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Acid Chloride Synthesis by the Palladium-Catalyzed Chlorocarbonylation of Aryl Bromides

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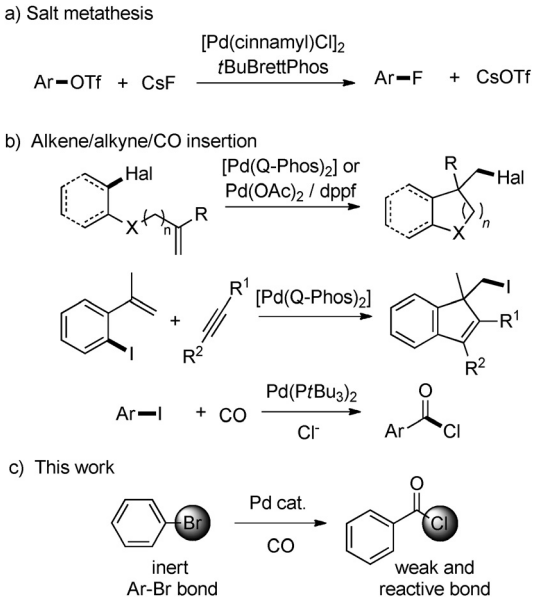
Abstract: We report a palladium-catalyzed method to synthesize acid chlorides by the chlorocarbonylation of aryl bromides. Mechanistic studies suggest the combination of sterically encumbered P*t*Bu$_3$ and CO coordination to palladium can rapidly equilibrate the oxidative addition/reductive elimination of carbon–halogen bonds. This provides a useful method to assemble highly reactive acid chlorides from stable and available reagents, and can be coupled with subsequent nucleophilic reactions to generate new classes of carbonylated products.

Introduction

Palladium-catalyzed bond-forming reactions have become among the most heavily exploited transformations in synthetic chemistry. A common feature of these reactions is the generation of a robust and inert C–C, C–N, or C–O bond, which together with the byproducts (e.g. metal salts) provide a strong driving force for reaction. In contrast, there has been recent interest in using palladium catalysis to create more reactive covalent bonds, such as carbon–halogen containing products. Hartwig illustrated this potential in the stoichiometric reductive elimination of aryl halides induced by sterically encumbered ligands.[1] Lautens, Buchwald, Tong, Jiang, and others have shown these reactions can be applied in catalysis, thereby allowing the efficient generation of carbon–halogen containing products.[2,3] These methods typically involve halide (or pseudohalide) metathesis (Scheme 1a) or alkene/alkyne insertion followed by reductive elimination (Scheme 1b). We have similarly reported that the palladium-catalyzed carbonylation of aryl iodides can allow the synthesis of acid chlorides.[4] In contrast to many the above examples, acid chlorides are themselves reactive towards oxidative addition to Pd^0 complexes.[5] However, the aryl iodide bond in the substrate is significantly weaker than in the acid chloride, and allows it to compete for addition to palladium.

From an energetic standpoint, the use of catalytic bond-forming reactions to convert stable building blocks into products that are themselves reactive can provide a useful approach in synthesis. In considering these features, we became interested in whether reactions such as carbonylations could be extended to form products with a weak and significantly more reactive bonds than in the substrate. A practical limitation of the catalytic synthesis of acid chlorides is its reliance on aryl iodides, which are often as expensive as acid chlorides, are unstable, and can be challenging to prepare. In contrast, aryl bromides are attractive building blocks in synthesis, less expensive, and, with the advent of cross-coupling reactions, are now generally available. Employing aryl bromides in palladium-catalyzed transformations is often a matter of overcoming the higher kinetic barrier for oxidative addition. However, an unusual challenge in this case is relative bond strengths, as the aryl bromide bond is not only stronger than that of aryl iodides (Ph–Br, Ph-I: 75 and 65 kcal mol^{-1}, respectively), but is also as strong as the C–Cl bond in the acid chloride product (PhCO–Cl: 74 kcal mol^{-1}).[6] More importantly, the aryl bromide substrate is orders of magnitude less reactive towards the Pd^0



Scheme 1. Catalytic sp^2- and sp^3-carbon–halogen bond-forming reactions.

