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Efficient Carbonylation of Aryl and Heteroaryl Bromides using a Palladium/Diadamantylbutylphosphine Catalyst

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Abstract: A general palladium-catalyzed alkoxycarbonylation of aryl and heteroaryl bromides has been developed in the presence of bulky monodentate phosphines. Studies of the butoxycarbonylation of three model substrates revealed the advantages of di-1-adamantyl-*n*-butylphosphine compared to other ligands. In the presence of this catalyst system various bromoarenes provided the corresponding benzoic acid derivatives (ester, amides, acids) in excellent yield at low catalyst loadings (0.5 mol% Pd or below).

Keywords: alkoxycarbonylation; aryl halides; benzoic acid esters; carbonylation; monodentate ligands

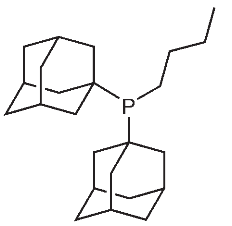
Introduction

Palladium-catalyzed carbonylations of aryl halides (or halide equivalents) represent a valuable tool for the selective introduction of carboxylic acid derivatives onto aromatic frameworks.[1] Originally, these reactions were established in the mid-1970s by the pioneering work of R. F. Heck and co-workers.[2] Since that time, carbonylations of haloarenes have found a number of applications in organic synthesis,[3] and even related industrial processes, such as the alkoxycarbonylation of a benzylic alcohol toward ibuprofen, have been realized on a multi-1000 ton scale.[4]

In the last decade, significant progress with respect to the development of more general and productive palladium catalysts for various coupling reactions has been reported. On the other hand, fewer improvements are known regarding the carbonylation of aryl halides. This is demonstrated by comparing known catalyst productivity (turnover number, TON), e.g., for a simple Suzuki reaction (in general TON = 100,000 to 1,000,000) and the carbonylation of bromoanisole (typically TON = 100).

The difficulty of more efficient palladium catalysis in the presence of a large excess of carbon monoxide is a result of the π-acceptor character of CO. Here, the activity of the catalyst towards oxidative addition is reduced, due to the binding of carbon monoxide to the metal centre. Moreover, clustering and agglomeration of Pd atoms is facile in the presence of CO, leading to non-active palladium species.[5] A solution to these problems can be the use of palladium catalysts containing the highly basic bidentate[6] or monodentate phosphines.[7] The drawbacks of these catalyst systems for larger scale applications are, however, the difficult synthesis and the highly sensitive nature of the often pyrophoric ligands.

For some time we have been involved in the development of novel palladium catalysts for various coupling reactions of aryl halides, which should be also applicable on an industrial scale.[8,9] Recently developed ligands from our side which fulfill this requirement include di-1-adamantylalkylphosphines,[10] and *N*-arylated 2-heteroaryldialkylphosphines.[11] The corresponding phosphines lead to highly active catalysts, but are comparably stable to air and moisture, and thus easy to handle. Based on our experience in carbonylation chemistry,[12] we started a program to explore the potential of these ligands in different carbonylation reactions of aryl halides. Initial results demonstrated the superiority of di-1-adamantylbutylphosphine (cata*CX*ium® A; Scheme 1) in formylation reactions with synthesis gas.[13] Here, we describe for the first time the use of these ligands in carbonylations, which led to a general and efficient palladium



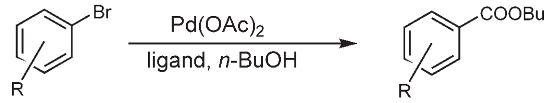
Scheme 1. Structure of di-1-adamantylbutylphosphine (cata*CX*ium® A).

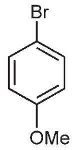
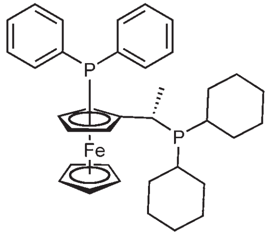
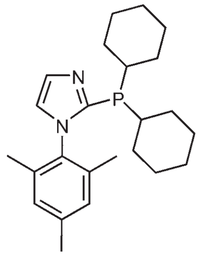
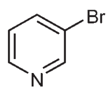
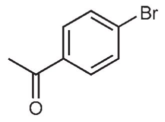
catalyst for alkoxy-, amino-, and hydroxycarbonylations of aryl and heteroaryl bromides.

