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Carbonylation of Aryl Halides: Extending the Scope of the Reaction

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Abstract:

Carbonylation reactions are being increasingly favoured in pharmaceutical chemistry for the atom-efficient introduction of carbonyl centres in aldehydes, acids, esters, and amides. Convenient procedures for simple aryl iodides and bromides are well established, and now the need is to develop improved conditions to allow the reactions to be extended to the more unreactive substrates, such as sterically hindered compounds and aryl chlorides. Sterically hindered compounds such as 2-iodo- or 2-bromo-*m*-xylenes can be converted using alkoxy and aminocarbonylation, while dehalogenation becomes a significant side reaction for reductive carbonylation. Less hindered compounds such as 2-iodo- or bromotoluene can be reacted successfully. Changing the aryl ligands of $PdCl_2\{Ph_2P(CH_2)_3PPh_2\}$ to alkyl groups improves the rate of oxidative addition but slows the carbonyl insertion step such that rates for the majority of aryl bromides are not improved by this change. Complexes such as $PdCl_2\{Cy_2P(CH_2)_3PCy_2\}$ offer better performance for alkoxy and aminocarbonylation of aryl chlorides. However, for reductive carbonylation dehalogenation is a significant side reaction. Increasing CO pressure results in additional CO coordination to the catalytic intermediates and slows the reaction, while the dehalogenation is little affected, so reaction selectivity suffers. Thus, CO pressure is a critical parameter, particularly for reductive carbonylation, in achieving the optimum performance.

Introduction

The introduction of functional groups into pharmaceutical intermediates is a vital part of synthesis and the modification of these groups allows many structural variations to be obtained. Aryl halides have been at the forefront of recent developments in coupling and so they are widely available as key intermediates. Improving the usefulness of aryl halides through extending the range of reactions that they can perform under mild conditions is therefore desirable. Carbonylation chemistry offers a variety of such reactions, allowing the formation of aldehydes, acids, esters, and amides.

We previously reported[1] on the reductive carbonylation of aryl halides using silanes as hydride donor. This work showed that under mild conditions (3 bar CO and 60–120 °C) it was possible to achieve high yields of the desired aldehydes. The reaction was demonstrated to perform satisfactorily for a range of aryl iodides and bromides bearing substituents with differing electronic properties. The results did however show sensitivity to steric influence, which has now been further investigated.

As part of generalising this study across a variety of catalytic carbonylation reactions the alkoxy- and aminocarbonylation reactions have also been studied. The alkoxycarbonylation is the most robust carbonylation reaction as evidenced by the much larger number of examples of this conversion,[2] and thus it is the most appropriate choice for catalyst evaluation. An improved route to amides is one of the most sought-after goals in pharmaceutical chemistry,[3] and aminocarbonylation is potentially a very valuable and simple means of preparing amides.

For each of the above reaction types, the adaptation of the chemistry to aryl chlorides has been investigated. The outstanding study performed in this area is that of Milstein et al.[4] They reported the use of a range of alkyldiphosphane complexes of palladium for carbonylation of aryl chlorides. Their study of the mechanism identified the oxidative addition of aryl chloride to the 14-electron $[L_2Pd]$ species as the rate-determining step, with the increased electron donation of the alkyl phosphane substituents, relative to aryl, being necessary to achieve an effective rate for this step. The amount of the catalytically active species is reduced by various equilibria involving coordination of further phosphane or carbonyl ligands, indicating that high pressures of CO should be avoided. The reductive carbonylation of aryl chlorides was found to proceed at 150 °C and 5 bar CO with sodium formate as hydride donor.

Bis(diphenylphosphanyl)alkane ligands were also the focus of work by Kim and Sen[5] on the aminocarbonylation of aromatic dichlorides (using 75 psig CO and 175 °C) and a patent by Nihon Nohyaku[6] for the preparation of carboxylic acids, although the conditions here were much harsher. Nomura et al. reported good yields of carboxylic acids with 5 bar CO at 180 °C using catalysts containing either mono- or bidentate cyclohexyl phosphane ligands.[7]

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The use of ferrocenylphosphanes[8] was investigated by Mägerlein, Indolese, and Beller, who identified 1-[2-dicyclohexylphosphanyl)ferrocenyl ethyldicyclohexylphosphane as the preferred ligand. This was effective for alkoxycarbonylation of chlorobenzene at ca. 145 °C, 1 bar CO, but requiring a 4-fold excess of phosphane ligand and the addition of excess base and molecular sieve. Moderate yields (15−50%) were obtained for carbonylation reactions (amino and alkoxy) of electron-deficient aryl chlorides using a Pd-carbene catalyst in DMA at 140 °C with atmospheric pressure CO gas.[9]

Some moderation of the conditions for 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 CO).[10,11] The addition of sodium iodide was also reported to allow milder conditions, where 5 psig CO and only 115 °C provided good yields for activated substrates, but incomplete reaction in other cases.[12] Conditions described by Indolese et al., 5 bar CO and 120 °C with formamide as the amine source, gave moderate yields for activated aryl chlorides.[13]

Most recently, the use of sodium phenoxide as an additive for assisting aminocarbonylation has been described.[14] Buchwald et al. selected 1,3- bis(dicyclohexylphosphanyl)propane (dcpp) as the most appropriate ligand for this alternative route to amides via alkoxycarbonylation. In the presence of sodium phenoxide the phenyl ester is initially formed and subsequently converted to the amide by acyl transfer to an amine catalysed by phenoxide. This allows reactions to be carried out at modest temperatures (100−120 °C) and pressures (0−1 bar CO).