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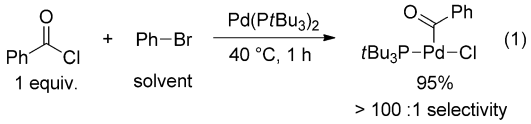
catalyst than acid chlorides. This can be seen in the reaction of $Pd(PtBu_3)_2$ with benzoyl chloride in bromobenzene solvent, which leads to the exclusive oxidative addition of the C–Cl bond [Eq. (1)].[7] This reaction would therefore require what is to our knowledge the unique use of palladium-catalyzed carbonylations to create a product that has both a weak bond and is orders of magnitude more reactive than the substrate, without becoming inhibited by product growth (Scheme 1c).



We describe below how sterically encumbered phosphines can overcome the relative barriers of aryl bromide and acid chloride oxidative addition. Mechanistic studies suggest this reflects the ability of phosphine and carbonyl-coordinated palladium to rapidly equilibrate the oxidative addition/reductive elimination of carbon–halogen bonds. From a synthetic perspective, coupling the catalytic formation of acid chlorides with their subsequent reactivity allows the application of carbonylations to nucleophiles not typically viable in this chemistry.

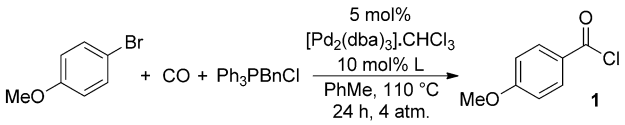
Results and Discussion

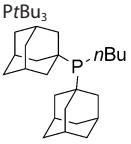
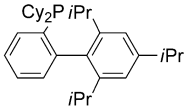
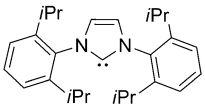
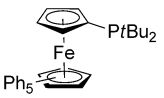
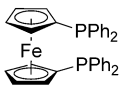
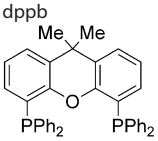
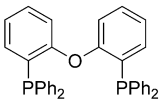
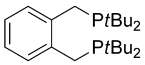
Catalyst development

Initial studies examined the reaction of the electron-rich 4-bromoanisole in the presence of chloride salts. The use of our previous conditions for aryl iodide carbonylation leads to a low yield of acid chloride together with catalyst decomposition (Table 1, entry 1). We therefore examined lower temperatures and higher catalyst loadings with a broad range of ligands, including trialkyl-, triaryl-, and dialkylarylphosphines, as well as N-heterocyclic carbenes (for the full scope of ligands, see Supporting Information). In contrast to our results with aryl iodides, a number of sterically encumbered ligands allow the formation of acid chloride in low yield (entries 5–8, and 10). The influence of ligand sterics on this reaction is dramatic: relative to $PtBu_3$ (entry 6), the slightly smaller $PtBu_2$(neopentyl) (entry 5) and P(1-adamantyl)$_2n$butyl (entry 7) lead to lower yields, while PCy_3, triarylphosphines, and aryldialkylphosphines show very little catalytic activity, nor do NHCs. As a palladium precipitate is generated during many of these reactions, chelating phosphines were also examined. While most of these are also inactive, the large bite angle Xantphos (entry 16) provides comparable yields to $PtBu_3$.

The limitation of even the best catalyst systems at approximately 50% conversion is presumably the result of product inhibition, as the acid chloride generated in the reaction can preferentially add to palladium relative to the aryl bromide substrate. In probing methods to overcome this limitation, we found that CO pressure can itself facilitate catalysis. Although added CO pressure has minimal influence with many of the ligands in Table 1, performing the catalytic reaction with the largest ligand, $PtBu_3$, at high CO pressure leads to high yield of acid chloride (Table 1, entry 19). Under these conditions, the catalyst loading can be lowered without a significant loss in activity, and proceeds equally well with $Pd(PtBu_3)_2$. Bu_4NCl can

