Palladium-catalyzed Chlorocarbonylation of Aryl (*pseudo*)Halides through *in situ* Generation of Carbon Monoxide

Philip Boehm, Sven Roediger, Alessandro Bismuto and Bill Morandi*

Dedication ((optional))

* Philip Boehm, Sven Roediger, Dr. Alessandro Bismuto and Prof. Dr. Bill Morandi
Laboratorium für Organische Chemie, ETH Zürich
Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland
E-mail: bill.morandi@org.chem.ethz.ch

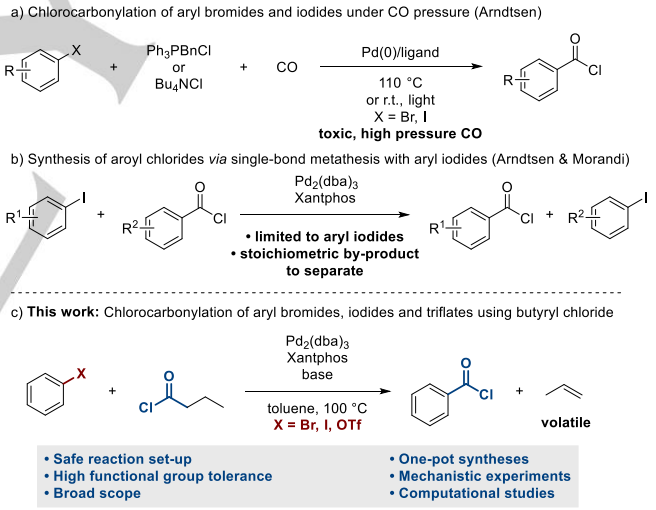
Supporting information for this article is given via a link at the end of the document.

Abstract: An efficient palladium-catalyzed chlorocarbonylation of aryl (*pseudo*)halides to access a wide range of carboxylic acid derivatives has been developed. The use of butyryl chloride as a combined CO and Cl source eludes the need for toxic, gaseous carbon monoxide, thus facilitating the synthesis of high-value products from readily available aryl (*pseudo*)halides. The combination of palladium(0), Xantphos, and an amine base is essential to promote this broadly applicable catalytic reaction. Overall, this reaction provides access to a great variety of carbonyl-containing products through *in situ* transformation of the generated aroyl chloride. Combined experimental and computational studies support a reaction mechanism involving *in situ* generation of CO.

Introduction

Transition-metal catalysis is an important tool for the efficient refinement of readily available chemical feedstocks into more functionalized products. Among those, carboxylic acid derivatives, aldehydes, and ketones are key intermediates often found in the syntheses of pharmaceuticals, agrochemicals, and other industrially relevant products.[1] An important route to access these products is the carbonylation of aryl halides. Since the seminal report from Heck and co-workers in 1974,[2] palladium-catalyzed carbonylation of aromatic halides has seen tremendous development.[1a,3] Most strategies make use of carbon monoxide as the carbonyl source in the presence of an appropriate nucleophile, *e. g.* alcohols, amines, thiols or organometallic species, for alkoxycarbonylation,[3,4] aminocarbonylation,[3,5] carbonylative Heck,[3,6] carbonylative Suzuki-Miyaura,[3,7] and carbonylative Sonogashira.[3,8]

However, due to the high toxicity and gaseous nature of carbon monoxide, the application of catalytic carbonylation reactions on a laboratory scale remains underdeveloped. These drawbacks can be overcome by the use of CO surrogates, such as formaldehyde, alkyl formates, formic anhydride, formamides, chloroform, aldehydes, or metal carbonyls.[9] Alternatively, an elegant solution developed by Skrydstrup and co-workers can be employed to generate CO *ex situ* in a two-chamber reactor, by-passing the storage and manipulation of exogenous CO. By using an acid chloride in one chamber of the reactor that can release CO under palladium catalysis, a great variety of carbonylation reactions can be performed in the second chamber of the reactor.[10] Still, some synthetically relevant carbonyl compounds remain challenging to access through transition metal-catalyzed carbonylation chemistry, mainly due to the intrinsic low reactivity of the corresponding nucleophiles. For instance, there is only one report, where unactivated arenes could be employed as nucleophiles in an intermolecular Friedel-Crafts type carbonylation of aryl iodides.[11] In addition, the broad spectrum of available catalytic systems for the carbonylation of aryl halides also brings along the necessity to employ tailor-made catalysts for each nucleophile or two catalyst systems as in the case of Skrydstrup.[3,9,10] These drawbacks can limit the flexibility of this strategy in target-oriented synthesis.



