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A Palladium-Catalyzed Carbonylation Approach to Acid Chloride Synthesis

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Supporting Information

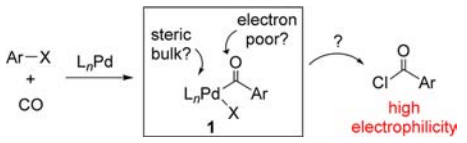
ABSTRACT: We describe a new approach to acid chloride synthesis via the palladium-catalyzed carbonylation of aryl iodides. The combination of sterically encumbered phosphines (P^tBu_3) and CO coordination has been found to facilitate the rapid carbonylation of aryl iodides into acid chlorides via reductive elimination from ($^tBu_3P$)(CO)Pd(COAr)Cl. The formation of acid chlorides can also be exploited to perform traditional aminocarbonylation reactions under exceptionally mild conditions (ambient temperature and pressure), and with a range of weakly nucleophilic substrates.

Acid chlorides are among the most versatile building blocks employed in synthesis, with examples ranging from simple ester, amide, or ketone formation, industrial polymerizations (e.g., Kevlar production),[1] peptide couplings,[2] Friedel-Craft acylations,[3] metal-catalyzed carbon−carbon bond formation,[4] and many others.[5] An important feature of acid chlorides is their high electrophilicity, which make them reliable acylating agents even with weak nucleophiles. Despite this utility, a significant challenge with acid chlorides is their own formation. Typical approaches to these compounds involve the reaction of carboxylic acids with halogenating reagents, such as PCl_3 and thionyl or oxalyl chloride. The latter are high energy, reactive species that must themselves first be generated, lead to the formation of significant chemical waste, and are hazardous; thionyl chloride and phosphorus trichloride are Schedule 3 substances under the Chemical Weapons Convention guidelines, while oxalyl chloride has similar physiological effects as phosgene. As such, acid chlorides are not particularly Green chemical reagents.

The difficulty associated with acid chloride formation has stimulated interest in other approaches to activated carboxylic acid derivatives (DCC, HOBt/HOAt couplings, anhydrides, etc).[6] One of the most efficient is the palladium-catalyzed carbonylation of aryl halides. This reaction was discovered by Heck nearly 40 years ago[7] and has since been found to provide a simple method to generate a range of carboxylic acid derivatives from organic halides and the available C1 source: CO.[8] Palladium-catalyzed carbonylations are reminiscent of simple acid chloride chemistry, where the putative palladium-aroyl intermediate **1** can undergo reactions with nucleophiles. A difference between these substrates is their electrophilicity. Palladium complex **1** is not nearly as reactive as acid chlorides and can require elevated temperatures and pressures for even simple alkoxy- and aminocarbonylations,[9] while reactions of weakly nucleophilic or bulky substrates are often unknown. This is presumably accentuated by the need for nucleophiles to first coordinate to the palladium center for subsequent reductive elimination.

In considering this reactivity, an alternative to traditional acid chloride synthesis would be to simply induce palladium intermediates **1** to undergo reductive elimination (Scheme 1).

Scheme 1. Palladium-Aroyl Complexes to Acid Chlorides



Early studies on palladium-catalyzed carbonylations of aryl halides postulated the generation of acid halides as reactive intermediates, though this was subsequently disproven by mechanistic and reactivity studies.[10] In different approaches, Buchwald and co-workers have reported that the *in situ* generation of electrophilic phenoxyesters by the use of phenoxides in aminocarbonylations[11] and oxidative carbonylations of alkenes or allyl chlorides to acid chlorides have been reported by Tsuji, Dent, Lambert, and others.[12] However, a method to generate acid chlorides via palladium-catalyzed aryl halide carbonylation has not been reported. Toward this end, we describe below how ligand influences can be exploited to induce the reductive elimination of acid chloride from palladium complexes of the form **1**. This allowed the design of what is to our knowledge the first catalytic synthesis of acid chlorides from aryl iodides, chloride, and CO. The ability to catalytically form acid chlorides can also be exploited to perform traditional carbonylation reactions under exceptionally mild conditions and with a range of often inaccessible nucleophiles.