Table 1. Ligand screening for catalytic acid chloride synthesis.[a,b]



Entry	L	Yield
1	$PtBu_3$	34[c]
2	PPh_3	2
3	P(*o*-tolyl)$_3$	2
4	PCy_3	0
5	$PtBu_2$(neopentyl)	41
6	$PtBu_3$	54 (56)[d]
7		11
8		5
9		0
10		39
11		4
12	dcpe	0
13	dppe	1
14	dppp	2
15	dppb	1
16		48 (47)[d]
17		5
18		0
19	$PtBu_3$	84[e] (74)[f]

[a] 4-Bromoanisole (47 mg, 0.25 mmol), Ph_3PBnCl (146 mg, 0.375 mmol), $[Pd_2(dba)_3]$·$CHCl_3$ (13 mg, 12.5 μmol), L (25 μmol), CO (4 atm), 2 mL PhMe, 110 °C, 24 h. [b] NMR yield. [c] 2.5 mol% $[Pd_2(dba)_3]$·$CHCl_3$, 130 °C. [d] 10 mol% $[PdL_2]$. [e] 10 mol% $[PdL_2]$, CO (20 atm.). [f] 5 mol% $[Pd(PtBu_3)_2]$, CO (20 atm.). dba = dibenzalacetone; dcpe = 1,2-bis(dicyclohexylphosphino)ethane; dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,2-bis(diphenylphosphino)propane; dppb = 1,2-bis(diphenylphosphino)butane.

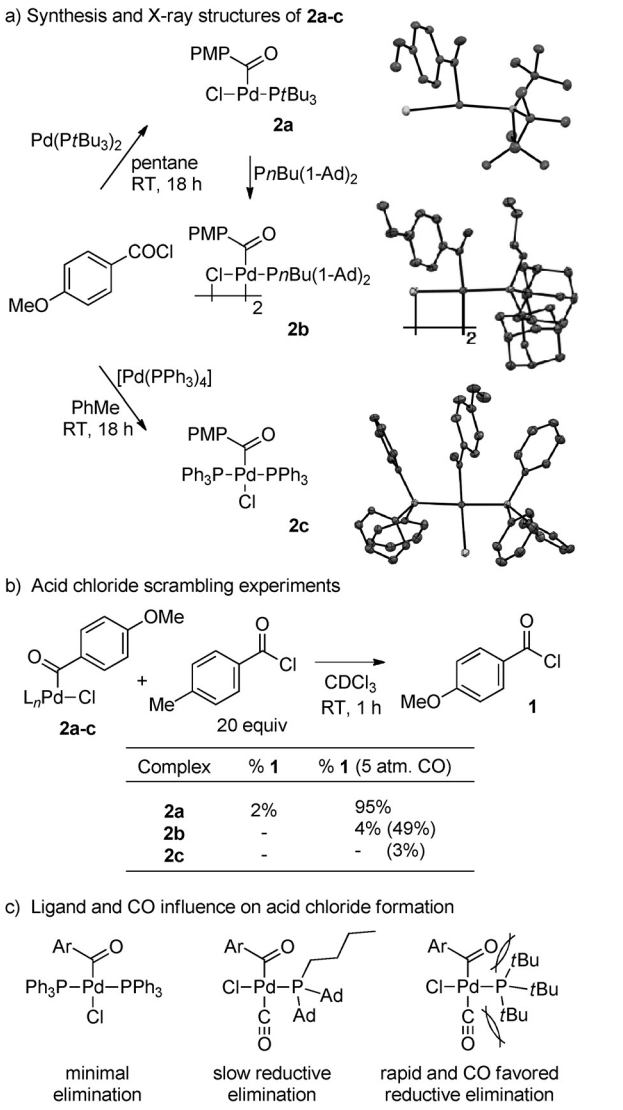
also be employed as a chloride source, albeit in diminished yields (see Supporting Information for other chloride sources).

