Letter

Palladium Catalyzed Carbonylation of Aryl Chlorides to Electrophilic Aroyl-DMAP Salts

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Palladium Catalyzed Carbonylation of Aryl Chlorides to Electrophilic Aroyl-DMAP Salts

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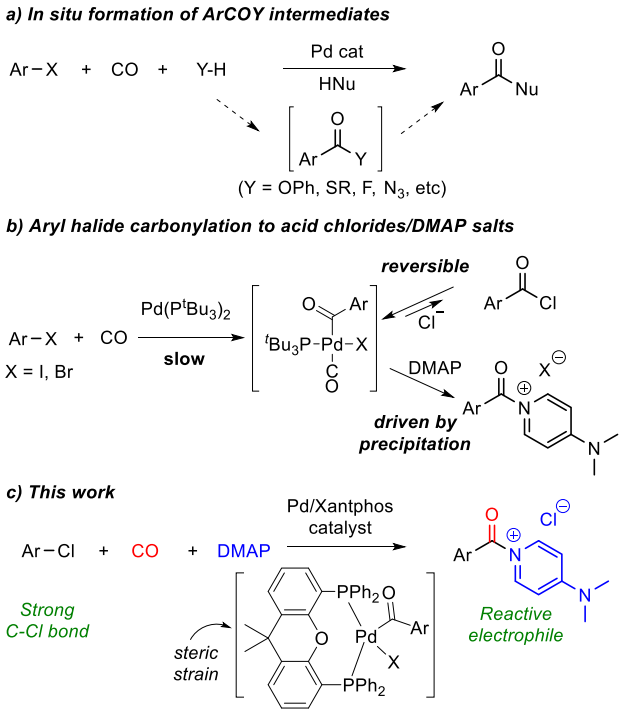
ABSTRACT: The palladium catalyzed carbonylative coupling of aryl chlorides and 4-dimethylaminopyridine (DMAP) to generate electrophilic aroyl-DMAP salts is described. In contrast to classical carbonylation reactions, which often require nucleophiles to react with weakly electrophilic palladium-acyl intermediates, the high electrophilicity of aroyl-DMAP salts allows the acylation of a broad range of substrates. This transformation is mediated by a palladium-Xantphos catalyst, and mechanistic studies suggest the combination of ligand steric strain together with Pd(0) stabilization allows both the reductive elimination of a reactive ArCO-DMAP product, and oxidative addition of the strong aryl-chloride bond. Overall, this transformation allows the generation of amides and esters from aryl chlorides with an array of nucleophiles, and with good functional group compatibility.

KEYWORDS Palladium catalysis, Carbonylation, Acylation, Aryl Chlorides, DMAP, Amides, Esters

Palladium catalyzed carbonylative coupling reactions have become of growing importance in organic synthesis.[1,2] Relative to classical methods to prepare carbonyl-containing products with activated carboxylic acid derivatives, which typically requires the use of synthetic, high energy reagents (e.g. carbodiimides, $SOCl_2$, PCl_3, etc), carbonylations offer a route to these same products using simply CO and organic halides. These transformations are postulated to proceed in a fashion similar to palladium catalyzed cross coupling reactions, wherein oxidative addition of an aryl halide generates a palladium-aryl complex that can undergo CO insertion followed by nucleophile coordination to palladium for reductive elimination.[3] While effective, the required addition of the nucleophile to palladium for elimination can also lead to limitations. For example, weakly coordinating or sterically encumbered nucleophiles can be difficult to employ in carbonylation reactions, and often require either pressing reaction conditions or are simply not viable reagents.[2] Buchwald, Skrydstrup, Grushin, and Manabe have previously demonstrated that the palladium catalyzed formation of aryl esters, thioesters, and related carbonylation products followed by the addition of stronger nucleophiles can be used to expand the scope of these transformations (Scheme 1a).[4-8] We have recently shown that aryl-iodides and -bromides can undergo carbonylation in the presence of a chloride anion to build-up highly electrophilic acid chlorides (Scheme 1b).[9,10] A P^tBu_3-coordinated palladium catalyst mediates this transformation, and is believe to allow the rapid and favor reductive elimination of the weak RCO-Cl bond as a mechanism to relieve steric strain.[11] By coupling the formation of acid chlorides with their high reactivity, a range of new classes of carbonylation products can be generated.