There are a number of complicating factors in inducing acid chloride reductive elimination from palladium(aroyl)(chloride) complexes. In contrast to the typical reductive elimination of C-C, C-N or C-O bonds, the carbon−chlorine bond in acid chlorides is weak (~70−80 kcal/mol),[13] suggesting that elimination from **1** will be energetically disfavored. Equally problematic is the re-oxidative addition of acid chlorides to palladium(0), which is much more rapid than that of the aryl halide substrate. Ligand effects may be useful in both of these areas. It is established that ligand bulk can favor reductive elimination as a mechanism to reduce strain,[14] including recent

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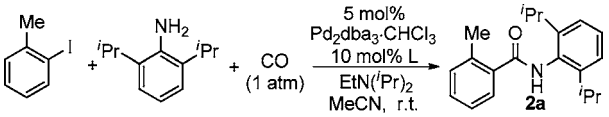
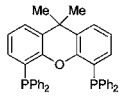
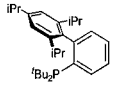
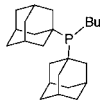
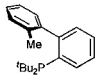
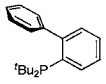
results with aryl- and alkyl-halogen bonds.[15] In addition, the aroyl ligand in **1** is electron poor, and an electron-deficient palladium may favor its selective elimination.

In order to probe for acid chloride formation uncomplicated by its re-addition to palladium, our initial studies explored the carbonylation of 2-iodotoluene in the presence of a bulky, noncoordinating trapping agent: 2,6-diisopropylaniline. These reagents have not been previously reported to undergo carbonylative coupling, likely due to their steric encumbrance and the poor coordinating ability of the aniline. However, this aniline can undergo rapid reaction with any acid chloride generated (eq S1). As anticipated, the palladium-catalyzed carbonylative coupling of these substrates is ineffective with many traditional catalysts, including ligands that are active in related aryl halide carbonylations with less encumbered substrates (Table 1).[16] In order to allow for the potential

Table 1. Ligand Screening for Aminocarbonylation[a]



#	Ligand	Yield **2a**[b] - Bu_4NCl[c]	#	Ligand	Yield **2a**[b] - Bu_4NCl[c]
1	PPh_3	- -			
2	P(*o*-tolyl)$_3$	- -	10		- 5%
3	PCy_3	- -			
4	dppp	- -			
5	dppe	- -	11		- 7%
6	dcpe	- -			
7		- -	12		- 7%
8		- -	13		- 12%
9	dppf	- -	14	P^{t}Bu$_3$	- 92%

[a]Iodotoluene (0.37 mmol), amine (0.25 mmol), EtN(^{i}Pr)$_2$ (0.37 mmol), Pd_2dba_3·$CHCl_3$ (12 μmol), L (25 μmol), 0.4 mL CH_3CN, 18 h. [b]NMR yield. [c]Bu_4NCl (0.25 mmol).

formation of acid chloride, Bu_4NCl was added as a chloride source to the reaction. Chloride had no beneficial effect with many of the ligands employed (entries 1−9), although sterically encumbered phosphines do form amide in trace amounts (entries 10−13). However, further increasing the steric bulk of the phosphine to P^{t}Bu$_3$ leads to a dramatic spike in catalytic activity and the near quantitative formation of amide **2a** (entry 14).

The chloride anion in the reaction above could play several potential roles. For example, halide sources including Bu_4NCl are well established to facilitate many palladium-catalyzed reactions (e.g., Jeffery conditions).[17] This is postulated to arise from weak association of halides to the Pd(0) catalyst, which can stabilize it toward precipitation or create anionic palladium catalysts. However, other common halide additives, such as Bu_4NBr and Bu_4NI, have no beneficial effect on this reaction (Table 2), while all chloride sources demonstrate increased activity. In addition, the effect of chloride anion is roughly proportional to chloride

Table 2. Halide Effect on Carbonylation[a]

