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Reviews

Palladium-Catalyzed Carbonylation—A Reaction Come of Age

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The palladium-catalyzed carbonylation of aryl and vinyl halides was first described more than 30 years ago by Richard Heck. However, limitations in the conditions originally described have meant that this reaction has achieved less prominence than the coupling reaction that also bears his name. Nevertheless, the attractiveness of this chemistry for forming carbonyl derivatives has led many researchers over the intervening years to attempt to increase the scope of the reaction beyond the originally described bromide, iodide, and triflate substrates, with conditions suited to large-scale application (particularly low pressure). To a large degree, this has now been achieved. This review describes the progress made regarding the selection of catalysts and conditions for this set of reactions, including illustrations from our own research. Reactions can now be carried out with aryl chlorides and tosylates bearing a range of substituents affecting both the electronic and steric properties of the substrate. The complexities of the reaction, represented by the interplay of catalyst, CO pressure, temperature, base, and solvent, make parallel screening desirable for optimization studies.

Introduction

Great progress has been made in recent years in extending the scope of palladium-catalyzed synthetic organic reactions,[1] primarily in the coupling of aryl and alkyl halides with a wide variety of nucleophilic reagents, including many organometallic derivatives. The diversity of these coupling systems is exemplified by the many named reactions of this type (Heck−Mizoroki, Suzuki−Miyaura, Sonogashira, Stille, Kumada, Negishi, Buchwald−Hartwig, and others). These reactions have particular applicability in complex organic synthesis to join together two functional components of the molecule. This has contributed to a change in synthetic schemes from largely linear (i.e., the successive elaboration of a single compound throughout the synthesis) to parallel synthesis of suitable components and their coupling at a late stage in the process. The latter approach generally provides a much more efficient and flexible process for the preparation of active pharmaceutical ingredients. With the success of the metal-based coupling chemistry (reactions involving copper, nickel, and other metals, as well as palladium, can often be used) has come renewed interest in the methods for forming the most suitable precursors for coupling or efficiently modifying the final structure at the end of the synthesis. The established methods often require stoichiometric reagents, giving poor atom efficiency and large amounts of waste. Recent emphasis on greener chemistry and improved sustainability has highlighted the benefits of catalytic processes.[2]

Interest in palladium-catalyzed reactions for organic synthesis received a major boost from the work of Richard Heck in the 1970s. Best known for the coupling reaction of aryl and vinyl halides with alkenes that carries his name, he also published a series of reports on carbonylation reactions[3−5] (sometimes referred to as Heck carbonylation) which have received considerable attention over the past 30 years. The reports describe reactions of aryl and vinyl halides with carbon monoxide to form acylpalladium intermediates, which are then converted by reaction with a nucleophile to products, typically carboxylic or keto acids, esters, amides, or aldehydes.

$$\mathrm{Ar{-}X + CO + Nu \rightarrow ArCONu + X}$$

$$\mathrm{Ar{-}X + 2CO + Nu \rightarrow ArCOCONu + X}$$

The reactions generally require added base to react with acid generated in the reaction (by deprotonation of alcohols and amines, for example) and to promote the formation of the Pd(0) species which initiates the reaction. This review will concentrate on describing the scope of these reactions and their mechanisms. Synthetic applications have been previously reviewed by Skoda-Földes and Kollár.[6] Palladium-catalyzed reactions have been set in the more generalized context of catalytic carbonylation by Beller and by Kollár.[7]

A large number of palladium catalyst precursors, mostly Pd(II) complexes but also a number of Pd(0) compounds, have been studied for carbonylation over the years. Catalysts can be obtained from fully formed complexes or prepared in situ using simple palladium compounds and ligand. A representative

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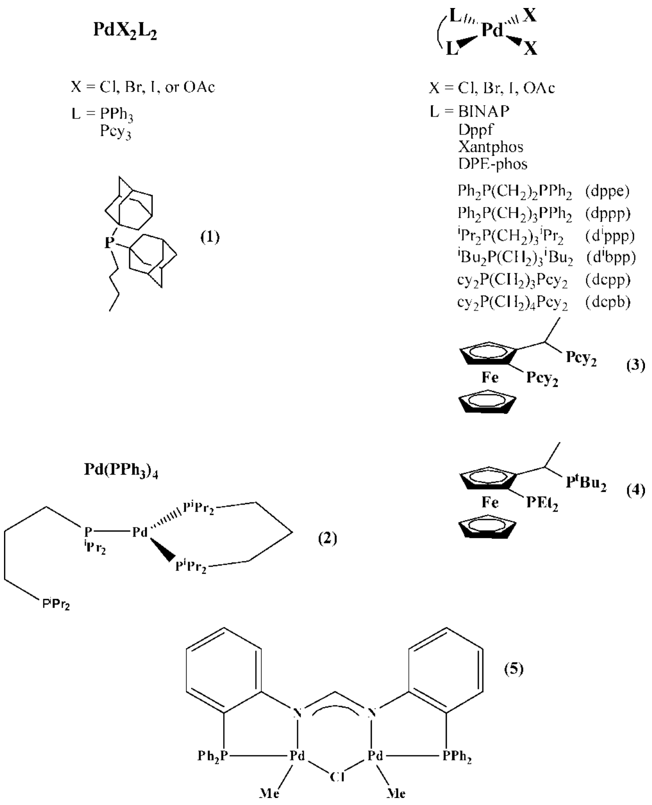

Figure 1. Representative catalysts for carbonylation.

selection of catalyst and ligands discussed in this review is shown in Figure 1.

Alkoxycarbonylation

The alkoxycarbonylation reaction is the most robust of the palladium-catalyzed carbonylation reactions because of the limited alternative reactions generated by ROH/RO^-. Heck reported that the reaction could be carried out readily for aryl and vinyl halides (I and Br) with >1 bar CO pressure and temperatures of >100 °C.[3] These mild conditions encouraged the widespread use of this reaction. Alkoxycarbonylation thus accounts for the majority of examples of industrial use of palladium-catalyzed carbonylation.[6]

Efforts to extend the applicability of this reaction naturally turned to activation of aryl chlorides. Significant progress was reported by Milstein in a series of papers.[8−11] He noted that it was the initial oxidative addition step which was rate limiting for these reactions. Increasing the electron density on palladium might be expected to improve the ease of oxidative addition; thus, he investigated the potential of the ligands $(alk)_2P(CH_2)_n$-$P(alk)_2$ (in particular $n = 3$, alk = ^iPr) as alternatives to the previously studied $Ph_2P(CH_2)_nPPh_2$. Characterization of the reaction product of $Pd(OAc)_2$ and $^iPr_2P(CH_2)_3P^iPr_2$ indicated an interesting structure (**2**) with one bidentate and one monodentate ligand[9] (see Figure 1). When it was reacted under 70 psi of CO at 150 °C, chlorobenzene could be converted to *n*-butyl benzoate in 89% isolated yield after 20 h. This system was studied in some detail in order to obtain mechanistic information, which is discussed below. Alper reported the conversion of chloroarenes to the corresponding carboxylic acids under biphasic conditions using $PdCl_2(Pcy_3)_2$ as catalyst, at 100 °C, under 1 atm of CO, but the reactions were slow (ca. 100 turnovers in 48−72 h),[12] and Nomura reported good yields of carboxylic acids using catalysts containing either mono- or bidentate cyclohexylphosphane ligands under 5 bar of CO at 180 °C.[13] The use of ferrocenylphosphanes was investigated by Beller, who identified {1-[2-(dicyclohexylphosphanyl)ferrocenyl]ethyl}dicyclohexylphosphane (**3**) as the preferred ligand.[14] This was effective for alkoxycarbonylation of chlorobenzene at ca. 145 °C and 1 bar of CO, but required a 4-fold excess of phosphane ligand and the addition of excess base and molecular sieve.

Some moderation of the conditions for the reaction of aryl chlorides was achieved by complexation of the aryl halide to a $Cr(CO)_3$ moiety, but for good yields reaction conditions were still quite harsh (>130 °C and >15 bar of CO).[15,16] The addition of sodium iodide was also reported to allow milder conditions, where 5 psig of CO and only 115 °C provided good yields for activated substrates (i.e., those having, additionally, electron-withdrawing substituents) but incomplete reaction in other cases.[17] While most studies have concentrated on bidentate ligands, Beller showed that the monodentate ligand di-1-adamantyl-*n*-butylphosphane (**1**) could be effective for the alkoxycarbonylation of aryl and heteroaryl bromides.[18] However, this ligand does not activate aryl chlorides for carbonylation.

Further improvement in catalyst performance was achieved by the use of bis(dicyclohexylphosphanyl)propane (dcpp) as ligand in conjunction with $Pd(OAc)_2$.[19] This catalyst provides good reactivity for the formation of benzoate esters under balloon pressure of CO and at ca. 100 °C.

Aryl halides are widely available as substrates, due to their value in coupling processes, but the ability to react their corresponding alcohols is also desirable. However, to be used in this reaction alcohols must first be converted to a more reactive derivative such as a sulfonate. The most reactive of the common derivatives is triflate, which undergoes carbonylation with activity on a par with aryl iodides. Thus, numerous examples of carbonylation of triflate derivatives have been reported.[20−24] Reactions of the cheaper and more readily crystallized sulfonates such as mesylate and tosylate have proved more difficult to achieve. However, some progress has been made recently. In 2006, Cai et al. published the use of a Josiphos analogue (**4**) with $Pd(OAc)_2$ to react *p*-fluorobenzenesulfonates

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Table 1. Methoxycarbonylation of Phenyl Tosylate

cat.	cat. loading (mol %)	temp (°C)	pressure CO (bar)	conversn (%)[a]	yield (%)
$PdCl_2$(dcpp)	2	140	0.5	100	88[b]
$PdBr_2$(dcpp)	2	100	0.5	66	42[b]
PdI_2(dcpp)	2	100	0.5	70	58[c]
$Pd(OAc)_2$(dcpp)	2	100	0.5	96	96
$PdCl_2$(d^ippp)	2	120	0.5	100	69[d]
$PdBr_2$(d^ippp)	2	120	0.5	100	91[e]
$PdCl_2$(d^ibpp)	2	120	0.5	100	53[f]
$PdBr_2$(dibpp)	2	120	0.5	100	59[g]

[a] Results reported as GC-MS normalized area. [b] 11% anisole. [c] 2% anisole. [d] 25% anisole. [e] 7% anisole. [f] 37% anisole. [g] 36% anisole.

and tosylates.[25] While there was little reactivity for conventional catalysts (some 100 compounds were studied), the preferred ligand gave 96% conversion when used at 4 mol % loading, 6 bar of pressure, and 135 °C for *p*-tolyl *p*-fluorobenzenesulfonate. This performance was bettered by results reported by Buchwald in 2008 for tosylates and mesylates.[26] Using dcpp and Pd $(OAc)_2$, he was able to react aryl tosylates at 100 °C with atmospheric pressure CO. Typically conversion was greater than 90% in 15 h. Thus, tosylate derivatives now are also convenient substrates for palladium-catalyzed carbonylation.

