Carbonylation

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Palladium-Catalyzed Aminocarbonylation of Aryl Chlorides at Atmospheric Pressure: The Dual Role of Sodium Phenoxide**

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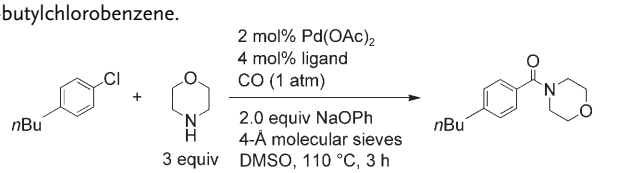
Since Heck's seminal reports in 1974, palladium-catalyzed carbonylation has emerged as an indispensable method for the regioselective installation of carbonyl functional groups and remains an area of active research.[1,2] Among the aryl halides, aryl chlorides are particularly attractive starting materials for these transformations, as they are both inexpensive and commercially abundant.[3] The relative chemical inertness of the aryl chlorides also makes them more challenging substrates,[3] and aryl chloride carbonylation methodologies remain underdeveloped compared to those of the more expensive aryl bromide,[4] iodide,[5] and triflate[6] variants.

In particular, only limited methods exist for the preparation of amides from unactivated aryl chlorides (aminocarbonylation). Nearly 20 years ago, Milstein and co-workers demonstrated that the bulky, electron-rich bidentate phosphine ligand bis(diisopropylphophino)propane (dippp) is an effective ligand in palladium-catalyzed aryl chloride carbonylation.[7a] However, the reaction requires high temperature (150 °C) and high CO pressure (70 psi). While highly significant, this study was limited in scope (it only included three examples of aminocarbonylation) and did not address functional-group compatibility, the effects of *ortho* substituents, or the use of reagents other than dialkyl amines. Moreover, the reaction conditions dramatically limit the utility of this method in preparative chemistry because of the high temperature, the need for specialized pressure reactors, and the dangers associated with handling pressurized CO. Recently, Beller and co-workers have shown that lower CO pressures can be used in aryl chloride carbonlyation reactions (1 bar) when electron-rich bidentate bisphosphine ligands based upon ferrocene are employed.[7b,c] However, like Milstein's report, this study focused primarily on the formation of esters (alkoxycarbonylation), with only a single aminocarbonylation (chlorobenzene and di-*n*-propylamine) being reported. Furthermore, reactions in this later study also required high reaction temperatures (145 °C). Finally, Lagerlund and Larhed have reported microwave conditions for aryl chloride aminocarbonylation.[7d] Although greater substrate scope was demonstrated in this study, hexacarbonylmolybdenum was required as a CO surrogate, and the reaction cannot be performed under standard thermal conditions. Like the previous reports, high temperatures (170 °C) are required. Thus, further development in this area is clearly needed.

Herein, we report a general and practical method for the aminocarbonylation of aryl chlorides. The reported reactions proceed at atmospheric CO pressure and moderate temperatures, and these conditions have been employed for a wide range of aryl chlorides and amines. Unlike many new methods employing palladium catalysis, successful development of this chemistry did not hinge on a particular precatalyst/ligand combination. Rather, the critical advance was the use of sodium phenoxide as the basic additive, which acts both as a base and as an acyl transfer agent, thereby facilitating an otherwise challenging transformation.

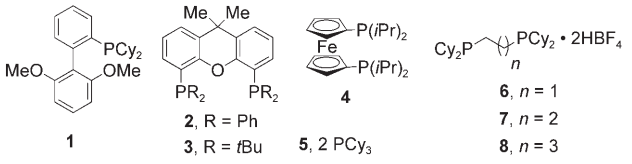
For the initial experiments, 4-*n*-butylchlorobenzene, 3-chloroanisole, and morpholine were chosen as test substrates, and reactions were conducted under balloons filled with CO (Tables 1 and 2). As was found in previous studies, ligand screening indicated that electron-rich, bulky bisphosphines were the most effective. Herein, 1,3-bis(dicyclohexylphosphino)propane[8] (dcpp) was the most efficient ligand of those screened, and it could be introduced as the air-stable tetrafluoroboric acid adduct. It is of note that, as in previous

Table 1: Optimization of atmospheric-pressure aminocarbonylation of 4-*n*-butylchlorobenzene.



Ligand	**1**	**2**	**3**	**4**	**5**[a]	**6**	**7**	**8**
Conversion [%]	6	1	6	8	7	61	92	14
Yield (GC) [%]	0	0	0	4	0	57	91	7

[a] $[(Cy_3P)_2PdCl_2]$ employed; Cy = cyclohexyl.



