates gave low product yields. The mechanism involves coordination of formamide with $AlMe_3$ and subsequent interaction with electron-rich nickel(0) species to give **58**. This is followed by the oxidative addition of the formyl C-H bond to the Lewis acid coordinated formamide to give **59**. Coordination of the alkyne gives **60** and subsequent hydronickelation give **61**. The arylalkyl group undergoes C-H activation to generate a five memebered nickelacycle **62** through transition state **65**. A second alkyne coordination and insertion generates the seven memebered nickelacycle **63** which underegoes reductive elimination to give the cycloadduct dihydropyridone **64** (Scheme 47).



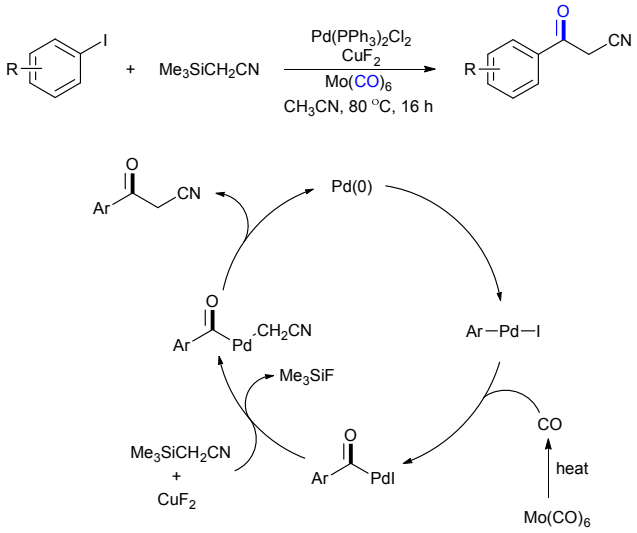
Scheme 47 [4+2] cycloaddition of *N,N*-bis(1-arylalkyl)formamides with alkynes.

12. Metal carbonyls

Metal carbonyls containing CO as the ligand find use in carbonylation reactions, as sources of CO, circumventing the need to use gaseous CO. As early as 1969, Corey and Hegedus reported the use of $Ni(CO)_4$ for the alkoxy and aminocarbonylation of vinyl halides[60] without the need to use gaseous CO. However from the viewpoint of safety and ease of handling, it is preferable to use solid sources of CO. In this relation, molybdenum hexacarbonyl has found predominant usage along with carbonyl compounds of other metals which will be reviewed in this section.

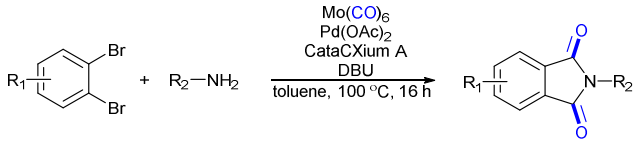
12.1 Molybdenum

In 2002, Larhed and co-workers reported the first example of carbonylation using $Mo(CO)_6$ as the CO source for palladium catalyzed carbonylation reactions.[61] There are a plethora of examples of carbonylation reactions using $Mo(CO)_6$ as the CO source under microwave and thermal conditions. Larhed's group has contributed substantially in this area and their as well as others' contribution has been excellently reviewed in 2012.[4] Hence this section will include reports after 2012 and which have not been covered in the above mentioned review. In 2012, Lee and co-workers reported the synthesis of benzoylacetonitriles by carbonylation of aryl iodides with trimethylsilylacetonitrile under palladium catalysis.[62] The use of CuF_2 as a fluoride activator in combination with the optimized conditions allowed the synthesis of a range of benzoylnitriles as part of the substrate study. The mechanism involving cleavage of the C-Si bond of trimethylsilylacetonitrile was proposed (Scheme 48).



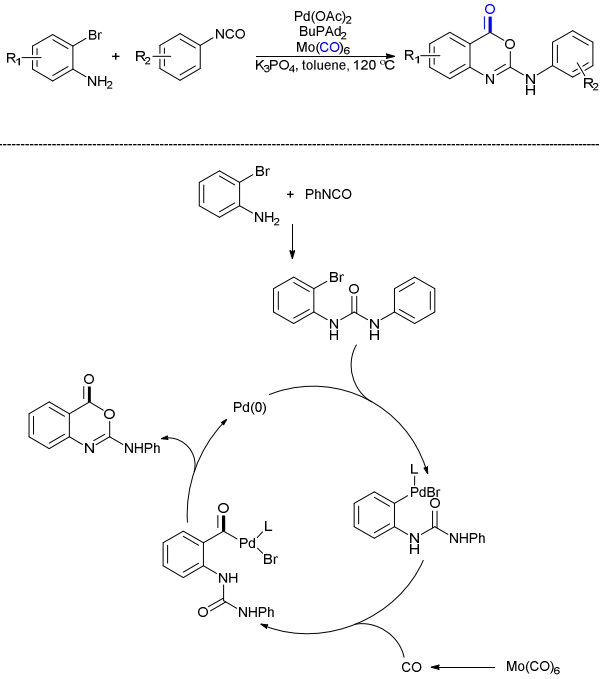
Scheme 48 Palladium catalyzed synthesis of benzoylacetonitrile using $Mo(CO)_6$.

In 2013 Wu *et al*. reported the synthesis of phthalimides by the carbonylative coupling of 1,2-dibromoarenes with primary amines using $Mo(CO)_6$.[63] After the optimization of the reaction conditions, $Pd(OAc)_2$ in combination with CataCXium A and DBU as the activator and base was found to be the best choice to obtain phthalimides in high yields. Screening of other metal carbonyls revealed that $Cr(CO)_6$ gave a 86% yield of phthalimide but was avoided given the high toxicity of chromium salts. A wide range of 1,2-dibromo(hetero)arenes could be carbonylatively coupled with different primary amines and a domino reaction mechanism based on Heck-type amidation was proposed (Scheme 49).



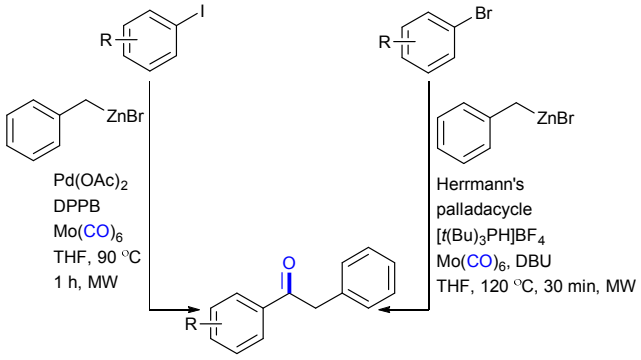
Scheme 49 Palladium catalyzed carbonylative synthesis of phthalimide using $Mo(CO)_6$.

The synthesis of 2-amino substituted benzoxazinones by the carbonylative coupling of 2-bromoaniline derivatives and phenylisocyanates using $Mo(CO)_6$ was reported again by Wu *et al*.[64] The combination of $Pd(OAc)_2$, CataCXium A and K_3PO_4 as the base in toluene came in as the optimized parameters. A range of substituted 2-bromoaniline derivatives and phenylisocyanates could be successfully coupled. The key step in the proposed mechanism involves the formation of urea from 2-bromoaniline and phenylisocyanate, followed by the conventional steps involved in a classical carbonylative mechanism to give the product. The authors postulated that molybdenum might act as a Lewis acid and coordinate with the acyl-Pd intermediate thereby assist in the formation of the product (Scheme 50).



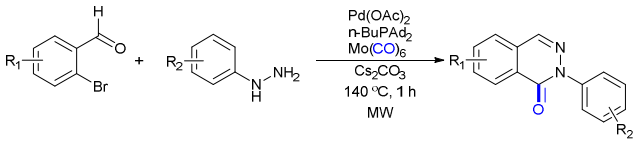
Scheme 50 Palladium catalyzed carbonylative synthesis of 2-amino substituted benzoxazinones using $Mo(CO)_6$.

Motwani and Larhed reported the synthesis of diarylated ethanones through the cross carbonylative Negishi coupling of aryl iodides and bromides with benzylzinc bromide under microwave conditions.[65] The aryl iodides could be coupled with $Pd(OAc)_2$-DPPB system at 90 °C in 1 hour whereas, the bromides required the use of Herrmann's palladacycle along with $[(t\text{-}Bu)_3PH]BF_4$ and could be coupled at 120 °C in 30 mins. Incidentally, this comes in as the first report for the carbonylative Negishi coupling using a solid CO source (Scheme 51).



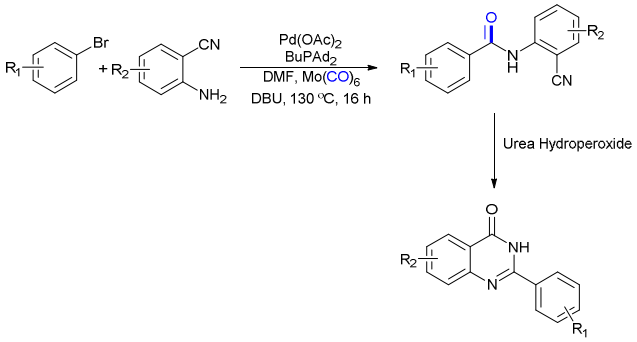
Scheme 51 Microwave assisted palladium catalyzed Negishi cross-coupling using $Mo(CO)_6$.

Reddy and co-workers reported the synthesis of phthalazinones and pyridopyridazinones from o-bromoarylaldehydes and arylhydrazines under microwave conditions.[66] $Pd(OAc)_2$-cataCXium A formed the active catalytic system and the reaction could be completed in one hour (Scheme 52).



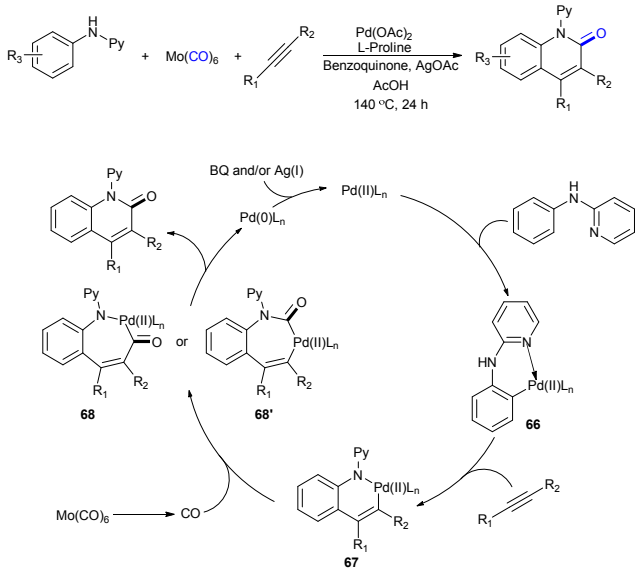
Scheme 52 Microwave assisted palladium-catalyzed synthesis of phthalazinones and pyridopyridazinones using $Mo(CO)_6$.

Wu *et al.* reported the synthesis of quinazolinones from *N*-(2-cyanoaryl) benzamides, which were synthesized by the carbonylative reaction between aryl bromides and 2-aminobenzonitriles using $Mo(CO)_6$.[67] The carbonylative synthesis of *N*-(2-cyanoaryl) benzamides was achieved using $Pd(OAc)_2$ and CataCXium A as the ligand in presence of DBU (1.5 equiv) as the base, which also acts as a promoter to release CO from $Mo(CO)_6$. The corresponding quinazolinones could be synthesized from the crude benzamides using urea hydroperoxide (Scheme 53).



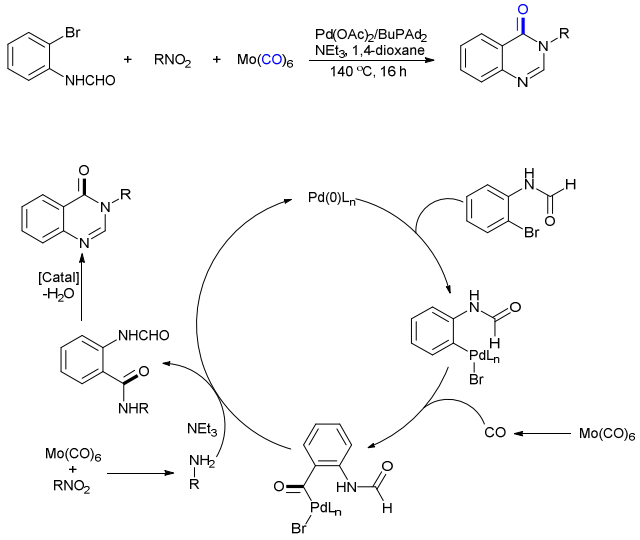
Scheme 53 Palladium catalyzed carbonylative synthesis of *N*-(2-cyanoaryl) benzamides and subsequent synthesis of the corresponding quinazolinones.

Chen *et al*. reported the synthesis of substituted 2-quinolinones through the carbonylative cyclization of *N*-aryl-pyridine-2-amines with internal alkynes.[68] The protocol involved a directing group (pyridine in this case) assisted intermolecular carbonylative C-H activation. During the course of the optimization studies, it was found out that molybdenum hexacarbonyl in conjunction with benzoquinone as the oxidant, silver acetate as the co-oxidant and L-proline as the ligand gave better yields than gaseous CO or other metal carbonyls. The proposed mechanism for the annulation reaction involved coordination of Pd(II) with pyridine nitrogen and C-H activation to give **66**. Alkyne insertion to **66** gave **67** which was followed by insertion of CO released from Mo(CO)6 to give **68** or **68′**. This in turn underwent reductive elimination to give the desired product and the Pd(0) generated was reoxidized by benzoquinone and/or AgOAc to Pd(II) (Scheme 54).