While there is little or no discrimination between catalysts differing in the choice of anionic ligands in reactions of aryl halides because of the large excess of halide provided by the substrate, the same is not true for the tosylate. In this case the only halide in the system is derived from the catalyst. Thus, one might expect to see differences among PdX_2L_2 species (X = Cl, Br, I, OAc; L = bidentate phosphane) in reactions of aryl sulfonates. This is indeed the case, as shown in Table 1 for the methoxycarbonylation of phenyl tosylate.

Examples of alkoxycarbonylation yielding acids or esters for a selection of aryl, vinyl, and heterocyclic halides and sulfonates are shown in Table 2. It can be noted that carbonylation activity of aryl halides is only slightly affected by electronic effects from additional substituents (affecting primarily the initial oxidative addition but also having an effect on the carbonyl insertion step),[27] but steric hindrance can have a profound influence on reaction rate, as discussed below with other aspects of the mechanism.

Aminocarbonylation

Improvement in the preparation of amides has been identified[2] as one of the most sought-after goals in pharmaceutical chemistry, and aminocarbonylation is potentially a very valuable and simple means of achieving this aim. This variant of the carbonylation reaction where an amine is chosen as the nucleophile has received less attention than alkoxycarbonylation, but the two reactions can often be conducted under very similar conditions. Heck reported the use of 1 atm of CO at 100 °C with $PdX_2(PPh_3)_2$ (X = Br, I) as a suitable catalyst.[4] These conditions have proved satisfactory for the reaction of aryl bromides and iodides, but until recently methods for aryl chlorides involved harsher conditions. Perry reported that the addition of iodide as a promoter assists the reaction of electron-deficient aryl chlorides, but this was not effective for electron-rich substrates.[28] The use of the dippp ligand by Milstein[9] and Sen[29] allowed reactions to be carried out at 150 and 175 °C, respectively. Work published by Buchwald illustrates an interesting way to circumvent this problem by first forming the phenyl ester in an alkoxycarbonylation reaction.[19] Excess phenoxide acts as a catalyst for a subsequent transamination reaction, generating the amide. Using dcpp ligand (as the tetrafluoroboric acid adduct) with atmospheric pressure CO, the temperature can be reduced to ca. 100 °C while maintaining a satisfactory rate. In the absence of phenoxide, the complex $[PdCl_2(dcpp)]$ reacts with the electron-deficient aryl chloride 4-chloroacetophenone at 120 °C and 5 bar of CO to give 100% GC yield, and chlorobenzene gives a slower but clean reaction with 76% GC yield at 140 °C and 5 bar of CO (see Table 3).

While the preparation of primary amides by aminocarbonylation is highly desirable, there has been a reluctance to conduct reactions requiring the handling of two very toxic gases, CO and NH_3. As an alternative, a number of reagents capable of acting as ammonia synthons have been described. Beller et al. noted the formation of dimethylamide byproduct in reactions carried out in dimethylformamide as solvent. They reasoned that similar reactions with formamide would yield the primary amines. This was found to be the case when reactions were carried out with aryl iodides or bromides at 120 °C under 5 bar of CO.[30] Given the low nucleophilicity of formamide, they proposed that the acyl group was transferred to formamide via an exchange involving the organic base, a suggestion that was supported by analysis of reaction solutions at intermediate points in the reaction. Alternative sources of ammonia that have been investigated are hexamethyldisilazane[31] and hydroxylamine.[32] A further alternative of providing the nitrogen from a Ti−N complex formed using N_2 was described by Mori.[33]

Our work with inorganic bases for both alkoxy- and aminocarbonylation encouraged us to try reactions using simple ammonium salts such as ammonium chloride. We were pleased to note that these reactions proceeded readily in good yield. Despite concerns regarding the low nucleophilicity of ammonia[34] and poor yields reported for ammonium acetate or aqueous ammonia,[32] the reactions gave high yields with only 1.1 equiv of NH_4Cl. In fact, the use of additional ammonium salt can prove detrimental due to inhibition of the reaction. Results are reported in Table 4.

It should be noted that while there is evident high reactivity for aryl mesylates and aryl tosylates (as indicated by complete reaction of the substrate), yields of the primary amide are low due to side reactions with as yet unidentified products. A significant amount of phenol is found, indicating cleavage of the O−S bond instead of the aryl O−C bond, interestingly generating conditions very similar to those achieved by Buchwald with the use of NaOPh as an additive.[19] Reaction of sterically inhibited 2-bromo-*m*-xylene gives complete conversion under slightly harsher conditions (125 °C, 1 bar of CO, 24 h) with PdX_2(dcpp) (X = Cl, OAc) but there is a significant yield of dimethylbenzoic acid as a second product, presumably through reaction with bicarbonate formed by neutralization of the ammonium salt. In these cases, further work is required to identify conditions for clean conversion to the desired amide.

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Table 2. Examples of Alkoxycarbonylation

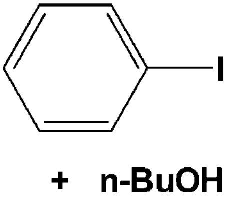
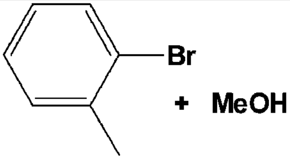
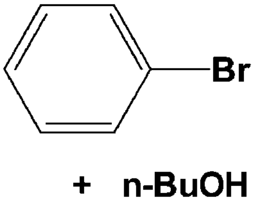
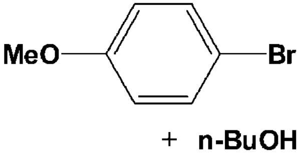
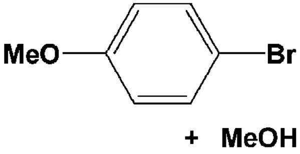
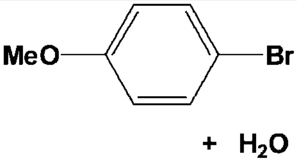
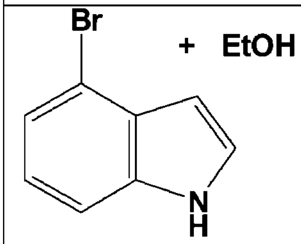
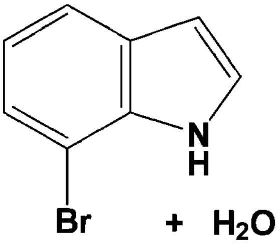
Substrate and reactant	Catalyst	Catalyst loading (mol % Pd)	Temp. (°C)	CO pressure (bar)	Reaction time (hours)	Yield (%)[a]	Ref.
	$PdI(Ph)(PPh_3)_2$	1.5	100	0[c]	30	96	3
	$PdCl_2$(dppp)	2	100	5	24	100	113
	$PdBr(Ph)(PPh_3)_2$	1.5	100	1	24	78	3
	$Pd(OAc)_2$ + **1**	0.5	115	5	16	97	18
	$PdCl_2$(BINAP)	3	100	3.5	16	96	70
	$Pd(OAc)_2$ + **1**	0.5	115	5	16	89	18
	$PdCl_2(PhCN)_2$ – dppf	1	130	25	20	98[b]	72
	$PdCl_2(PhCN)_2$ + dppf	1	130	25	20	67[b]	72

Table 2. Continued

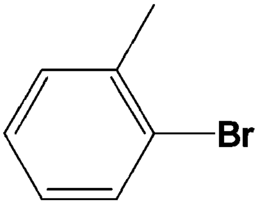
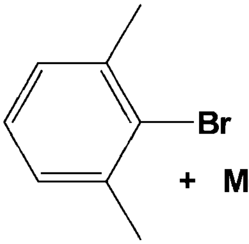
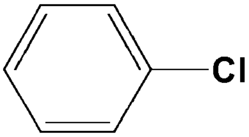
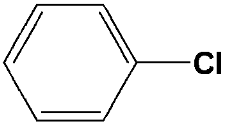
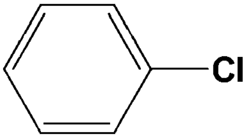
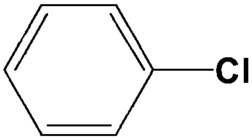
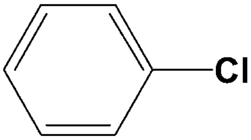
Substrate and reactant	Catalyst	Catalyst loading (mol % Pd)	Temp. (°C)	CO pressure (bar)	Reaction time (hours)	Yield (%)[a]	Ref.
 **+ MeOH**	$PdCl_2$(dcpp)	2	100	5	24	100	113
 **+ MeOH**	$PdCl_2$(dcpp)	2	130	2	24	86	113
 **+ n-BuOH**	Pd(d^{i}ppp)$_2$	1	150	5	20	100 (89^b)	9
 **+ n-BuOH**	$PdCl_2(PhCN)_2$ + **3**	0.5	145	3	16	99	14
 **+ EtOH**	$PdCl_2$(dcpp)	2	100	5	24	80	113
 **+ H_2O**	$PdCl_2(Pcy_3)_2$	0.03	180	5	2.5	97^b	13
 **+ H_2O**	$PdCl_2(PhCN)_2$ + **3**	0.5	145	1	16	84^b	14

