

Efficient heterogeneously catalyzed amidocarbonylation of bromoarenes based on a serinol-derived chelate diphosphine ligand

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Abstract

Although carbonylation of aryl halides is widely applied in synthesis, heterogeneous catalysts for this transformation are scarce. In order to heterogeneously catalyze the amidocarbonylation of bromoarenes, a polymer-supported catalytic system was assembled from Pd(dba)₂ and a polymer-bound diphosphine chelate, prepared via solid-phase synthesis from serinol. The system efficiently converts aryl bromides into carboxamides in a reaction with CO and aliphatic or aromatic amines. Comparison with other supported phosphine ligands demonstrated the superiority of the chelate diphosphine structure. Remarkably, partial complexation of the polymer-tethered ligating sites with Pd forms notably better catalytic systems than the full complexation. The reactivity pattern of the catalytic system points to the oxidative addition as the rate-determining step of the catalytic cycle.

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1. Introduction

The palladium-catalyzed carbonylation of aryl halides is widely applied in organic synthesis [1]. In general, soluble palladium complexes with phosphine or carbene ligands are used as the catalyst [2,3]. The choice of ligand allows the tuning of the catalytic activity and selectivity. Despite the potential benefits of using a heterogeneous catalyst in synthetic and industrial chemistry, there exist only a limited number of relevant examples of their use in these reactions [4,5]. While these catalytic systems functionalized iodoarenes and electron-deficient bromoarenes with high yields, only moderate yields were demonstrated for non-activated bromoarenes.

We recently reported the synthesis of sets of polymer-bound phosphine and phosphinite ligands from the common aminoalcohol template [6]. Fast screening of the Pd complexes of these ligands in the Heck reaction led to the demonstration of a promising reactivity of the complex of ligand **1** (Fig. 1) derived from serinol. Based on successful use of six-membered bisphosphine chelates in homogeneous carbonylations in the past [2b,c], we

decided to investigate the carbonylation reactions with the catalyst derived from **1**, choosing the amidocarbonylation reaction of bromobenzene as a model reaction (Scheme 1).

2. Experimental

2.1. General

All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Solvents were dried prior to use. Dry NMP was purchased from Sigma–Aldrich. Reagents were obtained from Sigma–Aldrich, Fluka, Strem Chemicals or Merck at the highest available purity and used as received. Pd(dba)₂ was prepared according to known procedure [7]. Merrifield resin and diphenylphosphinomethyl polystyrene resin were purchased from Novabiochem. All the supports used are 1% crosslinked divinylbenzene–styrene copolymer, 100–200 mesh, with loading 0.77–1.30 mmol/g. HPLC grade acetonitrile and water were purchased from Bio-Lab and Merck, respectively, and used after filtration. HPLC experiments were carried out using an Inertsil ODS-3v column on a Jasco instrument equipped with a UV–vis detector with acetonitrile and water as the eluting solvents.

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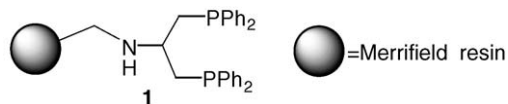
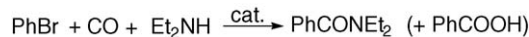


Fig. 1. Polymer-bound bisphosphine ligand derived from serinol.



Scheme 1. The model reaction.

^1H NMR (200, 400 MHz), ^{13}C NMR (50.4, 100.8 MHz) and ^{31}P NMR (81.3, 162.6 MHz) spectra were recorded on Bruker AVANCE-200 and AVANCE-400 spectrometers, in CDCl_3 or CDCl_3/TFA (1:1) using residual CHCl_3 (^1H , 7.26 ppm), or CDCl_3 (^{13}C , 77.0 ppm) as an internal standard. Gel-phase ^{13}C NMR (100.8 MHz) and ^{31}P NMR (162.6 MHz) spectra were recorded in benzene- d_6 , on a Bruker AVANCE-400 instrument using the solvent (^{13}C , 126.0 ppm) as an internal standard or H_3PO_4 , 85% (^{31}P , 0.0 ppm) as an external standard.

The yields of the polymer-bound ligands and complexes were determined using gel-phase ^{31}P NMR with an internal phosphorus-containing resin standard.

2.2. Synthesis: typical complexation procedure (for full complexation)

Bis(dibenzylideneacetone)palladium(0) (1.4 equiv.) was added to a suspension of **1** in THF. After 4 h of stirring, resin **2** was filtered off, washed with THF ($\times 3$) and DCM ($\times 2$) and dried in vacuo. Complexation efficiency: 100%. Gel-phase ^{31}P NMR (400 MHz, C_6D_6): δ 13.0 (m).