Scheme 54 Synthesis of 2-Quinolinones through palladium catalyzed carbonylative annulation of *N*-aryl-pyridine-2-amines with internal alkynes by C-H activation

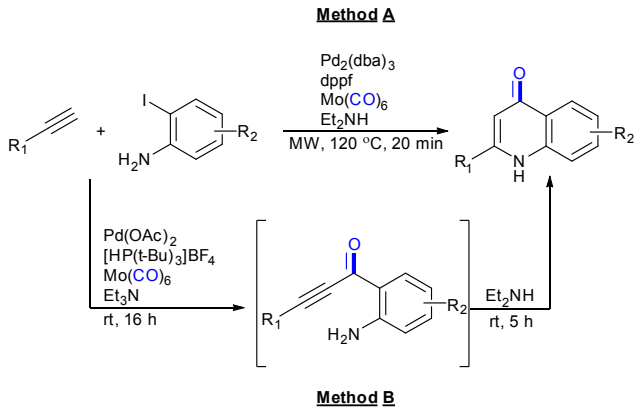
He *et al*. documented the palladium catalyzed synthesis of 4(3*H*)-quinazolinones from 2-bromoformanilides and nitrobenzene.[69] The use of $BuPAd_2$ as a ligand was critical for the success of the reaction as all other mono and bidentate ligands failed to generate the product in high yield. Interestingly, the reaction gave low product yields when gaseous CO was used. The reaction mechanism involved reduction of nitrobenzene to aniline and subsequent attack of aniline on the aryl palladium species generated by oxidative addition of aryl bromide, followed by cyclization. Interestingly, molybdenum hexacarbonyl had a dual role, wherein, it also acted as a reducing agent thereby reducing nitrobenzene to aniline completely and promoting the cyclization process leading to the synthesis of the quinazolinone product (Scheme 55).



Scheme 55 Palladium-catalyzed carbonylative synthesis of 4(3H)-quinazolinones from 2-bromoformanilides and nitroarenes/alkanes.

Recently, Larhed and co-workers reported the synthesis of 4−quinolones via palladium catalyzed carbonylative Sonogashira

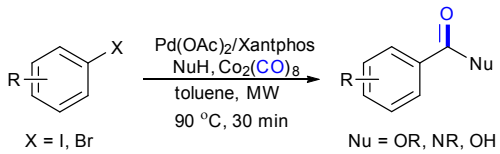
reaction using $Mo(CO)_6$.[70] They carried out the synthesis of 4-quinolones using two methods- one involving microwave heating, wherein the product formation took place in 20 min at 120 °C. The other method involved a two-step one pot procedure which could be carried out at room temperature for 16 h in which the corresponding alkynone was synthesized and was cyclized in presence of Et_2NH for 5 h to afford the quinolone. Since the second method took place at room temperature and harsh conditions were avoided, it allowed the coupling of nitro containing substrates which are normally reduced in presence of $Mo(CO)_6$. Further, the authors postulated that, since 2-quinolone was not formed under the reaction conditions, the carbonylative Sonogashira reaction took place first which was followed by the cyclization to afford the 4-quinolones (Scheme 56).



Scheme 56 Palladium catalyzed carbonylative Sonogashira cross-coupling followed by 4-quinolone synthesis.

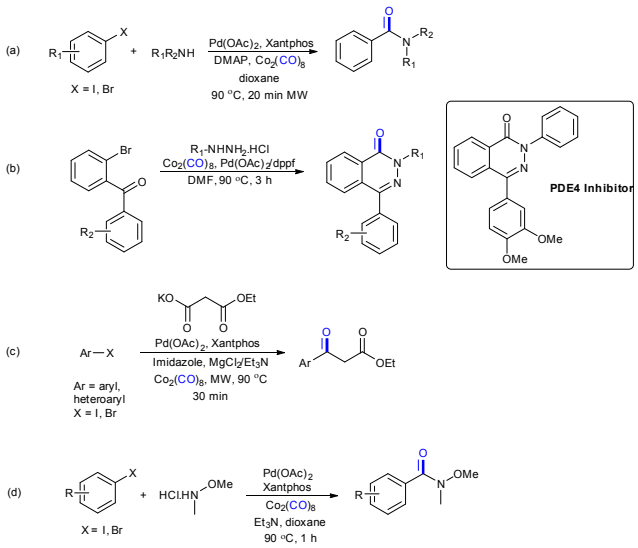
12.2 Cobalt

Dicobalt octacarbonyl ($Co_2(CO)_8$) is a useful alternative to molybdenum hexacarbonyl as a CO source. As compared to the latter (m.p. 150 °C) it has a low melting point of 55 °C and hence does not require high temperatures for the release of CO. Moreover functional groups susceptible to reduction (nitro) or cleavage (sulfone) in presence of molybdenum can be used in the presence of cobalt. In 2013, Elango and co-workers reported for the first time the use of cobalt carbonyl as a CO source in the palladium catalyzed alkoxycarbonylation of aryl halides under microwave conditions catalyzed by palladium.[71] The reaction led to the synthesis of esters in high yields using the $Pd(OAc)_2$-Xantphos system at 90 °C in just 30 mins. Further amines and water could also be used as a nucleophile to synthesize amides and carboxylic acid (Scheme 57).



Scheme 57 Microwave assisted carbonylation of aryl halides with different nucleophiles using $Co_2(CO)_8$.

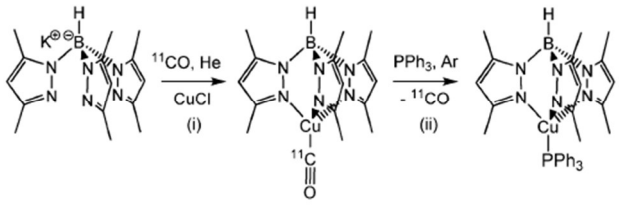
Baburajan and Elango later reported the aminocarbonylation of aryl iodides and bromides using the same system.[72] As part of the optimization study, metal carbonyls were screened and it was found out that cobalt carbonyl gave better yield as compared to molybdenum carbonyl at 90 °C. More importantly, nitro substituted aryl halides could be easily carbonylated without reduction of the nitro functionality (a, Scheme 58). Suresh *et al*. reported the synthesis of phthalazinones through the carbonylative cyclization of *o*-bromobenzaldehydes and *o*-bromobenzophenones with hydrazine.[73] It turned out that dppf ligand was needed for the products to be obtained in high yields. The synthesis of a selective PDE4 inhibitor was also reported (b, Scheme 58). The synthesis of β-keto esters by the carbonylation of aryl halides with potassium monoester malonate was reported by Baburajan and Elango under microwave conditions.[74] The choice of palladium source, ligand and imidazole as an additive were crucial for getting products in high yields (c, Scheme 58). Recently the synthesis of weinreb amides was reported by carbonylation of aryl and heteroaryl halides with *N*,*O*-dimethyl hydroxylamine (d, Scheme 58).[75]



Scheme 58 Carbonylative cross coupling reactions using $Co_2(CO)_8$.

12.3 Miscellaneous metal carbonyls

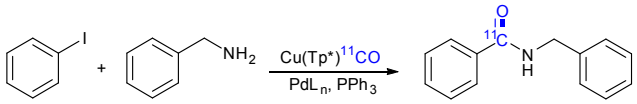
In 2009, Kealey *et al*. reported the use of copper-tris(3,5-dimethylpyrazolyl)-borate complex for effectively trapping ^{11}CO and subsequently using the CO trapped complex as a surrogate in palladium catalyzed carbonylation reactions for the synthesis of ^{11}C labelled amides and ureas.[76]



Scheme 59 (i) Trapping of ^{11}CO via the formation of Cu[Tp*]^{11}CO. (ii) ^{11}CO release by addition of triphenylphosphine. Reproduced from Ref. 76 with permission from The Royal Society of Chemistry.

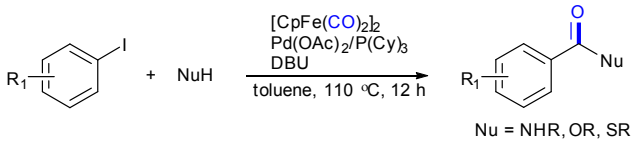
^{11}C is an important radionuclide used as a PET tracer due to the wide prevalence of carbon in biological systems. One of the best ways of accessing ^{11}C is through ^{11}CO which can be incorporated in biologically significant molecules through carbonylation reactions. But ^{11}CO has poor solubility in organic solvents and is

extremely diluted in inert carrier gases. These drawbacks were circumvented using chemical complexation with the copper-tris(3,5-dimethylpyrazolyl)-borate complex. It was found that, the simple addition of a phosphine ligand led to the rapid release of ^{11}CO from this complex (Scheme 59) and hence was used in the aminocarbonylation with aryl iodide leading to the synthesis of ^{11}CO labelled amide (Scheme 60).



Scheme 60 Palladium catalyzed carbonylative synthesis of ^{11}C labelled molecules using copper(I) scorpionate carbonyl complexes.

Nakaya *et al*. reported the alkoxy-, amino- and thiocarbonylation of aryl iodides using bis(cyclopentadienyldicarbonyliron) as a CO source.[77] The optimization study for aminocarbonylation revealed that 1.5 equivalent of ($[CpFe(CO)_2]_2$) gave quantitative yield of the product. On reducing the amount of ($[CpFe(CO)_2]_2$) to 0.38 equivalent, tricyclohexylphosphine is required to afford high yield. The role of DBU as a base is crucial for liberating CO from the complex. Further, for the thiocarbonylation, 1.5 equivalent of the iron complex was needed and DMAP as an additive increased the reactivity of secondary amines and primary alcohols (Scheme 61).



Scheme 61 Palladium catalyzed carbonylative coupling reactions of aryl iodides using bis(cyclopentadienyldicarbonyliron) as the CO source.

13. The two chamber system

The chemistry of CO surrogates saw a major breakthrough when Skrydstrup and co-workers at the Aarhus University in Denmark developed a two-chamber system for carrying out carbonylation chemistry (Figure 1).

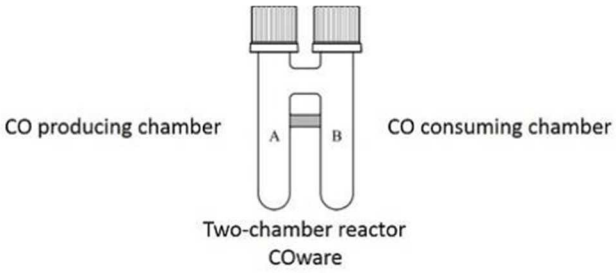
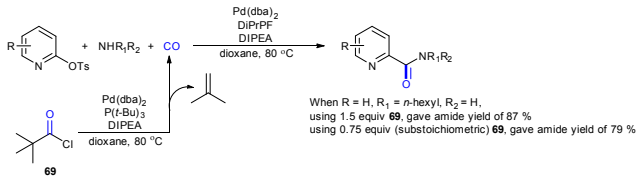


Figure 1 The two chamber reactor developed by Skrydstrup and co-workers. Reproduced with permission from A. Ahlburg, A. T. Lindhardt, R. H. Taaning, A. E. Modvig and T. Skrydstrup, *J. Org. Chem.*, 2013, **78**, 10310-10318. Copyright 2013 American Chemical Society.

One of the major drawbacks in the use of CO surrogates, is the *in situ* generation of CO, wherein the CO substitute, the starting materials and the transition metal catalyst are all present in a single pot. In such cases, there might be compatibility issues between the CO producing molecule and the CO consuming substrate, especially if the substrate molecule is complex and has a variety of functional groups present in it. The use of solid metal carbonyls helps circumvent this problem, however their use adds an extra metal to the system in a stoichiometric amount and hence is not desired. To overcome these problems, Skrydstrup and co-workers devised a two-chamber reactor in which the CO surrogate or CO releasing molecule is present in one chamber and the substrate which will get carbonylated is present in another chamber. The surrogate undergoes decarbonylation in the presence of a transition metal and the CO which is generated *ex situ* reacts with the substrates to give the carbonyl incorporated products. Newer CO releasing molecules/surrogates were also developed by the same group, which are more efficient than the conventional surrogates and deliver CO in sub-stoichiometric amounts, wherein CO can be considered as a limiting agent. Advantageously, these CO surrogates also can be isotopically labelled wherein the isotopically labelled carbon can be delivered to the product at a late stage in a multi-step synthesis. 9-Methyl-9*H*-fluorene-9-carbonyl chloride, which happens to be one of the surrogate developed by the group along with the two-chamber system are now commercially sold by Sigma Aldrich under the brand names of COgen and COware gas reactor respectively. The use of these surrogates and the reactions to which they are applied, along with the catalyst system used will be discussed in this section

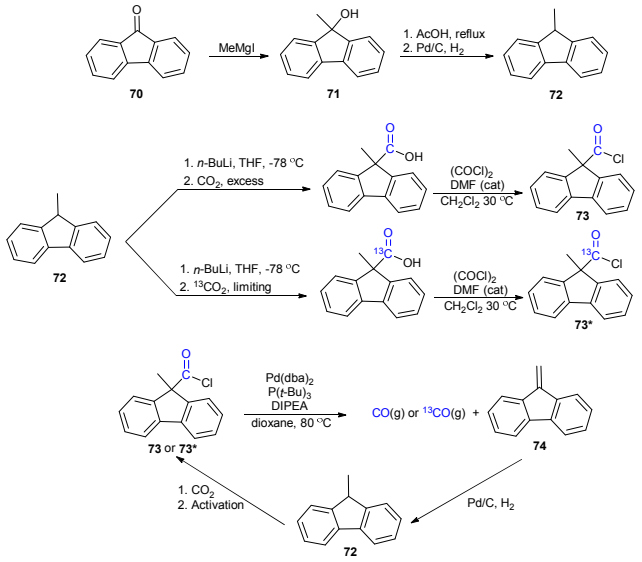
13.1 9-Methyl-9*H*-fluorene-9-carbonyl chloride (COgen)

In 2011, Skrydstrup and co-workers reported the aminocarbonylation of 2-pyridyl tosylates using pivaloyl chloride as a surrogate.[78] *Ex situ* generation of CO gas lead to the synthesis of different pyridyl amides in high yields. However the use of pivaloyl chloride had a few drawbacks. Being a liquid with a boiling point of 105 °C, its use in small scale synthesis, purification and isotopic labelling were cumbersome. Moreover after decarbonylation, isobutene is generated, whose presence in the reaction system can pose compatibility issue with the reactants. Generation of isobutuene also increases the overall pressure of the reactor (Scheme 62).