Mechanistic studies

The above studies suggest that the sterically encumbered P*t*Bu$_3$ ligand and CO pressure can favor both the reductive elimination of a weak and reactive ArCO–Cl bond, and at the same time the competitive activation of the significantly less reactive Ar–Br reagent. This catalyst is the same to that identified as being unique for acid chloride synthesis from aryl iodides.[4] Nevertheless, it is notable that a number of ligands can allow acid chloride formation from aryl bromides in moderate yield, which suggests that acid chloride reductive elimination may be more common than previously considered in carbonylations.

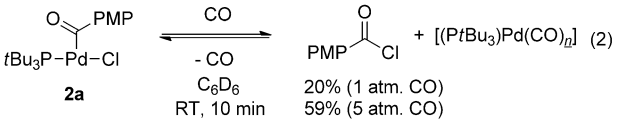
To gain a more complete mechanistic understanding of this reaction, we have prepared and structurally characterized a series of palladium–aroyl complexes, including that of the moderately active P(1-Ad)$_2$*n*Bu ligand, and compared it to complexes of highly active (P*t*Bu$_3$) and inactive (PPh$_3$) ligands (Scheme 2a). Unlike the rapid, room temperature reductive elimination of acid chloride from **2a** we have previously noted with aryl iodide trap [(P*t*Bu$_3$)Pd^0],[4] complexes **2a**–**c** do not undergo a similar exchange with the significantly less reactive aryl bromide substrate. However, these experiments probe two steps: the rate of elimination of acid chloride and of aryl halide addition to palladium. A more accurate method to examine reductive elimination from complexes **2** is by scrambling experiments. As shown in Scheme 2b, no reaction is observed between *p*-toluoyl chloride and any of these complexes alone, but the addition of CO initiates a rapid reaction with the P*t*Bu$_3$ complex **2a**, and the near quantitative liberation of *p*-anisoyl chloride after 1 h. The monophosphine complex **2b** undergoes slower exchange, and this rate becomes insignificant with the bis-PPh$_3$ complex **2c**.

The relative reactivity of these complexes parallels the catalytic activity in Table 1 (P*t*Bu$_3$ > P(1-Ad)$_2$*n*Bu ≫ PPh$_3$). It is also consistent with marked differences in the coordination environments of complexes **2a**–**c**. The larger catalytically active ligands in **2a** and **2b** generate monophosphine complexes that would be amenable for CO coordination, and CO-assisted reductive elimination.[4] Comparison of the structures of **2a** and **2b** provides potential insight into the significantly higher reactivity of **2a**. Relative to the pseudo-square-planar P(1-Ad)$_2$*n*Bu complex **2b**, the P*t*Bu$_3$ complex **2a** adopts a three-coordinate, T-shaped structure due to the disfavored occupation of the fourth coordination site on palladium by the three sterically congested *t*Bu units.[8] One possibility for the unusual ability of **2a** to undergo rapid reductive elimination may therefore be the steric strain induced upon CO association to palladium, which together with the withdrawal of electron density by CO leads to favorable, strain-relief reductive elimination of acid chloride. This phenomenon would be expected to be most pronounced with three large units on the phosphine (e.g. Table 1, entries 5, 6, and 10), relative to other seemingly large ligands lacking this tertiary steric bulk (entries 7–9).[9] Nevertheless, even moderately sized ligands such as P(1-Ad)$_2$*n*Bu can undergo acid chloride elimination at temperatures well below that of catalysis (Scheme 2b).



Scheme 2. a) Atoms are represented by Gaussian ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity and only half of palladium dimer **2b** shown. b) Data in brackets at 50 °C. PMP = *p*-methoxyphenyl.