The amino- and alkoxycarbonylation of aryl chlorides has been reported by Larhed et al., using $Mo(CO)_6$ rather than CO gas, under microwave irradiation.[15] Although the reaction times are short, the associated reaction temperatures are high (>170 °C). Conveniently, it was found that such reactions could be carried out in water with only minor amounts of benzoic acid byproduct formed.[16]

This long history of study reflects the desirability of establishing the most effective conditions for these transformations, while at the same time emphasising the complexities imposed by the multistep mechanism of the reaction. The results reported below represent our efforts to achieve a better understanding of the interplay of the many reaction variables.

Results

Studies of Milstein[4] and others have shown that chelating ligands often perform better than their monodentate counterparts in palladium catalysts used for carbonylation reactions. Also, they identified the bis(phosphanyl)propane ligands as more effective than the corresponding ethane- or butane-based ligands. As has been seen in coupling chemistry, replacing the phosphane aryl substituents with alkyl groups increases the electron donation to palladium and promotes the initial oxidative addition. However, there has been little comparative study of the catalysts obtained by changing these alkyl groups. Variations in performance might be expected from both electronic and steric effects. Therefore, the series of compounds illustrated in Figure 1 were prepared from commercially available secondary phosphanes using literature methods. These catalysts were used to supplement the commercially available materials **1**-**3**.

Our previous work[1] on reductive carbonylation studied electronic and substituent effects using simple groups unlikely to react under the chosen conditions. To extend this work we now report reactions illustrating the chemoselectivity of this method and some limitations imposed by steric hindrance. To demonstrate the selectivity of the reaction in the presence of a more reactive functional group, the reductive carbonylation of 4-bromostyrene was studied. The results are shown in Table 1. The main side products were those expected from reaction of the vinyl group with hydride, being ethyl benzene and ethyl benzaldehyde. Small amounts (<1%) of hydroformylation products were also formed. Thus, even without optimisation, our standard conditions can deliver very good selectivity for aldehyde formation versus hydrogenation or hydroformylation with better than 95% selectivity for the desired product.

Our previous work[1] and that of others (for example, refs 8, 14, and 17) has shown that the efficiency of carbonylation reactions can be markedly influenced by steric hindrance. While we obtained good yields for both 4-iodotoluene and 2-iodotoluene (96 and 97% yields, respectively) conditions giving complete conversion of 4-bromotoluene gave minimal conversion with 2-bromotoluene. Therefore, to study the conditions required to overcome this effect, comparisons were made using 2-halotolyl and 2-halo-*m*-xylyl derivatives. Initial reaction conditions taken from our previous work with **3** were extended to include other catalysts, and changes to the temperature and CO pressure were made. The results are reported in Table 2. It can be seen that adding the second "blocking" methyl group in 2-iodo-*m*-xylene makes it difficult to achieve high yields. The dehalogenation reaction becomes more significant, and potentially dominant. It seems that attack on the complex by the silane is less susceptible to steric hindrance than attack by CO. Adjusting the reaction conditions, for example increasing the CO pressure, decreasing the excess of silane, and changing the temperature, can improve the selectivity slightly (see Table 3), but this also increases the likelihood of other side reactions. A similar story is evident for the aryl bromide (see Table 2), but in this case the inhibition associated with the two methyl groups has a more marked effect on reactivity. Even a temperature

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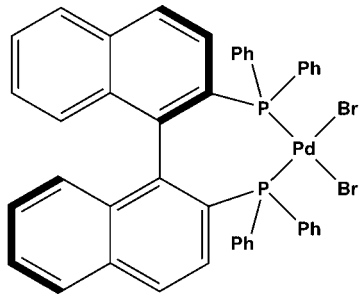

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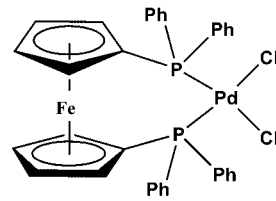

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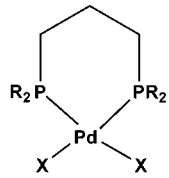
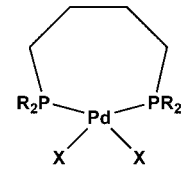
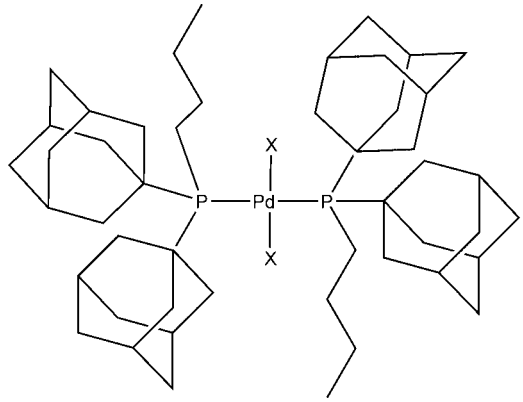




x = Cl	R = Ph	**3**	x = Cl	R = Ph	**14**
	i-C_3H_7	**4**		i-C_3H_7	**15**
	i-C_4H_9	**5**		t-C_4H_9	**16**
	t-C_4H_9	**6**		c-C_5H_9	**17**
	c-C_5H_9	**7**		c-C_6H_{11}	**18**
	c-C_6H_{11}	**8**			
	norbornyl	**9**			
x = Br	R = Ph	**10**	x = Br	R = i-C_3H_7	**19**
	i-C_3H_7	**11**		t-C_4H_9	**20**
	i-C_4H_9	**12**			
	t-C_4H_9	**13**			



