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Highly Selective Palladium-Catalysed Aminocarbonylation of Aryl Iodides using a Bulky Diphosphine Ligand

Verónica de la Fuente,[a] Cyril Godard,[a] Carmen Claver,[a,*] and Sergio Castillón[b,*]

[a] Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo s/n, 43007 Tarragona, Spain
Fax: (+34)-977-559-563; e-mail: carmen.claver@urv.cat
[b] Departament de Química Analítica i Orgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo s/n, 43007 Tarragona, Spain
Fax: (+34)-977-558-446; e-mail: sergio.castillon@urv.cat

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Abstract: An efficient methodology for the synthesis of amides *via* palladium-catalysed aminocarbonylation of aryl iodides is reported using the bulky *cis*-1,2-bis[(di-*tert*-butylphosphino)methyl]cyclohexane ligand under atmospheric pressure of carbon monoxide. Excellent conversions (up to 99%) and chemoselectivities (up to 99%) were obtained for a range of aryl iodides and amine nucleophiles. The effect of the substituents on the substrate and nucleophiles on the catalytic performance was investigated. An NMR study was also carried out and key intermediates of the catalytic cycle were detected and characterised.

Keywords: amide synthesis; diphosphines; α-keto amides; NMR studies; palladium-catalysed aminocarbonylation

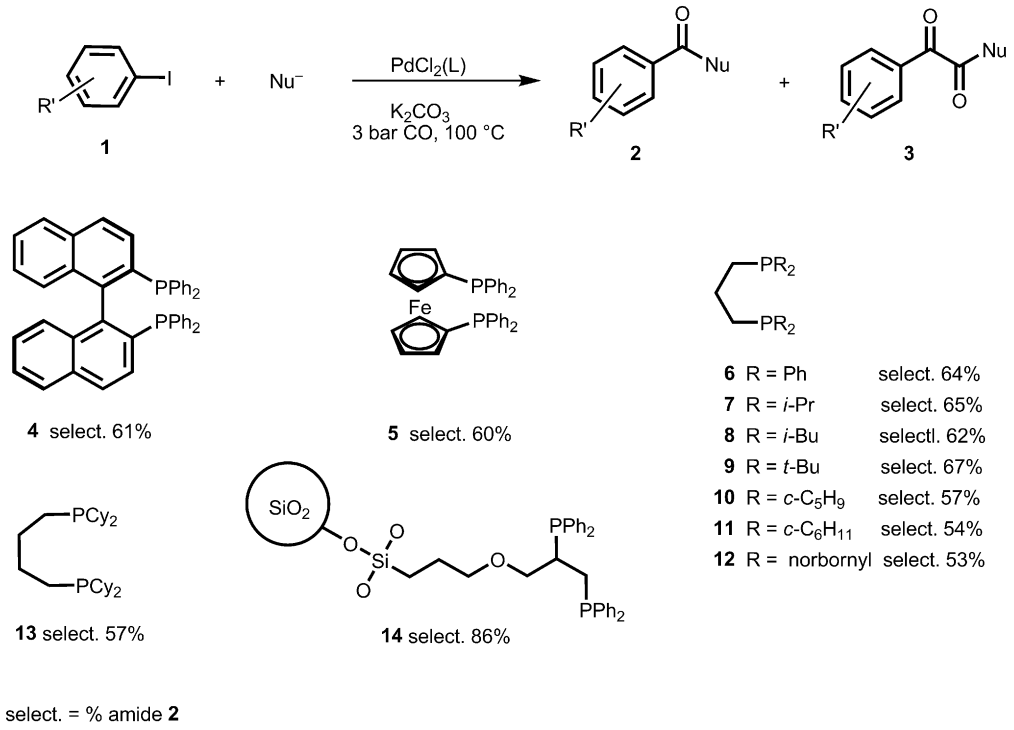
Introduction

The Pd-catalysed aminocarbonylation reaction provides an easy and practical method for the synthesis of amides, which are valuable products for the pharmaceutical industry.[1a,b] This reaction is used industrially to produce Lazabemide, a monoamine oxidase B inhibitor, in one step from 2,5-dichloropyridine.[1c] Although the Pd-catalysed aminocarbonylation, where the nucleophile is an amine, is related to the Pd alkoxycarbonylation, where the nucleophile is an alcohol, the former reaction has been much less studied. Heck first reported on palladium complexes $[PdX_2(PPh_3)_2]$ (X = Br, I) which were active in the Pd-catalysed aminocarbonylation of various aryl halides under 1 atm of carbon monoxide at 100 °C.[2] Later, various catalytic systems were reported for this process.[3–21] However, the Pd/PPh_3 remains the most efficient for this reaction.[15–17]