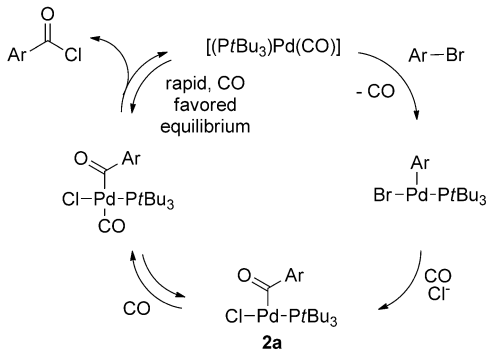
CO also appears to influence the thermodynamics of reductive elimination. Subjecting the P*t*Bu$_3$ complex **2a** to 1 atm. of CO without any trapping reagent results in the rapid equilibrium formation of acid chloride within minutes at ambient temperature [Eq. (2)]. Removal of CO regenerates **2a**, and increasing CO pressures further favors this equilibrium. These results suggest that CO can itself favor the formation of acid chloride elimination from **2a**, likely by generating an electron-poor Pd^0-



(2)

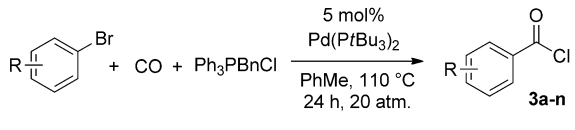
carbonyl complex that is less reactive towards the electrophilic acid chloride.[10] Complexes **2b** and **2c** undergo a similar CO-induced acid chloride elimination, but at significantly slower rates.[11]

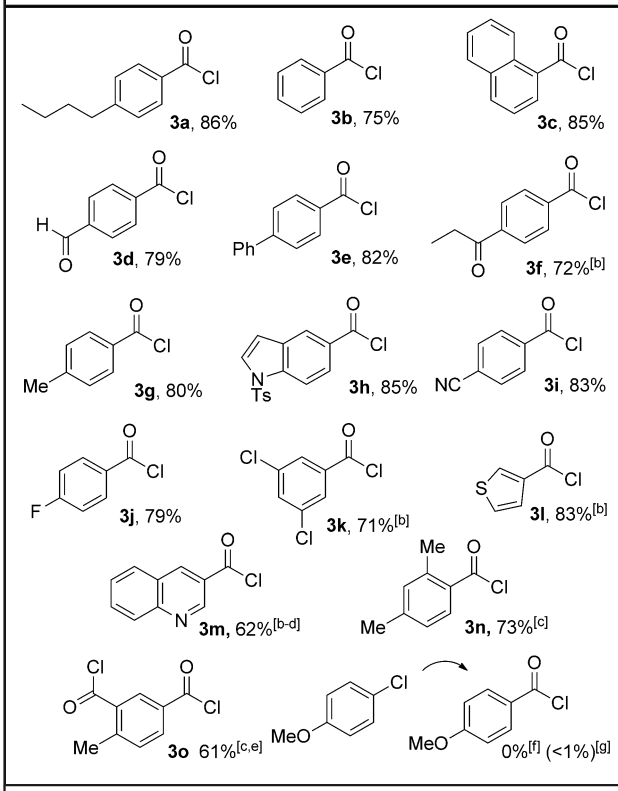
The rapid formation of acid chloride from **2a** with CO (within minutes at ambient temperature) shows that reductive elimination is unlikely to be rate-determining in catalysis. Preliminary kinetic experiments on the catalytic reaction are consistent with the stoichiometric studies. These show a linear rate dependence on CO pressure with the first order disappearance of aryl bromide (see the Supporting Information), and in situ ^{31}P NMR spectroscopic analysis (at 5 atm. CO) reveals that complex **2a** is the major catalyst resting state. Overall, these data suggest that the catalytic generation of acid chloride from aryl bromides proceeds by the reversible build-up of product and Pd^0 from **2a**. This equilibrium is favored by the large P*t*Bu$_3$ ligand (Scheme 2c) and high CO pressure.[12] In this scenario, catalyst turnover is dependent upon aryl bromide oxidative addition. The latter is also facilitated by sterically encumbered and strong donor ligands such at P*t*Bu$_3$. These mechanistic features are summarized in Scheme 3.



Scheme 3. Proposed catalytic cycle for aryl bromide chlorocarbonylation.