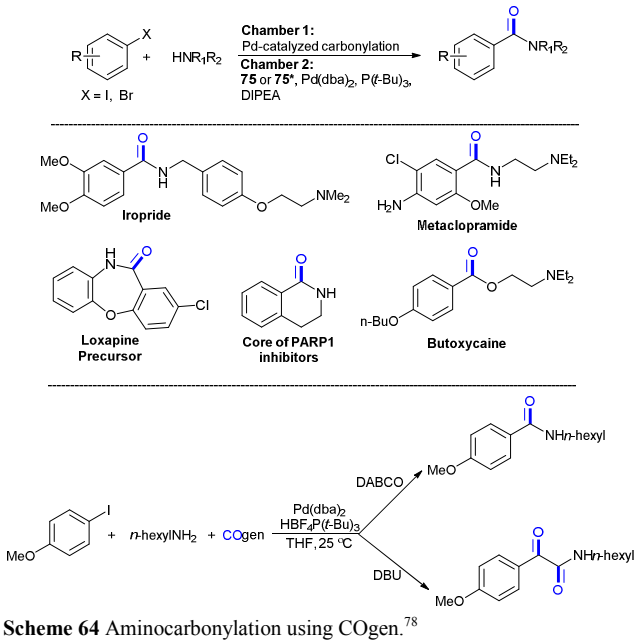
Scheme 62 Aminocarbonylation of 2-pyridyl tosylates using pivaloyl chloride.[78]

To overcome these problems, the authors developed a new solid, crystalline, stable and easy to handle CO surrogate. 9-Methyl-9*H*-fluorene-9-carbonyl chloride **73** was synthesized from 9-fluorenone **70** in 4 simple steps. The decarbonylation of this molecule generated 9-methylene-fluorene **74** which is non-volatile and can easily be reduced to 9-methyl-9*H*-fluorene **72**. This again can be converted to **73** or **73*** easily (Scheme 63).



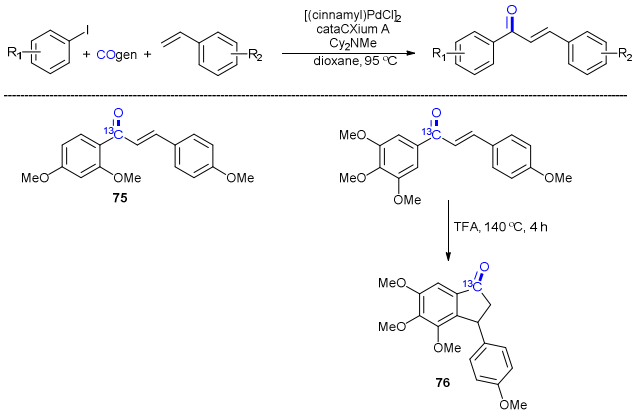
Scheme 63 Preparation of 9-Methyl-9*H*-fluorene-9-carbonyl chloride, CO release and its regeneration.[78]

A series of aryl iodides and bromides were aminocarbonylated by choosing an appropriate catalytic system to synthesis pharmaceutically significant molecules in high yields. ^{13}C-labelled molecules were also synthesized using the labelled surrogate. Noteworthy was the fact that all these reactions were conducted using the CO surrogate as a limiting reagent. Use of DBU and DABCO as bases allowed the reaction to be even conducted at room temperature. When DBU was used as a base, double carbonylation took place (Scheme 64).



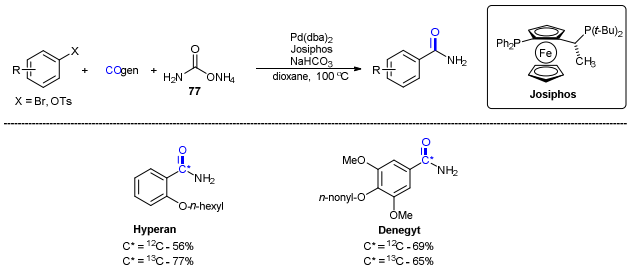
Scheme 64 Aminocarbonylation using COgen.[78]

Hermange *et al*. reported the carbonylative Heck protocol of aryl iodides leading to the synthesis of chalcone derivatives.[79] The combination of $[(cinnamyl)PdCl]_2$ as the palladium source and cataCXium A as the phosphine ligand forms an active catalytic system for the carbonylation. Interestingly, phosphine ligand loading of just 1 mol% is sufficient for getting high product yield. A range of aryl iodides and styrene derivatives could be smoothly coupled. The protocol was also applied for the synthesis of ^{13}C-labelled chalcone derivatives. ^{13}C-labelled diuretic drug, metochalcone **75** and indanone scaffold **76** could be synthesized (Scheme 65).



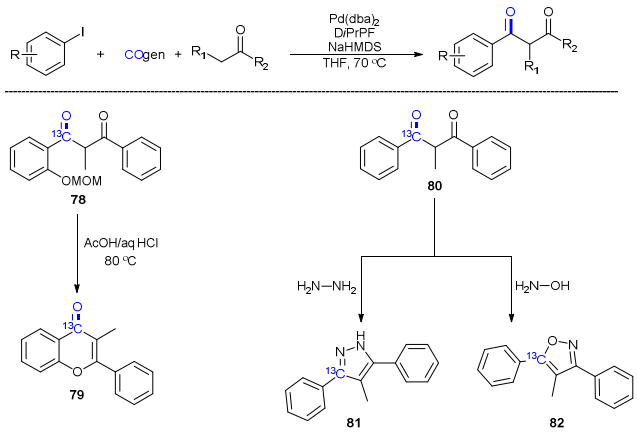
Scheme 65 Palladium catalyzed carbonylative Heck using COgen.

Later, Nielsen *et al*. reported the aminocarbonylation of aryl bromides and tosylates using COgen as the CO surrogate and ammonium carbamate **77** as the ammonia surrogate leading to the synthesis of primary amides.[80] The use of Josiphos ligand and adjustment of base to ammonium carbamate ratio to 1:1 resulted in the highest product yield. Aryl bromides and tosylate with varied functionalities were smoothly coupled. This protocol was also applied for the synthesis of ^{13}C labelled drugs- hyperan (antifungal) and denegyt (anticonvulsant) (Scheme 66).



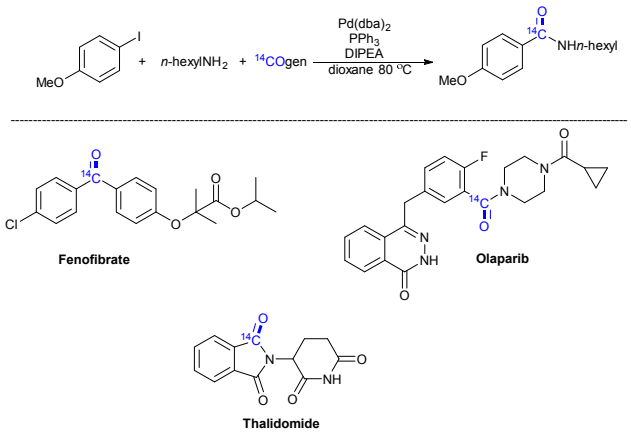
Scheme 66 Palladium catalyzed synthesis of primary amides using ammonium carbamate and COgen.

In 2012, the palladium catalyzed α-arylation of ketones with aryl halides was reported leading to the synthesis of 1,3-diketones.[81] The identification of the appropriate catalytic system and reaction conditions during the optimization study led to the synthesis of a variety of diketones from substituted aryl halides and ketones. Aryl iodides were smoothly coupled but aryl bromides were sluggish. Interestingly, when gaseous CO from a balloon was used, diketones were obtained in lower yields. ^{13}C-labelled diketones were also synthesized in which one carbonyl carbon of the diketone was isotopically labelled and later converted to labelled heterocycles. The MOM-protected labelled diketone **78** on hydrolysis of the MOM ether group and dehydrative cyclization gave the labelled flavone **79**, whereas the labelled ketone **80** gave labelled pyrazole **81** and isoxazole **82** (Scheme 67).



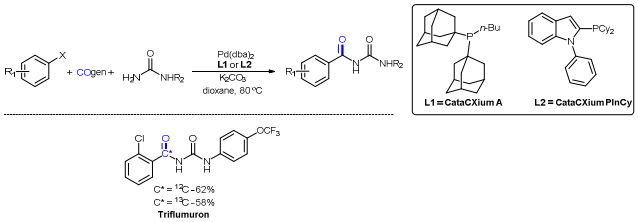
Scheme 67 Palladium catalyzed carbonylative α-arylation using COgen.

In 2012, Lindhardt *et al*. reported the synthesis of ^{14}C-labelled compounds using ^{14}CO which was in turn generated by the decarbonylation of ^{14}COgen.[82] ^{14}COgen was prepared from $^{14}CO_2$ using the aforementioned process (Scheme). The protocol was used for the synthesis of three drug molecules: olaparib, thalidomide, and fenofibrate, wherein the carbonylation could be carried out under mild conditions and allows the incorporation of the ^{14}C isotope in the final step of the synthesis (Scheme 68).



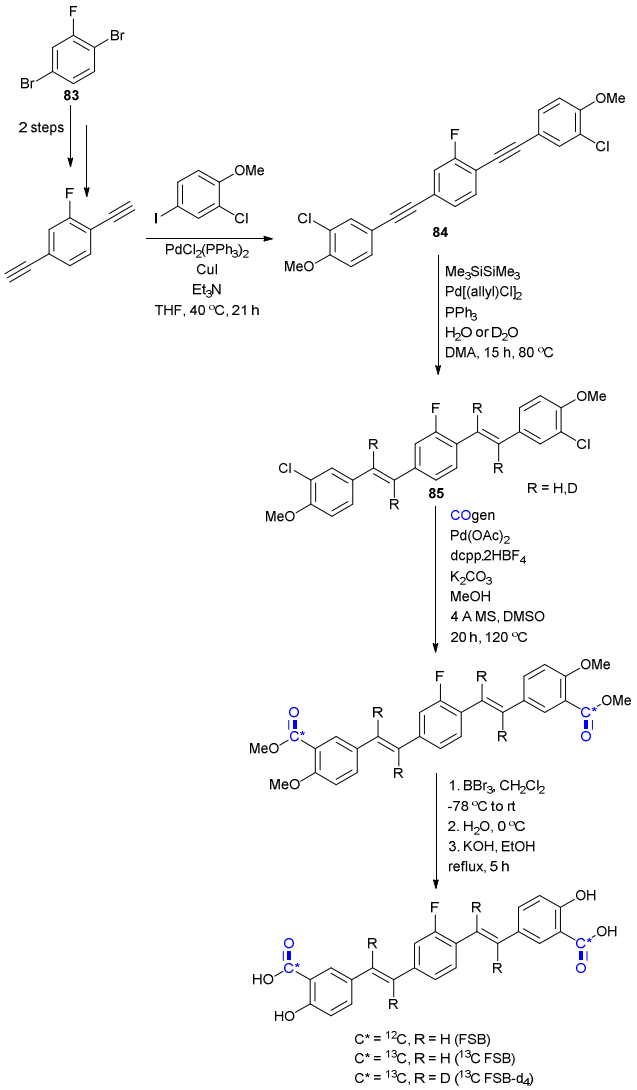
Scheme 68 Palladium catalyzed carbonylation reactions using ^{14}COgen.

Bjerglund *et al*. reported the carbonylation of monosubstituted ureas with aryl iodides and bromides leading to the synthesis of *N*-benzoylureas.[83] A catalytic system consisting of $Pd(dba)_2$ along with cataCXium A at just 5 mol% loading proved to be highly beneficial. In some cases, the reactions were sluggish and the use of cataCXium PInCy ligand resulted in a smooth reaction. The protocol was also used for the synthesis of ^{13}C-labelled ureas, including the insecticide triflumuron (Scheme 69).



Scheme 69 Palladium catalyzed *N*-acylation of monosubstituted ureas using COgen.

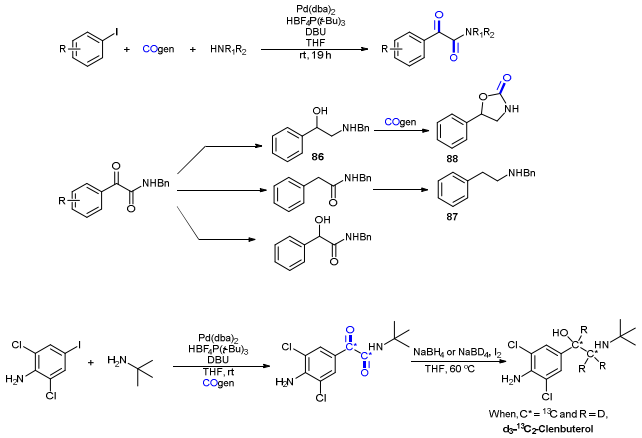
The synthesis of FSB ((*E*,*E*)-1-fluoro-2,5-bis-(3-hydroxycarbonyl-4-hydroxy)styrylbenzene) and its ^{13}C and deuterium labelled version, which is used as a tracer for the detection of Alzheimer plaques (β-amyloid fibrils and neurofibrillary tangles) was reported by Skrydstrup's group.[84] The multistep synthesis involved a double methoxycarbonylation reaction of an aryl chloride using COgen. Since carbonylation reactions of aryl chlorides require high temperature, a solvent screening study was done for the decarbonylation procedure and PEG-5000 was chosen as a high boiling solvent. The carbonylation protocol was optimized according to known procedures. The multistep synthesis consisted of a double-Sonogashira coupling of 1,4-dibromo-2-fluorobenzene **83** to give **84** followed by Shirakawa–Hayashi reduction of the alkyne functionality using H_2O/D_2O to give **85**. This was followed by the ^{12}C/^{13}C carbonylation, demethylation and base hydrolysis of the methyl esters to afford ^{12}C/^{13}C/^{13}C-d4 FSB (Scheme 70).



Scheme 70 Palladium catalyzed double alkoxycarbonylation of aryl chloride using COgen and isotope labelling of Fibril Binding Compound (FSB).