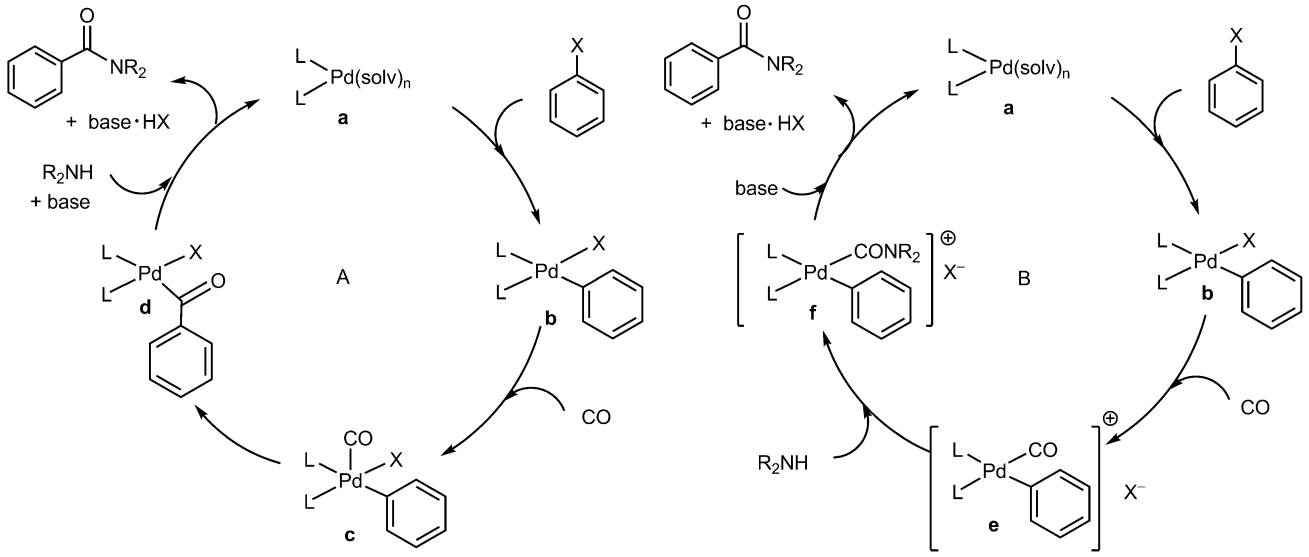
In this process, the use of bidentate phosphine ligands has been less explored, and mixtures of amides (**2**), α-keto amides (**3**) or dehalogenation products were usually obtained (Scheme 1).[18,22] Palladium complexes bearing ligands **4**–**13** afforded the corresponding amides with moderate chemoselectivities under 3 bar of carbon monoxide at 100 °C (Scheme 1).[22] Hang et al. reported the most efficient system using Pd/**14** as catalyst, achieving chemoselectivities up to 86% (Scheme 1).[18] The carbon monoxide pressure influences the chemoselectivity of the reaction since under low pressures, the formation of amides (**2** in Scheme 1) is favoured whereas high CO pressures are required for the synthesis of α-keto amides (**3**, Scheme 1).[18]

The catalytic cycle using monodentate phosphine ligands is now well established.[2–13] However, some uncertainty and disagreements remain in the last steps of the catalytic cycle.[2–13]

The most accepted mechanism for the aminocarbonylation reaction of aryl halides is presented in Scheme 2, A and consists of: (i) oxidative addition of the aryl halide at the Pd(0) species (**a**) to form the Pd(II) complex (**b**); (ii) coordination of carbon monoxide to give the pentacoordinated intermediate (**c**), (iii) carbonyl migratory insertion to yield the acyl palladium complex (**d**), and (iv) nucleophilic attack at the acyl produces the final product and regenerates the initial Pd(0) species. An alternative mechanism has also been proposed (Scheme 2, B) in which the nucleophilic attack occurs at the terminal Pd–CO of species (**e**) to form the intermediate (**f**), which produces the amide and the initial Pd(0) species *via* a reductive elimination step.[13]



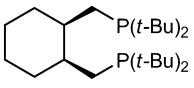
Scheme 1. Pd-catalysed aminocarbonylation of aryl iodides using Pd/diphosphine ligands.[18,22]



Scheme 2. Proposed mechanisms for the Pd-catalysed aminocarbonylation of aryl halides.[12,13]

However, to the best of our knowledge there are no mechanistic studies reported on Pd systems bearing bidentate phosphine ligands for this transformation.