X = Cl **21**
OAc **22**

Figure 1. **Catalyst structures.**

Table 1. **Chemoselectivity of reductive carbonylation of 4-bromostyrene**[a]

catalyst	bromoethylbenzene (%)	bromostyrene (%)	ethylbenzaldehyde (%)	vinylbenzaldehyde (%)
2	0.8	1.8	1.2	95.8
3	1.0	2.7	6.1	89.4
8	3.7	65.8	2.1	26.3

[a] Values reported as GC−MS normalised area. Method A: 4-bromostyrene (1 mmol); $HSiEt_3$ (2 mmol); Na_2CO_3 (1 mmol); DMF (5 mL); 2 mol % catalyst; 3 bar CO; 80 °C; 24 h.

increase of 30 °C is not sufficient to ensure complete reaction with most of the catalysts. As for the iodide, dehalogenation becomes the dominant reaction. It is noteworthy that catalysts **4** and **8** gave lower conversion than **3** (also the case for **8** and **3** for 4-bromostyrene, Table 1), indicating that these catalysts are significantly slower for this reaction than **3**. However, the high levels of dehalogenation occurring in these reactions make it unlikely that suitable conditions can be found for high yields from the reaction for severely sterically hindered aryl bromides.

In order to react aryl chlorides the increased bond strength C−Cl > C−Br > C−I requires harsher conditions to promote the oxidative addition, so the reaction temperature must be increased above that required for the bromides to maintain a reasonable reaction time. Also, increased electron donation from

Table 2. **Reductive carbonylation of sterically hindered aryl halides[a]**

catalyst	2-iodotoluene[b]	2-iodo-*m*-xylene[c]	2-bromotoluene[d]	2-bromo-*m*-xylene[e]
1	–	–	88 (6)	–
2	–	–	75 (9)	–
3	97(0)	8 (92)	82 (6)	1 (59)
4	–	16 (84)	26 (3)	9 (27)
5	–	10 (89)	29 (7)	–
6	–	–	42 (2)	1.7 (10)
7	–	12 (88)	58 (8)	12 (78)
8	–	30 (70)	32 (3)	14 (57)
9	–	13 (86)	30 (6)	21 (46)
14	–	–	60 (3)	–
15	–	3 (97)	–	6 (32)
17	–	3 (97)	–	–
18	–	5 (95)	–	7 (24)

[a] Values in parentheses indicate formation of arene (dehalogenation). Values reported as GC–MS normalised area. [b] Method A: 2-iodotoluene (3.6 mmol); $HSiEt_3$ (7.2 mmol) Na_2CO_3 (3.6 mmol); DMF (5 mL); 2 mol % catalyst; 3 bar CO; 60 °C; 18 h. [c] Method A: 2-iodo-*m*-xylene (1 mmol); $HSiEt_3$ (2 mmol); Na_2CO_3 (1 mmol); DMF (5 mL); 2 mol % catalyst; 3 bar CO; 100 °C; 24 h. [d] Method A: 2-bromotoluene (1 mmol); $HSiEt_3$ (2 mmol); Na_2CO_3 (1 mmol); DMF (5 mL); 2 mol % catalyst; 3 bar CO; 100 °C; 24 h. [e] Method A: 2-bromo-*m*-xylene (1 mmol); $HSiEt_3$ (2 mmol); Na_2CO_3 (1 mmol); DMF (5 mL); 2 mol % catalyst; 15 bar CO; 140 °C; 24 h.

Table 3. **Variation in yields with reaction conditions for reductive carbonylation of 2-Iodo-*m*-xylene[a]**

CO pressure (bar)	temperature (°C)	catalyst	conversion (%)	aldehyde (%)	*m*-xylene (%)
3	100	**3**	100	3	92
3	100	**8**	100	30	70
3	100	**9**	100	13	86
5[b]	90	**1**	90	35	34
5[b]	90	**2**	98	26	61
5[b]	90	**3**	99.5	16	64
5[b]	90	**8**	98	36	54
5[b]	90	**9**	98	41	49
15	110	**1**	100	33	67
15	110	**2**	100	54	46
15	110	**3**	100	24	76
15	110	**8**	100	33	66
15	110	**9**	100	56	44

[a] Method A. Values reported as GC–MS normalised area. [b] Only one equiv of $HSiEt_3$ added.