Scheme 1. Palladium-Catalyzed Carbonylative Formation of Electrophiles



In principle, an even more efficient approach to catalytic acid chloride formation would be the direct carbonylation of aryl chlorides. Relative to other aryl halides, aryl chlorides are inexpensive and broadly available building blocks, and their carbonylation would obviate the need for a chloride additive in the reaction. Unfortunately, the combination of a strong aryl-chloride bond and deactivating CO coordination often makes aryl chlorides much less

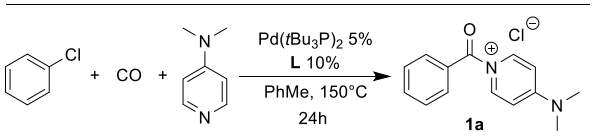
reactive towards palladium catalyzed carbonylation reactions.[2,12] This challenge is even more problematic in acid chloride synthesis due to the ability of the acid chloride product itself to re-add back to palladium more rapidly than the substrate (Scheme 1b). The latter limits catalyst activity with reactive aryl iodides,[13] and has to date made less reactive aryl chlorides not viable substrates in these reactions.

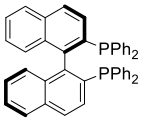
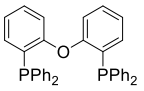
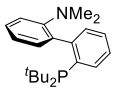
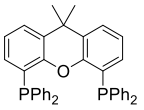
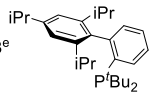
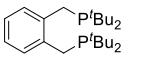
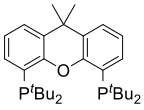
A potential approach to avoid these limitations with aryl chlorides would be to generate another class of potent electrophile: aroyl-DMAP (4-dimethylaminopyridine) salts (Scheme 1c). Aroyl-DMAP salts are common intermediates formed *in situ* to facilitate acylation reactions.[14] We have previously reported that aryl iodides and bromides can be carbonylated into these salts by using P^tBu_3-coordinated palladium catalysts to facilitate reductive elimination.[15] A useful feature of catalytically forming DMAP salt products is their ionic character, which can lead to their precipitation from non-polar solvents as easily isolable salts, and help drive the reaction under more mild conditions without product inhibition. We describe herein our efforts towards using aryl chlorides in this carbonylative coupling chemistry. In contrast to our previous results, these show that the sterically encumbered P^tBu_3 ligand is not sufficient to allow this transformation to occur with the less reactive aryl chloride bond. Nevertheless, modification to the catalyst system to stabilize palladium can allow the design of an efficient route to potent aroylating electrophiles form simple, inexpensive and commercially available substrates.

Our initial studies towards this reaction involved the carbonylation of chlorobenzene in the presence of DMAP with a $Pd(P^tBu_3)_2$ catalyst. Unfortunately, this does not lead to the formation of DMAP salt **1a** even under pressing conditions (Table 1, entries 1-3). The use of a range other monodentate phosphine ligands led to similar results (entries 4-8). This includes simple triaryl phosphines as well strong donor or sterically encumbered ligands, many of which have been employed in activation of aryl chlorides.[16] Instead, the aryl chloride reagent is observed intact at the end of the reaction.

In the reactions above, we noted the formation of significant amounts of Pd black precipitate at even early times of catalysis, suggesting that the oxidative addition of aryl chlorides in the presence of CO is not sufficiently rapid to compete with Pd(0) deactivation. We therefore turned next to chelate ligands, as these can more strongly coordinate to palladium in the presence of CO. The use of bidentate ligands such as dcpp and dppf, which have been found to allow carbonylations of aryl chlorides in other systems,[17] leads to the formation of trace amounts of product (entries 10, 11). However, increasing the ligand bite angle with Xantphos leads to a significant enhancement in catalytic activity, and the formation of DMAP salt **1a** in 67% yield (entry 14). Lower bite angle diphosphine ligands with similar electronic properties to Xantphos do not convert the aryl chloride in the desired product (entries 13), nor does the more electron rich ^{t}BuXantphos (entry 16). Increasing the temperature with Xantphos leads to the formation of **1a** in high yield (85%, entry 14).

Table 1 : Palladium-Catalyzed Carbonylation of PhCl with DMAP[a,b]

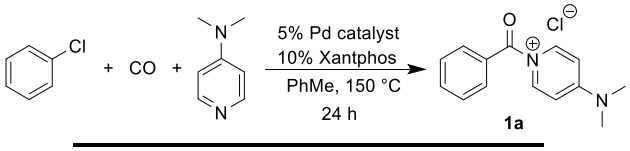


Entry	L	Yield (%)	Entry	L	Yield (%)
1	-	-	11	dcpp	7
2[c]	-	-			
3[d]	-	-	12		-
4[e]	PPh_3	-			
5[e]	$PoTolyl_3$	-	13		-
6[e]	$P(OPh)_3$	-			
7[e]		-	14		67, 85[d]
8[e]		-	15		-
9	dppe	-	16		-
10	dppf	5			

[a] PhCl (141 mg, 1.25 mmol), DMAP (30 mg, 0.25 mmol), $Pd(P^tBu_3)_2$ (6 mg, 12.5 μmol), ligand (25 μmol), CO (4 atm), toluene (1 ml), 150 °C, 24 h. [b] Isolated yield. [c] 100 °C. [d] 170 °C. [e] with $[Pd(allyl)Cl]_2$ (2 mg, 6.3 μmol).