Scheme 1. Context of this work.

To bypass these limitations and develop an operationally simple and unifying approach to access carbonyl containing products from aryl (*pseudo*)halides, the formation and *in situ* derivatization of aroyl chlorides presents an attractive alternative. Acid chlorides are highly versatile intermediates in organic synthesis and provide a platform for a wide range of subsequent transformations. Reactions of acid chlorides include formation of esters, amides, or ketones, as well as metal-catalyzed cross-coupling reactions[12] and peptide-couplings[13] amongst others.[14] Recently, Arndtsen and co-workers have shown the chlorocarbonylation of aryl iodides and bromides using pressurized carbon monoxide and a soluble chloride source (Scheme 1a).[15]

Arndtsen and our group independently developed a single-bond metathesis approach for the synthesis of acid chlorides from aryl

iodides, preventing the use of toxic, gaseous carbon monoxide (Scheme 1b).[16] Still, the conversion of less expensive aryl bromides and more readily available aryl triflates into the corresponding acyl chlorides could not be achieved, leaving this synthetic challenge unmet. Furthermore, the formation of stoichiometric amounts of aryl iodide byproduct were interfering with the purification of the acid chloride (*vide infra*).

In order to broaden the scope of the chlorocarbonylation and address the recurring purification issues, we reasoned that the use of butyryl chloride as an inexpensive CO and Cl source could be very attractive. Our group previously reported the use of this reagent, in a shuttle catalysis strategy,[17] as a source of HCl and CO in a hydrochlorocarbonylation of alkynes and alkenes.[18] We hypothesized that, in the presence of a base, we might divert this reaction mechanism to facilitate the chlorocarbonylation of aryl halides. A major benefit of this approach would be the release of a volatile by-product, propene, thus facilitating the purification of the final product. However, a major challenge in realizing this reaction, or any reaction involving two distinct electrophiles,[19] is to identify a suitable catalyst system which can mediate the oxidative addition of the two respective electrophiles with a similar rate to enable catalytic turnover.

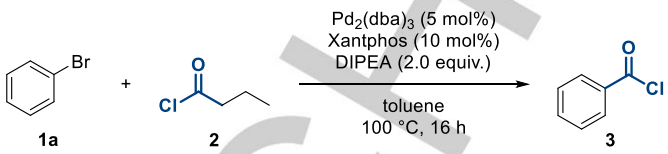
Herein, we report a general palladium-catalyzed chlorocarbonylation of aryl bromides, aryl iodides, and aryl triflates, using butyryl chloride as CO/Cl-donor in the presence of a base. We also provide key mechanistic and computational results, which lay down the groundwork for the development of new carbonylation reactions.

Results and Discussion

Evaluation of Reaction Conditions.

We began our investigations with bromobenzene (**1a**) and butyryl chloride (**2**) as benchmark substrates (Table 1). In a preliminary screening of monodentate and bidentate phosphines, as well as different Pd(0) sources, a first hit with $Pd_2(dba)_3$ and Xantphos was observed. After extensive evaluation of the reaction conditions, we found that a combination of $Pd_2(dba)_3$, Xantphos, and *N*,*N*-diisopropylethylamine (DIPEA) as a non-nucleophilic, sterically encumbered base in toluene at 100 °C gave the best result after a reaction time of 16 hours (see Supporting Information, Tables S1-S11). Amongst the aliphatic acid chlorides tested, butyryl chloride showed the highest yields.[20] The bidentate ligand Xantphos proved to be superior to all other tested ligands (entries 2 and 3), including sterically encumbered trialkylphosphines that showed good reactivity in prior examples of chlorocarbonylation.[15a,b] Other (amine) bases had a deleterious effect on the reaction outcome (entry 9 and 10). Since it is presumed that the reaction proceeds *via* the oxidative addition of Pd(0) into both butyryl chloride and aryl halide (*vide infra*), the rates of both processes have to match to avoid accumulation of one reaction intermediate.[19] By using 3 equivalents of bromobenzene, the relative reaction rates can be balanced, driving the reaction to high conversion and increasing the yield drastically (entry 12). The excess of aryl bromide is potentially required due to the preference of Pd(0) to oxidatively add into the weaker acyl C-Cl bond of both starting material and product.[15b,21] Inverting the stoichiometry of the reagents completely shuts down the reaction (entry 4). Changing the $Pd_2(dba)_3$ precatalyst to other Pd(0) sources gave a lower yield of the desired aroyl chloride (entry 5). Reactions conducted with decreased catalyst loading (entry 6) or temperature (entry 7) resulted in lower yield. Toluene emerged as the best solvent for this reaction (entry 8).[20]