Table 2. Continued

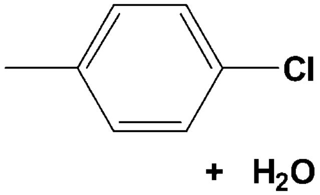
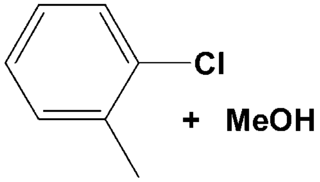
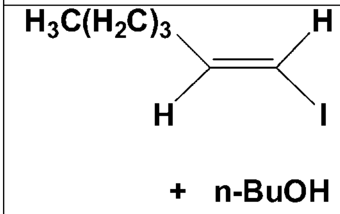
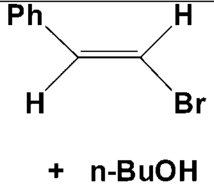
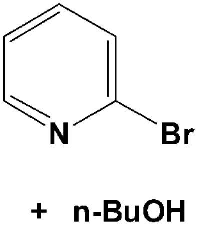
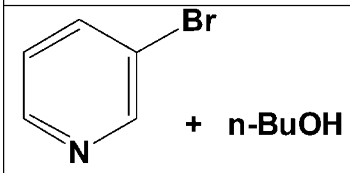
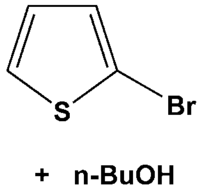
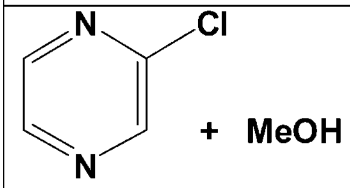
Substrate and reactant	Catalyst	Catalyst loading (mol % Pd)	Temp. (°C)	CO pressure (bar)	Reaction time (hours)	Yield (%)[a]	Ref.
	$Pd(d^tppp)_2$	1	150	5	20	79[b]	9
	$PdCl_2(d^ibpp)$	2	140	5	24	8	113
	$PdI_2(PPh_3)_2$	1.5	100	0[c]	2	83[b]	3
	$PdBr_2(PPh_3)_2$	1.5	100	0[c]	8	80[b]	3
	$Pd(OAc)_2$ + **1**	0.5	115	5	16	99	18
	$Pd(OAc)_2$ + **1**	0.5	115	5	16	91	18
	$Pd(OAc)_2$ + **1**	0.5	115	5	16	52	18
	$Pd(OAc)_2$ + $2PPh_3$	1	120	40	16	87	69

Table 2. Continued

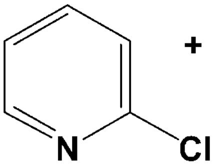
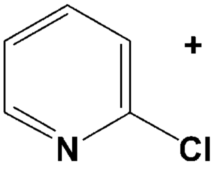
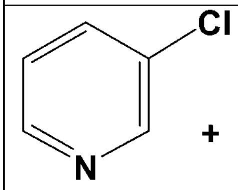
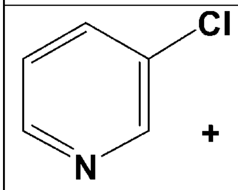
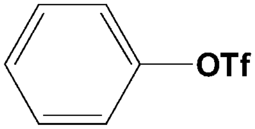
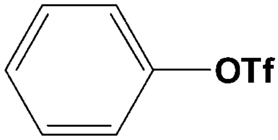
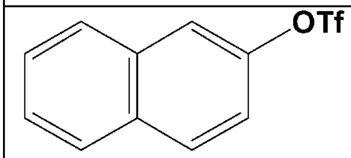
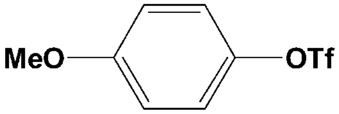
Substrate and reactant	Catalyst	Catalyst loading (mol % Pd)	Temp. (°C)	CO pressure (bar)	Reaction time (hours)	Yield (%)[a]	Ref.
 + MeOH	Pd(dba)$_2$ + 2PPh$_3$	2	150	40	16	79[b]	69
 + MeOH	PdCl$_2$(BINAP)	1	100	3.5	5	99	70
 + MeOH	Pd(dba)$_2$ + 2PPh$_3$	2	150	40	16	0	69
 + MeOH	PdCl$_2$(BINAP)	1	100	3.5	24	0	70
 + MeOH	PdCl$_2$(dppp)	2	80	0.5	24	72	114
 + MeOH	PdCl$_2$(dcpp)	2	80	0.5	24	35	114
 + MeOH	Pd(OAc)$_2$ + 2PPh$_3$	3	60	0[c]	2	78[b]	20
 + MeOH	Pd(OAc)$_2$(dppp)	3	70	0[c]	1	84	22

Table 2. Continued

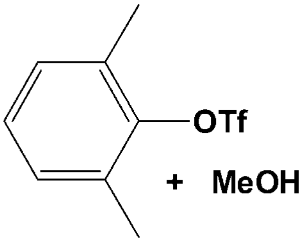
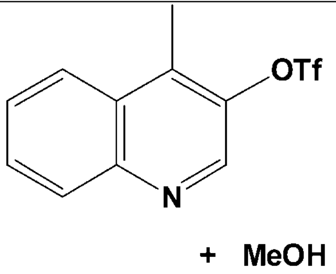
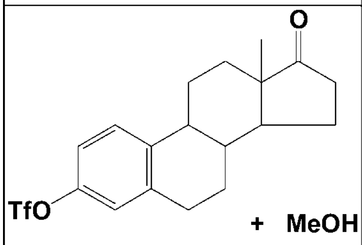
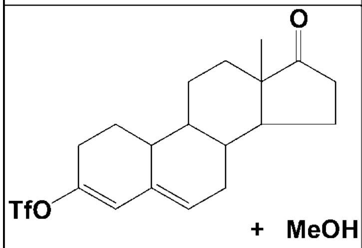
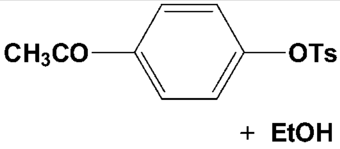
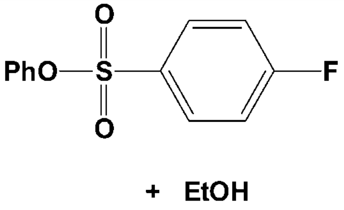
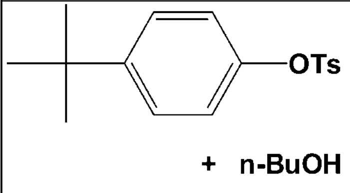
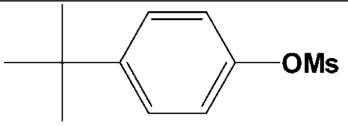
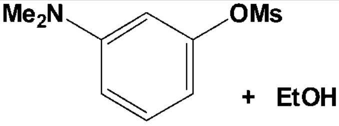
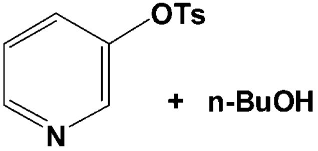
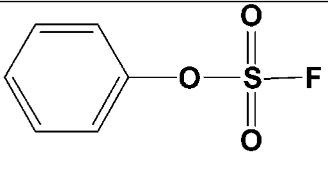
Substrate and reactant	Catalyst	Catalyst loading (mol % Pd)	Temp. (°C)	CO pressure (bar)	Reaction time (hours)	Yield (%)[a]	Ref.
	$Pd(OAc)_2(dppp)$	3	70	0[c]	2	87	22
	$Pd(OAc)_2$ + dppf	1.5	60	0[c]	1	70[b]	21
	$Pd(OAc)_2$ + $2PPh_3$	3	60	0[c]	2	81[b]	21
	$Pd(OAc)_2$ + $2PPh_3$	3	25	0[c]	3	83[b]	20
	$PdCl_2$ + dppp	4	150	10	3	74[b]	111
	$Pd(OAc)_2$ + **4**	4	135	6	20	96[b]	25
	$Pd(OAc)_2$ + dcpp.$2HBF_4$	2	100	0[c]	15	99	26

Table 2. Continued

Substrate and reactant	Catalyst	Catalyst loading (mol % Pd)	Temp. (°C)	CO pressure (bar)	Reaction time (hours)	Yield (%)[a]	Ref.
 + n-BuOH	$Pd(OAc)_2$ + dcpp.2HBF$_4$	2	100	0[c]	15	>99	26
	$Pd(OAc)_2$ + dcpp.2HBF$_4$	4	80	0[c]	20	86[b]	26
	$Pd(OAc)_2$ + dcpp.2HBF$_4$	2	90	0[c]	15	82[b]	26
 + MeOH	$Pd(OAc)_2$ + dppp	3	60	0[c]	2	88[b]	112

[a] GC yield unless indicated. In some cases low values represent incomplete conversion with high selectivity; see the original reference. [b] Isolated yield. [c] Atmospheric pressure.

This approach can also be conveniently applied to the preparation of dimethylamides as an alternative to using dimethylamine solution.