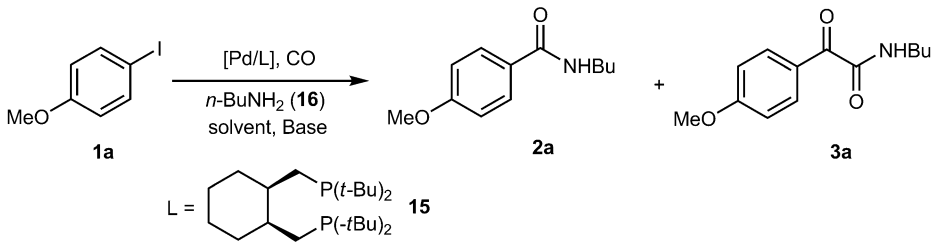
Here, we report the successful use of a palladium catalytic system bearing the bidentate phosphine ligand **15** (Figure 1) in the Pd-catalysed aminocarbonylation of aryl iodides. This system was recently reported by our group in the Pd-catalysed methoxycarbonylation of ethene and is the most active and selective system reported to date.[23]



15

Figure 1. *cis*-1,2-Bis[(di-*tert*-butylphosphino)methyl]cyclohexane.

Table 1. Pd-catalysed aminocarbonylation of 1-iodo-4-methoxybenzene in the presence of *n*-butylamine: optimisation of reaction conditions.[a]



Entry	Pd precursor	Solvent	Conversion [%][b]	Selectivity **2a**/**3a**[b]
1[c]	Pd_2dba_3	CH_2Cl_2	12	99/1
2	Pd_2dba_3	CH_2Cl_2	96	99/1
3	Pd_2dba_3	THF	59	99/1
4	Pd_2dba_3	toluene	76	94/6
5	$Pd(OAc)_2$	CH_2Cl_2	92	99/1
6	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	CH_2Cl_2	95	99/1

[a] [Pd] (0.01 mmol), ligand **15** (0.011 mmol), aryl iodide (0.5 mmol), pyridine (1 mmol), *n*-butylamine (1.2 mmol), solvent (1 mL), CO (1 bar), 45 °C and 14 h.
[b] Determined by ^{1}H NMR and GC-MS.
[c] Without base.

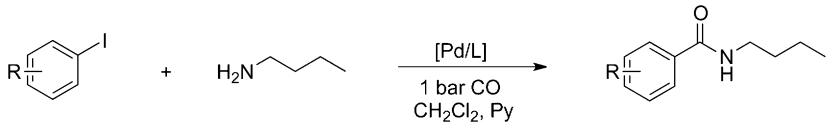
Results and Discussion

The catalytic reaction conditions were optimised using 1-iodo-4-methoxybenzene as substrate and *n*-butylamine as nucleophile (Table 1).

The first reaction was performed under atmospheric carbon monoxide pressure in refluxing dichloromethane in the absence of base, achieving low conversion but excellent chemoselectivity to the amide product **2a** (entry 1, Table 1).

Using pyridine as base, excellent conversion and chemoselectivity to **2a** were obtained (entry 2, Table 1). The effect of the solvent was examined, achieving the highest activity when dichloromethane was used. The chemoselectivity remained excellent in all cases (entries 2–4, Table 1). A decrease in conversion was observed when THF and toluene were used as solvents (entries 3 and 4, Table 1), which is in agreement with previously reported results.[17]

Table 2. Pd-catalysed aminocarbonylation of aryl iodides with *n*-butylamine.[a]



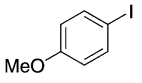
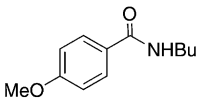
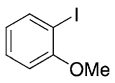
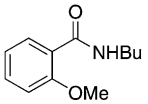
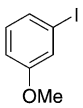
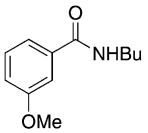
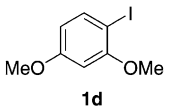
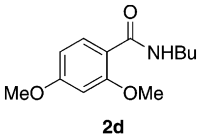
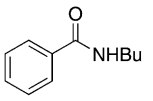
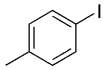
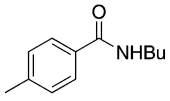
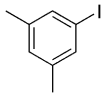
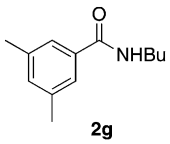
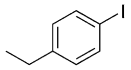
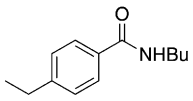
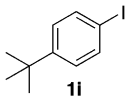
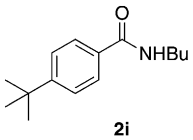
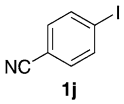
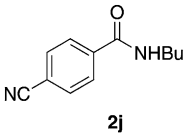
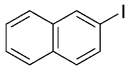
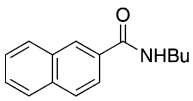
Entry	Aryl iodide	Product	Conversion [%][b]	Selectivity [%][b]
1	 **1a**	 **2a**	96	99
2	 **1b**	 **2b**	85	99
3	 **1c**	 **2c**	76	99