Table 4. **Reductive carbonylation of 4-chloroacetophenone[a]**

CO pressure (bar)	temperature (°C)	catalyst	conversion (%)	aldehyde (%)	acetophenone (%)
5	110	**3**	0	0	0
5	110	**7**	12	0	12
5	110	**8**	5	0	5
3	120	**3**	36	0.3	22
3	120	**7**	42	0	27
3	145	**7**	100	0	100
3	145	**8**	100	0	100

[a] Method A: values reported as GC–MS normalised area.

the ligand to palladium enhances the oxidative addition, so improved performance is expected for the alkyl-substituted bisphosphanes in comparison to the aryl-substituted derivatives. However, reaction of the electron-deficient aryl chloride 4-chloroacetophenone (see Table 4) carried out at 110–145 °C with 3–5 bar CO shows increasing conversion with temperature but with dehalogenation as the dominant reaction. Attempts to react an unactivated compound such as chlorobenzene were even less successful with complete formation of the arene. As was seen for the aryl bromides, the carbonylation steps are less favoured by the alkyl-substituted ligands compared to the aryl-substituted ones, and so the reduced rate here leads to more competition from reaction of the hydride donor with the aryl intermediate. Increasing the CO pressure in an effort to promote carbonyl insertion rather than dehalogenation results in a reduction in conversion (due to increased binding of CO by the catalytic intermediates) and no improvement in selectivity. Increasing the temperature results in the appearance of amide side products formed from dimethylamine, this arising from catalysed decarbonylation of the dimethylformamide solvent.

Other reagents have been reported for reductive carbonylation. Beller et al. have reported[18] that *n*-butyldi(adamantyl)phosphane ligand with palladium acetate is effective for the reductive carbonylation of aryl bromides under CO/H_2. The bidentate ligands dppf and dppp (i.e., precursors to **2** and **3**) were reported to be ineffective under these conditions. This has been verified in this study, with further results for **4** and **8** (yields <1%) for 2-bromotoluene and 4-*tert*-butylbromobenzene, while yields were ca. 50% for **22**, under 2 bar 1:1 CO/H_2 at 100 °C in toluene with TMEDA as base. However, catalysts **21** and **22** were ineffective under the standard conditions for alkoxy- and aminocarbonylation reported here (for example, yield <1% for alkoxycarbonylation of phenyl triflate with methanol at 0.5 bar CO at 80 °C, whereas yields of methyl benzoate for **1**, **2**, and **3** are all >60%). Good yields with these ligands can be obtained under different conditions (3:1 ligand/Pd, TMEDA as base and pressures >5 bar CO at elevated temperature, 115 °C).[19] The implications of this for our understanding of the mechanism of the reaction are discussed below.

Alkoxycarbonylation is the most robust of this series of carbonylation reactions due to the weakness of the interaction of the alcohol (in comparison with an amine or hydride donor) with the palladium catalyst. Carbonylation reactions are sensitive to the choice of base, and preference may differ depending on the nature of the nucleophile, i.e. the alcohol, amine, or hydride donor. Our previous work identified the benefits of sodium carbonate in reductive carbonylation in DMF. Screening of a selection of bases for the alkoxycarbonylation of 4-chloroacetophenone (see Table 5) showed that the inorganic bases are

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Table 5. **Influence of base on alkoxycarbonylation of 4-chloroacetophenone with ethanol**[a]

base	4-acetobenzoic acid ethyl ester (%)
Na_2CO_3	98
K_2CO_3	98
KOAc	74
K_3PO_4	53
KF	70
Cs_2CO_3	47
NaOEt	34
NEt_3	27
NEt^iPr_2	28
DMAP	29

[a] Method B: 4-chloroacetophenone (3.6 mmol); ethanol (1 mL); base (1 equiv); NMP (5 mL); 2 mol % **3**; 5 bar CO; 120 °C; 24 h. Values reported as GC−MS normalised area.

also superior to amines for this reaction. However, although sodium and potassium carbonate perform equally well in this example, over a series of reactions potassium carbonate was preferred to sodium carbonate for further exploration of alkoxycarbonylation.

As shown above, carbonylation reactions are affected by steric factors. However, in contrast to the reductive carbonylation, more intense conditions do allow reactivity to be obtained for alkoxycarbonylation without significant dehalogenation. Thus although the reaction temperature is increased by 30 °C to complete the reaction of 2-bromo-*m*-xylene in comparison with 2-bromotoluene, good selectivity is maintained as shown in Table 6. It can be seen that even for **8** temperatures of 120 °C or greater and higher catalyst loadings (ca. 5 mol %) are required to achieve good conversion with electron-neutral or electron-rich substrates. This compares with 100 °C reported by Buchwald using dcpp ligand[14] in alkoxycarbonylation with phenoxide (but with rigorous exclusion of water and air). The yields of esters are also good, in contrast to reductive carbonylation with $HSiEt_3$ where dehalogenation occurred. Optimisation of the conditions of temperature and pressure should allow the reaction to give high yields for most aryl chlorides. It should be noted that comparison of NMP, commonly used here, with DMSO as solvent, as suggested by Buchwald,[14] showed no significant difference in rate or selectivity.

Although there are fewer reports of aminocarbonylation than of alkoxycarbonylation,[2] the conditions for the two reactions are similar, reflecting the similarity in their mechanisms. Conditions for aryl bromides and iodides have been established, but there are few reports on the reaction of aryl chlorides. A notable recent report is the work of Buchwald et al. with the addition of sodium phenoxide.[14] However, in our work we have concentrated on the simpler, direct procedure and have taken only basic precautions to minimise exposure to moisture to better reflect an industrial setting. Initial attempts to carry out reaction with diethylamine in DMF as solvent resulted in a mixture of amides due to release of dimethylamine from the solvent. Therefore, NMP was used as solvent in all further work on aminocarbonylation. As for the alkoxycarbonylation, a series of substrates were studied to determine the relative performance of the catalysts for sterically demanding substrates and aryl chlorides. The results are shown in Table 7. While steric factors clearly inhibit the reactivity in aminocarbonylation, increasing