Reductive Carbonylation

Of these carbonylation reactions, the one with perhaps the greatest potential is the formation of aldehydes, due to the wide range of derivatives that can be obtained by their further conversion. However, the conditions established by Heck were not readily applicable to industrial operation, since they involved high pressure (greater than 80 bar of 1/1 CO/H_2).[5] The other conditions, a temperature of 80−150 °C and $PdX_2(PPh_3)_2$ (X = Cl, Br, I) as catalyst at ca. 1% loading, with aromatic hydrocarbon as solvent and tertiary amine as base, were all acceptable for large-scale implementation; therefore, the reaction has since attracted interest with the aim of overcoming the pressure limitation. Since palladium reacts readily with carbon monoxide at low pressure, it was evident that the key change required was to provide a more effective hydride donor. This was demonstrated by the work of Stille using Bu_3SnH.[35−37] He reported the conversion of aryl iodides, bromides, and triflates to aldehydes under mild conditions: 1−3 bar of CO and 50 °C with $Pd(PPh_3)_4$ as catalyst.[37] However, direct reduction of the aryl halide to the arene often proved to be an inconvenient side reaction, requiring control by slow addition of the tin reagent and an increase in the CO pressure. He noted that electron-donating or -withdrawing substituents on the aryl halide had no effect on the reaction, while steric effects were more significant. Product contamination with tin residues is often an issue for applications in pharmaceutical synthesis; therefore, other investigators continued to seek alternative hydride sources. Pri-Bar and Buchman demonstrated that silanes were suitable hydride donors with reactivity under conditions similar to those for the stannanes (3 mol % of $Pd(PPh_3)_4$ as catalyst, 3 bar of CO, 80−110 °C).[38] Their preferred reagent was polymeric material: poly(methylhydrosiloxane) (PMHS). While this reagent is versatile and cheap, its tendency to form a gel during reactions has restricted its widespread application. Hidai studied monomeric silanes such as Et_3SiH.[39] This was in conjunction with bimetallic catalyst systems based on Pd/Ru and Pd/Co. In an effort to optimize the reaction conditions, Kotsuki[40] compared Et_3SiH and Oct_3SiH, finding that Et_3SiH was more reactive and therefore, in some cases, prone to the formation of the arene as a major byproduct. As in the work of Stille, they found it necessary to control the addition of silane during the course of the reaction in order to maximize the yield.

Given the multitude of factors influencing this reaction, parallel screening techniques are ideally suited to optimization of the conditions. We have reported the results of such a study,[41] adopting the conditions exemplified by Kotsuki but with a single

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(35) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7175.

(36) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.

(37) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452.

(38) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1984**, *49*, 4009.

(39) Misumi, Y.; Ishii, Y.; Hidai, M. *Organometallics* **1995**, *14*, 1770.

(40) Kotsuki, H.; Datta, P. K.; Suenaga, H. *Synthesis* **1996**, *94*, 470.

(41) Ashfield, L.; Barnard, C. F. J. *Org. Process Res. Dev.* **2007**, *11*, 39.

Table 3. Examples of Aminocarbonylation

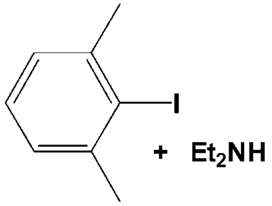
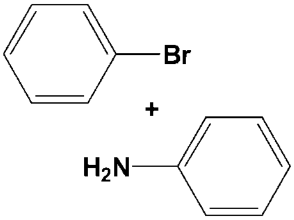
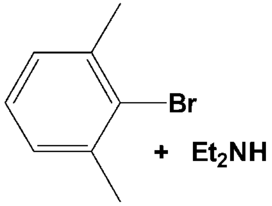
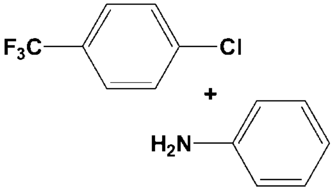
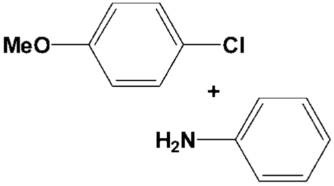
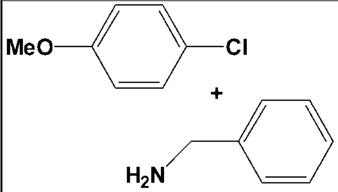
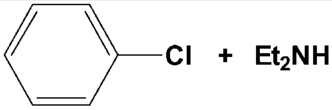
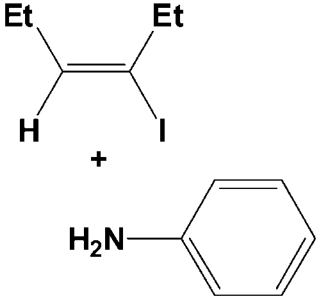
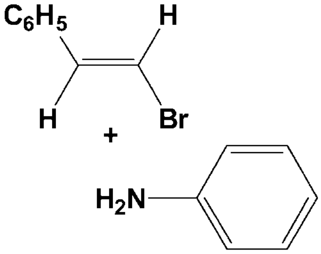
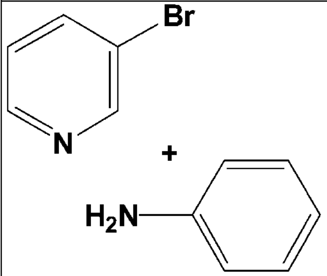
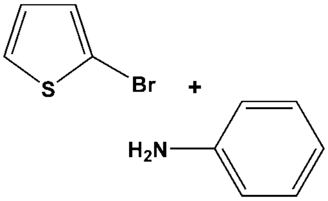
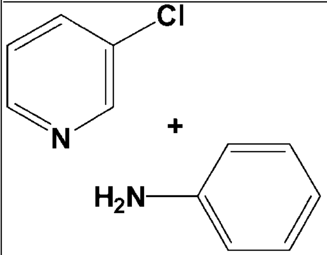
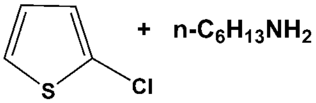
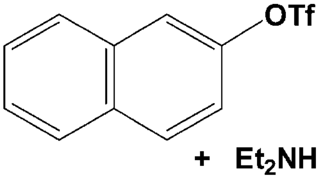
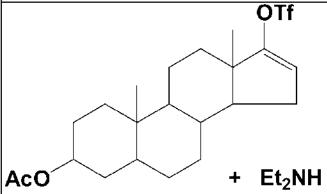
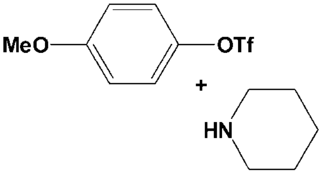
Substrate and reactant	Catalyst	Catalyst loading (mol % Pd)	Temp. (°C)	CO pressure (bar)	Reaction time (hours)	Yield (%)[a]	Ref.
	$PdCl_2$(dppp)	2	100	3	24	64	113
	$PdBr(Ph)(PPh_3)_2$	1.5	100	0[c]	3.5	94 [b]	4
	$PdCl_2$(dcpp)	2	140	5	24	71	113
	$PdCl_2(PPh_3)_2$ + dppe + NaI	3	115	0.3	24	78[b]	28
	$PdCl_2(PPh_3)_2$ + dppe + NaI	3	115	0.3	24	0	28
	$Pd(OAc)_2$ + dcpp.2HBF_4 + NaOPh	2	110	0[c]	15	98[b]	19
	$PdCl_2$(dcpp)	2	140	5	24	76	113
	$PdI_2(PPh_3)_2$	1.5	100	0[c]	1.5	71[b]	4

Table 3. Continued

Substrate and reactant	Catalyst	Catalyst loading (mol % Pd)	Temp. (°C)	CO pressure (bar)	Reaction time (hours)	Yield (%)[a]	Ref.
	$PdBr_2(PPh_3)_2$	1.5	60	0[c]	3	81[b]	4
	$PdBr_2(PPh_3)_2$	1.5	100	0[c]	5.5	65[b]	4
	$PdBr_2(PPh_3)_2$	1.5	100	0[c]	2	63[b]	4
	$Pd(OAc)_2$ + dcpp.2HBF$_4$ + NaOPh	2	100	0[c]	15	92[b]	19
	$Pd(OAc)_2$ + dcpp.2HBF$_4$ + NaOPh	2	100	0[c]	15	99[b]	19
	$Pd(OAc)_2$ + 2PPh$_3$	3	60	0[c]	2	78[b]	21
	$Pd(OAc)_2$ + 2PPh$_3$	3	25	0[c]	1	91[b]	20
	$Pd(OAc)_2$ + dppf	3	80	0[c]	1	59[b]	21

[a] GC yield unless indicated. In some cases low values represent incomplete conversion with high selectivity; see the original reference. [b] Isolated yield. [c] Atmospheric pressure.

Table 4. Formation of Primary Amides

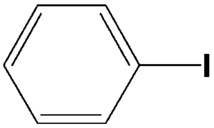
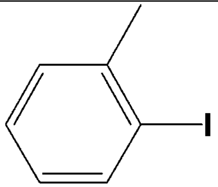
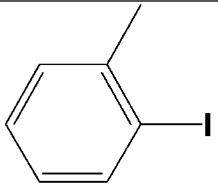
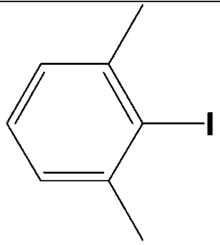
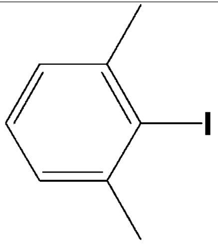
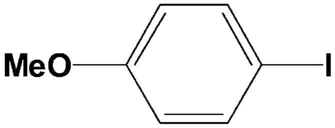
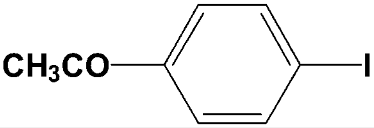
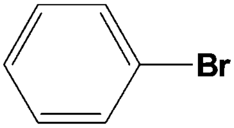
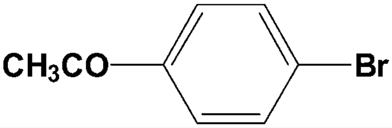
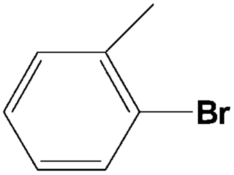
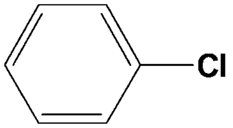
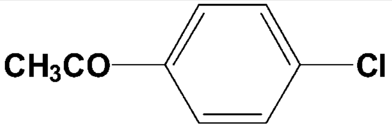
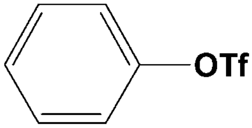
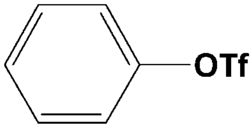
Substrate	Catalyst[a]	Temperature (°C)	CO pressure (bar)	Reaction time (hours)	Yield (%)[b]
	PdCl$_2$(dppf)	75	3	24	97
	PdCl$_2$(dppf)	75	3	24	97
	PdCl$_2$(dcpp)	80	1	24	12[c]
	PdCl$_2$(dppf)	75	3	24	88
	PdCl$_2$(BINAP)	80	1	24	89
	PdCl$_2$(dppf)	75	3	24	96
	PdCl$_2$(dppf)	75	3	24	99
	PdCl$_2$(dppp)	100	3	24	99
	PdCl$_2$(dppp)	100	3	24	100
	PdCl$_2$(dppf)	100	3	24	42

Table 4. Continued

Substrate	Catalyst[a]	Temperature (°C)	CO pressure (bar)	Reaction time (hours)	Yield (%)[b]
	$PdCl_2$(dcpp)	120	1	24	95
	$Pd(OAc)_2$(dcpp)	100	1	24	98
	$PdCl_2$(dppp)	80	3	6	100
	$PdCl_2$(dcpp)	80	3	6	9[d]

[a] Conditions: catalyst loading 2 mol %, reaction carried out using 1 mmol of substrate, 1.1 mmol of NH_4Cl, and 2 mmol of K_2CO_3 in 1-methyl-2-pyrrolidinone (5 mL). [b] Yield reported as GC-MS normalized peak area. [c] Conversion 18%. [d] Conversion 9%.