Results and Discussion

Initially, the alkoxycarbonylation of 4-bromoanisole (deactivated aryl bromide) with *n*-butanol was investigated in the presence of nine different phosphines (Table 1, entries 1–9). Typically all experiments were carried out in a 6-fold parallel autoclave (reaction volume 4 mL), which allows fast testing of catalysts and variation of reaction conditions. In order to ensure reproducibility some experiments have been repeated on a 300 mL scale. For practical relevance the carboxylation experiments were carried out with 0.5 mol% catalyst loading at 115 °C and 20 bar of carbon monoxide. For the stabilization of the palladium catalyst and to prevent the formation of palladium

Table 1. Butoxycarbonylation in the presence of different ligands.[a]



Entry	(Hetero)aryl bromide	Ligand	TMEDA [equivs.]	Time [h]	Conversion by GC [%]	Yield by GC [%]
1		cata*CX*ium® A	0.6	18	96	94
2		PPh_3	0.6	18	18	18
3		$P(t\text{-}Bu)_3$	0.6	18	100	93
4		PCy_3	0.6	18	2	2
5		dppf	0.6	18	97	84
6		dppp	0.6	18	32	29
7		dppb	0.6	18	34	30
8			0.6	18	46	40
9			0.6	18	79	70
10		cata*CX*ium® A	0.75	12	86	69
11		$P(t\text{-}Bu)_3$	0.75	12	74	56
12		cata*CX*ium® A	0.75	12	88	79
13		$P(t\text{-}Bu)_3$	0.75	12	80	65

[a] *Reaction conditions:* 2 mmol bromo(hetero)arene, 0.5 mol% $Pd(OAc)_2$, 1.5 mol% ligand, 2 equivs. hexadecane (internal standard), 2 mL *n*-butanol, 20 bar CO, 115 °C.

carbonyl clusters a three-fold excess of the ligand (P/Pd = 3:1) was used.

As shown in Table 1 di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A) and $P(t\text{-}Bu)_3$ permit efficient butoxycarbonylation of 4-bromoanisole (93–94%; Table 1, entries 1, 3). 1,1′-Bis(diphenylphosphino)ferrocene (dppf) and the dicyclohexyl-2-(*N*-mesityl)imidazolylphosphine gave slightly lower yields (70–84%) of the desired product (Table 1, entries 5, 9). On the other hand PPh_3, PCy_3 and standard bidentate ligands such as 1,3-bis(diphenylphosphino)propane (dppp) or 1,4-bis(diphenylphosphino)butane did not lead to high conversion (<50%) and ester formation (2–30%) (Table 1, entries 2, 4, 6, 7). Comparing entries 4 and 9 demonstrates the importance of sterically hindered substituents on the phosphorus atom. Due to the similar performance of di-1-adamantylbutylphosphine and $P(t\text{-}Bu)_3$ both ligands were tested further with 3-bromopyridine and 4-bromoacetophenone. Here a higher yield of the corresponding ester was obtained with di-1-adamantylbutylphosphine as ligand. Interestingly aryl keto esters resulting from double carbonylations were observed as side products (5–10%) in these reactions. Therefore, we studied the influence of the carbon monoxide pressure more closely (Figure 1).

Excellent conversion (97%) and selectivity (>99%) is obtained already at 5 bar.[14] High conversion is seen up to 50 bar, however the selectivity is continuously decreased due to the formation of the double carbonylated product. At higher CO pressure also deactivation of the catalyst becomes more pronounced.

Next, we investigated the general scope of our catalyst system for the alkoxycarbonylation of different aryl and heteroaryl bromides (Table 2). High conversion (>95%) and excellent selectivity (>98%) were observed for the alkoxycarbonylation of various mono-substituted aryl bromides such as 3-[12c] and 4-bromoanisoles, 4-bromobenzonitrile, 4-(dimethylamino)-bromobenzene, 4-bromo-chlorobenzene, and 3,4,5-trifluorobenzene (Table 2, entries 3, 4, 6, 9, 15, 16). In general, there is no difference between electron-rich substrates (bromoanisoles, bromoaniline) and electron-deficient ones (bromobenzonitrile). 2-Bromobenzonitrile (86%), 1-bromo-3,4-methylendioxobenzene (83%), and 2,5-bis(trifluoromethyl)benzene (71%) also reacted well. The method works also with different heteroaryl halides (3-bromothiophene, 3-bromobenzothiophene, 2-[15] and 3-bromopyridine[12c], 6-bromoquinoxaline). At this point it is important to note that heteroaromatic carboxylic acid derivatives are particularly useful intermediates for the synthesis of a number of agrochemicals.[16] With respect to minimization of the catalyst loading one should note that the model reaction of 4-bromoanisole works well at a 0.05 mol% Pd loading, however, a further decrease of palladium resulted in a significant decrease of conversion.