1

2, R = Ph
3, R = *t*Bu

4

5, 2 PCy_3

6, *n* = 1
7, *n* = 2
8, *n* = 3

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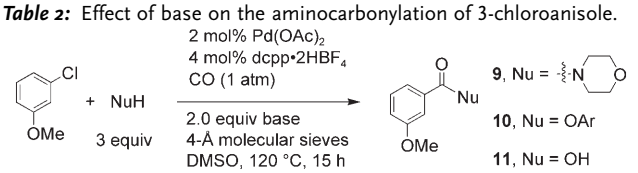
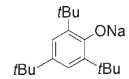
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

studies, a three-carbon linker between the phosphorous atoms proved optimal.[7a–c] We believe that the ligand having this linker, in addition to being electron-rich and bulky, may be a critical requirement of the ligands in these transformations.[9] Further optimization revealed that anhydrous DMSO was the optimal solvent. In general, exclusion of extraneous water, accomplished through the use of activated 4-Å molecular sieves, was necessary to obtain high yields.

As mentioned above, the identity of the base proved critical to the success of the carbonylation reaction (Table 2). Initial screening of standard basic additives failed to provide

Table 2: Effect of base on the aminocarbonylation of 3-chloroanisole.



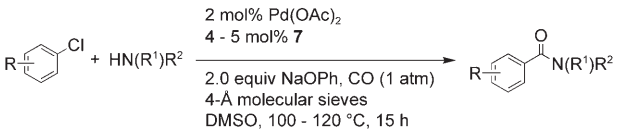
Entry	Base	Conversion ArCl [%]	Yield [%] 9	10	11
1	nPr_3N	11	11	–	–
2	Na_2CO_3	94	52	–	38
3	Cs_2CO_3	>99	8	–	n.d.[a]
4	K_3PO_4	>99	62	–	n.d.
5	DBU	78	25	–	n.d.
6	Na_2CO_3/25% PhOH	>99	70	–	n.d.
7	PhONa	>99	>99	–	–
8		>99	76	22	–
9		80	60	<2	n.d.

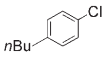
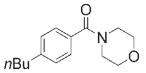
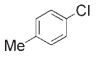
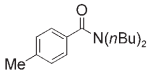
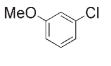
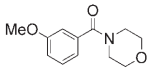
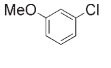
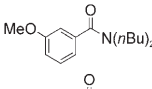
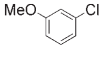
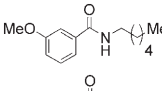
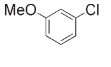
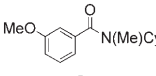
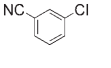
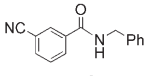
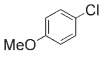
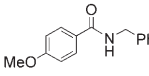
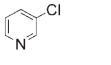
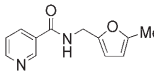
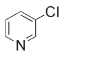
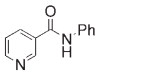
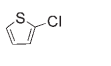
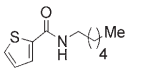
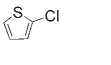
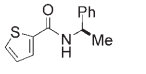
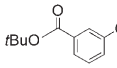
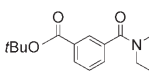
[a] Not determined.

high yields of the desired amide product. The use of sodium carbonate resulted in the formation of a significant amount of carboxylic acid. On the other hand, the use of anhydrous organic bases, such as tri-*n*-propylamine or 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), resulted in very low conversion of the aryl chloride. We hypothesized that the problematic step in the catalytic process might be transfer of the acyl group from the palladium center to the amine and decided to explore additives that might act as acyl transfer agents to facilitate this process. Consistent with this reasoning, the addition of phenol to the reaction mixture provided a modest increase in the observed yield of amide **9**. The use of anhydrous sodium phenoxide (NaOPh) as base resulted in even more dramatic improvements, providing complete conversion of the aryl chloride and an excellent yield of the desired amide. Sterically hindered phenoxides were also examined but did not perform as well.

To determine the scope of this process, many different aryl chlorides and amines were employed as substrates (Table 3). Primary, secondary, and aromatic amines are all readily converted into amides. Additionally, electron-rich, -neutral, and -poor aryl chlorides are all compatible with these aminocarbonylation conditions. Aryl chlorides with *ortho* substituents were also well-tolerated (Table 3, entry 15). For

Table 3: Substrate scope of atmospheric-pressure aminocarbonylation with **7**.[a,b]



Entry	ArCl	Amine	Product	Yield [%]
1				88[c,d]
2		$(nBu)_2NH$		79[e]
3				88
4		$(nBu)_2NH$		85[e]
5				93[f]
6				97[c,g]
7		Cy(Me)NH		93[e,h]
8				65
9				98[d]
10				92
11				92
12				99
13		 99% *ee*		94
14				75
15				86[c,d]