Table 2. Palladium-catalyzed carbonylation of aryl bromides to acid chlorides.[a]





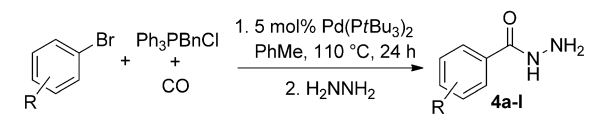
[a] Aryl bromide (1.25 mmol), Ph_3PBnCl (1.9 mmol), Pd(P*t*Bu$_3$)$_2$ (31.9 mg, 62.5 μmol), 20 atm. CO, PhMe (10 mL), 110 °C, 24 h; isolated yield of the derivatized products (see Supporting Information). [b] 7.5 mol% Pd(P*t*Bu$_3$)$_2$; [c] 48 h; [d] 15 mol% P*t*Bu$_3$ added. [e] ^{1}H NMR yield of ester derivative of **3o**. Determined by comparison to data reported in ref. [14]. [f] Standard conditions using 4-methoxychlorobenzene. [g] In neat chlorobenzene solvent at 150 °C.

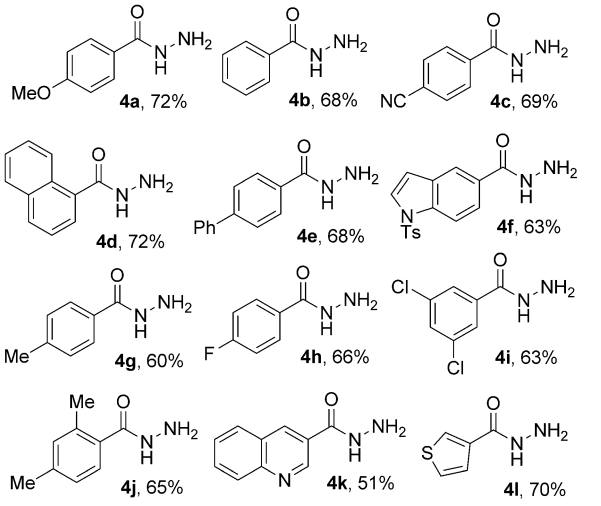
Scope of catalysis

As shown in Table 2, a range of aryl bromides can be carbonylated into acid chlorides with this catalyst system.[13] This includes arenes with functionality such as aldehydes (**3d**), nitriles (**3i**), and ketones (**3f**). Heteroaromatic aryl bromides, which are much more available and stable than their iodide counterparts, are also compatible in this reaction manifold (**3k**, **3l**). For nitrogen-containing **3m**, additional P*t*Bu$_3$ is required to accelerate the slow reaction, presumably due to the competitive coordination of the pyridine moiety to the catalyst. Substitution at the *ortho*-position is tolerated (**3n**), although the reaction is slightly more sluggish, likely as a result of the slower oxidative addition with the bulkier aryl bromide. Unsymmetrical dibromides can also be carbonylated to diacid chlorides (**3o**). Interestingly, only minimal monoacid chloride is generated from this reagent, even at short reaction times,[14] which suggests the first chlorocarbonylation facilitates a rapid second carbonylation to form **3o**. Conversely, the more atom-economical carbonylation of aryl chlorides to acid chlorides is not kinetically viable, even with this optimized catalyst system. The latter presumably reflects the extreme kinetic challenge of activating aryl chloride bonds in the presence of reactive ArCOCl. Overall, considering the low cost and broad availability of aryl bromides, and the other reagents (CO, Cl^-), this provides an effective method to assemble aromatic or heteroaromatic acid chlorides.

The catalytic generation of acid chlorides offers the potential to apply aryl bromide carbonylations to new classes of substrates. A traditional limitation in Pd-catalyzed carbonylations is the scope of nucleophiles that can be employed. For example, sterically encumbered, weakly nucleophilic, or palladium-reactive substrates have traditionally proven problematic in carbonylations. This is believed to arise from the limited electrophilicity of in situ generated palladium–acyl intermediates, and the required initial coordination of nucleophiles to palladium for reductive elimination.[15] In contrast, as acid chlorides

Table 3. Synthesis of benzohydrazides by carbonylation.[a]





[a] 1. Procedure from Table 2; 2. hydrazine hydrate (85%, 0.6 mL), 0 °C, 2 h.