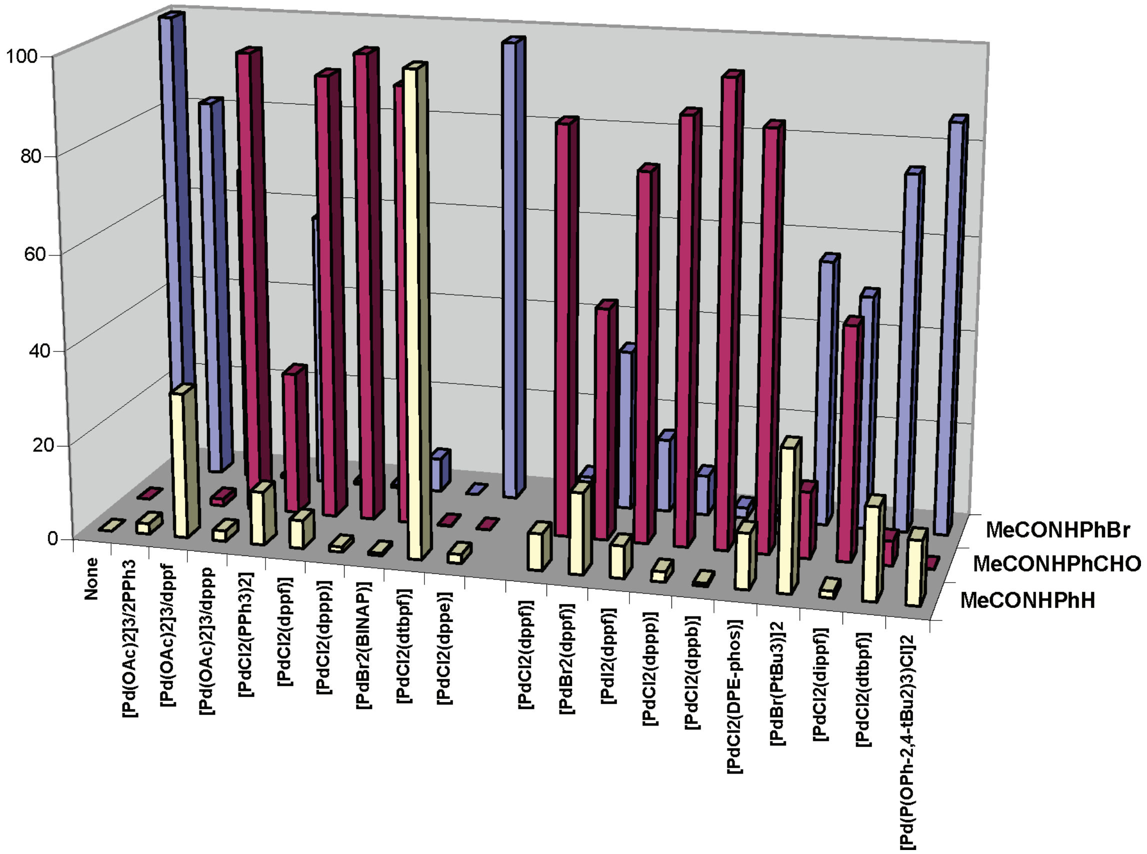


Figure 2. Reductive carbonylation of 4-bromoacetanilide with a variety of catalysts (conditions: 90 °C; 6 bar of CO; Et_3SiH; Et_3N; DMF).

addition of silane at the beginning of the reaction. Using 4-bromoacetanilide as substrate, the effect of different catalyst precursors was studied as shown in Figure 2. While good activity was seen for both mono- and bidentate ligands, the bidentate ligands dppp, dppf, and BINAP proved the best choice, as previously found in many studies. Catalyst precursors can be formed in situ but it is generally more convenient to use the complexes, where the ligands are stabilized through complexation. Of a range of silanes (Et_3SiH, Oct_3SiH, $^iPr_3SiH$, Ph_3SiH, $(EtO)_3SiH$, and polymethylhydrosiloxane), only Et_3SiH and Oct_3SiH performed well. Of a selection of bases, sodium carbonate gave the best yield, with tertiary amines also performing well. Preferred solvents were polar aprotic media, such as DMF, NMP, DMSO, and MeCN. As noted above in the work of Stille, the electronic properties of substituents of the aryl halide have less effect than is seen in coupling reactions, while steric effects are more pronounced. Examples of both aryl iodides and bromides are given in Table 5. It can be seen that while one ortho substituent slightly reduces the reactivity, the presence of a second ortho substituent has a marked effect. Possible reasons for this will be discussed below in relation to the proposed mechanism.

The tolerance for a wide variety of functional groups has been of considerable benefit in palladium-catalyzed coupling chemistry, and this also applies in carbonylation reactions. This can be illustrated by a study of the carbonylation of 4-bromostyrene. Varying the concentration of the reactant in addition to changing the catalyst shows that it is possible to obtain >90% conversion to the desired 4-vinylbenzaldehyde, with the major byproduct arising from reduction of the vinyl group (Table 6). One functional group that is often a cause of complications in carbonylation is the nitro group. With palladium catalysis this is readily reduced by carbon monoxide in a reaction that may proceed via a nitrene intermediate and/or isocyanate.[1] With an appropriately placed alkene substituent, this can form indoles (see below), but in the presence of aryl bromides or iodides various products may be formed. While most aryl iodide and bromide substituents are more reactive for carbonylation than nitro groups, allowing reasonable yields of nitro-substituted ester and amide products to be obtained,[4,42,43] under reductive conditions the yields are generally poor.[37,41] Even when using a CO/H_2 gas mixture (see below), 4-nitrobromobenzene proved highly resistant to formation of the aldehyde.[44,45]

Selectivity between the different halides is also possible. Under most conditions aryl chlorides are inert, so that their presence in the molecule does not present a challenge, but with both aryl iodide and bromide present it is also possible to selectively react the former with little conversion of the latter. An increase of ca. 20−30 °C is required to achieve the same rate of conversion for an aryl bromide compared to the corresponding aryl iodide, and so, for example, 4-bromoiodobenzene is converted to 74% 4-bromobenzaldehyde under 3 bar of CO at 60 °C for 18 h, using $PdCl_2$(dppp) in DMF with Na_2CO_3 as base with 20% of the substrate unreacted when the reaction was stopped (i.e., 92% selectivity).[41]

Other researchers have returned to the original conditions described by Heck, recognizing that hydrogen provides a low cost source of hydride. Beller et al. discovered that the reaction could be run at moderate pressures (ca. 5 bar) if the very bulky monodentate phosphane ligand di-1-adamantyl-*n*-butylphosphane (**1**) was used.[44] As with all the other systems described here, there is good reactivity for aryl iodides and aryl bromides, but this system is not effective for the conversion of aryl chlorides. Results to date have shown that the activity under these conditions is highly specific to this ligand: for example, for 4-bromoanisole the bidentate ligand dppp is reported to yield only 1% product in comparison with 92% for (**1**) under unoptimized conditions. There is no clear direction as to how the activity of (**1**) for aryl chlorides could be improved.

Other systems that have been investigated include the use of formate as the hydride source. Pri-Bar and Buchman used this reagent with 3 mol % of $Pd(PPh_3)_4$ as catalyst at 125 °C and 50 psi of CO for the conversion of bromobenzenes to the corresponding aldehydes.[38,46] Milstein reacted chlorobenzene in the presence of formate with $Pd(d^{i}ppp)_2$ at 150 °C and 5 bar to yield 95% benzaldehyde.[10] Other groups have attempted to carry out the reaction using solid reagents as sources of CO, an approach particularly directed toward laboratories where there are safety restrictions on the use of CO gas. Work with $Mo(CO)_6$ has been described by Larhed in a series of papers on the use of microwaves to enhance this chemistry.[47−51] While the reaction times are dramatically shortened by the use of microwaves, the temperatures reached are higher than required by normal procedures. Conveniently, it was found that aminocarbonylation reactions could be carried out in water with only minor amounts of benzoic acid byproduct formed.[52,53] Cacchi has reported that acetic formic anhydride (either added directly or formed in situ from acetic anhydride and formate) can be used in both reductive[54] and alkoxycarbonylation[55] reactions. The involvement of mixed anhydride intermediates was previously proposed by Pri-Bar.[46]

Double-Carbonylation Reactions

The high yields established for amino- and alkoxycarbonylation might give the impression that alternative products of this reaction do not arise. However, under the appropriate conditions a double-carbonylation reaction occurs, leading to keto amides, acids, and esters. The reactions may be carried out under conditions very similar to those for the single carbonylation, but generally under a significantly higher pressure of CO. (Fortunately, most single-carbonylation reactions can be carried out at CO pressures only marginally above atmospheric pressure, thus allowing high selectivity to be achieved.) The distribution of products has been studied by several researchers, but a recent example is the work of Buchwald and Jensen.[56] Using a microreactor to carry out a study of the effect of temperature and CO pressure on the aminocarbonylation of 3-iodoanisole and 4-bromobenzonitrile using $Pd(OAc)_2$ and Xantphos as catalyst, they showed that the ratio of single- to double-carbonylation products decreases with CO pressure ranging from 5 to 15 bar and increases with temperature for 100−150 °C. However, in this study the highest yield of the keto amide was modest, typically 60−70%.