Table 6. **Comparison of catalysts for alkoxycarbonylation of aryl halides**[a]

catalyst	2-iodo-*m*-xylene + MeOH[b]	2-bromotoluene + MeOH[c]	2-bromo-*m*-xylene + MeOH[d]	4-chloroacetophenone + MeOH[e]	chlorobenzene + EtOH[f]	4-chloroanisole + MeOH[g]	2-chlorotoluene + MeOH[h]
1	90 (9)[i]	99.3	–	–	–	–	–
2	100[e]	99.7	0.2 (7)	4	–	–	–
3	100	100	1 (6)	11	–	–	–
4	100	98.6	47 (51)	3	78 (13)	40 (39)	2 (27)
5	95 (3)[i]	97.8	68 (32)	44	76 (10)	39 (31)	8 (41)
6	–	–	31 (14)	1	–	1 (7)	2 (6)
7	–	–	67 (33)	–	–	34 (52)	2 (19)
8	100	–	86 (14)	99	80 (8)	38 (49)	0.4 (28)
14	–	–	–	15	–	–	–
15	–	–	–	36	–	–	–
17	–	–	51 (49)	–	–	–	–
18	–	–	56 (44)	–	–	–	–

[a] Values reported as GC−MS normalised area. Values for arene are given in parentheses. [b] Method B: 2-iodo-*m*-xylene (1 mmol); methanol (1 mL); K_2CO_3 (1 equiv); DMF (5 mL); 2 mol % catalyst; 5 bar CO; 100 °C; 24 h. [c] Method B: 2-bromotoluene (1 mmol); methanol (1 mL); K_2CO_3 (1 equiv); NMP (5 mL); 2 mol % catalyst; 5 bar CO; 100 °C; 24 h. [d] Method B: 2-bromo-*m*-xylene (1 mmol); methanol (1 mL); K_2CO_3 (1 equiv); NMP (5 mL); 2 mol % catalyst; 2 bar CO; 130 °C; 24 h. [e] Method B: 4-chloroacetophenone (1 mmol); methanol (1 mL); K_2CO_3 (1 equiv); NMP (5 mL); 2 mol % catalyst; 5 bar CO; 100 °C; 24 h. [f] Method B: chlorobenzene (3.6 mmol); ethanol (1 mL); K_2CO_3 (1 equiv); NMP (5 mL); 2 mol % catalyst; 5 bar CO; 100 °C; 24 h. [g] Method B: 4-chloroanisole (1 mmol); methanol (1 mL); K_2CO_3 (1 equiv); NMP (5 mL); 2 mol % catalyst; 5 bar CO; 140 °C; 24 h. [h] Method B: 2-chlorotoluene (1 mmol); methanol (1 mL); K_2CO_3 (1 equiv); NMP (5 mL); 2 mol % catalyst; 5 bar CO; 140 °C; 24 h. [i] Reaction in NMP as solvent.

Table 7. **Comparison of catalysts for aminocarbonylation of aryl halides[a]**

	2-iodo-*m*-xylene[b]		2-bromo-*m*-xylene[c]		4-chloroacetophenone[d]		chlorobenzene[e]	
catalyst	conversion (%)	GC yield (%)	conversion (%)	GC yield (%)	conversion (%)	GC yield (%)	conversion (%)	GC yield (%)
1	100	61	37	27	52	45	2	2
2	100	60	8	5	18	8	3	2
3	100	64	40	35	38	20	12	11
4	100	65	84	46	44	40	42	41
5	100	62	44	23	56	54	20	19
6	100	67	70	37	38	30	9	8
7	100	57	98	54	96	95	62	61
8	100	54	100	71	100	100	77	76
9	100	53	80	44	25	18	42	41
18	100	57	93	77	75	64	75	64

[a] Main byproduct ketoamide formed by double carbonylation. [b] Method C: 2-iodo-*m*-xylene (1 mmol); $HNEt_2$ 0.2 mL, 2 equiv); K_2CO_3 (1 equiv); NMP (5 mL); 2 mol % catalyst; 3 bar CO; 100 °C; 24 h. [c] Method C: 2-bromo-*m*-xylene (1 mmol); $HNEt_2$ (1 mL); K_2CO_3 (1 equiv); NMP (5 mL); 2 mol % catalyst; 5 bar CO; 140 °C; 24 h. [d] Method C: 4-chloroacetophenone (1 mmol); $HNEt_2$ (1 mL); K_2CO_3 (1 equiv); NMP (5 mL); 2 mol % catalyst; 5 bar CO; 120 °C; 24 h. [e] Method C: chlorobenzene (1 mmol); $HNEt_2$ (1 mL); K_2CO_3 (1 equiv); NMP (5 mL); 2 mol % catalyst; 5 bar CO; 140 °C; 24 h.