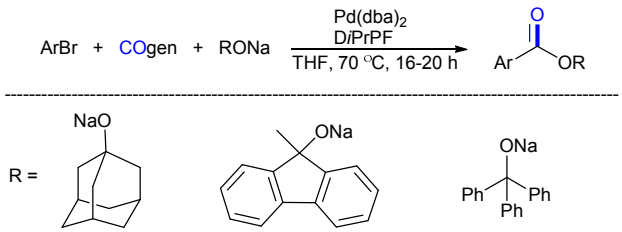
The double carbonylation of aryl iodides with amines leading to the synthesis of α-ketoamides was documented by Nielsen *et al*.[85]

A wide range of aryl iodides and amines were smoothly coupled. The protocol was also extended for the synthesis of biologically important motifs such as β-amino alcohols **86**, phenethylamines **87** and 2-oxazolidinones **88** from ketoamindes. Starting from 2,6-dichloro-4-iodoaniline, the authors also carried out the synthesis of d_3-$^{13}C_2$-Clenbuterol in a two-step sequence. This comes in as the first general procedure for the $^{13}C_2$-labeling of the ethyl moiety of phenethylamines which in turn is useful for the detection of phenethylamine derivatives with the help of techniques like isotope dilution mass spectrometry (Scheme 71).



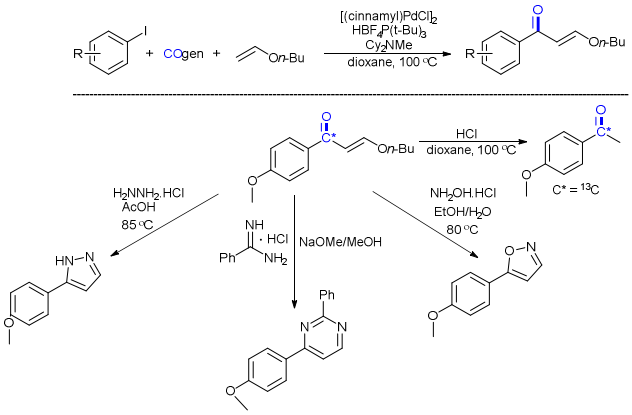
Scheme 71 Palladium catalyzed double carbonylation using COgen and synthesis of $^{13}C_2$ labelled phenethylamines.

Xin *et al*. reported the synthesis of tertiary esters by the alkoxycarbonylation of aryl bromides using sodium *tert*-alkoxides as nucleophiles.[86] The reaction afforded high ester yields only in the presence of D*i*PrPF ligand. A wide variety of aromatic and heteroaromatic bromides were successfully coupled with sodium salts of bulky alcohols like 1-adamantol, 9-methyl-9-fluorenol and triphenylmethanol (Scheme 72).



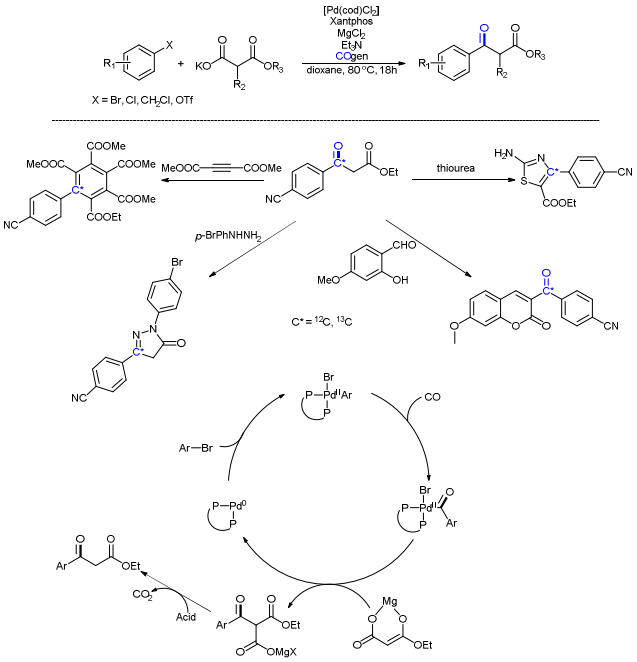
Scheme 72 Synthesis of tertiary esters through the palladium catalyzed alkoxycarbonylation of aryl bromides using COgen.

Later the carbonylative Heck reaction of vinyl ethers with aryl iodides was reported.[87] The keto vinyl ethers subsequently synthesized are 1,3-ketoaldehyde surrogates, which can be transformed into varied heterocyclic moieties and aryl methyl ketones. After optimizing the catalytic system by choosing the appropriate palladium source and ligand, aryl iodides were smoothly coupled. The protocol was then used for the synthesis of heterocyclic moieties and ^{13}C labelled aryl methyl ketones (Scheme 73).



Scheme 73 Palladium catalyzed carbonylative Heck reaction for the synthesis of monoprotected 1,3-ketoaldehydes using COgen.

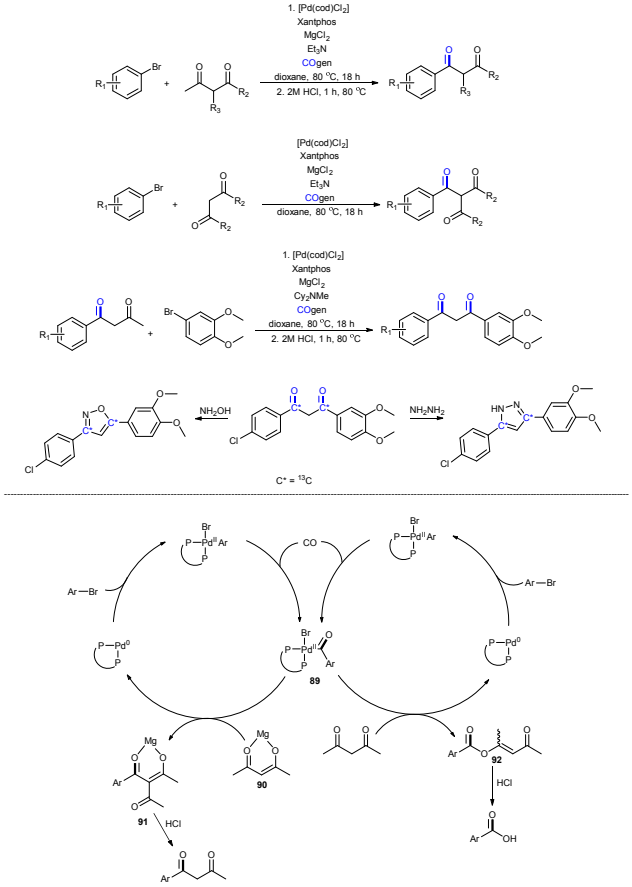
In 2013, Korsager *et al*. reported the synthesis of β-keto esters by the carbonylative coupling of aryl halides and triflates with potassium monoester malonates.[88] The catalytic system required the use of Xantphos ligand along with $MgCl_2$ and Et_3N for high product yields and was utilized for the synthesis of a range of β-ketoesters. Interestingly, the catalytic system allowed the use and coupling of aryl and benzyl chlorides as well. The reaction was smoothly conducted even for the gram scale synthesis of esters. Use of ^{13}COgen resulted in the synthesis of ^{13}C-labelled ketoesters which were successfully transformed to ^{13}C-labelled heterocycles through diverse transformations. A mechanism for the transformation was proposed (Scheme 74).



Scheme 74 Palladium catalyzed carbonylative synthesis of β-keto esters using COgen.

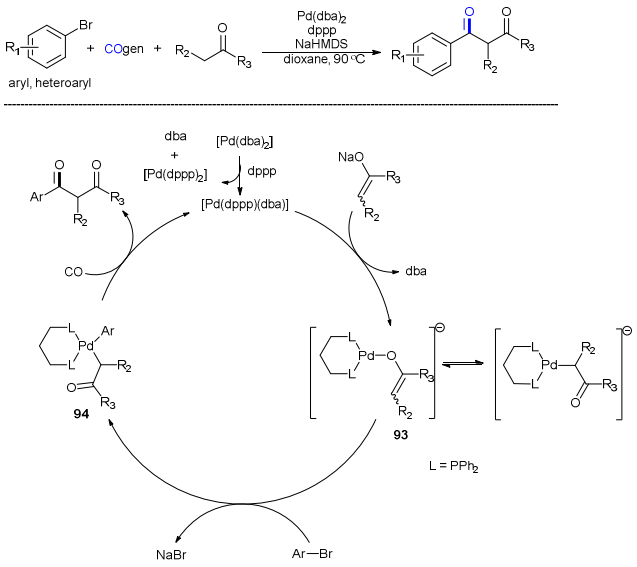
The carbonylative coupling of aryl bromides with acetylacetone for the synthesis of 1,3-diketones was reported.[89] The reaction was a two-step process, wherein the carbonylation lead to the synthesis of the triketone which selectively underwent deacetylation in the presence of 2M HCl to afford the diketone. The protocol also included the synthesis of triketone derivatives,

1,3-diaryl-1,3-propandiones and a scale up process. The double ^{13}C-labelled 1,3-diaryl-1,3-propandione was subsequently converted to double ^{13}C-labelled heterocycle derivatives. The key step in the proposed mechanism involves the attack of the $MgCl_2$-activated complex **90** on the acyl palladium intermediate **89** through a nucleophilic acyl substitution or by ligand exchange followed by reductive elimination to give **91**. This undergoes deacetylation with HCl to give the diketone product. In absence of $MgCl_2$, competing attack through the more reactive oxygen gives the vinyl benzoate **92** which upon acidic treatment gives benzoic acid (Scheme 75).



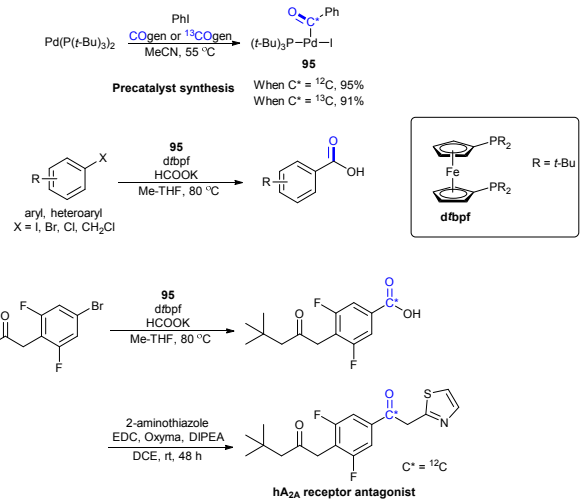
Scheme 75 Synthesis of 1,3-diketones by palladium catalyzed carbonylative coupling of aryl halides with acetylacetone.

In continuation of their previous work involving the carbonylative α-arylation of ketones with aryl iodides[81], the scope was extended to aryl bromides.[90] The use of the $Pd(dba)_2$-DPPP system was found to be optimal in conjunction with the use of NaHMDS as base to form the sodium enolate of the ketone. A wide variety of aryl, heteroaryl bromides and ketones were successfully coupled to give 1,3 diketones. A detailed mechanistic study utilizing ^{31}P and ^{13}C NMR spectroscopy techniques was undertaken to determine the catalytic cycle. The study showed that the catalytic cycle is different from the one proposed for the classical carbonylation and involves the generation of [Pd(dppp)(enolate)] anion **93** from [Pd(dppp)(dba)] in the presence of the sodium enolate of the ketone. This is followed by the oxidative addition of the aryl bromide to give [Pd(Ar)(dppp)(enolate)] **94**. CO insertion and subsequent reductive elimination give the 1,3-diketone product (Scheme 76).



Scheme 76 Palladium catalyzed carbonylative a-arylation of ketones with aryl bromides using COgen.

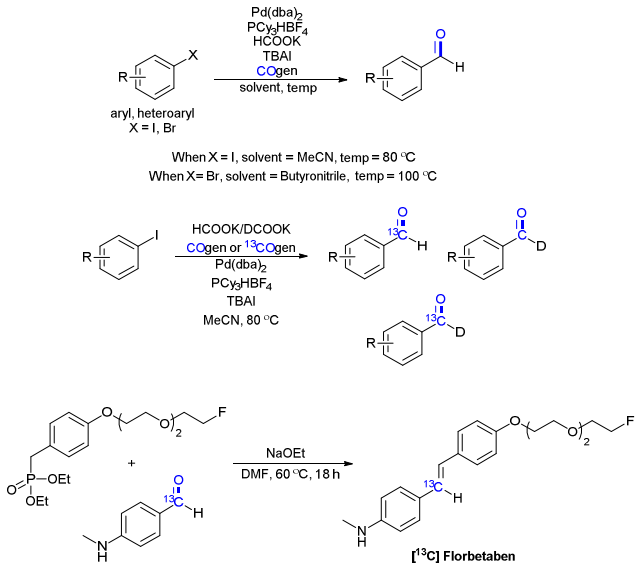
Korsager *et al*. reported the hydroxycarbonylation of aryl halides leading to the synthesis of aryl carboxylic acids.[91] Based on previous reports, potassium formate was used, which forms formic anhydride, which subsequently decomposes to yield the carboxylic acid. The use of d*t*bpf in combination with $Pd(dba)_2$ provided high yields of carboxylic acid. The authors also synthesized an air stable acyl-Pd(II) precatalyst **95**, which would not only behave as the active catalyst but also deliver CO acting as the surrogate, thereby removing the need for a two chamber system and simplifying the operation. Aryl bromides with varied functionalities and electron deficient aryl chlorides and benzyl chloride were successfully transformed into the corresponding acids. The precatalyst was applied for the synthesis of a potent and selective human A_{2A} receptor antagonist based on the hydroxycarbonylation protocol (Scheme 77).



Scheme 77 Palladium catalyzed hydroxycarbonylation of aryl halides using a Pd(II) precatalyst prepared from COgen.

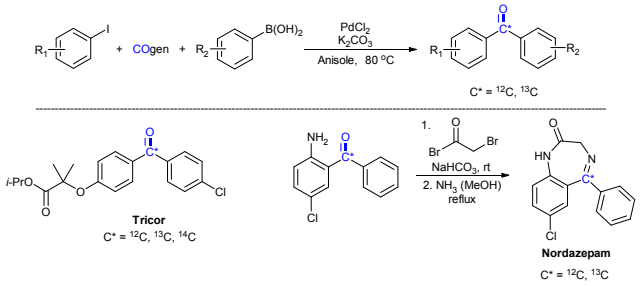
Synthesis of aldehydes by the reductive carbonylation of aryl

iodides and bromides was reported using potassium formate as the *in situ* hydride source.[92] The use of TBAI as a phase transfer catalyst was needed for utilizing formate in the reaction system. After identifying PCy_3HBF_4 at 5 mol% loading as the ligand for getting aldehydes selectively and with high yields, aryl iodides were successfully coupled. Aryl bromides could be coupled at a higher temperature. Use of ^{13}C-labelled COgen and DCOOK allowed the synthesis of aldehydes labelled at the carbonyl carbon as well as double isotopically labelled aryl aldehydes. The synthesis of ^{13}C-labelled florbetaben, a β-amyloid binding compound was achieved (Scheme 78).