are highly electrophilic reagents, their catalytic generation can allow the extension of palladium-catalyzed carbonylations to nonclassical coupling partners.[16] As an example, simple hydrazine is an attractive building block in synthesis but rarely employed in palladium-catalyzed coupling reactions,[17] including carbonylations, due in part to the ability of this small nucleophile to coordinate and interfere with bond activation.[18,19] As shown in Table 3, the in situ generation of acid chloride followed by hydrazine addition can provide a straightforward route to form benzohydrazide derivatives. A diverse range of aryl- and heteroaryl bromides can be employed in this one pot, two-step chemistry, each of which undergo rapid reaction with the in situ formed acid chloride. In light of the rich and highly-developed chemistry of acid chlorides, this approach should prove viable in the synthesis of many products typically inaccessible by carbonylations.

Conclusion

In summary, we have described the preparation of acid chlorides by carbonylation from aryl bromides. In contrast to traditional approaches to acid chloride synthesis with high energy and toxic halogenating agents (e.g. $SOCl_2$, PCl_3), or the use of aryl iodides, this reaction provides an approach to these electrophiles from reagents that are inexpensive, readily available, and stable (aryl bromides, CO, Cl^-). Catalyst effects are found to be critical for the generation of the weak and reactive acid chloride bond, with both sterically encumbered P*t*Bu$_3$ and CO required to achieve rapid and favored reductive elimination. Considering the growing significance of palladium-catalyzed bond-forming reactions, their application to assemble reactive products such as acid chlorides from stable building blocks could provide a useful general direction for such systems. Studies directed towards the latter are currently underway.

Experimental Section

In a steel Parr autoclave in a nitrogen glovebox was added 4-bromoanisole (234 mg, 1.25 mmol), benzyltriphenyl phosphonium chloride (727 mg, 1.88 mmol, 1.5 equiv), Pd(P*t*Bu$_3$)$_2$ (32 mg, 0.062 mmol, 5 mol%) and a stir bar. The autoclave was placed in a Parr system, then charged with carbon monoxide by evacuating and filling the system three times, and finally pressurized to 20 atm CO. The reaction was then heated to 110 °C for 24 h with a stirring rate of 600 RPM. The vessel was then allowed to cool to room temperature, the headspace was evacuated and the vessel was brought back into the glovebox. The product solution was filtered over a fine sintered glass frit to remove the insoluble phosphonium salt, the solid rinsed with toluene (3×1 mL), and the reaction solution derivatized.

Acknowledgements

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Keywords: acid chloride · carbonylation · mechanism · palladium · reductive elimination

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[6] BDE values can vary with the technique employed. Those quoted used the same method: a) Ph-Br BDE: R. J. Kominar, M. J. Krech, S. J. W. Price,

Can. J. Chem. **1978**, *56*, 1589; b) Ph-I BDE: R. J. Kominar, M. J. Krech, S. J. W. Price, *Can. J. Chem.* **1976**, *54*, 2981; c) PhCO-Cl BDE: M. Szwarc, J. W. Taylor, *J. Chem. Phys.* **1954**, *22*, 270; for other sources: d) Y. R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca Raton, **2007** and references therein.

[7] While the rate constant for PhBr oxidative addition to $Pd(PtBu_3)_2$ is not known due to complications of product decomposition, the half-life of this reaction is approximately 6.5 h at 70 °C (F. Barrios-Landeros, B. P. Carrow, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 5842), relative to ca. 10 min for PhCOCl at 25 °C. Conversely, PhI oxidative addition rates suggest an approximate half-life of 25 min in neat PhI at 25 °C (F. Barrios-Landeros, B. P. Carrow, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 8141).

[8] Related [RCOPdX(L)] complexes: a) S. Korsager, R. H. Taaning, T. Skrydstrup, *J. Am. Chem. Soc.* **2013**, *135*, 2891; b) S. Bontemps, J. S. Quesnel, K. Worrall, B. A. Arndtsen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8948; *Angew. Chem.* **2011**, *123*, 9110; c) D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard, T. Skrydstrup, *J. Am. Chem. Soc.* **2010**, *132*, 7998; d) A. G. Sergeev, A. Spannenberg, M. Beller, *J. Am. Chem. Soc.* **2008**, *130*, 15549.