Table 2. (Continued)

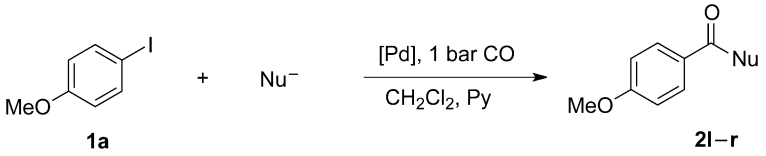
Entry	Aryl iodide	Product	Conversion [%][b]	Selectivity [%][b]
4	 **1d**	 **2d**	95	99
5	 **1e**	 **2e**	95	99
6	 **1f**	 **2f**	91	99
7	 **1g**	 **2g**	85	99
8	 **1h**	 **2h**	92	99
9	 **1i**	 **2i**	99	99
10	 **1j**	 **2j**	94	99
11	 **1k**	 **2k**	77	99

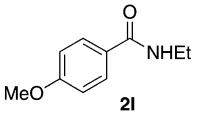
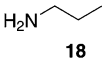
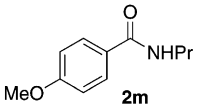
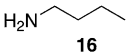
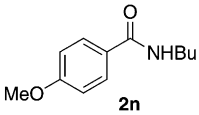
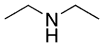
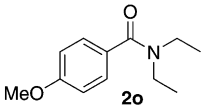
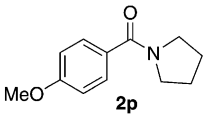
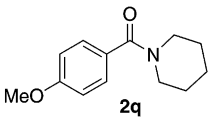
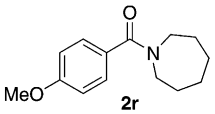
[a] Pd_2dba_3 (0.005 mmol), ligand (0.011 mmol), aryl iodide (0.5 mmol), pyridine (1 mmol), *n*-butylamine (1.2 mmol), dichloromethane (1 mL), CO (1 bar), 45 °C and 14 h.
[b] Determined by ^{1}H NMR and GC-MS.

Other palladium precursors such as $Pd(OAc)_2$ or $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ were tested and also gave excellent conversions and chemoselectivities (entries 2 *vs.* 5 and 6, Table 1).

Next, a range of aryl iodides was used as substrates (Table 2). For all the substrates used, conversions between 85–99% and total chemoselectivities were achieved, showing that this catalytic system is suitable for the selective transformation of a wide range of aryl iodide substrates. For *ortho*- and *meta*-iodoanisoles (entries 2 and 3, Table 2), the conversions slightly decreased when compared to that obtained with the *para* isomer of this substrate. The position of the substituent therefore only affects the conversion of the reaction. Interestingly, the reaction of the 2,4-dimethoxy derivative afforded exclusively the corresponding amide in 95% conversion (entry 4, Table 2). When iodobenzene **1e** was used as substrate, excellent conversion and selectivity to the formation of the amide **2e** were achieved (entry 5, Table 2). When substrates **1f**, **1h**, **1i** with alkyl groups at the *para*-position of aryl group (entries 6, 8 and 9, Table 2) were used, the conversions were between 91 and 99% together with 99% chemoselectivity. For 3,5-dimethyl-1-iodobenzene **1g**, 85% conversion into the amide **2g** was achieved (entry 7, Table 2). When an electron-withdrawing substituent such as −CN was present at the *para*-position, the conversion and selectivity remained excellent (94% and 99%, respectively) (entry 10, Table 2).