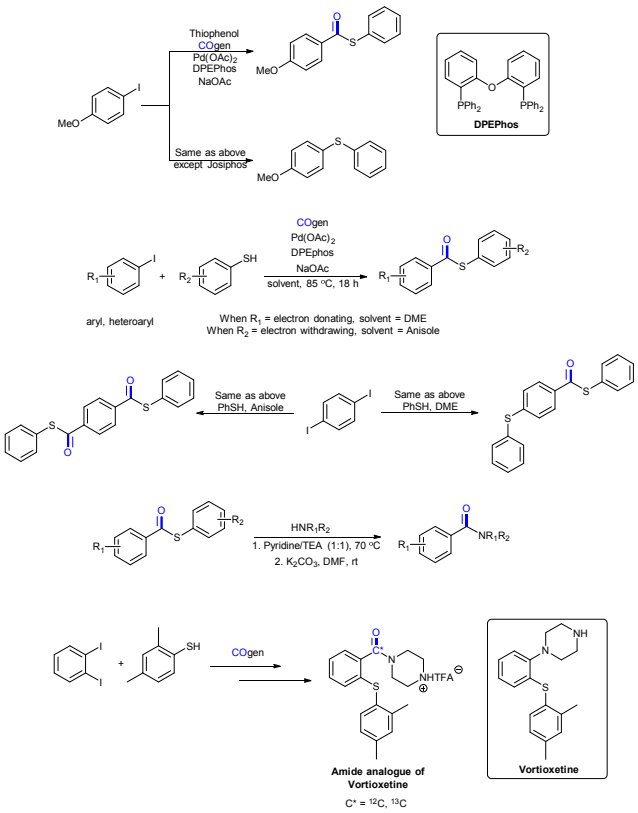
Scheme 78 Reductive carbonylation of aryl halides using COgen.

Ahlburg *et al*. reported the carbonylative Suzuki coupling of aryl iodides leading to the synthesis of benzophenone derivatives.[93] The reaction could be carried out in the presence of oxygen, without degassing and drying solvents, thus making the use of glovebox and the need for inert atmosphere redundant. The protocol was used for the ^{12}C- and ^{13}C-labelled synthesis of pharmaceutical drugs: Nordazepam and Tricor (Scheme 79).



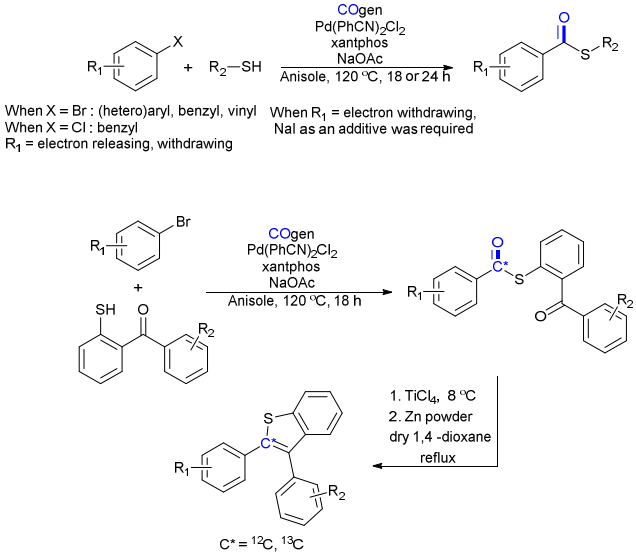
Scheme 79 Palladium catalyzed carbonylative Suzuki-Miyaura coupling using COgen.

Burhardt *et al*. reported the thiocarbonylation of aryl iodides with aryl and alkyl thiols leading to the synthesis of thioesters.[94] The chemoselectivity of the reaction was highly dependent on the choice of ligand and solvent used. It was observed that in the presence of Josiphos, the thioether was formed exclusively even in the presence of CO, while changing the ligand to DPEphos afforded the thioester in a reversal of chemoselectivity. Moreover, DME as a solvent worked for the carbonylation of electron rich aryl iodides, whereas anisole was required for the electron deficient ones. Interestingly, the diiodobenzene substrates gave a thiocarbonylation-thioarylation sequence in DME, while changing the solvent to anisole resulted in a double thiocarbonylation. The thioesters were successfully transformed to amides and a ^{13}C-labelled amide version of the antidepressive agent, vortioxetine was also synthesized (Scheme 80).



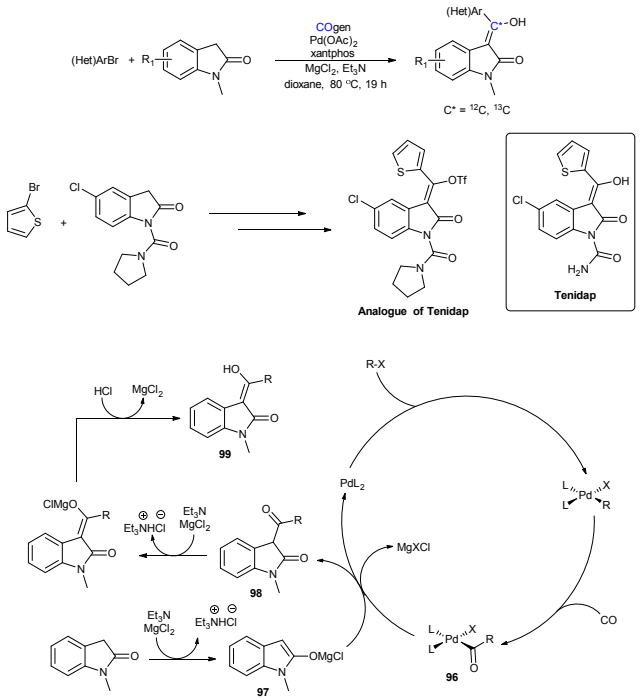
Scheme 80 Palladium catalyzed thiocarbonylation of aryl iodide using COgen.

The scope of the thiocarbonylation was expanded by carrying out the reaction with aryl, benzyl, vinyl bromides and benzyl chlorides.[95] Again the choice of the solvent and the catalytic system was crucial for the chemoselectivity of the reaction towards the synthesis of thioesters. Anisole was the solvent of choice for the conversion. Addition of iodide salts was necessary for making electron deficient aryl bromides react. The protocol was also extended to the synthesis of ^{13}C-labelled benzothiophenes via a sequential thioester preparation and McMurry coupling (Scheme 81).



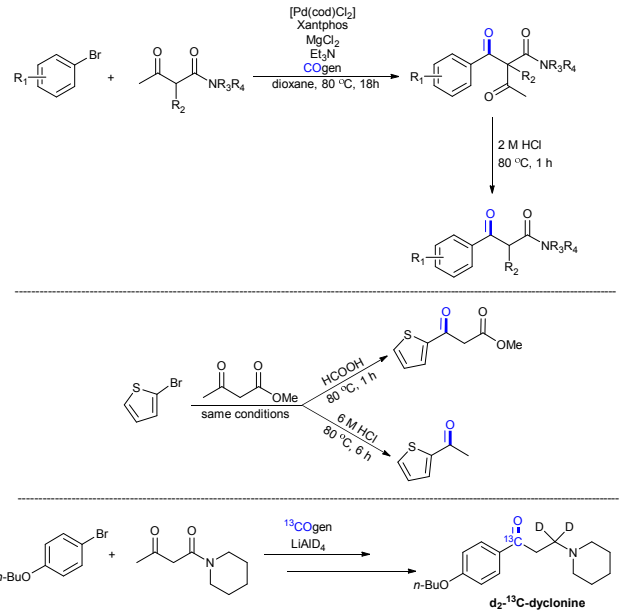
Scheme 81 Palladium catalyzed thiocarbonylation of aryl, benzyl, vinyl bromides and aryl chlorides using COgen.

In 2014, Lian *et al*. reported the carbonylative α-arylation of 2-oxindoles with aryl and heteroaryl bromides leading to the synthesis of 3-acyl-2-oxindoles.[96] The presence of $MgCl_2$ with Et_3N was essential for promoting C-acylation. Even benzyl chlorides could be used as substrates after optimizing reaction conditions for bromides. The synthesis of ^{13}C-labelled acyl oxindoles and an analogue of tenidap, a potent cyclooxygenase inhibitor was carried out. A mechanism involving the role of the magnesium enolate of 2-oxindole behaving as the nucleophile was proposed. The key steps in the mechanism involve the formation of the palladium-acyl intermediate **96** by the oxidative addition of the halide followed by CO insertion. Enolate **97** is formed by coordination of oxindole with $MgCl_2$ followed by deprotonation by Et_3N. This undergoes either a nucleophilic acyl-type substitution, or a ligand exchange with the halide followed by reductive elimination to give the ketoamide **98**. A second deprotonation by the combination of $MgCl_2$ and Et_3N followed by acidic workup gives the 3-acyl-2-oxindole **99** (Scheme 82).



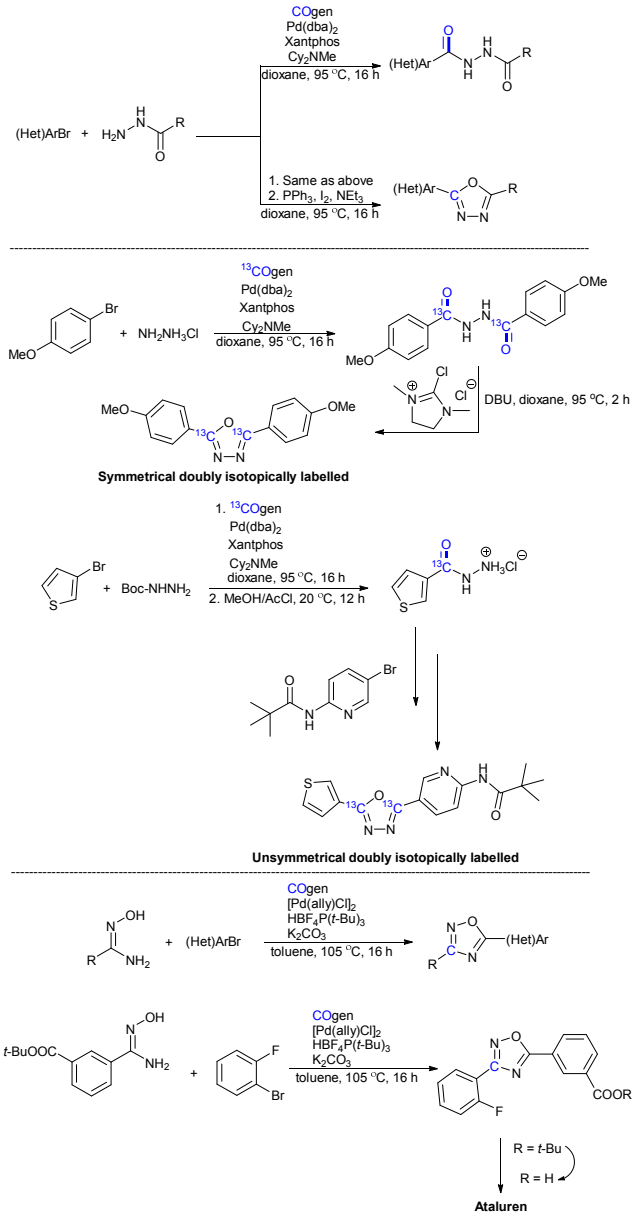
Scheme 82 Synthesis of 3-acyl-2-oxindoles by the palladium catalyzed carbonylative a-arylation of 2-oxindoles with (hetero)aryl bromides.

Andersen *et al*. reported the carbonylative coupling of aryl bromides with *N*-substituted acetoacetamides followed by an acid-mediated deacetylation work-up to afford β-keto amides.[97] The reaction conditions were similar to the previous mentioned reports involving deacetylation. Further the same methodology was extended for the synthesis of β-keto esters and thioesters and depending on the conditions chosen for the acidic work-up, the ester or the corresponding ketone could be generated. Using ^{13}C-labelled COgen, the protocol was used for the synthesis of d_2-^{13}C-dyclonine (Scheme 83).



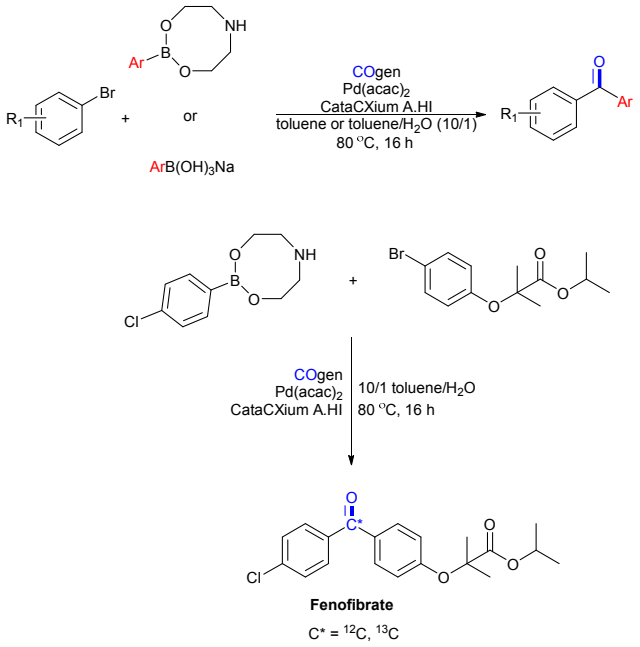
Scheme 83 Palladium catalyzed carbonylative-deacetylative process for the synthesis of β-ketoamides using COgen.