Table 8. **Concentration effects in carbonylation**

substrate	concn (M)	CO pressure (bar)	temperature (°C)	catalyst	catalyst loading (mol %)	product	yield (%)
4-bromostyrene	0.2	3	80	**3**	2	vinylbenzaldehyde	89.4
4-bromostyrene	1.0	3	80	**3**	2	vinylbenzaldehyde	82.3[a]
Chlorobenzene	0.2	5	140	**8**	5	ethyl benzoate	80.4[b]
Chlorobenzene	0.7	5	140	**8**	2	ethyl benzoate	95.8

[a] Main byproduct 4-ethylbenzaldehyde. [b] Main byproducts benzene and benzaldehyde.

the reaction temperature can give satisfactory yields without significant dehalogenation. However, in some cases the double carbonylation yielding the ketoamide does become a significant side reaction, but for the aryl chlorides there was no evidence for the ketoamide byproduct. Comparison of the catalysts gives similar results to the alkoxycarbonylation: where oxidative addition is easy, the arylphosphane derivatives perform well. However, when improved oxidative addition is required, **8** is generally the preferred catalyst, although for particular compounds one of the other alkylphosphane catalysts may perform better.

While the detrimental effect of high CO pressure on Pd-catalysed carbonylation has been noted previously, there has been little reporting on the study of this important variable, with most authors reporting work in a narrow pressure range. The need to achieve the correct pressure can be shown by the alkoxycarbonylation of chlorobenzene. With 2 mol % **4** at 120 °C the yield at 5 bar CO is encouraging (13%), but if the pressure is reduced to 2 bar CO, the reaction slows markedly (ca. 1% yield), whereas increasing the pressure to 15 bar CO results in almost complete shut-down of the reaction. Similar results have been seen in other cases. It seems likely that the anion bound to palladium is an important factor in determining the optimum pressure, and a more extensive study of this topic is warranted. Certainly, the affect of pressure should be included as part of any initial evaluation of a carbonylation process.

In order to maximise productivity it is generally best to operate at the maximum convenient concentration. However, concentration can sometimes influence the selectivity of the reaction. Examples of differences in the effect of concentration are shown in Table 8. Therefore, substrate concentration is another parameter that should be thoroughly investigated during reaction optimisation.

Discussion

While individual substrates may differ in the preferred choice of catalyst, base and solvent combinations, the previously reported results for the reductive carbonylation of aryl bromides and iodides suggest that PdX_2(dppp), PdX_2(dppf) or PdX_2-(BINAP) (X = Cl or Br) with sodium carbonate as base in DMF as solvent is a reasonable starting point for reductive carbonylation. The results presented here offer further insight into the effects of substrate variation, as well as catalyst choice, on the reaction conditions.

Increasing electron donation from the phosphane ligand to promote the oxidative addition step has been well studied in coupling chemistry.[20] However, the results for 4-bromostyrene and for other aryl iodides and bromides, comparing the results for **3** and **8**, indicate that the carbonylation step is slowed by this change (for further discussion, see below). For the majority of aryl bromides reaction of the aryl-palladium intermediate with carbon monoxide is much faster than reaction with hydride leading to very good selectivity versus dehalogenation. This remains true for 4-bromostyrene with regard to carbonylation versus reduction of the alkene. However, when the carbonylation is slowed by steric effects, or by strong electron donation from the ligand, then the dehalogenation reaction becomes dominant. The high levels of conversion of the 2-halotoluene and 2-halo-*m*-xylene compounds confirm that the oxidative addition still proceeds satisfactorily with the sterically demanding substrates. However, the low yield of carbonyl products indicates that attack by CO on the intermediate aryl complex is strongly inhibited. This may be understood in terms of the

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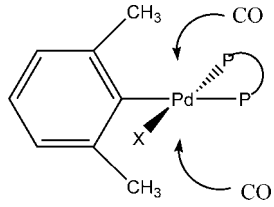

Figure 2. **Steric influence on binding of carbon monoxide.**

standard associative mechanism for CO substitution reactions, with substitution of one phosphorus donor being required before the migratory insertion takes place. The initial coordination of CO must take place along the axial coordinate of the square planar complex as illustrated in Figure 2. To minimise steric interactions in the plane, the aryl group will lie vertically and therefore the methyl substituent will sit over the axial site. With one methyl group there is still one axial site readily available and the reaction, though slowed, proceeds well, while with methyl groups blocking both axial sites the reaction is severely hindered. Rotation of the methyl groups away from the axial sites correspondingly increases steric interaction in the plane, also adversely affecting the reaction. (An alternative proposal of initial coordination of CO at an axial site has been considered by Albaneze et al.,[17] but does not seem to provide a straightforward explanation of these results.) While it might be assumed that increasing the CO pressure would promote carbonylation versus reductive dehalogenation, this also leads to further CO coordination, which depletes the level of active intermediates in the catalytic cycle, and overall the reaction is slowed. Compensating through increasing the temperature increases the rate of side reactions. Determination of the optimum pressure for these reactions should therefore be a major feature of process development.

In contrast to coupling reactions, the final step in the alkoxy- and aminocarbonylation mechanism (see Figure 3) is attack by the nucleophile on the acyl palladium complex rather than reductive elimination.[4a] These results were confirmed by Moser et al.[21] in an IR study of the formation of [PdBr-(COC_6H_5)(PPh_3)$_2$] from [PdBr(C_6H_5)(PPh_3)$_2$] and CO which also established that the acyl group in the former is stable to decarbonylation. The contribution of base in generating the appropriate nucleophile (e.g., methoxide) for attack on the benzoyl complex is significant.