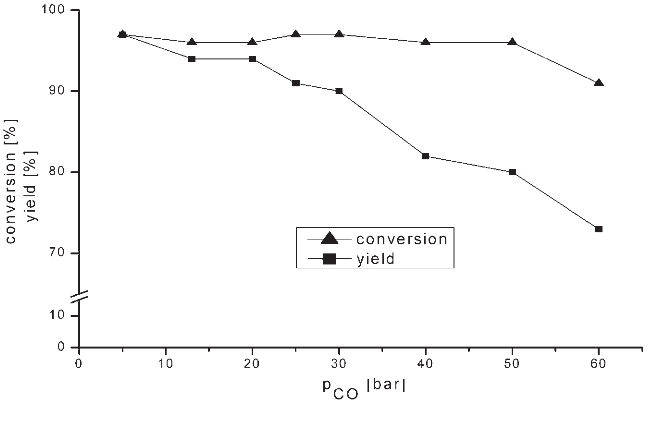


Figure 1. Influence of the carbon monoxide pressure on conversion and yield. *Reaction conditions:* 2 mmol 4-bromoanisole, 0.5 mol% $Pd(OAc)_2$, 1.5 mol% cata*CX*ium® A, 0.6 equivs. TMEDA, 0.2 equivs. hexadecane (internal standard), 0.3 mL *n*-BuOH, 115 °C, 16 h.

Finally, we also studied the reaction of 4-bromoanisole with different nucleophiles (Table 3). In addition to methanol, ethanol, primary and secondary amines, as well as pyrrole and water led to good yield (64–89%) and good to excellent selectivity (73–>99%).

Conclusions

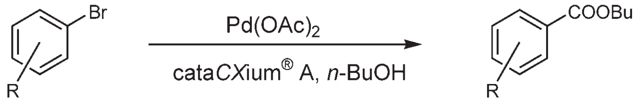
In conclusion, we have presented a general carbonylation procedure for the synthesis of aromatic and heteroaromatic esters, amides, and acids from the corresponding bromides. Best results are obtained at comparatively low pressure (5 bar) using cata*CX*ium® A as ligand. Due to the efficiency and easy handling of the catalyst we believe that this novel carbonylation protocol will allow one to perform such reactions on an industrial scale.[17]

Experimental Section

General Remarks

Butanol and toluene were purified by distillation from CaH_2 and from Na. Unless otherwise noted, all reagents were used as received from commercial suppliers. Silica gel column chromatography was performed with 230–400 mesh ASTM silica gel from Merck. Melting points were recorded on a Galen III (Cambridge Instruments) and are uncorrected. IR spectra of solids were recorded using KBr plates or KBr pellets on a Nicolet Magna 550. Mass spectra were obtained on an AMD 402/3 of AMD Intectra (EI, 70 eV). NMR data were recorded on a Bruker ARX 400 with a QNP probe head (^1H, 400.13 MHz; ^{13}C, 100.61 MHz) at 25 °C. GC analyses were performed on an HP 6890 equipped with a HP-5 capillary column (5% diphenylsiloxane,

Table 2. Butoxycarbonylation of various aryl and heteroaryl bromides.[a]



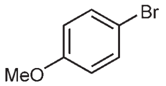
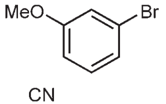
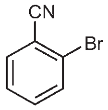
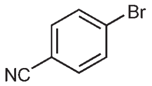
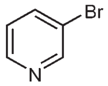
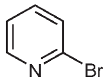
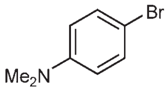
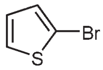
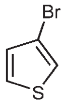
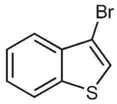
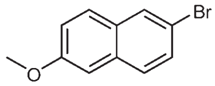
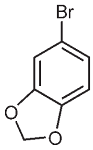
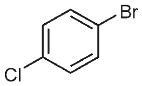
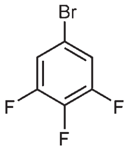
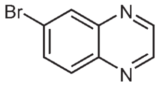
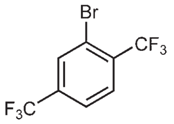
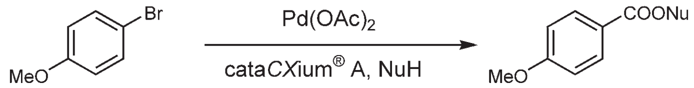
Entry	Bromo(hetero)arene	$Pd(OAc)_2$ [mol%]	cata*CX*ium® A [mol%]	Temperature [°C]	Conversion[b] [%]	Ester[b] [%]	Selectivity[b] [%]
1		0.01	1	125	39	34	87
2		0.05	1	125	85	82	96
3		0.5	1.5	115	97	97	100
4		0.5	1.5	115	100	99	99
5		0.5	1.5	115	100	86	86
6		0.5	1.5	115	100	98	98
7		0.5	1.5	115	100	91	91
8		0.5	1.5	115	100	99	99
9		0.5	1.5	125	100	99	99
10		0.5	1.5	115	69	52	75
11		0.5	1.5	115	100	84	84
12		0.5	1.5	115	100	99	99
13		0.5	1.5	115	100	99	99
14		0.5	1.5	115	86	83	96
15		0.5	1.5	115	100	99	99
16		0.5	1.5	115	96	94	98
17		0.5	1.5	115	100	98	98