For partial complexation, the same procedure with the suitably adjusted amount of $\text{Pd}(\text{dba})_2$ was used.

2.3. Catalysis: typical catalytic procedure

Bromobenzene (0.053 ml, 0.5 mmol, 1 equiv.), diethylamine (0.2 ml, 2.0 mmol, 4 equiv.) and triethylamine (0.07 ml, 0.5 mmol, 1 equiv.) were added to the suspension of **2** (0.0125 mmol, 0.025 equiv. of Pd, two phosphines per Pd assumed) in 1 ml of NMP. The reaction was carried out in a pressure reactor. After evacuating the reactor and filling it with 70 psi of CO, the mixture was stirred overnight at 150 °C. The suspension was filtered and washed with acetonitrile. The filtrate was diluted with acetonitrile and analyzed by HPLC. For characterization, the solvent was evaporated and the product isolated from the mixture by column chromatography on silica gel with hexanes/EtOAc as eluents.

3. Results and discussion

During the preliminary studies, we found that only the catalyst prepared from $\text{Pd}(\text{dba})_2$ is active (Scheme 2). Presumably, complex **2** is formed under the complexation conditions. Gel-phase ^{31}P demonstrated a single broad multiplet at 13 ppm, in accordance with the value expected from the literature data [8].

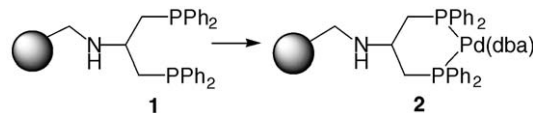
Scheme 2. Reagents and conditions: $\text{Pd}(\text{dba})_2$, THF, 4 h.

Table 1

The amidocarbonylation reaction of bromobenzene and diethylamine catalyzed by **2**^a

Entry	Catalyst 2 (%)	Temperature (°C)	Pressure (psi) ^b	Conversion (%)	Yield (%) ^c
1	10	150	70	100	91
2	5	150	70	100	95
3	2.5	150	70	100	89
4	1	150	70	74	72
5	1	110	70	42	40
6	1	150	40	42	40
7 ^d	10	150	70	86	81

^a Reaction conditions: 0.5 mmol bromobenzene, 2.0 mmol diethylamine, 0.7 mmol triethylamine and **2** in 2 ml NMP, 17 h.

^b Initial pressure at room temperature.

^c HPLC yield.

^d Catalyst recycled from entry 1.

In a series of experiments catalyst loading, temperature and pressure were optimized (Table 1). The results demonstrated that reasonable conversion and yield can be obtained even with 2.5% (molar) of the catalyst (Table 1, entry 3), although a higher catalyst percentage leads to somewhat better yields (Table 1, entries 1 and 2). Even with 1% catalyst, a 74% conversion of bromobenzene was achieved (Table 1, entry 4). Initially, benzoic acid, a product of the benzamide hydrolysis or, alternatively, a direct hydroxycarbonylation, was always present in the product mixture. Addition of molecular sieves to the reaction mixture practically eliminated this problem.

Moderate conversion could be achieved at an even lower temperature or CO pressure (Table 1, entries 5 and 6). In the experiment performed with a sufficient amount of resin (tens of milligrams) we were able to recycle the catalyst, albeit with somewhat reduced activity (Table 1, entry 7).

We decided to compare the activity of catalyst **2** with other supported phosphine complexes of the $\text{Pd}(\text{dba})_2$ fragment. Ligands **3** and **4** (Fig. 2), the synthesis of which we reported previously [6,9], and a commercially available phosphine, resin **5**, were complexed with $\text{Pd}(\text{dba})_2$ to yield the corresponding complexes (**6**, **7**, **8**) with 100% conversion.

The results of amidocarbonylation with these ligands (Table 2) demonstrate clear superiority of catalyst **2** over others

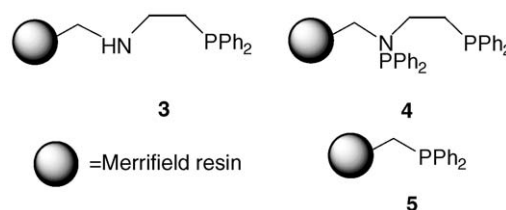
Fig. 2. Polymer-bound ligands compared with **1** in this study.