Table 3. Pd-catalysed aminocarbonylation of 1-iodo-4-methoxybenzene with different nucleophiles.[a]



Entry	Nucleophile	Product	Conversion [%][b]	Selectivity [%][b]
1	 **17**	 **2l**	89	99
2	 **18**	 **2m**	91	96
3	 **16**	 **2n**	96	99
4	 **19**	 **2o**	99	99
5	 **20**	 **2p**	92	99
6	 **21**	 **2q**	97	99
7	 **22**	 **2r**	83	99

[a] Pd_2dba_3 (0.005 mmol), ligand **15** (0.011 mmol), aryl iodide (0.5 mmol), pyridine (1 mmol), nucleophile (1.2 mmol), dichloromethane (1 mL), CO (1 bar), 45 °C and 14 h.
[b] Determined by ^1H NMR and GC-MS.

When 1-iodonaphthalene was used as substrate the conversion was 77% (entry 11, Table 2). Interestingly, these results show that the presence of substituents with distinct electronic and/or steric properties on the substrate does not affect the chemoselectivity of the reaction.

To extend the scope of this process, various primary and secondary amines were tested as nucleophiles (Table 3). Conversions of 83–96% and chemoselectivities of 96–99% (entries 1–7, Table 3) were achieved. The results obtained with primary (**16**–**18**) or secondary amines (**19**–**22**) were very similar in terms of chemoselectivity (entries 1–3 *versus* 4–7) although the use of bulky amines leads to a decrease of the conversion (entry 7).

These results show that the palladium system bearing the bulky electron-rich bidentate phosphine ligand **15** constitutes a very efficient catalytic system for the palladium-catalysed aminocarbonylation of a wide range of aryl iodides and nucleophiles under mild conditions. However, this system was found to be inactive when aryl bromides and chlorides were used as substrates.

NMR Study of the Pd-Catalysed Aminocarbonylation of 1-Iodo-4-methoxybenzene using the P,P Ligand 15

In order to gain information about the mechanism of the Pd/**15**-catalysed aminocarbonylation reaction of aryl iodides, an NMR study was carried out (Figure 2).

First, the palladium precursor [$Pd_2(dba)_3$] was treated with ligand **15** in toluene at room temperature for 20 min and a ^{31}P-{^1H} NMR spectrum was recorded at this temperature. A singlet at 22.5 ppm was detected