The synthesis of *N,N′*-diacylhydrazines by carbonylatively coupling aryl bromides with acylhydrazines using COgen was reported.[98] The reaction could be catalyzed by $Pd(dba)_2$ in combination with Xantphos and Cy_2NMe as the base. The diacylhydrazines were subsequently dehydrated using the combination of PPh_3/I_2 to afford 1,3,4-oxadiazoles in one pot. Further, two different strategies were used for the synthesis of symmetrical and non-symmetrical doubly isotopically ^{13}C-labelled 1,3,4-oxadiazoles. The authors also documented the synthesis of 1,2,4-oxadiazoles by coupling amidoximes with aryl bromides in presence of CO and the best reaction conditions were identified. This protocol was used for the synthesis of Ataluren, a molecule in late stage chemical trials for the treatment of Duchenne muscular dystrophy and cystic fibrosis (Scheme 84).



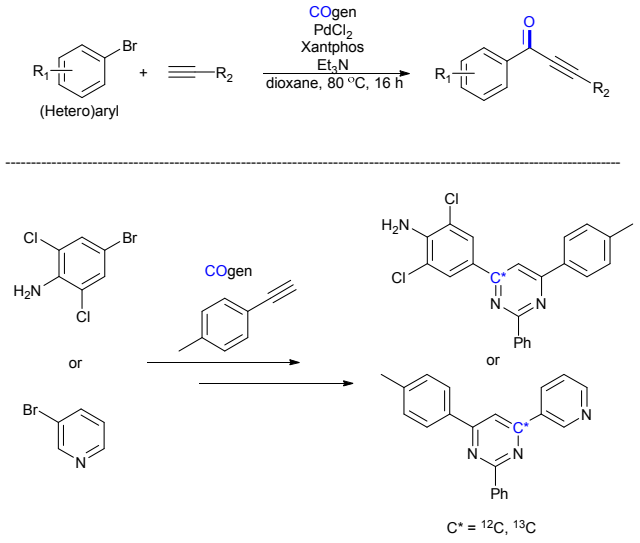
Scheme 84 Palladium catalyzed carbonylative synthesis of *N,N′*-diacylhydrazine and subsequent synthesis of 1,2,4- and 1,3,4-oxadiazoles using COgen.

Bjerglund *et al*. reported that the carbonylative Suzuki−Miyaura coupling of aryl bromides could be carried out under base free conditions by employing sodium phenyltrihydroxyborate and aryl DABO boronates as organometallic nucleophiles.[99] The latter is used in cases when the former cannot be synthesized from certain arylboronic acids. Aryl, heteroaryl bromides and arylboronic acid equivalents could be successfully coupled under the $Pd(acac)_2$-CataCXium A·HI system. The synthesis of ^{13}C-labelled triglyceride and cholesterol regulator drug, fenofibrate was achieved (Scheme 85).



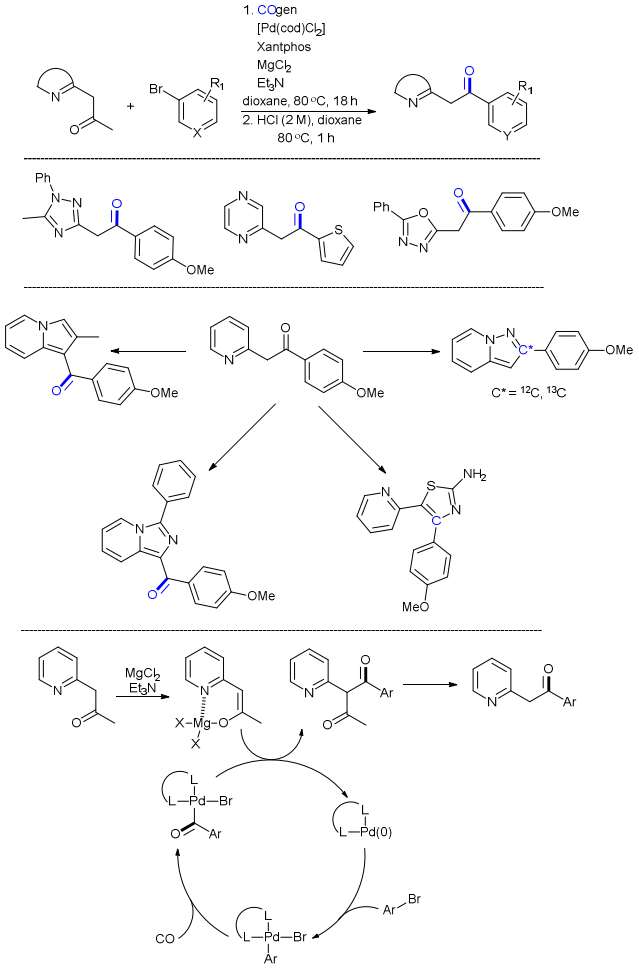
Scheme 85 Base free palladium catalyzed Suzuki-Miyaura coupling of aryl bromides with boronic acid derivatives using COgen.

Neumann *et al*. reported the carbonylative Sonogashira coupling of aryl bromides.[100] Using a simple Pd-Xantphos system, ynones were synthesized effectively. The synthesis of ^{13}C-labelled pyrimidine derivatives was carried out in two steps from the synthesized ynones (Scheme 86).



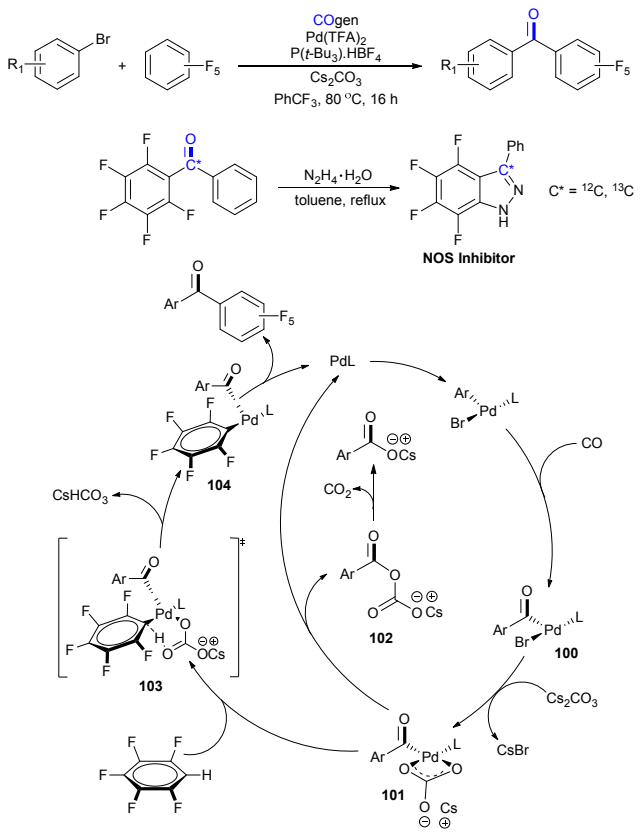
Scheme 86 Palladium catalyzed carbonylative Sonogashira coupling of aryl bromides using COgen.

Jusseau *et al*. reported the synthesis of 1-(het)aryl-2-(2-pyridyl)ethanones by the carbonylative coupling of (2-pyridyl)acetones with aryl bromides followed by an acid promoted deacetylation step.[101] The optimization studies revealed that, [Pd(cod)Cl_2] in conjunction with Xantphos, $MgCl_2$ and Et_3N in dioxane gave the best product yields. Further, the deacetylation step could be carried out in presence of 2 M HCl at 80 °C for 1 h. After the test reactions revealed that the position of the nitrogen atom is essential for proper reactivity, a range of 5- and 6-membered (2-azaaryl)acetone derivatives containing the pyridazine, pyrimidine, pyrazine, benzothiazole, 1,2,4-triazole and 1,3,4-oxadiazole skeleton were synthesized and subjected to the carbonylative coupling, thus affording varied heteroaromatic derivatives. The 1-(het)aryl-2-(2-pyridyl)ethanones were further subjected to different transformations, thus leading to the synthesis of multi(hetero)aromatic derivatives. A mechanism for the carbonylative coupling was proposed which involved the formation of the Mg-enolate as the key intermediate (Scheme 87).



Scheme 87 Palladium catalyzed carbonylative coupling of (2-azaaryl)acetone derivatives with (hetero)arylbromides using COgen.

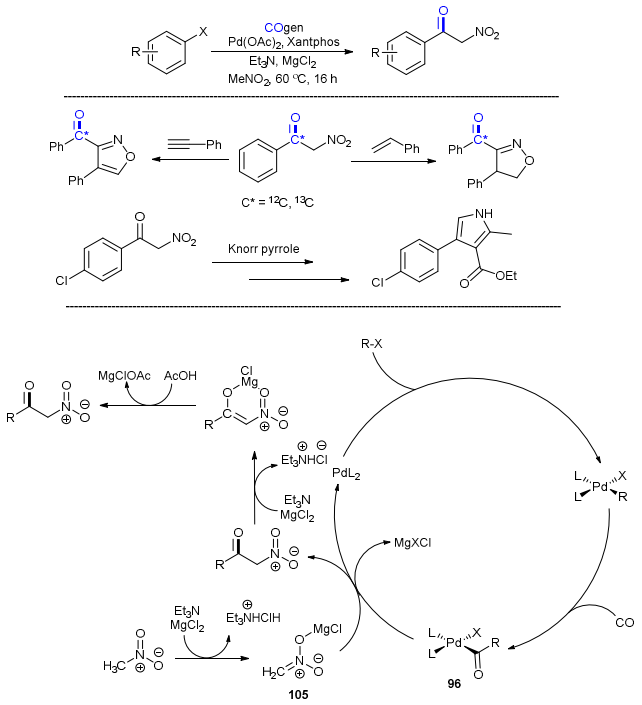
Lian *et al*. reported the first intermolecular C(sp2)-H carbonylation of polyfluoroarenes with aryl bromides using COgen.[102] Incidentally, the reaction was carried out without the assistance of directing groups under mild conditions. The combination of Pd(TFA)$_2$ with the bulky ligand P(*t*-Bu)$_3$, Cs_2CO_3 as the base in trifluorotoluene turned out to be the optimized parameter and lead to the synthesis of benzopolyfluorophenone in high yields. The effect of various substituents present on aryl bromide on the reaction yield was studied and the presence of electron-withdrawing groups caused the product yield to drop as compared to electron-releasing groups. The variation of the number of fluorine atoms on the polyfluoroarene was studied and the product yield drops as the number of fluorine atoms are replaced by hydrogen atoms or alkyl groups. The protocol was also used for the synthesis of ^{13}C-labelled benzopolyfluorophenone which in turn was used for the synthesis of a labelled potent nitric oxide synthases (NOS) inhibitor. The mechanism proposed involves the oxidative insertion of the aryl bromide to Pd(0) followed by coordination and insertion of CO to give the acylpalladium complex **100**. This is followed by a counterion exchange between Cs_2CO_3 and Br to give complex **101**. This complex can undergo a reductive elimination to give complex **102** which undergoes decarboxylation to give aryl carboxylic acid which is observed as a major side-product. But if C-H activation is faster, intermediate **104** is formed through transition state **103** which undergoes reductive elimination to afford the desired product (Scheme 88).



Scheme 88 Palladium catalyzed carbonylative coupling of aryl bromides and polyfluoroarenes through C-H activation using COgen.

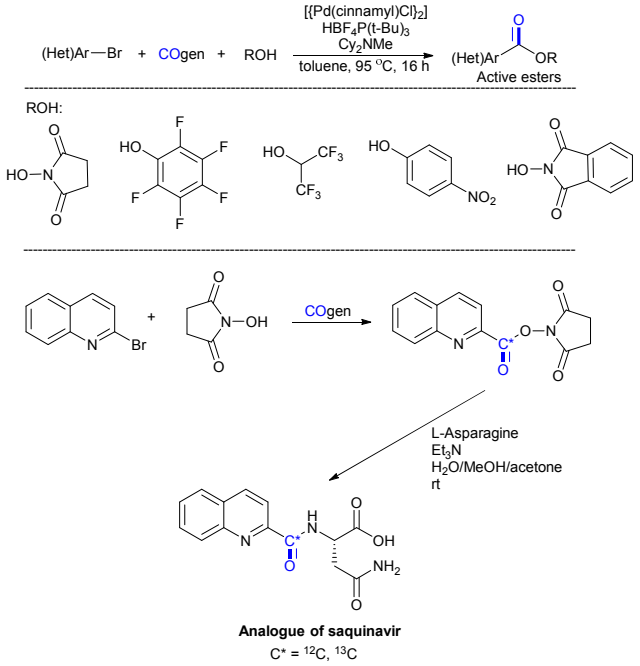
The carbonylative α-arylation of nitromethane with aryl halides resulting in the synthesis of α-nitro ketones was reported again by Lian *et al*.[103] Pd(OAc)$_2$ in combination with Xantphos in presence of $MgCl_2$ and Et_3N formed part of the optimized reaction

parameters. Incidentally, the reaction could be conducted in nitromethane under neat conditions without the addition of any solvent. A range of aryl iodides and bromides were successfully carbonylated and α-nitro ketones being versatile synthons in organic synthesis, the protocol was extended for the synthesis of ^{13}C-labelled isoxazoline and isoxazole through a [3+2] dipolar cycloaddition and pyrrole through the Knorr pyrrole synthesis (Scheme 89). The mechanism involves the formation of the nitronate carbanion **105**. The oxophilic coordination of magnesium chloride to nitromethane facilitates deprotonation by a mild base and encourages product formation through C-acylation rather than O-acylation. The product being more acidic is deprotonated by combination of $MgCl_2$ and Et_3N and the product is generated after an acidic workup.