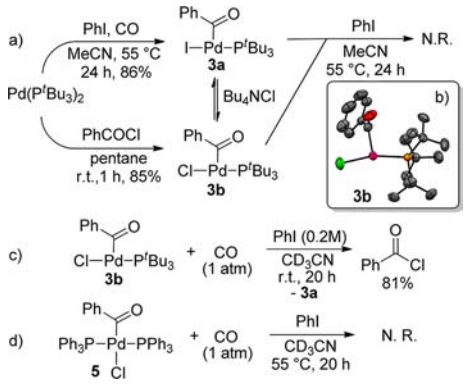
entry	halide	conc. (M)	yield **2a**[b]
1	Bu_4NCl	0.25	95%
2	Bu_4NBr	0.25	5%
3	Bu_4NI	0.25	1%
4	Ph_3PBnCl	0.25	89%
5	PPNCl	0.25	62%
6	Bu_4NCl	0.12	51%
7	Bu_4NCl	0.025	14%

[a]Table 1 conditions, Pd(P^{t}Bu$_3$)$_2$ cat. (25 μmol). [b]NMR yield.

concentration (Table 2) and well beyond that of the palladium catalyst (5 mol %). This suggests a more specific role of chloride.

To better understand these effects, stoichiometric experiments were performed on the putative palladium-aroyl intermediates **3a** and **3b** (Scheme 2). The iodide complex **3a** can be generated by

Scheme 2. Stoichiometric (P^{t}Bu$_3$)Pd(COPh)X Reactivity



the carbonylation of phenyl iodide with Pd(P^{t}Bu$_3$)$_2$.[18] The addition of Bu_4NCl to **3a** leads to the equilibrium formation of **3b**. However, a more quantitative approach is via the reaction of benzoyl chloride with Pd(P^{t}Bu$_3$)$_2$. Single crystal X-ray crystallography was performed on **3b** (Scheme 2b). This complex adopts a monomeric T-shaped geometry at palladium, with the benzoyl ligand *trans* to the open coordination site. The coordinatively unsaturated palladium is stabilized by an agostic interaction with a P^{t}Bu$_3$ C−H bond, as has been reported for related compounds.[18,19]

Warming of the iodide complex **3a** shows no evidence for the generation of acid halide products, even in the presence of excess phenyl iodide to trap any resultant (P^{t}Bu$_3$)Pd(0). Similar results were observed with the chloride complex **3b** and with **3a** in the presence of Bu_4NCl. These suggest that the reductive elimination of acid halide either is not kinetically viable or is thermodynamically disfavored. However, the addition of CO (1 atm) to the palladium-benzoyl(chloride) complex results in the rapid and near quantitative formation of benzoyl chloride, along with the phenyl iodide oxidative addition product **3a** (Scheme 2c).

These data show that the combined influence of P^{t}Bu$_3$, Cl^-, and carbon monoxide can allow the rapid elimination of benzoyl chloride. Considering that chloride exchange with the iodide complex **3a** is rapid (Scheme 2a) and the P^{t}Bu$_3$ bound **3b** has an empty coordination site, we postulate that acid chloride forms from complex **3b** with CO association (**4**, Scheme 3).[20] The ability of P^{t}Bu$_3$ to mediate this transformation may arise from its size and donor ability, which both creates a coordination site on

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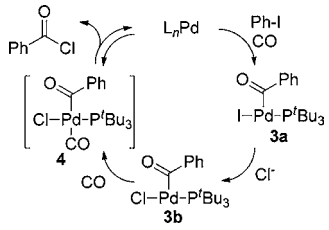
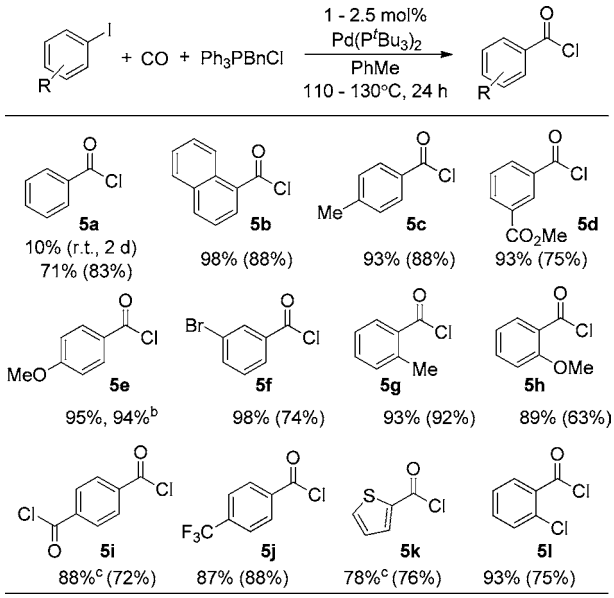
Scheme 3. Mechanism of Acid Chloride Formation