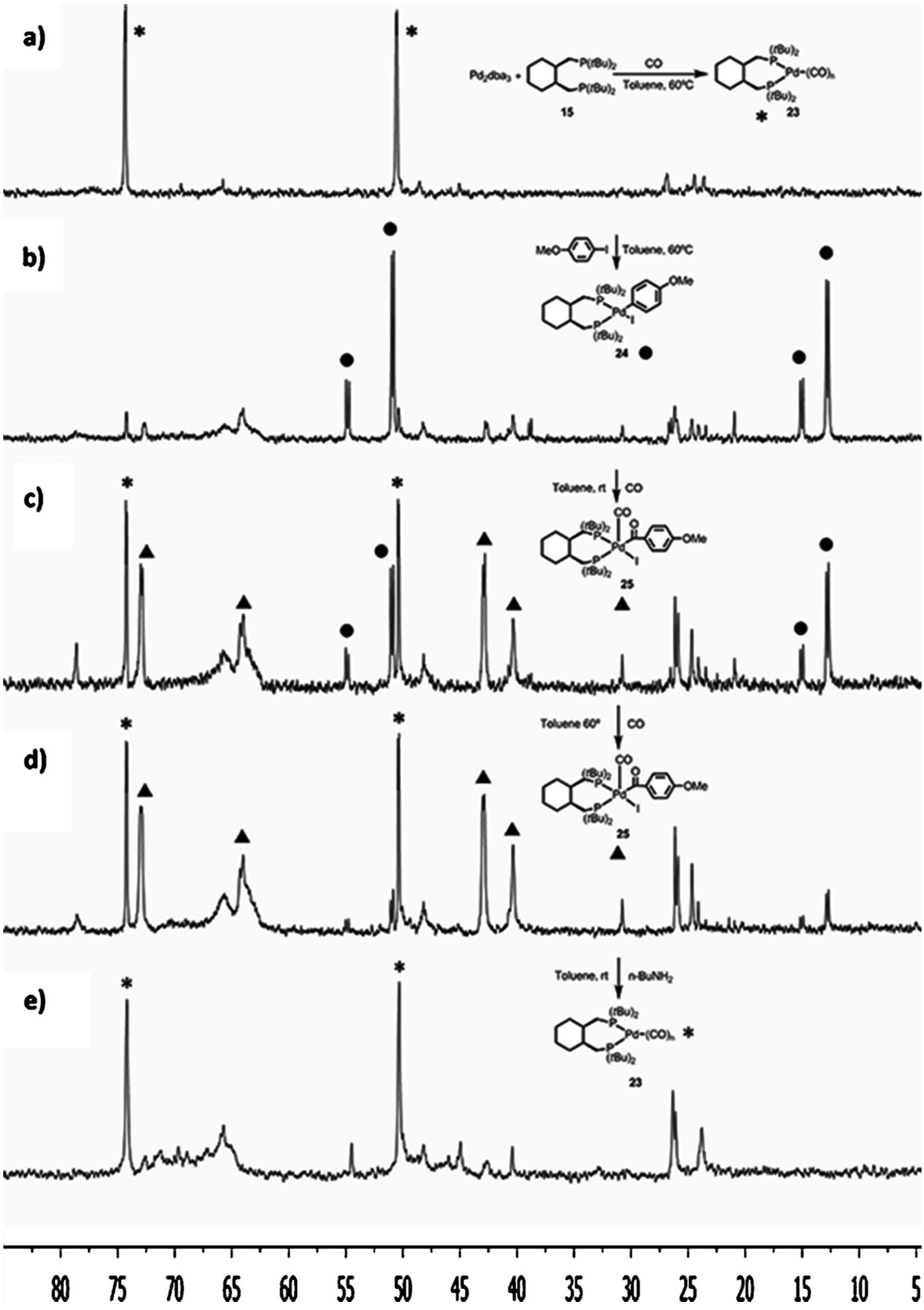
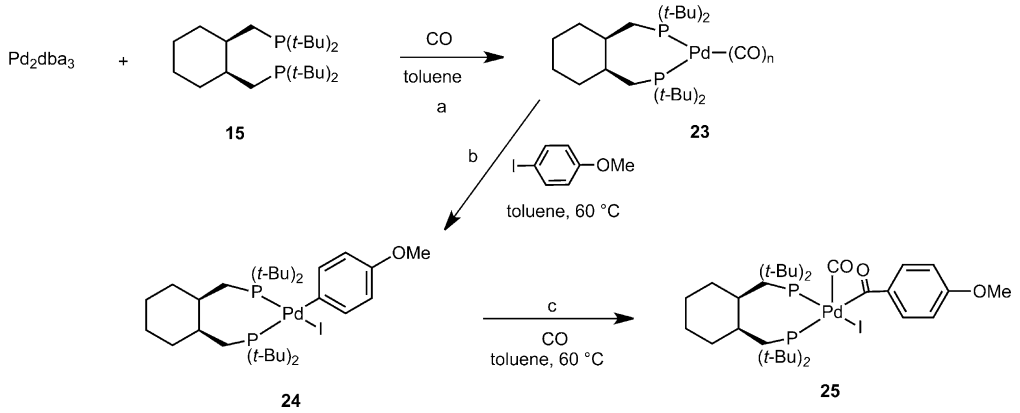


Figure 2. $^{31}P\{^{1}H\}$ NMR spectra: **a)** of the Pd_2dba_3/**15** under 1 bar of CO in toluene at −90 °C; **b)** of the Pd_2dba_3/**15** under 1 bar of carbon monoxide plus addition of 1-iodo-4-methoxybenzene under nitrogen in toluene at −90 °C after being heated for 1 h at 60 °C; **c)** the previous solution pressurised with 1 bar of CO at −90 °C; **d)** the previous solution pressurised with 1 bar of CO and heated at 60 °C for 15 minutes; **e)** addition of *n*-butylamine to the previous solution at room temperature and spectrum acquired at −90 °C.



Scheme 3. Reaction carried out with Pd/**15**.

and readily assigned to the free diphosphine **15**. When the temperature was decreased to −90 °C, two singlet signals were detected at 24.2 and 22.1 ppm, corresponding to both boat and chair conformers of the free ligand. It was therefore concluded that under these conditions the coordination of **15** to Pd does not occur. This is in agreement with previous findings by our group in the Pd-catalysed methoxycarbonylation reaction.[23]

However, when carbon monoxide was bubbled through a toluene solution containing [$Pd_2(dba)_3$] and **15** (Scheme 3, a), the colour of solution changed immediately from purple to dark green.