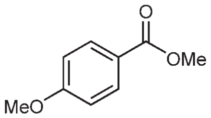
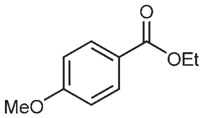
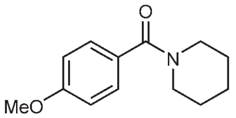
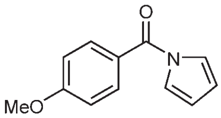
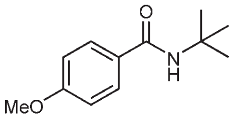
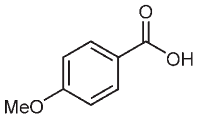
Table 2. (Continued)

Entry	Bromo(hetero)arene	$Pd(OAc)_2$ [mol%]	cata*CX*ium® A [mol%]	Temperature [°C]	Conversion[b] [%]	Ester[b] [%]	Selectivity[b] [%]
18		0.5	1.5	115	82	71	87

[a] *Reaction conditions:* 2 mmol bromo(hetero)arene, 0.75 equivs. TMEDA, 0.2 equivs. hexadecane (internal standard), 2 mL *n*-butanol, 5 bar CO, 16 h.
[b] Determined by GC.

Table 3. Carbonylation of 4-bromoanisole with different nucleophiles.[a]



Entry	Nucleophile	Temperature [°C]	Product	Yield by GC [%]	Selectivity by GC [%]
1	MeOH	115		78	99
2	EtOH	115		86	99
3	piperidine	115		63	85
4	pyrrole	125		64	80
5	*t*-butylamine	115		73	73
6	H_2O[b]	115		89	98

[a] *Reaction conditions:* 2 mmol 4-bromoanisole, 0.5 mol% $Pd(OAc)_2$, 1.5 mol% cata*CX*ium® A, 0.75 equivs. TMEDA, 0.2 equivs. hexadecane (internal standard), 0.2 mL toluene, 1.8 mL nucleophile, 5 bar CO, 30 bar N_2, 16 h.
[b] 0.4 mL H_2O in 1.6 mL 1,4-dioxane.

95% dimethylsiloxane, L=30 m, d=250 μm, d_{film}=0.25 μm) and an FID detector. Quantitative GC analyses were referenced to internal hexadecane. All new compounds were characterized by ^1H and ^{13}C NMR spectroscopy, IR, and high resolution MS (see Supporting Information). The following compounds have already been reported in the literature: butyl esters (Table 2, entries 4,[12c] 7,[12c] 8[15]), methyl and ethyl esters (Table 3, entries 1,[18] 2[18]) and amides (Table 3, entries 4,[19] 5[20]).

General Procedure for the 6-fold Parallel Autoclave

A 50 mL Schlenk flask was charged with $Pd(OAc)_2$ (22.5 mg, 0.5 mol%), cata*CX*ium® A (108 mg, 1.5 mol%) and *n*-butanol (20 mL). Subsequently, hexadecane (1.17 mL, internal GC standard) and TMEDA (*N,N,N′,N′*-tetramethylethylenediamine) (2.25 mL, 15 mmol) were added. 2.34 mL of this clear yellow stock solution were transferred to the 6 vials (4 mL reaction volume) equipped with a septum, a small cannula, a stirring bar and 2 mmol of the corresponding aryl bromide. The vials were placed in an alloy plate, which was transferred to a 300 mL autoclave of the 4560 series from Parr Instruments® under an argon atmosphere. After flushing the autoclave three times with CO a pressure of 5 bar CO was adjusted at ambient temperature and the reaction was performed for 16 h at 115 °C. Before and after the reaction an aliquot of the reaction mixture was subjected to GC analysis for determination of yield and conversion.

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