The first reports of this reaction for keto amide products appeared in 1982[57−59] and were soon followed by more detailed mechanistic studies to ascertain whether the product was formed from the same catalytic pathway as the single-carbonylation product. It was shown through the use of ^{13}CO and by the

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Table 5. Examples of Reductive Carbonylation

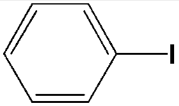
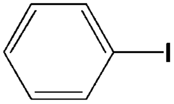
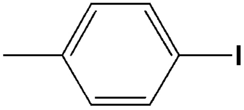
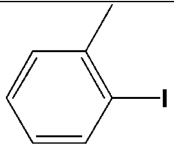
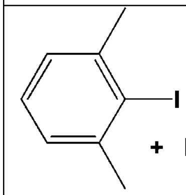
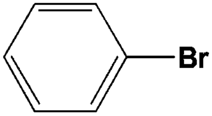
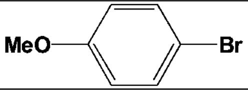
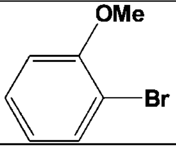
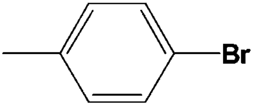
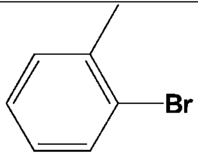
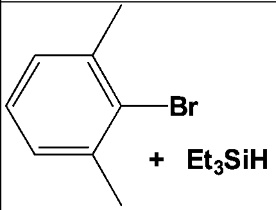
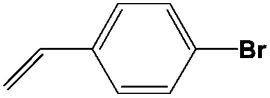
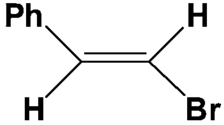
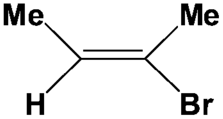
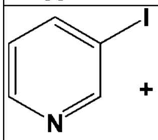
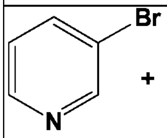
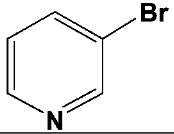
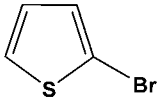
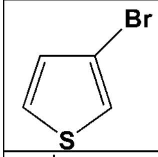
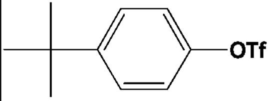
Substrate and reactant	Catalyst	Catalyst loading (mol % Pd)	Temp. (°C)	Pressure (CO or CO/H_2) (bar)	Reaction time (hours)	Yield (%)[a]	Ref.
	$PdI_2(PPh_3)_2$	3	125	100 (1:1 CO:H_2)	9	95	5
 + n-Bu_3SnH	$Pd(PPh_3)_4$	4	50	0[b]	2-4	95	35
 + Et_3SiH	$PdCl_2$(dppp)	2.5	60	3	18	96	41
 + Et_3SiH	$PdCl_2$(dppp)	2.5	60	3	18	97	41
 + Et_3SiH	$PdCl_2$(dppp)	2	100	3	24	30[c]	113
	$PdBr_2(PPh_3)_2$	3	125	90 (1:1 CO:H_2)	24	94	5
	$Pd(OAc)_2$ + **1**	0.33	100	5 (1:1 CO:H_2)	16	96	44
	$Pd(OAc)_2$ + **1**	0.33	100	5 (1:1 CO:H_2)	16	63	44
 + Et_3SiH	$PdCl_2$(dppp)	2.5	90	3	18	92	41
 + Et_3SiH	$PdCl_2$(dppp)	2	100	3	18	82	113

Table 5. Continued

Substrate and reactant	Catalyst	Catalyst loading (mol % Pd)	Temp. (°C)	Pressure (CO or CO/H_2) (bar)	Reaction time (hours)	Yield (%)[a]	Ref.
	$PdCl_2$(dcpp)	2.5	140	3	18	14[d]	113
 + Et_3SiH	$PdCl_2$(dppf)	2	80	3	24	95	113
	$PdBr_2(PPh_3)_2$	3	80	95 (1:1 CO:H_2)	26	94	5
	$Pd(OAc)_2$ + **1**	0.5	100	7.5 (1:1 CO:H_2)	16	98	45
 + Et_3SiH	$PdCl_2$(dppp)	2.5	60	3	18	100	41
 + Et_3SiH	$PdCl_2$(dppp)	2.5	90	3	18	100	41
	$Pd(OAc)_2$ + **1**	0.33	100	5 (1:1 CO:H_2)	16	77	44
	$Pd(OAc)_2$ + **1**	0.25	100	5 (1:1 CO:H_2)	16	66	44
	$Pd(OAc)_2$ + **1**	0.33	100	5 (1:1 CO:H_2)	16	82	44
 + Oct_3SiH	$Pd(OAc)_2$ + dppp	2	70	0[b]	22	77[e]	40

[a] GC yield unless indicated. [b] Atmospheric pressure. [c] 70% *m*-xylene. [d] Isolated yield.

synthesis of the proposed intermediate complexes that there is no insertion into the palladium—acyl bond and that the double-carbonylation product is formed via an acyl carbamoyl intermediate and then subsequent reductive elimination to form the keto amide.[60−62] Yamamoto suggested that there may be significant changes in the mechanism between aryl iodide and bromide substrates and amino and alkoxy products due to a change in the rate-determining step (in some cases oxidative addition, in others nucleophilic attack on coordinated CO).[63,64] He proposed that the single- and double-aminocarbonylation

Table 6. Chemoselectivity of Reductive Carbonylation of 4-Bromostyrene[a]

cat.	bromoethylbenzene (%)	bromostyrene (%)	ethylbenzaldehyde (%)	vinylbenzaldehyde (%)
$PdCl_2$(dppf)	0.8	1.8	1.2	95.8
$PdCl_2$(dppp)	1.0	2.7	6.1	89.4
$PdCl_2$(dcpp)	3.7	65.8	2.1	26.3

[a] Values reported as GC-MS normalized area. Method A: 4-bromostyrene (1 mmol); $HSiEt_3$ (2 mmol); Na_2CO_3 (1 mmol); DMF (5 mL); 2 mol % catalyst; 3 bar of CO; 80 °C; 24 h. Adapted with permission from: Barnard, C. F. J. *Org. Process Res. Dev.* **2008**, *12*, 566.

products are formed via the aryl carbamoyl intermediate $PdAr(CONR_2)L_2$ rather than via $PdX(COAr)L_2$, while the single- and double-alkoxycarbonylation products are formed via the common intermediate $[PdI(COAr)L_2]$, with substitution of iodide by alkoxide prior to reductive elimination[64] rather than nucleophilic attack on the acyl ligand, as initially suggested by Heck.[3] This will be discussed in more detail below. The reaction was soon extended to α-keto acids[65] and esters.[66,67] A highly efficient ligand **4** (see Figure 1) for this reaction giving up to 10^5 turnovers and selectivities >90% was reported in 2003, although there were limitations on the range of nucleophiles/amines suitable for achieving this performance.[68]

Other Reactants

In addition to applications involving aryl, benzylic, and vinyl halides, carbonylation reactions have been widely applied to heteroaryl halides. The polarizing effect of the heteroatom can result in increased reactivity for heteroaryl chlorides compared with the aryl counterparts. For example, Takeuchi reported the formation of amides and esters from 2-chloropyrazine or 2-chloropyridine, while 3-chloropyridine was unreactive under the same conditions (20−40 bar of CO, 120 °C).[69] Similarly, Albaneze-Walker reported reactivity for 2-chloropyridines under milder conditions (50 psi of CO, 100 °C) using $PdCl_2$(BINAP) as catalyst, but again 3-chloropyridine was inert under those conditions.[70] Beller has reported on the carbonylation of many heteroaryl chlorides[71] and was able to show that carbonylation of unprotected bromoindoles could be achieved with a range of N and O nucleophiles.[72] Neither the presence of the acidic NH proton nor the free indole nitrogen interferes with the reaction.

A major advantage of palladium-catalyzed synthetic procedures is their compatibility with a wide range of subsidiary functional groups on the reactive partners. However, some functionalities stable for coupling reactions can prove reactive under carbonylation. This applies particularly to the nitro group. This group can react with carbon monoxide, transferring the oxygen atoms to form carbon dioxide in a series of steps. This can result in the formation of several products,[73,74] with synthetically the most useful reactions being the preparation of indoles, indazoles, and benzimidazoles.[75−83] The formation of heteroaryl compounds such as lactones and benzimidazoles has been carried out in a similar fashion using aryl halide and triflate precursors.[84−89]

The presence of sulfur nucleophiles is often detrimental to reactions catalyzed by late-transition-metal catalysts due to the formation of stable, catalytically inert compounds. Tables 2, 3, and 5 indicate good yields with thiophene derivatives, and Alper has reported that thiocarbonylation of aryl iodides can be carried out successfully using thiols in phosphonium salt ionic liquids.[90] Typical reaction conditions were 200 psi of CO at 100 °C with $Pd(OAc)_2/PPh_3$ as catalyst and Et_3N as base. Alkoxycarbonylation has also been studied in ionic liquid media employing a Pd benzothiazole carbene catalyst.[91]

The use of arylboronic acids to provide the nucleophile in Pd-catalyzed carbonylation was reported by Castanet, resulting in a convenient route to α-pyridyl ketones.[92] Careful choice of the catalyst and reaction conditions allows good selectivity to be obtained over the formation of the biaryl by direct coupling. Organoborates react with aryl bromides under carbonylation conditions to give esters.[93]

In addition to aryl halides and sulfonates a variety of other easily activated aryl compounds can be used as starting materials: e.g., iodoxyarenes[94] or diazonium compounds.[95]

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Reactions of Vinyl Arenes

The low reactivity of palladium complexes for hydroformylation when compared with rhodium compounds suggests that forcing conditions would be required for alkoxycarbonylation of vinyl arenes. This is indeed the case, as reported in a number of studies aimed at the asymmetric synthesis of esters. A recent review of this area by Godard describes many, often unsuccessful, attempts to achieve high regioselectivity for the branched product combined with good enantioselectivity.[96] The ready coordination of CO to palladium is expected to restrict the secondary interactions of the substrate with the metal that are required to deliver high enantioselectivity. Only one study has been reported where the reaction was found to proceed at low pressure and provide high regioselectivity and enantioselectivity.[97] As yet, this reaction has not been widely applied.