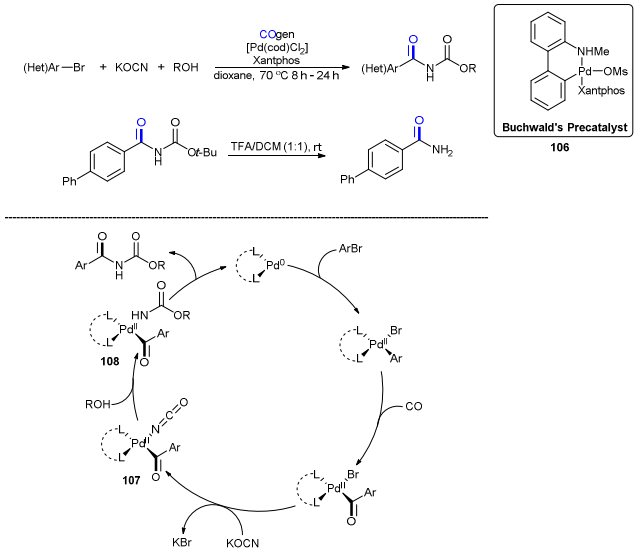
Scheme 89 Palladium catalyzed carbonylative a-arylation of nitromethane with aryl halides using COgen.

Almeida *et al*. carried out the alkoxycarbonylation of aryl and heteroaryl bromides with a range of oxygen nucleophiles that include N-hydroxysuccinimide (NHS), pentafluorophenol (PFP), hexafluoroisopropanol (HFP), 4-nitrophenol and *N*-hydroxyphthalimide for the synthesis of active esters.[104] Such esters play a key role in the synthesis of natural products, pharmaceuticals and peptides. The methodology was also applied for the synthesis of a ^{13}C-labelled precursor of saquinavir, a HIV-protease inhibitor (Scheme 90).



Scheme 90 Palladium catalyzed alkoxycarbonylation of aryl bromides for the synthesis of active esters using COgen.

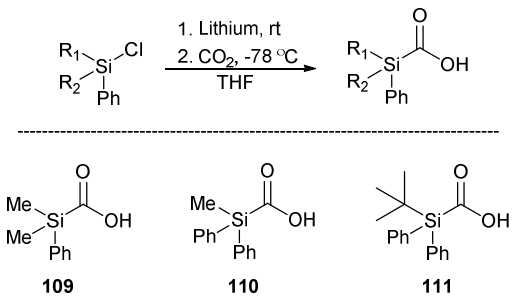
Very recently, Yin *et al*. reported the synthesis of *N*-acylated carbamates through a four component palladium catalyzed carbonylative coupling of aryl bromides with potassium cyanate and alcohols.[105] The optimization studies revealed that [Pd(cod)Cl_2] (5 mol%) in conjunction with Xantphos (5 mol%) gave the highest product yield and the reaction reached completion in 8 h at 70 °C. However using Buchwald's Pd-Xantphos palladacyclic precatalyst **106** allowed the reaction to be conducted at 50 °C resulting in a 89% isolated yield of the product. A range of (hetero)aryl bromides and alcohols could be successfully coupled and the protocol was extended for the synthesis of primary amides by the acid mediated deprotection of a Boc-protected amide. The mechanism proposed involves the formation of the acyl-Pd complex from the aryl halide followed by a subsequent ligand exchange with KOCN to form the isocyanate complex **107**. These complexes reluctantly undergo reductive elimination and hence the alcohol adds to the cyanate ligand to form the carbamate ligated complex **108** which undergoes reductive elimination to furnish the acyl carbamate (Scheme 91).



Scheme 91 Palladium catalyzed carbonylative synthesis of acyl carbamates using COgen.

13.2 Silacarboxylic Acid

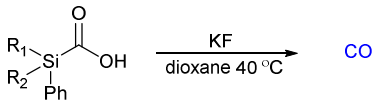
In an endeavour to develop alternate crystalline CO releasing molecules (CORMs), Skrydstrup's group reported the use of silacarboxylic acids as potent CO surrogates for the first time in 2011.[106] The use of silacarboxylic acids was envisioned considering earlier work on boranocarbonates as CO releasing molecules and the fact that the former would be easier to synthesize and handle vis-à-vis the latter. Moreover, considering the fluorophilicity of the silicon atom, the role of a fluoride source for decarbonylation of the acid at ambient temperature was envisaged. The acids were synthesized from chlorosilanes and carbon dioxide in a two-step process (Scheme 92).



Scheme 92 Synthesis of silacarboxylic acids.[106]

During the optimization studies it was found that, methyldiphenyl silacarboxylic acid underwent decarbonylation the fastest in the presence of substoichiometric amounts of KF as the activator (Table 6).

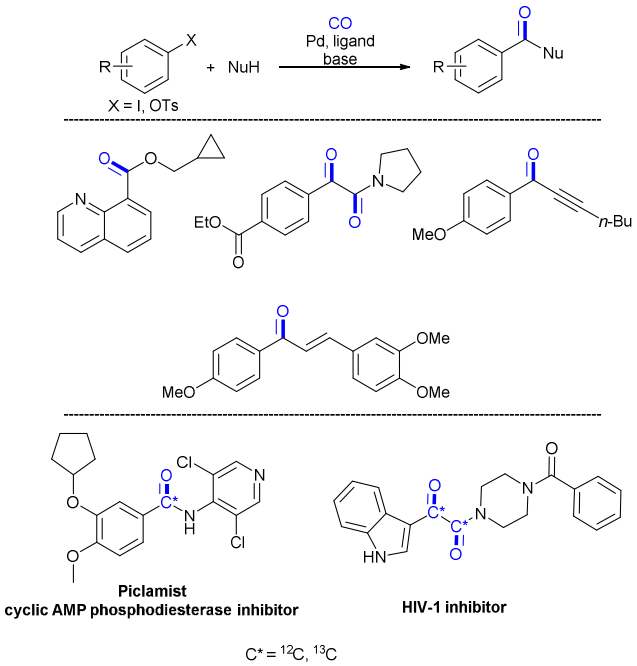
Table 6 Decarbonylation of silacarboxylic acids using KF.[106]



Entry	Precursor	Time (min)	Gas yield (%)
1	**109**	12	90
2	**110**	10	95
3	**111**	20	97

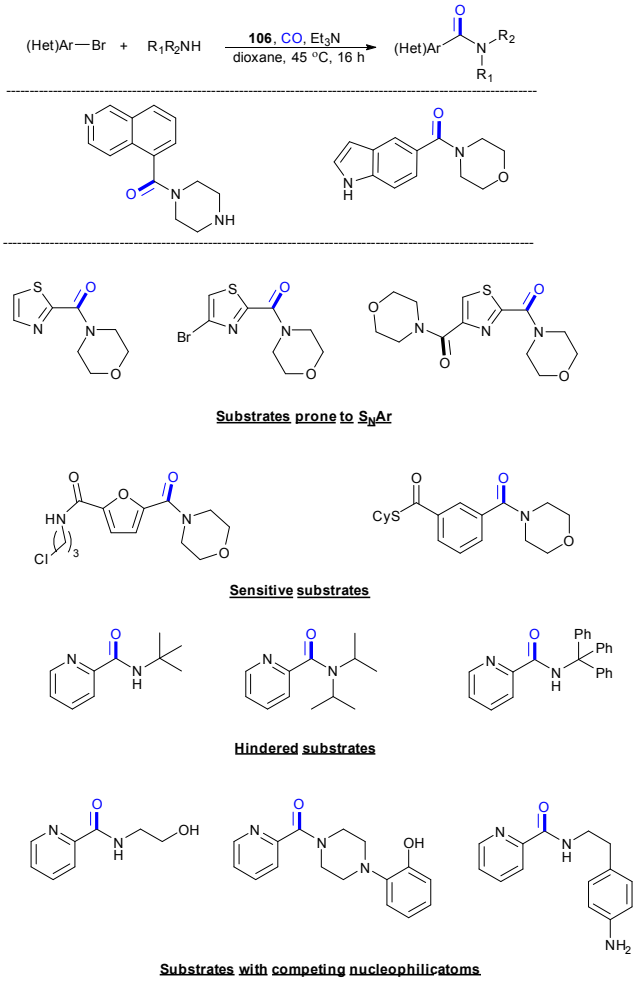
silacarboxylic acid (0.33 mmol) and KF (0.36 mmol) in dioxane (3 mL).

It was also the easiest to purify through recrystallization and hence was chosen for further studies. A range of classical carbonylation reactions (alkoxy, amino, carbonylative Heck, Sonogashira) were performed after choosing the appropriate catalytic system and solvent. Isotopically labelled silacarboxylic acid was used to synthesize two labelled pharmaceutically significant molecules (Scheme 93).



Scheme 93 Palladium catalyzed carbonylation reactions using silacarboxylic acid.[106]

In 2014, Friis *et al*. reported a Xantphos ligated palladacyclic precatalyst **106** for the aminocarbonylation of aryl and mainly heteroaryl bromides using silacarboxylic acid.[107] The highlight of the protocol was that, the reaction could be carried out at a temperature of 45 °C and also allowed the carbonylation of difficult heteroaryl bromides, substrates prone to S_NAr type reactions as well as containing sensitive functionalities (Scheme 94).



Scheme 94 Palladacyclic precatalyst catalyzed aminocarbonylation of (hetero)aryl bromides using silacarboxylic acid.

The comparison of the activity of the precatalyst with traditional palladium sources showed that the latter could provide quantitative conversion only at 80 °C, whereas the precatalyst showed good yield at 40 °C and a quantitative conversion at 50 °C (Figure 2).

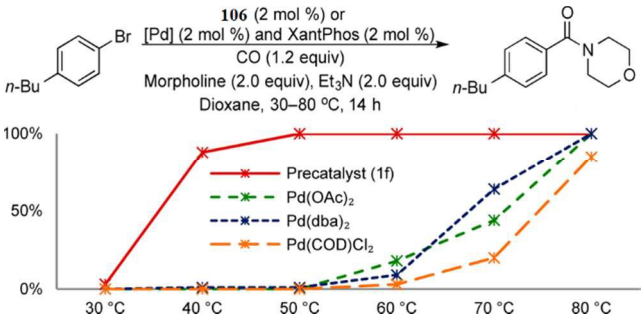
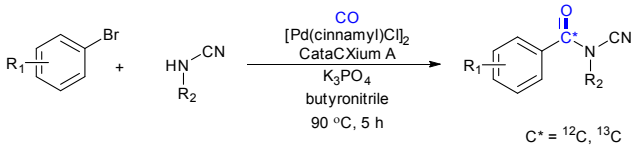


Figure 2 Comparison of the activity of precatalyst with conventional palladium sources. Reproduced with permission from S. D. Friis, T. Skrydstrup and S. L. Buchwald, *Org. Lett.*, 2014, **16**, 4296-4299. Copyright 2014 American Chemical Society.

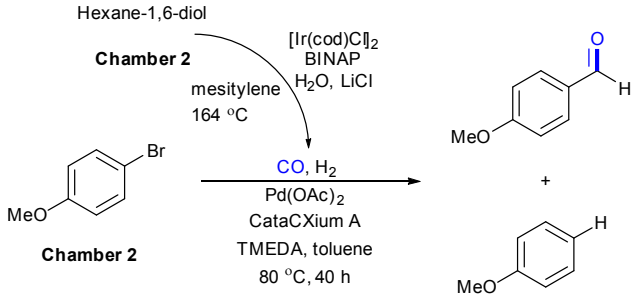
Lian *et al*. documented the preparation of *N*-acyl cyanamides by the carbonylative coupling of aryl bromides with *N*-alkyl cyanamides.[108] [Pd(cinnamyl)Cl]$_2$ in conjunction with cataCXium A proved to be an active catalytic system. The methodology was also used for the synthesis of ^{13}C-labelled acyl cyanamides using ^{13}C-silacarboxylic acid (Scheme 95).



Scheme 95 Palladium catalyzed carbonylative synthesis of cyanamides using silacarboxylic acid.

13.3 Alcohol

In 2012, Olsen and Madsen reported an iridium-*rac*-BINAP catalyzed dehydrogenative decarbonylation of primary alcohols which results in a one carbon atom shorter alkane with the simulataneous liberation of syn gas.[109] The mechanism is presumably involves two separate catalytic cycles with the iridium(I)-BINAP species, where the first removes molecular hydrogen from the primary alcohol and the second cleaves carbon monoxide from the resulting aldehyde. Thus, this protocol, wherein the alcohol serves as a source of syngas was applied by Madsen and co-workers for the reductive carbonylation of 4-bromoanisole leading to the synthesis of 4-anisaldehyde in a two-chamber system.[110] After screening various alcohols, it was found that hexane-1,6-diol was the best choice (Scheme 96).

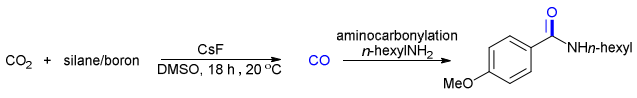


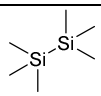
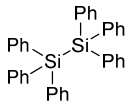
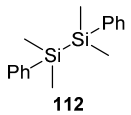
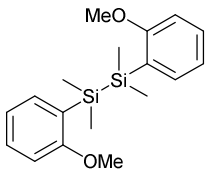
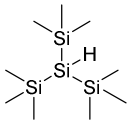
Scheme 96 Palladium catalyzed reductive carbonylation using hexane-1,6-diol.

13.4 Carbon dioxide

Recently, Lescot *et al*. reported a highly efficient methodology for the transition metal free reduction of CO_2 to CO catalyzed by cesium fluoride in the presence of a stoichiometric amount of disilane in DMSO at room temperauture.[111] Use of non-hygroscopic potassium hydrogen fluoride (KHF_2) (CsF is hygroscopic and hence an inert atmosphere is required), allowed the reduction to be conducted in a non-inert atmosphere. Use of potassium fluoride at an elevated temperature also resulted in the quantitative production of CO. A variety of silanes- disilanes, trisilanes, silylborane- maintained the efficiency of the reduction, whereas bis(pinacolato)diboron was inefficient indicating that a silicon atom is necessary for the fluoride source to carry out reduction (Table 7).