Table 2
The amidocarbonylation of bromobenzene with diethylamine using different catalysts^a

Entry	Catalyst	Conversion (%)	Yield (%) ^b
1	2	100	89
2	6	14	8
3	7	31	29
4	8	34	32

^a Reaction conditions: 0.5 mmol bromobenzene, 2.0 mmol diethylamine, 0.7 mmol triethylamine and the catalyst (0.012 mmol Pd) in 2 ml NMP under 70 psi CO, 150 °C, 17 h.

^b HPLC yield.

in this reaction. Notably, ligand **1** is a bidentate phosphine ligand, while the others are not (ligand **4** is not truly a bidentate phosphine since one of the phosphorus-containing groups is actually an amidophosphine). Obviously, there is a clear advantage to using bidentate over monodentate phosphine ligands in this catalytic system. It is known that the chelate effect can increase the activity of the catalyst, and thus, lead to better performance [2c,10].

In order to further test the catalytic activity of **2**, amidocarbonylation with different amines and aryl bromides was studied (Table 3). The reactions were carried out under the aforementioned optimized conditions with 2.5% of the catalyst. All benzamides were obtained with high yields. Remarkably, the use of aromatic amines (Table 3, entries 1 and 3) led to high yields. While the aryl bromide with an electron-withdrawing substituent (Table 3, entry 4) was, under these conditions, fully converted into the correspondent amide, a slight decrease in conversion of the aryl bromide with an electron-donating substituent was observed (Table 3, entry 5). This result reflects the ease of oxidative addition of the various bromides and may point to oxidative addition as the rate-determining step of the catalytic cycle [11].

An additional parameter, examined after the aforementioned studies, was the influence of the partial complexation of the ligand-functionalized resin on the catalytic reaction outcome. Remarkably, Table 4 demonstrates that the increase of the P:Pd complexation ratio has a dramatic effect on the yield of amidocarbonylation. Thus, the 72% yield observed with a 2:1 ratio (fully complexed system, entry 1) turns into quantitative yield for an 8:1 ratio (partial complexation, on average one in four sites is occupied by Pd, entry 3). Qualitatively, we observed

Table 3
The amidocarbonylation reaction with different aryl bromides and amines^a

Entry	Amine	Aryl bromide	Conversion (%)	Yield (%) ^b
1	PhNH ₂	PhBr	92	87
2	PhCH ₂ NH ₂	PhBr	100	97
3	<i>p</i> -ClC ₆ H ₄ NH ₂	PhBr	100	97
4	Et ₂ NH	<i>p</i> -OHCC ₆ H ₄ Br	99	97 ^c
5	Et ₂ NH	<i>p</i> -CH ₃ C ₆ H ₄ Br	83	65

^a Reaction conditions: 0.5 mmol aryl bromide, 2.0 mmol amine, 0.7 mmol triethylamine and 0.012 mmol **2** in 2 ml NMP under 70 psi CO, 150 °C, 17 h.

^b HPLC yield.

^c Part of the product is oxidized to mono-*N,N*-diethylamide of terephthalic acid.

Table 4
The amidocarbonylation of bromobenzene with diethylamine using different complexation ratios of Pd(dba)₂ to **1**^a

Entry	P:Pd ratio	Conversion (%)	Yield (%) ^b
1	2:1	74	72
2	4:1	80	80
3	8:1	100	98

^a Reaction conditions: 0.5 mmol bromobenzene, 2.0 mmol diethylamine, 0.7 mmol triethylamine and the catalyst (0.005 mmol Pd) in 2 ml NMP under 70 psi CO, 150 °C, 17 h.

^b HPLC yield.

reduced precipitation of Pd black when a partially complexed resin was used as a catalyst. Obviously, additional empty ligating sites help in the recapture of ‘naked Pd(0)’ fragments which dissociate from the bisphosphine ligands due to high temperature. This has a stabilizing effect on the catalyst, prolongs its life and increases the conversion and yield of the reaction. A similar effect of improved catalytic performance, upon increasing the P:Pd ratio, was reported for supported monodentate phosphines in the Heck reaction [12], but never for bidentate ligands or carbonylation processes.

4. Conclusions

We have described a novel supported catalytic system for amidocarbonylation of aryl bromides. The superiority of the complex over various relevant analogues was demonstrated. Furthermore, we exposed the positive effect of partial complexation on the performance of the catalyst, probably as a result of reduced precipitation of Pd metal from the system. Some of our results point to the oxidative addition step of the cycle as the rate-determining step. Studies directed at additional improvement of the stability and recyclability of the catalyst, as well as expanding the scope of the carbonylation reactions catalyzed by this system, are underway.

Acknowledgments

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