The changes to the choice of preferred catalyst and the conditions for carbonylation of different substrates arise from the conflicting requirements for the oxidative addition and carbonylation steps. Milstein reported that for aryl chloride carbonylation oxidative addition is the rate-determining step. However, work on cross-coupling reactions has shown that oxidative addition for aryl bromides and chlorides can occur readily at room temperature with appropriate catalysts.[20] Therefore, for many of these reactions oxidative addition is clearly not the rate-limiting step. This must be one of the steps involved in the formation of the acyl ligand (CO binding/phosphane displacement or CO insertion). Promotion of the oxidative addition by increasing electron density on palladium will increase the capability of the palladium for back bonding to the π-accepting ligands CO and aryl. The barrier to combining these ligands will rise, slowing this step. For example, as noted above, the reductive carbonylation of bromo- and iodo- substrates proceeds more readily for **3** than for **8** under circumstances where the carbonylation step(s) are rate-determining. However, for aryl chlorides oxidative addition is limiting for **3**, while the situation is less clear for **8**, where it seems likely that the carbonylation is the slowest part of the catalytic cycle. Because of the conflicting requirements for these two essential parts of the cycle, it seems unlikely that there will be the same dramatic improvement in carbonylation catalysts as has been seen for cross-coupling. Nonetheless, optimisation of conditions (catalyst, base, solvent, pressure, temperature) still allows Pd-catalysed carbonylation to be an extremely effective means for the conversion of aryl halides to other functional groups.

Comparison of the results for bidentate bis(phosphanyl)propane complexes with those of monodentate *n*-butyldi(adamantyl)phosphine suggests significant mechanistic differences between the reductive carbonylation carried out in the presence of hydrogen or silane. The former complexes perform well in silane-based reductive carbonylation, in alkoxy- and aminocarbonylation but do not give significant product with hydrogen-based methodology. The reverse is true for the monodentate phosphine complexes, which perform very poorly in alkoxy- and aminocarbonylation under the conditions described in this paper. This suggests that a monophosphane Pd−P species plays a much greater role in the hydrogen-based reductive carbonylation. For the chelating bis(phosphanyl)propane, ring-opening is anticipated to allow CO complexation prior to insertion into the Pd−Aryl bond. However, binding of hydrogen in a similar manner is not expected. In contrast, for hydrogen coordination a readily available vacant coordination site, associated with complete dissociation of one phosphane, is required. It is likely that the bidentate phosphane catalyst performs better than the monophosphane one in amino- and alkoxycarbonylation due to the assistance that the second phosphane offers in promoting the carbonyl insertion. The improved performance of *n*-butyldi(adamantyl)phosphine in amino- and alkoxycarbonylation with the presence of excess ligand[19] also supports this suggestion.

Comparing the performance of the catalysts indicates that both alkyl- and aryl-substituted phosphane palladium complexes are required to give effective reaction across a wide range of substrates. The simple phenylphosphane derivatives **1**−**3** are highly effective for aryl iodides and bromides, while catalysts such as **8** generally perform better for aryl chlorides. Comparing the propane- and butane-based ligands, the results are in accordance with those of Milstein et al., who showed that catalyst activity varies with chelate ring size 6 > 7 ≫ 5. However, within the series of phosphanylpropane derivatives the order of activity is less easily rationalised. Evidently, the cyclohexyl derivative provides the optimum compromise of electron donation and steric influence for most substrates, although occasionally another derivative may perform better. It is our assumption that it is mainly the steric match to the substrate that is causing these changes in relative performance. Chloro- and bromo- forms of the catalysts perform equally well since the substrate provides a great excess of halide over that originally present in the catalyst.