palladium for the π-acid CO to associate and together with steric crowding may favor reductive elimination. For comparison, the analogous benzoyl chloride palladium complex **5** with two PPh_3 ligands lacks this coordination site and does not undergo reductive elimination even at elevated temperature (Scheme 2d).

These effects can also be applied in catalysis. The addition of **3b** (5 mol %) to phenyl iodide, 5 atm CO, and Bu_4NCl leads to the slow catalytic build-up of benzoyl chloride to 10% after 2 days at ambient temperature (Table 3, **5a**). This represents an unusual

Table 3. Palladium-Catalyzed Synthesis of Acid Chlorides[a]



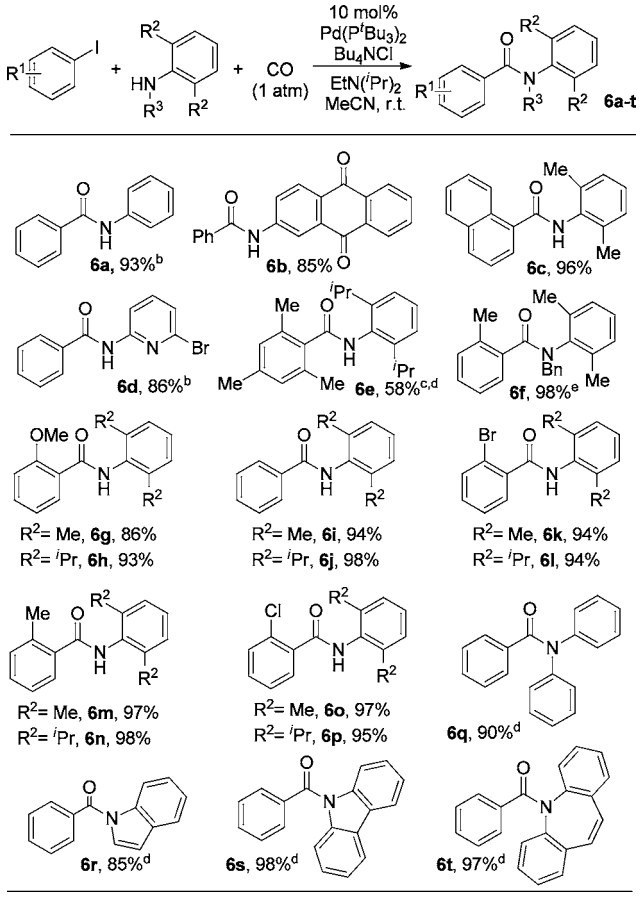
[a]Isolated yield: aryl iodide (4 mmol) Ph_3PBnCl (4.4 mmol), 1% $Pd(P^tBu_3)_2$, 110 °C, 50 atm CO, 24 h, (NMR yield: 4 atm CO, 130 °C, 2.5% $Pd(P^tBu_3)_2$). [b]0.1 mol % $Pd(P^tBu_3)_2$. [c]48 h.

palladium-catalyzed bond forming reaction, where oxidative addition/reductive elimination steps are used to generate a product (acid chloride) that is much more reactive toward the palladium catalyst than the starting material (aryl iodide).[21] The rate of acid chloride formation slows as the reaction proceeds (Figure S1) presumably due to the competitive reverse reaction: the reoxidative addition of acid chloride to Pd(0). *In situ* ^{31}P NMR analysis reveals that the palladium catalyst remains intact as the precursor to reductive eliminaton (**3b**). Thus, simply heating the reaction can overcome this kinetic product inhibition, resulting in a clean catalytic route to generate benzoyl chloride from phenyl iodide and CO (Table 3).