The unique ability of Xantphos to allow catalysis of this reaction raises a number of mechanistic questions.[18,19] Firstly, the transformation employs a $Pd(P^tBu_3)_2$ precursor, which therefore has P^tBu_3 as well as Xantphos present in the reaction. Replacing the $Pd(P^tBu_3)_2$ catalyst with other palladium precursors such as $[Pd(allyl)Cl]_2$ or Pd_2dba_3 leads to a significant loss in product yield (Table 2, entries 1, 2). This can be partially recovered by the addition of P^tBu_3 (entries 3, 4). While these data suggests that the P^tBu_3 ligand may play a direct role in the reaction together with Xantphos, an alternative is the ease of activation and greater solubility of $Pd(P^tBu_3)_2$ in the non-polar reaction solvent. This was demonstrated by preparing the Xantphos-coordinated palladium catalyst precursor (Xantphos)Pd(COPh)Cl (**2a**).[7, 19] The use of **2a** as catalyst leads to the formation of **1a** in similar yields than with $Pd(P^tBu_3)_2$/Xantphos and with no side products (entry 7).

Table 2. Palladium Catalyst Precursors for the Synthesis of Aroyl-DMAP Salts[a]



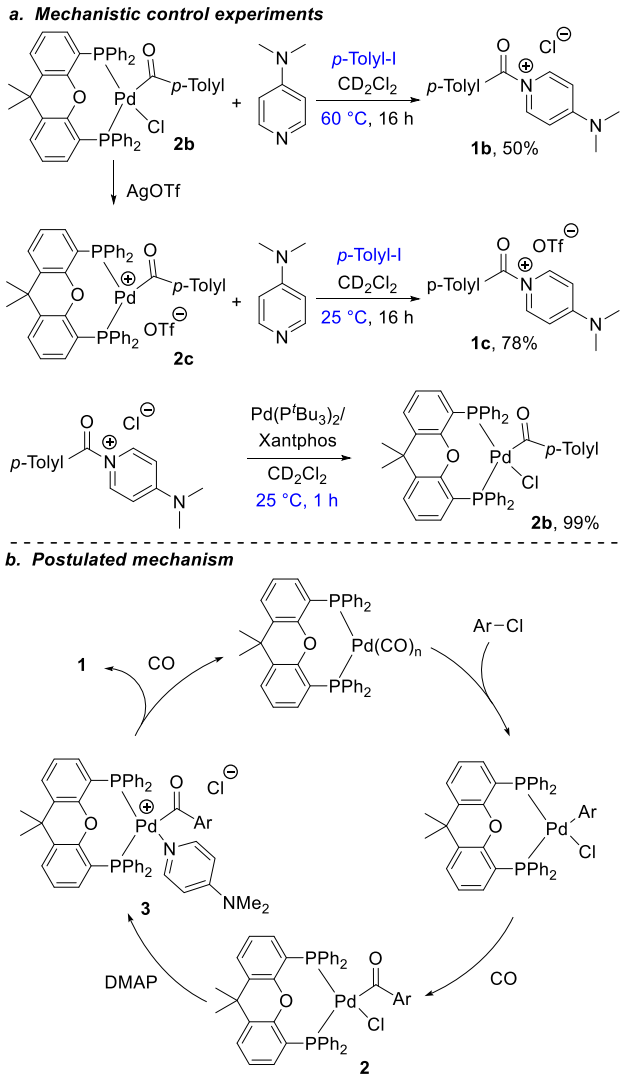
Entry	Pd catalyst	Yield (%)[b]
1	$Pd_2(dba)_3CHCl_3$	3
2	$[Pd(allyl)Cl]_2$	31
3	$Pd(dba)_3CHCl_3$ / 10% P^tBu_3	27
4	$[Pd(allyl)Cl]_2$ / 10% P^tBu_3	63
5	$PdCl_2$	9
6[c]	$Pd(Xantphos)_2$	44
7[c]	(Xantphos)Pd(COPh)Cl (**2a**)	75

[a] PhCl (141 mg, 1.25 mmol), DMAP (30 mg, 0.25 mmol), Pd (5 %, 12.5 μmol), xantphos (14 mg, 25 μmol), 4 atm CO, 1 mL toluene, 150 °C, 24 h. [b] Isolated. [c] No Xantphos added.