Mechanisms

Many mechanistic studies have been carried out on this series of related carbonylation reactions and yet still some uncertainty and disagreements remain regarding the later steps of the mechanism. Partly, this is because the several steps of the reaction offer numerous alternative pathways, whose relative rates vary in association with the following: (a) the choice of catalyst precursor (electronic and steric effects of ligands), (b) the base, affecting concentration of the nucleophilic anion and influencing reductive elimination of HX from Pd, (c) the substrate (choice of halide plus electronic and steric factors) and reactant, (d) the solvent (effectiveness of stabilization of charge separated transition states and charged intermediates), and (e) carbon monoxide pressure (leading to multiple binding of CO to Pd) and the presence of other potential ligands.

This makes it extremely difficult to extend the conclusions of study of one reaction to others, and in some cases apparently conflicting conclusions may be reached from the study of different substrates or catalysts.

A simple outline for the mechanism is shown in Figure 3 describing the main steps: (i) catalyst formation, (ii) oxidative addition, (iii) carbon monoxide binding, (iv) carbonyl insertion, (v) nucleophilic attack, and (vi) product release. An alternative to carbonyl insertion is nucleophilic attack on Pd−CO to form a carbamate or carboxylate ligand and then reductive elimination for product release. Each of these steps will now be discussed in more detail.

(i) Catalyst Formation. Many of the catalyst precursors recommended for carbonylation are Pd(II) species, which must first be reduced to active Pd(0) species. A similar situation arises for many of the catalysts described for coupling. This reaction is often influenced by the choice of base (assisting reduction) and the presence of added ligand. Catalysts formed in situ will often be prepared using ligand to metal ratios greater than 2, and even in reactions where the overall ratio is 2 or less dissociation in subsequent reaction steps generates free ligand. Furthermore, the 14-electron species believed to be the reactive intermediate for oxidative addition will also be in equilibrium with carbonyl species[98] and anionic species.[99] The formation of a number of carbonyl species (mono- and multinuclear) has been shown by the study of the reaction of $PdCl_2(PPh_3)_2$ with methanol and amines under CO in the absence of aryl halide,[98] and they lead to the formation of esters when iodobenzene is added.[100]

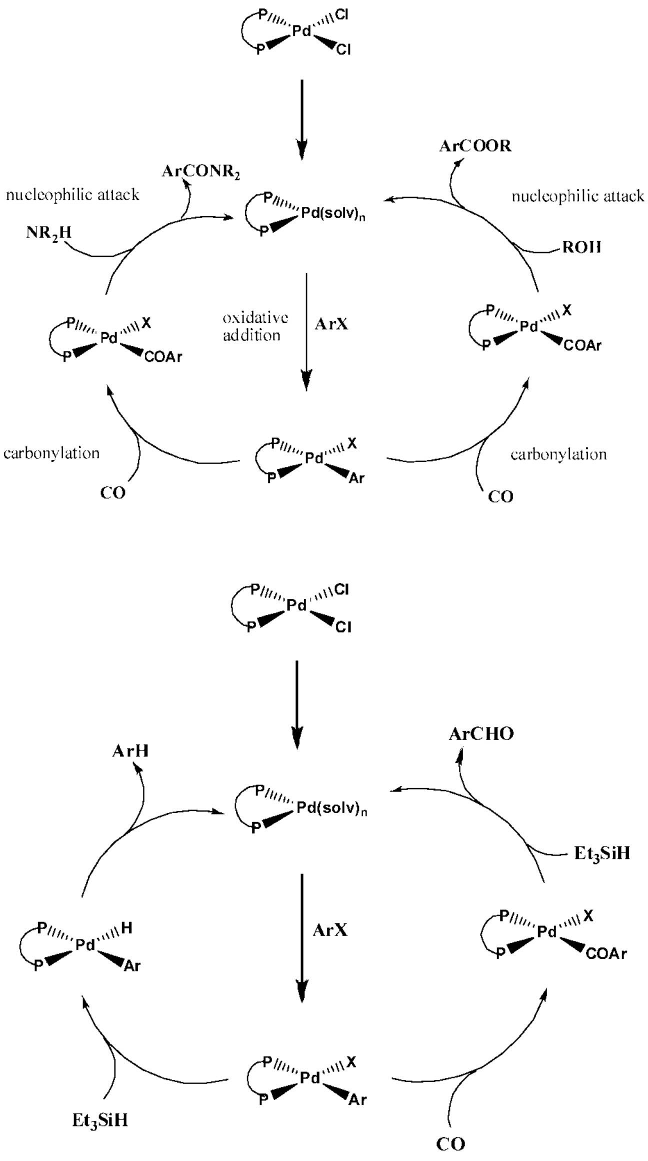

Figure 3. Simplified mechanisms for alkoxycarbonylation, aminocarbonylation, and reductive carbonylation via silane.

Carbonyl ligands reduce the electron density of the metal by back-donation, and so these species are generally not active for oxidative addition.[11] For the bidentate phosphane ligands the equilibria are more complex, as the second ligand gives rise to a tridentate structure, isolated and characterized by Milstein for $Pd(d^ippp)_2$, which is in equilibrium with a number of other forms. These various equilibria with anion, CO, and phosphane are illustrated in Figure 4. The availability of palladium to the catalytic cycle can be significantly diminished by these equilibria, especially under high pressures of CO, reducing reaction rates. Both steric and electronic factors influence the equilibria with additional ligands, thus initiating the complex interplay of factors that govern the preferred choice of catalyst for any particular reaction. Osborn found that a remarkably narrow range

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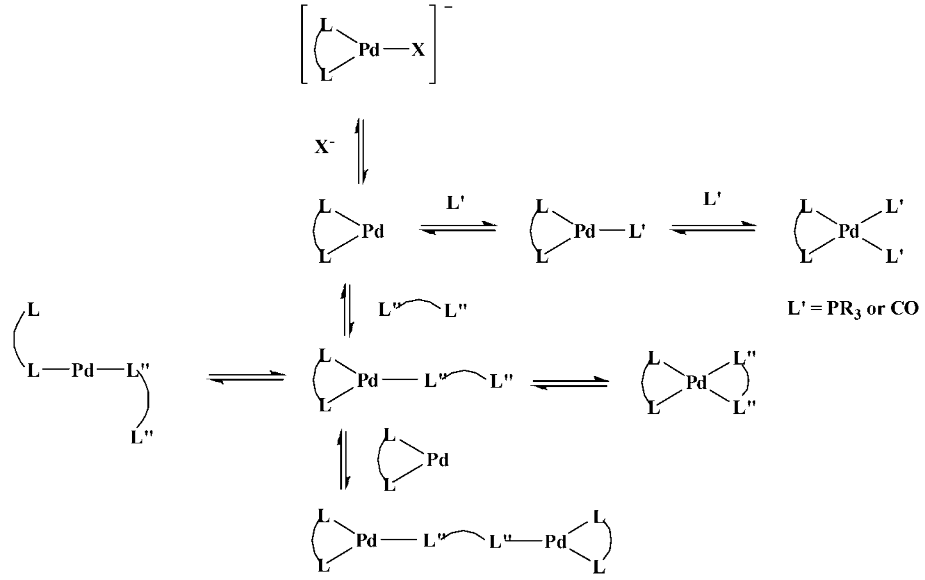

Figure 4. Precatalytic equilibria for PdL_2 systems.

for phosphane cone angle of 160−180° was necessary for good catalytic activity, with the reduction in the amounts of $Pd(PR_3)_n$ (n = 3, 4) being one feature involved in determining this range.[101] This correlates with the marked difference in carbonylation behavior often seen for cyclohexyl and *tert*-butyl phosphane derivatives, with the latter giving comparatively poor performance.

(ii) Oxidative Addition. The first step of the catalytic cycle is the oxidative addition of the aryl or vinyl compound to a palladium(0) species. This step is common to most palladium-catalyzed organic chemistry and, as a consequence of the interest in coupling chemistry, it has been thoroughly investigated, in both experimental and theoretical studies. Increases in electron density on palladium reduce the activation energy for the formation of the palladium(II) organometallic intermediate.[11,102−104] Thus, while aryl-substituted bisphosphanes are suitable ligands to promote the oxidative addition of aryl iodides and bromides, stronger electron donation from alkyl-substituted phosphanes is required to accelerate the oxidative addition of aryl chlorides. Osborn reported that a minimum pK_a value of 6.5 for the phosphane is necessary.[101] The oxidative addition step for chlorobenzene and other aryl chlorides was reported to be rate limiting by Milstein in his study of Pd(d^{i}ppp)$_2$ as catalyst.[9] Osborn also studied the oxidative addition of chlorobenzene to $Pd(OAc)_2(Pcy_3)_2$ and concluded that this would not be rate limiting in many cases.[101] In studies of C−C coupling mechanisms it has been shown that steric bulk significantly accelerates oxidative addition,[105] and this is another factor behind the limiting cone angle values observed by Osborn.

It is shown by the low conversion of aryl iodides and triflates (see Tables 2 and 4) with $PdCl_2$(dcpp) that when oxidative addition occurs readily and is not the rate-determining step, then $PdCl_2$(dppp) is a more effective catalyst. It is evident that the carbonylation steps are favored by less electron density on palladium; for example, carbonylation of $PdBr(Ph)(PPh_3)_2$ is 140-fold faster than that for $PdBr(Ph)(PEt_3)_2$.[27]

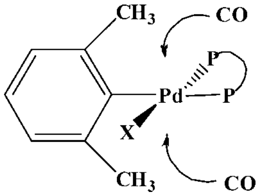

Figure 5. Steric influence on the binding of carbon monoxide. Reprinted with permission from: Barnard, C. F. J. *Org. Process Res. Dev.* **2008**, *12*, 566. Copyright 2008 American Chemical Society.