A range of aryl iodides can be efficiently carbonylated to acid chlorides with this catalyst system. Electron-deficient and electon-rich aromatics can participate in this reaction, as can sterically bulky substrates (**5b**, **5g**) and even heteroaryl iodides (**5k**).[22] Carbonylation can also be performed on diiodobenzene, allowing the synthesis of commercially relevant terephthaloyl chloride (**5i**). These reactions proceed with minimal side products and form acid chlorides in near quantitative isolated yields with most substrates.[23] Elevated CO pressure allows the isolation of these acid chloride products via simple filtration of the insoluble halide salts and precipitation of the palladium catalyst, although moderate pressures are also viable. The catalyst loading can also be decreased to 0.1 mol % without adverse effect on the yield (**5e**). Overall, this provides an effective method to generate acid chlorides from CO and Cl^-.

In addition to generating acid chlorides, we noted from the stoichiometric experiments that the all of the basic steps in catalysis, oxidative addition of aryl iodide, CO insertion, and reductive elimination, occur rapidly at ambient temperature and 1 atm CO. Similarly, acid chlorides can undergo rapid reactions with a range of substrates. Together, these can provide a route to carry out carbonylative coupling reactions without the pressing temperatures and pressures typically needed in these reactions and with a variety of often challenging nucleophiles. As illustrated in Table 4, a diverse range of amidocarbonylations can be performed at simply ambient conditions (1 atm carbon monoxide, room temperature). These include functionalized, sterically encumbered, and electron-poor amines, many of which are not typically viable in this reaction or, if known (e.g., **6a**), require elevated temperatures and/or CO pressures.[9] Weakly nucleophilic substrates, such as diarylamines, which do not

Table 4. Ambient Temperature and Pressure Palladium-Catalyzed Aminocarbonylations[a]



[a]Table 1, entry 14 conditions, isolated yield. [b]5 mol % $Pd(P^tBu_3)_2$. [c]0.5 mmol aryl iodide, 0.75 mmol amine. [d]65 °C. [e]40 °C.

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proceed in other carbonylation reactions,[24] also undergo clean coupling (**6q**). The formation of acid chlorides also allows the use of other, even less nucleophilic substrates in carbonylation. Nitrogen-containing heterocycles are known to react with acid chlorides but are rarely applied in palladium-catalyzed carbonylations, likely due to their poor nucleophilicity and coordinating ability.[25] As shown in **6r**–**6s**, these substrates can all be effectively aroylated in high yields. The mild heating required for the latter is not due to catalysis but to the sluggish reaction of these heterocycles with acid chlorides (eqs S3, S4). As far as we are aware, this represents a novel platform to perform aminocarbonylations under ambient conditions with a broad range of reagents.

In conclusion, these results demonstrate a new approach to construct acid chlorides via the palladium-catalyzed carbonylation of aryl halides. This transformation is mediated by combination of the bulky, electron-rich P^tBu_3, chloride, and carbon monoxide coordination, which together allows the rapid reductive elimination of acid chloride under mild conditions. Considering the availability of aryl halides and the diverse utility of acid chlorides, this approach should prove equally applicable to the efficient generation of a range of acid chlorides or acid chloride-derived products. Studies directed toward the latter are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) Reductive elimination may also occur via an ionic $(P^tBu_3)(CO)_nPd(COPh)^+ Cl^-$. Catalytic acid chloride formation proceeds at similar rates in polar (acetonitrile) and nonpolar (toluene) solvents, consistent with a neutral intermediate. Nevertheless, an ionic pathway cannot be ruled out.

(21) The addition of a 1:1 mixture of phenyl iodide and benzoyl chloride (1:1) to $Pd(P^tBu_3)_2$ results in exclusive acid chloride oxidative addition to form the benzoyl complex **3a** (eq S2).

(22) Under similar conditions, aryl bromides can also be partially carbonylated but at diminished rates and yields, presumably due to the stronger Ar-Br bond. Further investigations of this reaction are currently underway.

(23) The lower isolated yields for **5a**, **5j**, **5k** are due to the volatility of the product. *In situ* ^{1}H NMR spectra show the near quantitative formation of these compounds.

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