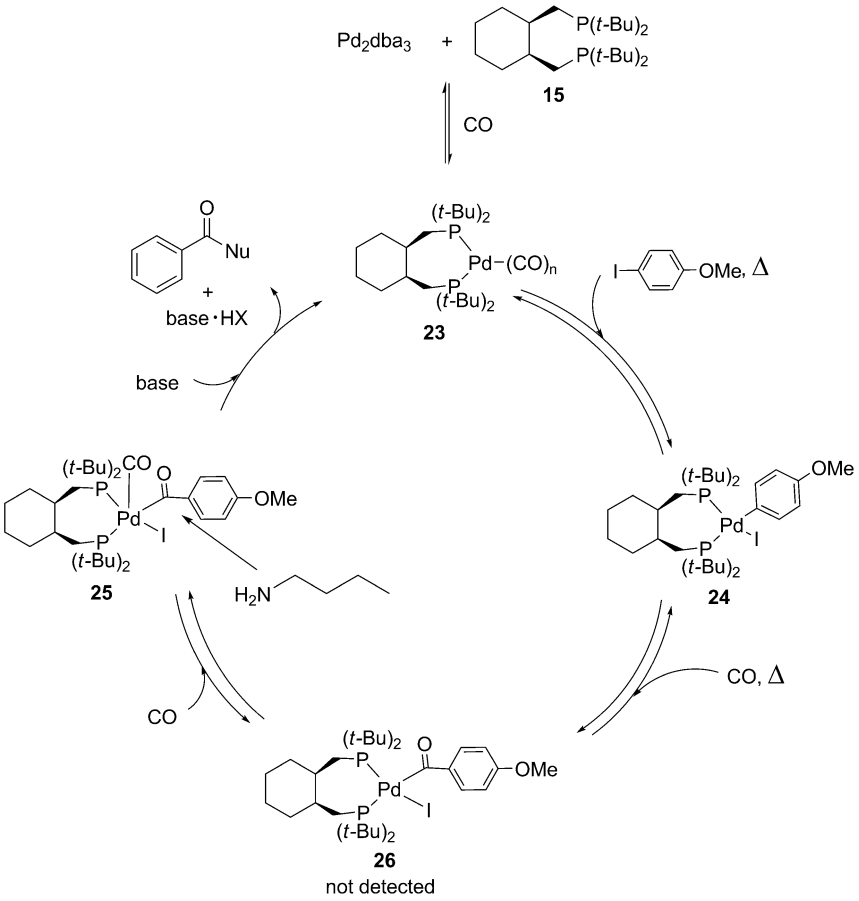
The $^{31}P\{^1H\}$ NMR spectrum of this solution at room temperature showed two new broad signals at 68.0 and 51.2 ppm. In addition, resonances corresponding to the oxidised ligand (64.3–62.8 ppm) were also detected. When the temperature was decreased to −90 °C, the broad signals resolved into two doublets at 74.2 and 50.4 ppm ($^2J_{P,P}=11$ Hz) (Figure 2, a), that were attributed to a palladium complex containing two conformationally inequivalent phosphorus atoms. The two signals corresponding to the free ligand were again detected. When a $^{13}C\{^1H\}$ NMR spectrum was recorded at −60 °C, a broad signal at 195.3 ppm was observed. The resonance was assigned to the palladium carbonyl diphosphine complex (**23**) according to previous reports in Pd-catalysed aminocarbonylation reaction (Scheme 3, a).[24] However, the coordination of a solvent molecule to the Pd centre of **23** cannot be discarded.

This result indicated that in the presence of carbon monoxide, the coordination of the bidentate ligand **15** to palladium rapidly yields the complex **23**. In the absence of CO no palladium/phosphine species were detected, probably due to the slow reactivity of the Pd complex under these conditions. Indeed, previous results from our group showed that $Pd_2(dba)_3$ slowly reacts in the presence of **15** to form [Pd(dba)(**15**)].[23]

At this point, 20 equivalents of 1-iodo-4-methoxybenzene with respect to palladium were added, and the solution was then heated for 1 hour at 60 °C and again cooled to −90 °C. The $^{31}P\{^1H\}$ NMR spectra acquired at this temperature showed the complete disappearance of the signals for **23**, while two new sets of two doublets at 54.8 and 15.0 ppm ($^2J=14$ Hz) and at 50.9 and 12.8 ppm ($^2J=14$ Hz) (ratio 3.5:1), were detected (Figure 2, b). These signals were attributed to the boat and chair conformers of the ligand in complex **24** (Scheme 2, b). Related isomers were previously detected in Pd-ethyl complexes.[23]

These isomers could also be detected by ^1H NMR *via* the presence in the aromatic region of two set of signals, at 8.18 and 6.46 ppm ($^3J=12.4$ Hz) for the major isomer and at 8.06 and 6.14 ppm ($^3J=12.4$ Hz) for the minor species. Additionally, in the $^{13}C\{^1H\}$ NMR spectra recorded at −60 °C, the four signals arising from quaternary aromatic carbons corresponding to two isomers, were detected at 164.2, 162.4, 161.8 and 161.1 ppm. No signals corresponding to CO containing species were detected.