[a] Reaction conditions: 2 mol% $Pd(OAc)_2$, 4–5 mol% **7**, 1 mmol aryl chloride, 3 mmol amine, 2 mmol NaOPh, 150 mg 4-Å molecular sieves in DMSO (1 mL) at 100 °C for 15 h. [b] Yields (of isolated product) are an average of two runs. [c] Reaction time 4 h. [d] Reaction temperature 110 °C. [e] Reaction temperature 120 °C. [f] Reaction time 3 h. [g] Less catalyst used: 0.5 mol% $Pd(OAc)_2$, 2 mol% **7**. [h] 4 equiv of amine used.

these substrates, the reactions proceeded at 100–110 °C. The combination of a primary amine and an electron-poor aryl chloride can be successfully transformed to the corresponding benzamide in 4 h using only 0.5 mol% catalyst (Table 3, entry 6). Not surprisingly, acyclic secondary amines require higher temperatures to afford complete transformation to the desired amide (Table 3, entries 2, 4, and 7). However, in no case were temperatures in excess of 120 °C required, which is a considerably lower temperature than in previously reported conditions. While methyl esters underwent amidation under

these reaction conditions, other functional groups, such as the *t*-butyl ester and nitrile groups, remained intact (Table 3, entries 8 and 14). Heteroaryl chlorides, such as 3-chloropyridine and 2-chlorothiophene, were converted into the corresponding benzamides without complications (Table 3, entries 10–13).

To gain evidence for the proposed role of NaOPh in these transformations, the reaction of 3-chloroanisole and di-*n*-butylamine was monitored using in situ IR spectroscopy. In the initial kinetic experiments, $Pd(OAc)_2$ (2 mol%) and **7** (4 mol%) were used as the catalytic additives. These reactions displayed a variable initiation period, presumably owing to the reduction of $Pd(OAc)_2$ to Pd^0. To improve reproducibility in the kinetic experiments, we prepared [(dcpp)PdPhCl] (**12**) from dcpp and $[(Ph_3P)_2PdPhCl]$ as the monotoluene solvate. Using **12** (2 mol%) and **7** (2 mol%) as the precatalyst eliminated the initiation period.

Figure 1 shows the reaction profile as determined by in situ IR spectroscopy resulting from the combination of 3-chloroanisole, di-*n*-butylamine, and NaOPh under catalytic conditions at 120°C. A signal at 1736 cm^{-1}, corresponding to

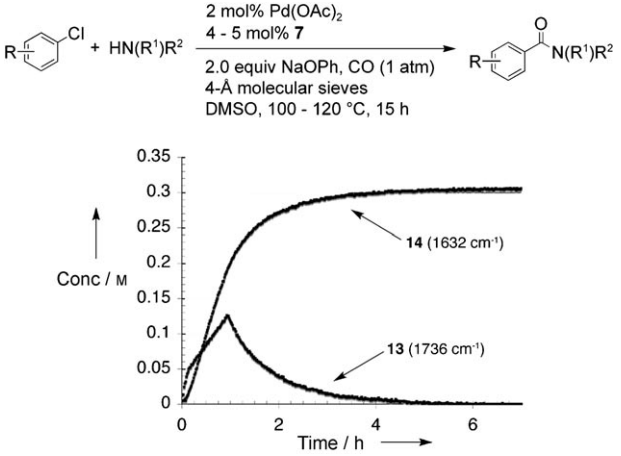
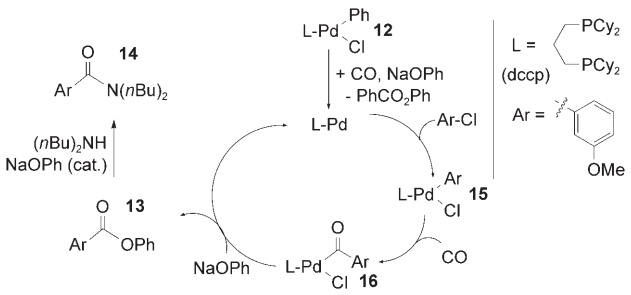


Figure 1. Kinetic profile for the reaction of di-*n*-butylamine and 3-chloroanisole.

phenyl 3-methoxybenzoate **13**, was observed at the beginning of the reaction. This signal reached a maximum intensity after about 1 h, and then slowly decayed. Additionally, a signal at 1632 cm^{-1}, corresponding to amide **14**, was observed a few minutes after the beginning of the reaction and continued to increase in intensity for approximately 5 h. At the end of the reaction, the aryl chloride and **13** had been completely consumed, and **14** was formed in 88% yield (determined by GC). Thus, as predicted, phenyl ester **13** appears to be an intermediate in the formation of amide **14**.