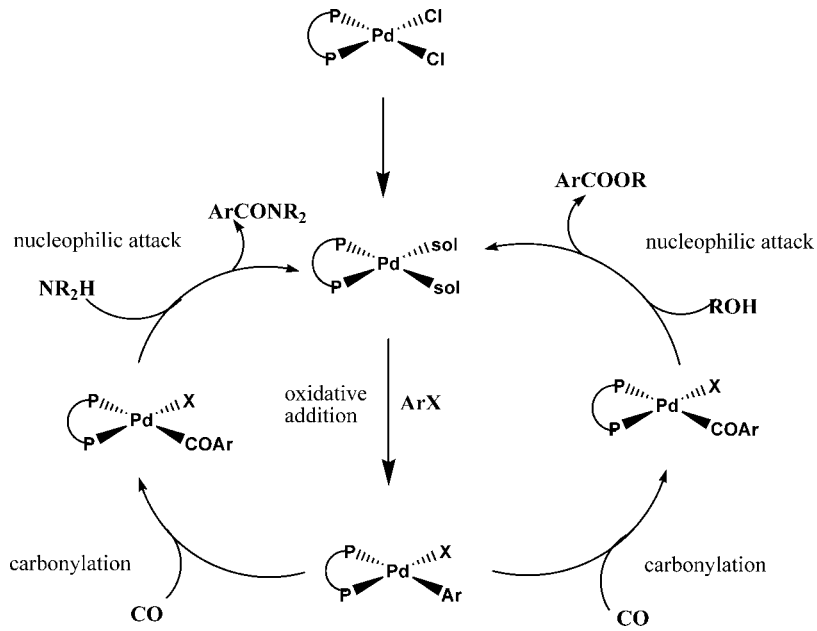

Figure 3. **Outline mechanism for alkoxy- and aminocarbonylation.**

Conclusion

The results presented here can be understood using the conventional model for the mechanism of palladium-catalysed carbonylation. Consideration of the main steps in the model as described in Figure 3 indicates that a range of catalysts are required to deliver optimum performance for the different aryl halides. It is evident that the rate-determining step in the mechanism can differ, depending on the substrate, the catalyst, and the nucleophile. Thus, for aryl iodides and bromides, where the oxidative addition occurs readily, the less electron-donating phenyl phosphane derivatives perform well by achieving faster carbonylation steps, while for aryl chlorides more electron-donating alkylphosphanes are required to promote the oxidative addition even though they slow the carbonylation steps. Once the reagents and catalyst have been selected, to optimise the reaction for a given conversion the concentration and relative amounts of reactants and catalyst need to be determined (in addition to defining the most appropriate combination of temperature and CO pressure) to achieve the best selectivity and a suitable rate. If the CO pressure is too high, the reaction is slowed. Compensating for this by using a higher temperature will generally lead to reductions in selectivity, for example through increased dehalogenation. However, with the availability of parallel screening equipment such optimisation can now be carried out expediently.

Experimental Section

All solvents and reagents were obtained from commercial suppliers and used without further purification. Unless indicated, catalysts and ligands may be obtained from Johnson Matthey Catalysts or Alfa Aesar. Bisphosphane ligands were prepared in accordance with literature procedures[22] from $PH(alkyl)_2$ (Strem). Complexes [PdX_2(bisphosphane)] (X = Cl or Br) were prepared by stirring together [PdX_2(cod)] and the ligand in acetone overnight at ambient temperature. The products were collected by filtration and used without further purification. Materials were characterised by elemental analysis (University of Strathclyde) and IR and in some cases by NMR spectroscopy (see Supporting Information).

Reactions were performed in a Baskerville 10 × 30 mL multicell pressure reactor rated to 50 bar and 200 °C. In contrast to the work of Buchwald et al.,[14] no stringent precautions (e.g., flame-dried glassware, glovebox, etc.) were taken to avoid contact with air or moisture. Catalyst, substrate, reagent, base, and solvent were measured into reaction tubes in air. After transfer of the tubes to the autoclave, this was sealed and then purged four times using nitrogen and four times with CO, before charging to the required pressure at ambient temperature. There was a slight increase in pressure during initial heating, which then returned to the set pressure as CO was consumed. This pressure was then maintained at the reported value using additional CO for the remainder of the reaction time. Analysis of the reaction mixture was carried out by GC−MS using a Perkin-Elmer AutoSystem XL gas chromatograph with TurboMass mass spectrometer. Conditions used: 1.0 μL sample injection, columns: 30 m × 0.25 mm DF 0.25 μm Elite Series PE-5MS, 30 m × 0.32 mm DF 0.25 μm Elite Series PE-35MS or 30 m × 0.32 mm DF 0.25μm PE-Wax, injection port 320 °C, initial temperature 130 °C, hold 4 min, ramp at 30 °C/min to 300 °C, hold 5 min, split ratio 100/1, MS scan 40.0 to 600.0 EI+ (centroid). A lower initial temperature of 50 °C was used where dehalogenation was suspected and separation of volatile arenes was required. For these screening runs no isolation of the products was attempted, but previous work has shown that aldehyde,[1] ester,[23] and amide[14] products may be isolated with excellent recovery by routine methods.

General Procedure for the Reductive Carbonylation of Aryl Halides (Method A). To each reactor tube was added substrate (1 mmol) catalyst (20 μmol) and Na_2CO_3 (1−1.1 mmol) DMF (5 mL) and Et_3SiH (0.324 mL, 2 mmol). Once

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sealed inside the reactor, the system was purged with nitrogen (pressurising to 3−4 bar and venting four times) and then repeating with CO. The autoclave was pressurised with CO and heated to the desired temperature. The reaction was stirred under these conditions for 24 h with additional CO added to maintain the set pressure. The reactor was allowed to cool and the reaction mixture was filtered and the filtrate analysed by GC−MS to determine conversion and yield of the aldehyde.

General Procedure for Alkoxycarbonylation of Aryl Halides (Method B). To each reactor tube was added substrate (1 mmol) catalyst (20 μmol) K_2CO_3 (1−1.1 mmol) and NMP (5 mL), and alcohol (1 mL). Once sealed inside the reactor, the system was purged with nitrogen (pressurising to 3−4 bar and venting four times) and then repeating with CO. The autoclave was pressurised with CO and heated to the desired temperature. The reaction was stirred under these conditions for 24 h with additional CO added to maintain the set pressure. The reactor was allowed to cool and the reaction mixture was filtered and the filtrate analysed by GC−MS to determine conversion and yield of the ester.

General Procedure for Aminocarbonylation of Aryl Halides (Method C). To each reactor tube was added substrate (1 mmol) catalyst (20 μmol) NMP (5 mL) and diethylamine (1 mL). Additional base (typically K_2CO_3 1 mmol) was added if desired. Once sealed inside the reactor, the system was purged with nitrogen (pressurising to 3−4 bar and venting four times) and then repeating with CO. The autoclave was pressurised with CO and heated to the desired temperature. The reaction was stirred under these conditions for 24 h with additional CO added to maintain the set pressure. The reactor was allowed to cool and the reaction mixture was filtered and the filtrate analysed by GC−MS to determine conversion and yield of the amide.

Supporting Information Available

Details of the elemental analysis for catalysts synthesised as part of this work; selected ^{31}P NMR data. This information is available free of charge via the Internet at http://pubs.acs.org.

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