A series of mechanistic experiments were performed to gain further insight into this transformation. Monitoring the catalytic reaction of Table 1 by periodic ^1H and ^{31}P NMR analysis shows no evidence for the palladium-aroyl complex (**2**), and instead we see signals assigned as free P^tBu_3 and $(Xantphos)_2Pd$ (Figure S1). This observation is unlike previous results with aryl iodide carbonylation to aroyl-DMAP salts,[15] where the catalyst resting state is a palladium-aroyl complex, and suggests that reductive elimination from a Xantphos coordinated palladium intermediate is no longer rate limiting in catalysis. To further probe this step, the palladium-aroyl complex **2b** was prepared by the reaction of Xantphos/Pd_2dba_3 and acid chloride.[19] As shown in Scheme 2a, heating this complex together with DMAP and aryl iodide (the later to trap the resultant Pd(0)) to 60 °C, well below catalyst temperatures, leads to the elimination of **1b** in 50% yield.[20] In addition, the conversion of **2b** to its triflate salt, which would presumably favor the coordination to DMAP to palladium, results in the rapid, room temperature formation of **1c**.

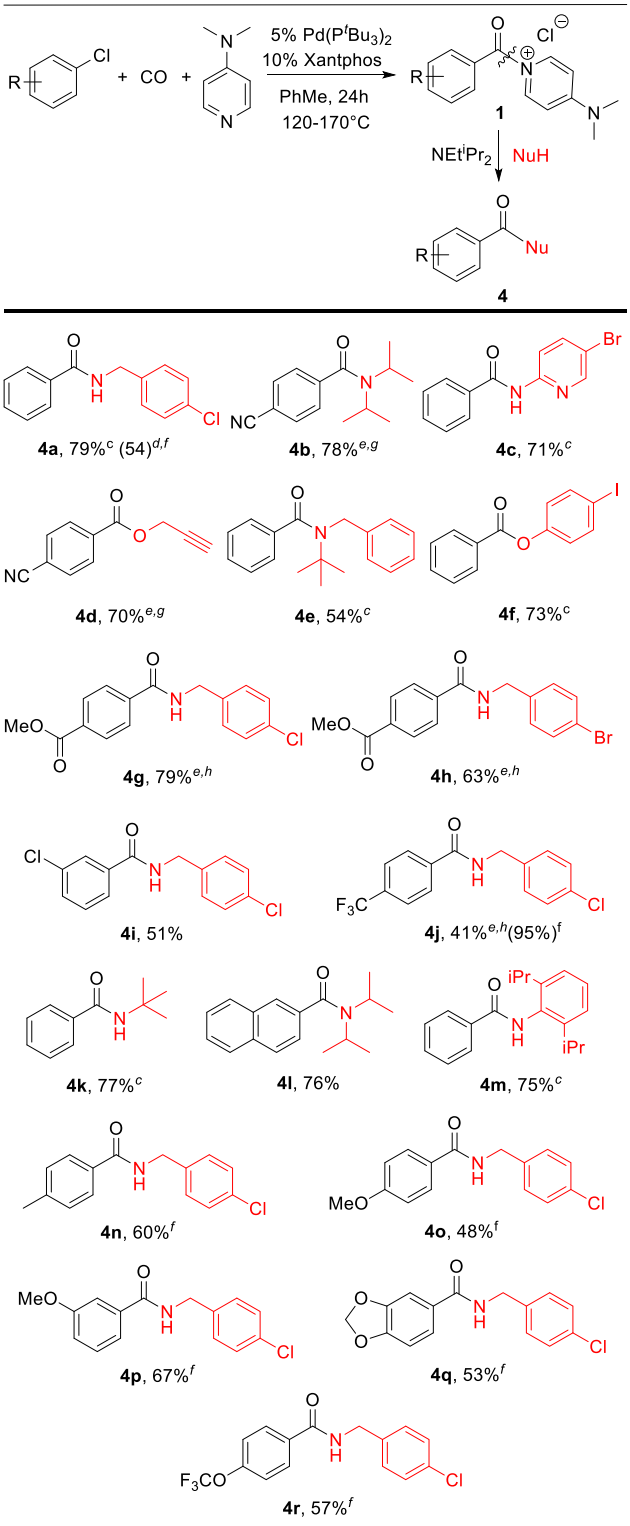
Together, the data above is consistent with the mechanism shown in Scheme 2b. In this, the coordination of the chelating Xantphos ligand to palladium creates a Pd(0) complex sufficiently stabilized in the presence of carbon monoxide to mediate a rate limiting aryl chloride oxidative addition. While a range of bidentate ligands could in principle stabilize palladium(0) towards precipitation, a second important feature of Xantphos is its large bite angle.[21] We postulate that the steric encumbrance of Xantphos creates a bidentate alternative to the P^tBu_3 ligand to favor the reductive elimination of the reactive aroyl-DMAP bond kinetically competent. As demonstrated in the more rapid reaction of **2c** relative to **2b** (Scheme 2a), the latter may occur via DMAP coordination to palladium to generate the cationic DMAP-palladium complex **3**, which undergoes reductive elimination of **1** under mild conditions. Alternatively, the direct attack of DMAP on the electrophilic acyl ligand is also possible. The insolubility of the aroyl-DMAP product in toluene makes this step irreversible, and helps drive product formation and catalyst turnover. The importance of this precipitation driving the reaction forward is also shown in Scheme 2a, where the use of a solvent in which the DMAP salt **1b** is soluble (CD_2Cl_2) leads to its rapid, ambient temperature re-oxidative addition to Pd(0).