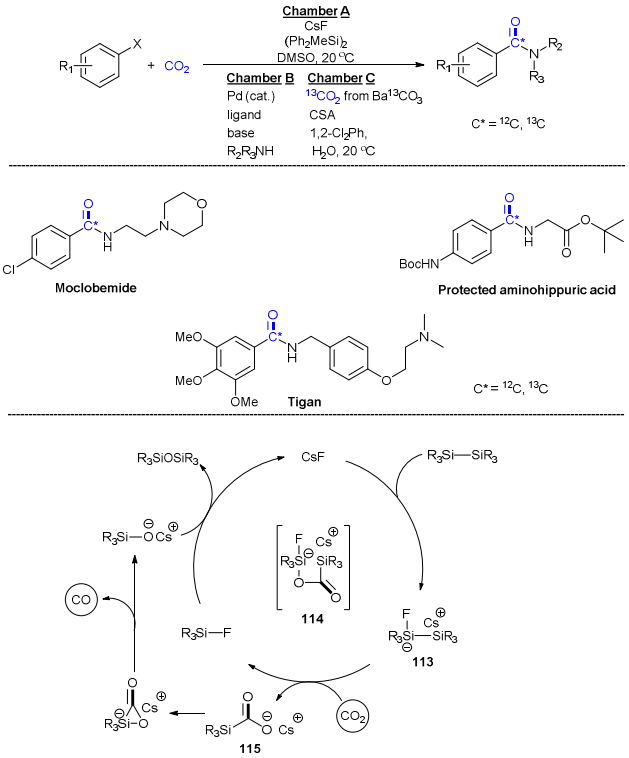
Table 7 Screening of silanes and boron for reduction of CO_2.[111]



Entry	Reducing agent	Amide % conv (% yield)[b]
1		7
2		0
3	 **112**	100(90%)
4		0
5		90(78%)
6	pinB—Bpin	0
7	pinB—$SiMe_2$Ph	89(67%)
[c]8	**112**	[d] 63, [e] 100(92%)

[a] Conditions: Chamber A was loaded with silane or boron (0.5 mmol), CsF (0.05 mmol), DMSO (3 mL), and last CO_2 (21 mL, 0.85 mmol) by injection through the septum. Chamber B was loaded with p-iodoanisole (0.50 mmol), *n*-hexylamine (1 mmol), $Pd(dba)_2$ (0.025 mmol), PPh_3 (0.050 mmol), Et_3N (1 mmol), and dioxane (3.0 mL). Reaction mixture in Chamber B was stirred at 80 °C for 18 h and in Chamber A at 20 °C for 18 h. [b] ^1H NMR conversion. [c] KHF_2 (0.05 mmol), [d] 20 °C, [e] 30 °C

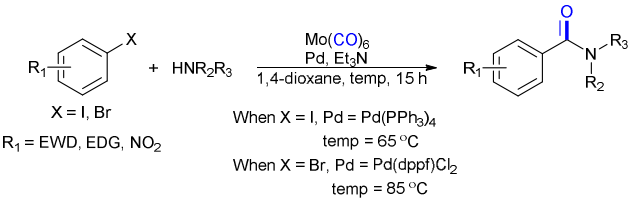
The CO so produced from CO_2 was applied for the carbonylation of various aryl halides leading to the synthesis of pharmaceutically important molecules in the two-chamber reactor. CO_2 was injected in one chamber and underwent reduction in the presence of the fluoride salt and silane. The CO so produced reacted with the substrates in the other chamber where the catalytic system was appropriately chosen. In order to synthesize the labelled compounds, a three chamber system was chosen, in which $Ba^{13}CO_3$ reacted with camphorsulfonic acid in the first chamber generating $^{13}CO_2$ which got reduced to ^{13}CO in the second chamber and subsequent carbonylation took place in the third chamber. Such a three chamber system did not reduce the efficiency of the process and the carbonylated products were generated in high yields. A mechanism for the reduction of CO_2 with CsF and disilane was proposed. CO_2 either reacts with a free silyl anion or a hypervalent species **113** by fluoride coordination. Subsequent CO_2 insertion into **113** generates the *O*-silylated silacarboxylic acid **114**. Liberation of the silacarboxylate generates the cesium salt **115**, which presumably undergoes a Brook rearrangement to liberate CO and a silyloxide. Subsequent generation of the disiloxane from attack of the siloxide on silyl fluoride regenerates the cesium fluoride (Scheme 97).



Scheme 97 CsF catalyzed reduction of CO_2 to CO and subsequent palladium catalyzed carbonylation.[111]

13.5 Metal carbonyl

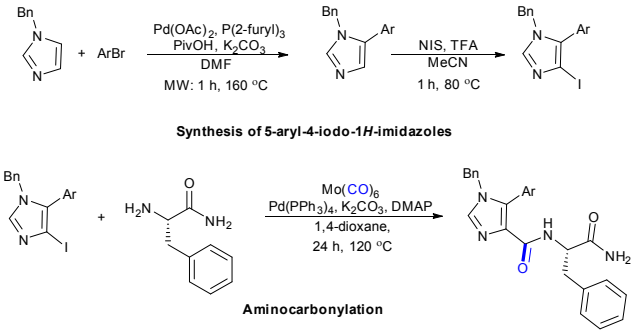
In 2012, Larhed and co-workers took advantage of the two-chamber system to carry out aminocarbonylation of nitro substituted aryl iodides and bromides with molybdenum hexacarbonyl as the solid CO source.[112] When the same process was carried out in one pot, the nitro functionality underwent substantial reduction in presence of molybdenum. The advantage of this protocol, wherein $Mo(CO)_6$ and the substrates to be carbonylated are in two different chambers is that, it allows the carbonylation to proceed smoothly with the nitro group remaining intact. DBU was chosen as the activator to release CO from the metal carbonyl and an appropriate catalytic system allowed the carbonylation of a wide variety of substituted aryl iodides and bromides with primary, secondary amines and anilines (Scheme 98).



Scheme 98 Palladium catalyzed aminocarbonylation of nitro substituted aryl halides using $Mo(CO)_6$.

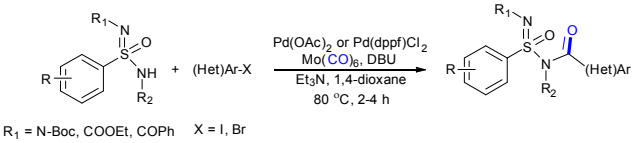
In 2013, Skogh *et al*. reported the aminocarbonylation of 5-aryl-4-iodo-1*H*-imidazoles with an amino acid amide (amide of phenyl alanine) nucleophile leading to the synthesis of 5-aryl-1-benzyl-1*H*-imidazole-4-carboxamides using $Mo(CO)_6$.[113] The starting material prior to the carbonylation reaction was prepared in a two-step manner starting from 1-benzyl-1*H*-imidazole which

underwent a microwave assisted C-5 arylation followed by a regioselective C-4 iodination. Hence the protocol serves as a way to synthesize imidazole containing phenylalanine based peptidomimetics. Interestingly, this work comes in as the first reported example of the aminocarbonylation of an imidazole scaffold with an amino acid nucleophile using a metal carbonyl as a CO surrogate (Scheme 99).



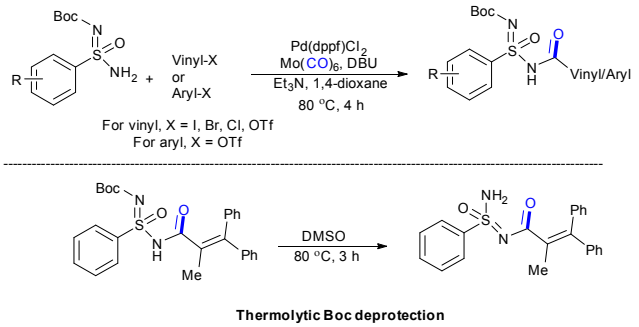
Scheme 99 Aminocarbonylation of 5-aryl-4-iodo-1*H*-imidazoles with amino acid amide using $Mo(CO)_6$.

Borhade *et al*. reported the synthesis of aryl and heteroaryl acyl sulfonimidamides by the carbonylative coupling of sulfonimidamides with aryl halides using $Mo(CO)_6$.[114] Interestingly, the optimization studies revealed that, the carbonylation of *N*-Boc protected sulfonimidamide with 4-iodoanisole using $Mo(CO)_6$ in a two-chamber system gave a better product yield as compared to gaseous CO(75 psi) and using $Mo(CO)_6$ in one pot under microwave irradiation. After optimizing the reaction conditions, a range of aryl and heteroaryl acyl sulfonimidamides were synthesized (Scheme 100).



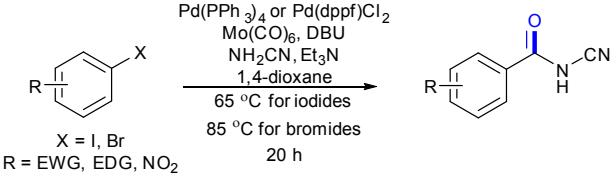
Scheme 100 Palladium catalyzed carbonylation synthesis of (hetero)aryl acyl sulfonimidamides.

Expanding the previous protocol for the synthesis of aryl and heteroaryl acyl sulfonimidamides, Wakchaure *et al*. reported the synthesis of *N*-(α,β-unsaturated acyl)-substituted sulfonimidamides through the carbonylative coupling of *N*-Boc protected sulfonimidamides with vinyl/(hetero)aryl halides and triflates.[115] In addition, a thermolytic Boc deprotection of *N*-(α,β-unsaturated acyl) sulfonimidamides was also carried out (Scheme 101).



Scheme 101 Palladium catalyzed carbonylative synthesis of vinyl and aryl acyl sulfonimidamides.

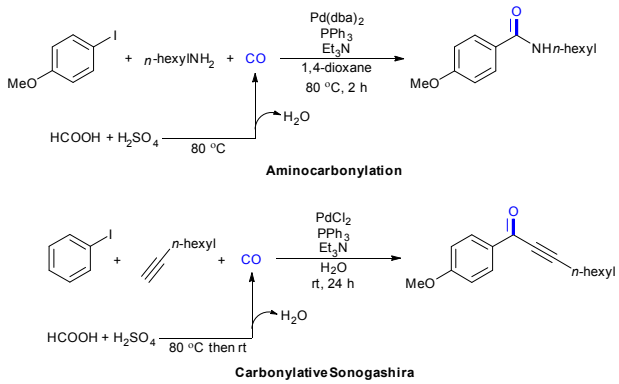
Mane *et al*. reported the synthesis of *N*-cyanobenzamides by the aminocarbonylative coupling of cyanamides with aryl hallides using $Mo(CO)_6$ (Scheme 102).[116]



Scheme 102 Palladium catalyzed carbonylative synthesis of *N*-cyanobenzamides.

13.6 Formic acid

In 2013, Brancour *et al*. reported the aminocarbonylation and carbonylative Sonogashira of aryl iodides by the generation of CO from the decomposition of formic acid in presence of sulfuric acid (Morgan reaction).[117] Interestingly, the Sonogashira carbonylation reaction could be performed in water and at room temperature (Scheme 103).



Scheme 103 Palladium catalyzed amino- and Sonogashira carbonylation using HCOOH.

The carbonylation could also be carried out using a continuous flow process involving a "tube-in-tube" reactor wherein the outer stainless steel tube provides the carbonylation flow and the formic acid decomposition takes place in the inner gas-permeable Teflon AF 2400 (Figure 3).

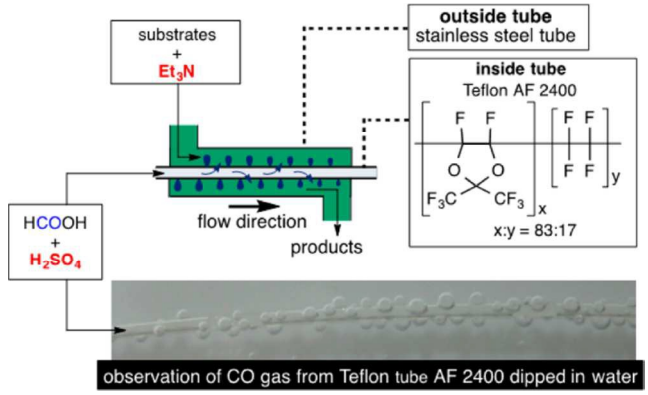


Figure 3 Schematic diagram of the *ex-situ* flow carbonylation using tube-in-tube reactor. Reproduced with permission from C. Brancour, T.

Fukuyama, Y. Mukai, T. Skrydstrup and I. Ryu, *Org. Lett.*, 2013, **15**, 2794-2797. Copyright 2013 American Chemical Society.

The continuous process and the two-chamber system elegantly establish the fact that strong acids can be simultaneously used with amine bases in the aminocarbonylation reaction thereby circumventing the need to mix them.

14. Summary and Outlook

This review describes the chemistry of surrogates reported over the last decade. There has been advancement in the discovery of new reactions which can be carried out using traditional surrogate molecules and also greater emphasis on the discovery of newer molecules and methodologies for carrying out carbonylation chemistry. Milder reaction conditions have been developed, wherein, for example, few formyl group containing molecules (formate esters and *N*-formylsaccharin) can be completely decarbonylated in a very short span of time and at relatively lower temperatures. Further, the two-chamber system removes the need to mix the surrogate molecule and the substrate and hence allows broader substrate tolerance and synthesis of ^{13}C, ^{14}C-labelled molecules. However, most of the protocols rely on the use of expensive second row transition elements, particularly palladium, and hence, it will be imperative to discover protocols using the less expensive first row transition elements. Avoiding the use of pre-functionalized substrates contributes to step economy and economic viability. Reports on the carbonylative coupling through C-H activation are few and is an important area which needs to be explored. The addition of phosphine ligands, stoichiometric quantities of surrogate molecule activators and bases lead to a less economical protocol with simultaneous generation of waste, thus compromising on atom economy. Hence the newer protocols developed should address these issues. The cheapest and the most abundant source of CO is still CO_2 and methodologies incorporating the production of CO through the reduction of CO_2 will contribute to sustainability. Additionally, carbohydrates and biomass, which happen to be benign and renewable sources of CO offer bright opportunities in the future for carbonylation chemistry. Heterogeneous catalysts for carbonylation reactions using CO surrogates are less explored as compared to the analogous carbonylation using gaseous CO. Development of such processes will allow catalyst product separation and catalyst recyclability, thus bringing down the overall cost of the process and hence allowing it to be extrapolated to the industrial scale. Finally, development of protocols with low catalyst loading need to be taken care of, wherein turnover number (TON) and turnover frequency (TOF) of the catalyst can be reported which will be the true measure of the efficiency and robustness of the catalyst used in such a process.

Notes and references

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