To further confirm the intermediacy of the ester, we examined the kinetics of the conversion of ester **13** to amide **14**. Surprisingly, combining ester **13** and di-*n*-butylamine in DMSO at 120°C resulted only in the very slow formation of amide **14** ($t_{1/2} \approx 10$ h). However, when the same reaction was conducted in the presence of NaOPh (1 equiv), rapid conversion ($t_{1/2} \approx 12$ m) of ester **13** to amide **14** was observed.[10]

The above observations suggest that sodium phenoxide is playing two distinct roles in the formation of amide **14** (Scheme 1). First, owing to its greater nucleophilicity com-



Scheme 1. Proposed reaction pathway for reactions involving acyclic secondary amines.

pared to di-*n*-butylamine, NaOPh intercepts the palladium acyl species resulting from oxidative addition of the aryl chloride and migratory insertion of CO[11] and leads to the formation of **13**.[12,13] We suspect that this lower energy pathway, involving intermediate ester **13**, is the critical feature that allows lower operational temperatures in this method compared to previously reported systems that employ similar ligand/metal systems. Second, NaOPh acts as a Brønsted base in catalyzing the conversion of the intermediate phenyl ester to the amide product. The phenoxide anion may also play a role as a ligand to the metal center by displacement of chloride. However, at this point we have no evidence to support this suggestion. Ongoing studies are directed at further elucidation of these subtle mechanistic details.

In conclusion, we have developed a general, practical protocol for the aminocarbonylation of aryl chlorides at atmospheric pressure of CO. Electron-deficient, -neutral and -rich aryl chlorides were all successfully transformed into the corresponding amides. Primary, α-branched primary, cyclic secondary, acyclic secondary, and aryl amines were all productive in the reaction. Furthermore, the process tolerates functional groups and utilizes an inexpensive, air-stable, and commercially available ligand salt. Like previous studies in this area, the optimal ligand proved to be an electron-rich bulky bisphosphine. However, the critical innovation in this process was the use of sodium phenoxide as the basic additive. In addition to acting as a base, this reagent facilitates acyl transfer through the formation of phenyl esters as intermediates and catalyzes the conversion of phenyl ester into the final amide product. This route has resulted in lower reaction temperatures and CO pressures in the aminocarbonylation process, which greatly improves both the practicality and safety profile of this transformation, and for the first time has resulted in a general method for the aminocarbonylation of aryl chlorides. The dual role of NaOPh revealed during this study underscores the concept that ligands alone, while important for success in developing a method, are not the only reaction parameter that needs to be considered. In this case, consideration of the potential reactive intermediates

resulted in the introduction of an unusual basic additive and allowed alternate reaction pathways to proceed, resulting in the successful development of this methodology.

Experimental Section

General procedure (NOTE: Carbon monoxide should only be handled in a well-ventilated fume hood.): An oven-dried culture tube (18 × 150 mm, VWR) or screw-cap test tube equipped with a teflon-coated magnetic stir bar was charged with 4-Å molecular sieves and sealed with a 14/20 rubber septum (inverted) or screw cap and teflon-lined septum. The tube was then evacuated, heated for about 1 min with a Bunsen burner or for about 2–3 min with a heat gun to activate the molecular sieves; the tube was then backfilled with argon and allowed to cool. Subsequently, the tube was taken into a glovebox (a needle was inserted in the septum or the septum was removed upon entering the antechamber) and charged with anhydrous NaOPh (2 mmol, 2 equiv, 232 mg). The tube was resealed inside the glovebox and removed. The solid reagents were added in air by briefly removing the rubber septum: $Pd(OAc)_2$ (2 mol%, 0.02 mmol, 0.02 equiv, 4.5 mg) and 1,3-bis(dicyclohexylphosphino)propane·2 HBF_4 salt (**7**, 4–5 mol%, 0.04–0.05 mmol, 0.04–0.05 equiv, 24.5–30.6 mg). After the addition of all solid reagents, the rubber septum was secured by wrapping with electrical tape. Next, all liquid reagents were added by syringe: DMSO (1 mL), aryl chloride (1 mmol, 1 equiv; aryl chlorides which were solids at room temperature were added during the initial charge), and amine (3 mmol, 3 equiv). Once all reagents were added, a balloon was connected to the reaction vessel using a short length of rubber tubing (ca. 1 in.), a needle adapter, and a 20 G needle. The inert atmosphere was then exchanged for carbon monoxide by briefly exposing the reaction vessel to vacuum (1–2 s) and backfilling with carbon monoxide; the balloon was inflated with CO(g) directly following this atmosphere exchange. The reaction tube was then submerged in a preheated oil bath (100–120 °C). The reaction mixture was heated while being stirred vigorously for 15 h or until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with methylene chloride or ethyl acetate (ca. 10 mL), filtered through a plug of celite (eluting with methylene chloride or ethyl acetate), and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel.

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