Scheme 2. Control Experiments and Proposed Mechanism of Catalysis



Finally, with a catalytic method to prepare aroyl-DMAP salt **1a** in hand, we have probed the ability of this system to allow aryl chloride to be used in challenging carbonylation reactions. As an example, weakly nucleophilic and sterically encumbered substrates such as sterically hindered anilines and secondary amines have not been found to be viable coupling partners in typical aryl chloride

Table 3. Palladium Catalyzed Carbonylative Coupling via Aroyl DMAP Salts[a,b]



[a] Aryl chloride (1.25 mmol), DMAP (30 mg, 0.25 mmol), Pd(P^{t}Bu$_3$)$_2$ (6 mg, 12.5 µmol), xantphos (14 mg, 25 µmol), 4 atm CO, 1 mL toluene, 150 °C, 24 h, then addition of NuH (0.38 mmol), NEt^{i}Pr$_2$ (65 mg, 0.50 mmol), 1 mL MeCN, 25 °C, 4-16 h. [b] Isolated yield, DMAP as limiting reagent, [c] 170 °C, [d] 0. 37 mmol aryl chloride, [e] 10 mol% Pd(P^{t}Bu$_3$)$_2$, [f] 10 mol% Pd(P^{t}Bu$_3$)$_2$, NaPF$_6$ (63 mg,0.375 mmol), [g] 130 °C, [h] 120 °C.

carbonylations, presumably do to the weak coordinating ability of these substrates to palladium. However, aroyl-DMAP salts are potent electrophiles. Thus, the addition of this amine to an *in situ* generated **1** can allow the build-up of a range of secondary and tertiary amides from aryl chlorides, amine and CO (Table 3, **4b**,**e**,**k**,**l**,**m**).[22] Alternatively, nucleophiles incorporating palladium reactive functionalities, which would be challenging to employ in carbonylative coupling reactions, can also be incorporated into this system. Examples of the latter include nucleophiles containing other aryl chlorides (**4a**,**g**,**i**,**j**) or even aryl-bromides and -iodides (**4c**,**f**,**h**) or terminal alkynes (**4d**). A range of either electronically neutral or activated aryl chlorides can participate in this chemistry (**4a–m**). Electron rich aryl chlorides are also viable substrates with the addition of $NaPF_6$ (**4n-r**). The latter is postulated to aid in the build-up of **1** by creating a more reactive cationic acyl complex **2** (e.g. Scheme 2a).[23] While catalysis is typically performed with an excess of aryl chloride to drive the build-up of **1**, the reaction can also be accomplished with near stoichiometric aryl chloride at slightly lower yields (**4a**, 54%). These reactions are generally complete within 24 hours, and provide the amide or ester products in good overall yields.

In conclusion, we have developed a novel carbonylation of aryl chlorides into aroyl-DMAP salts. This transformation is driven by the use of the large bite angle Xantphos ligand, which can both stabilize palladium towards precipitation and, at the same time, favor product elimination. Overall, this provides an efficient method to create electrophilic aroyl-DMAP salts, and new classes of carbonylation products, from broadly available aryl chlorides.

ASSOCIATED CONTENT

Details of experimental procedures and ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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