(iii) CO Binding. The next step in the mechanism is the introduction of carbonyl ligand into the coordination sphere. This occurs very rapidly for simple phenyl complexes,[27] but it is the interaction with carbon monoxide that accounts for the high sensitivity of these reactions to steric features of the substrate. The formation of xylene as a major product of attempts to carbonylate 2-bromo-*m*-xylene (for example, see Table 5) illustrates that oxidative addition to palladium is not the rate-limiting factor for this reaction; rather, it is the difficulty of coordinating CO to palladium. As shown in Figure 5, in the sterically constrained environment around palladium the aryl group will lie in the vertical plane. This brings the 2,6-dimethyl substituents into positions close to the axial binding sites of palladium. It is these sites that provide access for coordination of CO in the standard associative mechanism for ligand substitution. Thus, when one ortho substituent is present, there is only modest hindrance of the reaction, since the second axial site remains open. Once the second site is restricted, CO binding is strongly inhibited. Twisting of the aryl ligand away from the vertical plane will increase strain in the ligand plane, thus maintaining the high activation energy for this step. There are seven possible structures for the five-coordinate intermediate formed by CO binding. The carbonyl insertion reaction requires the cis location of the carbonyl and aryl ligand; thus, two structures are most likely for the intermediate (see Figure 6). The presence of at least two isomers is suggested by IR data.[27]

It is also possible that the reaction could proceed by an alternative route, as proposed by Yamamoto. He suggests that the carbonyl ligand is attacked by the nucleophile, forming a carbamate or carboxylate group, and the product then arises from reductive elimination of this ligand and the aryl group. As the

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Figure 6. Trigonal intermediates preceding carbonyl insertion.

reductive elimination also requires cis positioning of the carbamate/carboxylate and aryl group, the same structures are most likely for the trigonal intermediate. The equilibrium of the five-coordinate intermediate and corresponding four-coordinate species has been studied by Heck.[27] One ligand must be lost, and this is most likely one of the neutral phosphane donors rather than the halide. For bisphosphane ligands the equilibrium for this displacement will be affected by the stability of the chelate ring, and this accounts for the trend of reactivity of the bisphosphanes (C3 > C4 ≫ C2 bridge) observed by Milstein.[9]

(iv, v) Carbonyl Insertion or Nucleophilic Attack at CO. In his initial work on carbonylation, Heck proposed that carbonyl insertion would be the next step. The combination of the cis-related carbonyl and acyl groups leads to a vacant site, where binding of an additional neutral ligand stabilizes the acyl intermediate. This could be another carbonyl ligand or the return of a previously displaced phosphane. It is likely that the balance between these two possibilities is significantly affected by CO pressure, with coordination of the phosphane being dominant at low pressure. In most cases, the formation of this intermediate is essentially irreversible, as suggested by Heck[3] and demonstrated by Moser[106] for $PdBr(COPh)(PPh_3)_2$ and by Milstein[8] for $PdCl(COCH_2Ph)(PMe_3)_2$ using ^{13}CO. However, in the study of $[PdCl(COPh)(Pcy_3)_2]$ Osborn reported reversibility,[101] emphasizing again that changes in the electron donation and steric properties of the phosphane ligand can significantly alter the reactivity of the intermediates in this process.

The rate of the carbonyl insertion step will be strongly influenced by the strength of the Pd−carbonyl and Pd−aryl bonds. While an element of back-donation is involved in the bonding of both of these ligands, this is much more pronounced for the former. Electron-withdrawing substituents in the 4-position slightly decrease carbonylation rates compared with electron-donating groups, with the same trend being determined for the rates of aryl migration in the related complexes $PtR(X)CO(PR_3)$.[27] Increased electron density on palladium provided by the coordination of alkyl-substituted bisphosphanes results in increased back-donation to the carbonyl ligand and slowing of this step. Therefore, as noted above, in reactions where the oxidative addition occurs rapidly and is not rate determining (aryl iodides, triflates, and many aryl bromides) aryl-substituted bisphosphanes will often yield faster reactions than the corresponding alkyl analogues. The two possibilities of direct formation of the acyl complex from the five-coordinate intermediate $PdR(X)CO(PR_3)_2$ and indirect formation via $PdR(X)CO(PR_3)$ following dissociation of PR_3 have been considered by Heck, with rate constants favoring the indirect route, although this path is inhibited by excess phosphane.[27]

In support of the alternative pathway involving nucleophilic attack on the carbonyl ligand proposed by Yamamoto, he noted that more acidic alcohols give faster reaction rates, and competitive studies with EtOH and Et_2NH in the presence and absence of CO gave exclusively ester and keto amide products, respectively.[64] The low reactivity of $PdCl(CO_2Me)(PPh_3)_2$ with iodobenzene[107] was taken by Hidai and co-workers as evidence for the carbonyl insertion route.[98] Other evidence for the carbonyl insertion mechanism was obtained by Milstein from the study of $PdCl(CH_2Ph)(PMe_3)_2$.[8] Given that carbonyl insertion reactions of model palladium complexes occur very rapidly even at room temperature,[108] in contrast to the long reaction times (several hours) at elevated temperature for carbonylation reactions, and that the formation of the acyl group is essentially irreversible, it seems likely that the carbonyl insertion reaction will prevail for single-carbonylation reactions yielding acids, esters, and amides. The different situation for double-carbonylation reactions is discussed below.

(vi) Product Formation. The reaction of the acyl complex with the chosen nucleophile can then occur either by direct attack of the nucleophile at the acyl carbon or by initial bonding to palladium followed by reductive elimination. The former route was suggested by Heck in his initial work and is believed to be dominant for most alkoxy- and aminocarbonylations. However, Yamamoto concluded that kinetic data for reactions of $PdI(Ph)(PPh_3)_2$ supported the latter mechanism.[64] A full understanding of this step remains to be achieved.

Studies of reductive elimination indicate that this occurs following initial dissociation of one neutral ligand from a cis complex, leading to a trigonal transition state.[109,110] Elimination from a T-shaped transition state is forbidden on symmetry grounds. Results for Pd(dppe) complexes indicate that even this stable chelate will dissociate one donor atom to generate sufficient monodentate ligand to allow an effective rate, although slower than for PPh_3.[109] Other bidentate bisphosphanes would be expected to give more dissociation due to reduced stability of the chelate ring. Phosphane dissociation shows solvent dependency, with polar solvents favoring dissociation.[110]

For the reductive carbonylation in the presence of silane, it is likely that the hydride is transferred to palladium in an exchange reaction. This difference from reaction with hydrogen, where oxidative addition of H_2 is expected, could account for the lack of reactivity of bidentate ligands in the moderate pressure reaction with syngas in comparison with the satisfactory performance of the diadamantyl-*n*-butylphosphane ligand.[44] The more ready dissociation of one monophosphane to provide another coordination site may permit the oxidative addition of hydrogen under mild conditions. Our studies of complexes containing diadamantyl-*n*-butylphosphane suggest that, in contrast, they do not perform well in the silane reduction.[111] Good reactivity for these ligands has been established for alkoxycarbonylation of aryl iodides and bromides, although the conditions are somewhat harsher (6 bar of CO and 120 °C) than would be required by bidentate phosphane catalysts.[18]

Several of the intermediates in this mechanism can react further with CO, yielding mononuclear dicarbonyl and polynuclear carbonyl species.[98] This accounts for the unusual behavior of this reaction, alluded to above, with regard to pressure. While there can be no carbonylation in the absence of CO, above a few atmospheres of pressure the reaction is slowed dramatically, indicating that the concentration of active

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intermediates is being reduced by the additional coordination of CO. Indeed, it is likely that in the past carbonylation has been abandoned as a reaction choice for converting aryl halides because too high a pressure of CO was used, in the mistaken belief that this would drive the reaction forward. It is also evident in studies of the reaction with ammonium salts that there is also some sensitivity to the presence of excess nucleophile, which also results in a slowing of the reaction.

As a consequence of the many features and pathways of the mechanism(s) described above, particularly the competitive binding of CO, phosphane ligand, and the nucleophile to the several reaction intermediates, it is difficult to predict the preferred reaction conditions for any one substrate and nucleophile. While some aspects are clear, such as the need for strongly electron donating bisphosphane ligands for reaction of aryl chlorides and less strongly donating ligands for most aryl iodides and triflates, other factors such as steric influences of the ligands and substrates can have a major effect on these reactions. Modern techniques of parallel screening are therefore highly beneficial for the rapid identification of the most suitable combination of catalyst, solvent, and base and the appropriate reaction conditions, particularly the optimum temperature and CO pressure, to achieve high selectivity and an appropriate reaction time. However, in most cases it is possible to identify conditions that lead to very high yields under mild conditions suitable for industrial application.

Conclusion

Palladium-catalyzed coupling reactions are now a mainstay of pharmaceutical and fine chemical synthesis. However, this is not the limit of the transformations that can be carried out using palladium catalysis, with carbonylation offering a range of options for generating a variety of functional groups capable of further elaboration. The original reaction conditions defined by Heck over 30 years ago have been modified through the identification of a broader range of catalyst precursors to allow the reaction to be conducted under mild conditions. Now it is practical in many cases to operate the reaction with cheap aryl chloride or tosylate substrates at low pressures of carbon monoxide (<3 bar) and moderate temperatures (ca. 100 °C). This allows the use of conventional plant equipment in an industrial setting. The previously established compatibility of palladium-catalyzed chemistry with the presence of a wide variety of other functional groups as substituents in the molecules demonstrated by coupling reactions is only slightly diminished for carbonylation. Clearly the combination of palladium-catalyzed coupling and carbonylation reactions for synthesizing complex molecules offers an extremely attractive opportunity for atom-efficient preparations and it is anticipated that carbonylation will come to represent another major use of palladium catalysts in industrial applications.

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