[9] The more accessible coordination site in **2a** may also facilitate CO association and elimination. However, we see no evidence for CO binding to **2a**, even at elevated pressures, which suggests this association is not favored. Similarly, excess $PtBu_3$ does not affect the rate of elimination, which suggests $PtBu_3$ is not displaced by CO.

[10] For other examples of CO-induced reductive elimination: a) R. Pulukkody, S. J. Kyran, R. D. Bethel, C.-H. Hsieh, M. B. Hall, D. J. Darensbourg, M. Y. Darensbourg, *J. Am. Chem. Soc.* **2013**, *135*, 8423; b) Y. Gloaguen, L. M. Jongens, J. N. H. Reek, M. Lutz, B. de Bruin, J. I. van der Vlugt, *Organometallics* **2013**, *32*, 4284; c) M. Montag, I. Efremenko, R. Cohen, L. J. W. Shimon, G. Leitus, Y. Diskin-Posner, Y. Ben-David, H. Salem, J. M. L. Martin, D. Milstein, *Chem. Eur. J.* **2010**, *16*, 328; d) N. M. West, S. Reinartz, P. S. White, J. L. Templeton, *J. Am. Chem. Soc.* **2006**, *128*, 2059; for a computational study of the role of palladium electronics on C–X reductive elimination:e) Y. Lan, P. Liu, S. G. Newman, M. Lautens, K. N. Houk, *Chem. Sci.* **2012**, *3*, 1987.

[11] See the Supporting Information for details.

[12] As acid chloride builds up in catalysis, the equilibrium elimination in Equation (2) will become disfavored. As such, the role CO pressure may be to make this step kinetically viable near the end of the reaction (Table 1, entry 19).

[13] Due to the similar boiling points and solubility of aryl bromides and acid chlorides, acid chlorides were converted to the corresponding esters for isolation and characterization (see the Supporting Information for details).

[14] ^{1}H NMR spectroscopic analysis of crude mixture at 24 h shows 36% diacid chloride relative to 14% monoacid chloride, and 50% starting material, by comparison to known ester derivatives: a) L. Anzalone, J. A. Hirsch, *J. Org. Chem.* **1985**, *50*, 2128; b) K. S. Song, S. K. Lee, M. J. Kim, H. J. Seo, J. Lee, S. H. Lee, M. E. Jung, E. J. Son, M. Lee, J. Kim, J. Lee, *ACS Med. Chem. Lett.* **2011**, *2*, 182.

[15] Carbonylations typically show significant nucleophile scope limitations relative to acid chlorides. For reviews, see: a) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1; b) R. Grigg, S. P. Mutton, *Tetrahedron* **2010**, *66*, 5515; c) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4114; *Angew. Chem.* **2009**, *121*, 4176.

[16] For alternative approaches to expanding the scope of carbonylations, see: a) T. Ueda, H. Konishi, K. Manabe, *Org. Lett.* **2013**, *15*, 5370; b) M. N. Burhardt, R. H. Taaning, T. Skrydstrup, *Org. Lett.* **2013**, *15*, 948; c) T. Ueda, H. Konishi, K. Manabe, *Org. Lett.* **2012**, *14*, 5370; d) D. A. Watson, X. Fan, S. Buchwald, *J. Org. Chem.* **2008**, *73*, 7096.

[17] R. J. Lundgren, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 8686; *Angew. Chem.* **2010**, *122*, 8868.

[18] We are aware of only one report of hydrazine in carbonylative coupling, and this required high Pd loading (30 mol%), 150 °C, and was performed on a 2–3 mg scale: a) F. Karimi, B. Langstrom, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2111; b) unsuccessful use: D. Marosvölgyi-Haskó, A. Petz, A. Takács, L. Kollár, *Tetrahedron* **2011**, *67*, 9122.

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