Next, the solution was pressurised with 1 bar of carbon monoxide at room temperature and a $^{31}P\{^1H\}$ NMR spectrum was recorded at −90 °C. Signals corresponding to species **23** (at 74.2 and 50.4 ppm, $^2J=11$ Hz) and **24** at 54.8 and 15.0 ppm ($^2J=14$ Hz) and 50.9 and 12.8 ppm ($^2J=14$ Hz) (ratio 3.5:1) were readily detected. Additionally, two new sets of signals appeared as doublets at 72.9 and 42.8 ppm with a coupling constant of $J_{P,P}=26$ Hz. Two other broad singlets were detected at 63.9 and 40.3 ppm (Figure 2, c) and attributed to a palladium complex containing two conformationally inequivalent phosphorus atoms. The two signals corresponding to the free ligand were also detected. When the solution was heated for 15 min at 60 °C, the signals corresponding to the complex **24** were not detected anymore (Figure 2, d). Broad signals corresponding to the ligand oxide and to the free ligand **15** at 65 ppm and at 26 ppm were also present. In the $^{13}C\{^1H\}$ NMR spectra, two broad signals at 218 and 197 ppm were detected. These values are in agreement with the



Scheme 4. Proposed mechanism for the Pd-catalysed carbonylation of aryl iodides with the catalytic system Pd/**15**.

chemical shift of an acyl and a terminal CO group, respectively (Scheme 2, c).[24] In this context the two sets of signals present in the $^{31}P\{^{1}H\}$ NMR spectrum were attributed to the two conformers of the penta-coordinated carbonyl-acyl species **25**. The ^{1}H NMR spectrum showed two doublets at 7.91 and 6.13 ppm with a coupling constant of 13 Hz indicating again the presence of a unique acyl species.

Interestingly, when the solution containing **24** was pressurized with CO (1 bar), the species **23** was again observed, thus suggesting that the oxidative addition process is reversible. Indeed, the absence of nucleophile in this experiment rules out the regeneration of **23** through completion of the catalytic cycle. However, the presence of traces of water that could act as nucleophile and form the hydroxycarbonylation product cannot be discarded.

Next, *n*-butylamine (20 equiv.) was added at room temperature to the solution and the corresponding $^{31}P\{^{1}H\}$ NMR spectra exhibited broad signals previously attributed to **23**. When the mixture was cooled down to −90 °C the two doublets at 74.2 and 50.3 ppm, corresponding to **23**, were again detected (Figure 2, e).

Based on these results, a possible mechanism for the Pd-catalysed carbonylation of aryl iodides with the catalytic system Pd/**15** is proposed (Scheme 4). These results suggest that the species **23** is the resting state of the cycle under these conditions and undergoes oxidative addition of the substrate to form the complex **24** at 60 °C. Then, carbon monoxide coordination and insertion into the Pd−Ar bond affords the acyl species **25**, which yields the aminocarbonylated product after the nucleophilic attack.

Conclusions

The catalytic system Pd/**15** is very efficient in the Pd-catalysed aminocarbonylation of aryl iodides and provides high conversions and total selectivity to amides for a wide range of aryl iodides and amine nucleophiles under mild conditions. This is the most active and selective system reported to date for a broad range of substrates and nucleophiles.

In this study, the steric and electronic properties of the aryl substrates were observed to not affect the selectivity and only slightly impact on the conversion.

The NMR study described here led to the identification and characterisation of several intermediates of the catalytic cycle.

Experimental Section

General Procedure for the Pd-Catalysed Aminocarbonylation of Aryl Iodides

A tube was charged under an N_2 atmosphere with the corresponding aryl iodide (0.5 mmol), Pd_2dba_3 (0.005 mmol), the bidentate ligand **15** (0.011 mmol), pyridine (1 mmol) and the amine nucleophile (1.2 mmol) in dichloromethane (1 mL). Then, the tube was purged and pressurised with 1 bar of carbon monoxide. The reaction mixture was stirred at 45 °C for 14 h. After the reaction, the mixture was filtered over celite, and washed with water (3 × 5 mL). The organic phase was dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed under reduced pressure. The conversion and chemoselectivity were determined by GC-MS chromatography.

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