Table 1. Optimization of reaction conditions for aryl bromides.[a]



1a 2 3

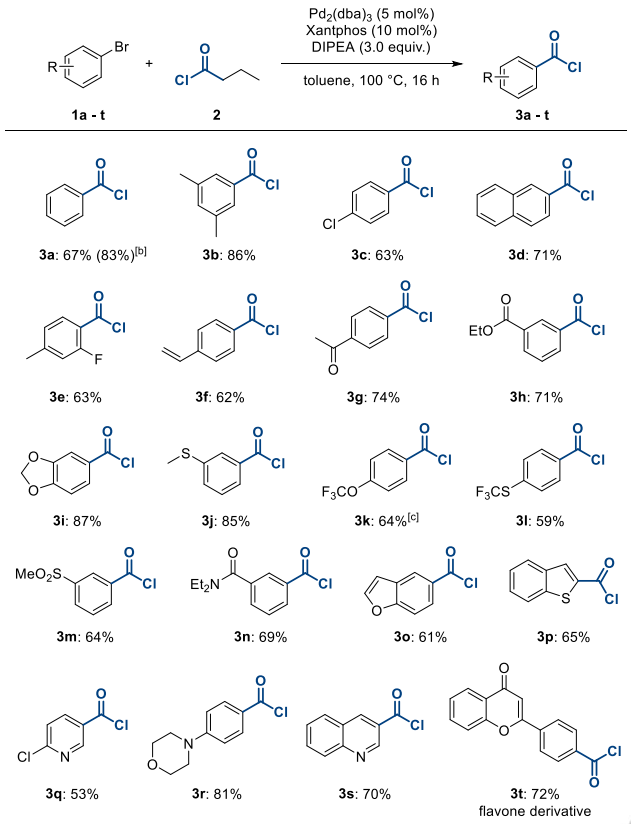
Entry	Deviations from above	Yield [%][b]
1	none	25
2	P^{t}Bu$_3$ instead of Xantphos	18
3	BrettPhos instead of Xantphos	2
4	3.0 equiv. of butyryl chloride	traces
5	10 mol% $Pd(PPh_3)_4$ instead of $Pd_2(dba)_3$	18
6	2.5 mol% $Pd_2(dba)_3$, 5 mol% Xantphos	20
7	80 °C instead of 100 °C	10
8	1,4-dioxane instead of toluene	23
9	2.0 equiv. of NEt_3 instead of DIPEA	8
10	2.0 equiv. of K_3PO_4 instead of DIPEA	-
11	3.0 equiv. of DIPEA	31
12	**3.0 equiv. of bromobenzene**	**83**[c]

[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.25 mmol), $Pd_2(dba)_3$ (5 mol%), Xantphos (10 mol%), DIPEA (2.0 equiv.), toluene (1.25 mL) at 100 °C, 16 h. [b] GC yield of the corresponding methyl ester using *n*-dodecane as internal standard. [c] 3.0 equiv. DIPEA used.

Chlorocarbonylation of Aryl Bromides and Aryl Triflates.

With these optimized reaction conditions in hand, we moved on to explore the substrate scope of the chlorocarbonylation of aryl (*pseudo*)halides which could not be used as electrophiles in previous examples of CO-free chlorocarbonylation.[16] Starting with aryl bromides, a wide variety of aroyl chlorides could be successfully accessed through this methodology (Table 2). Indeed, aryl bromides bearing either electron-neutral (**3a** and **3d**), electron-rich (**3b**, **3i**, and **3r**), or electron-poor (**3c**, **3g**, **3h**, **3j**, **3k**, **3l**, **3m**, and **3n**) substituents were tolerated under the reaction conditions, giving the desired aroyl chlorides in good yield. The chlorocarbonylation proved to be efficient in the presence of heterocyclic compounds, such as pyridine, quinoline, benzofuran, or benzothiophene (**3o**, **3p**, **3q**, and **3s**). Notably, a styrene derivative was tolerated under the reaction conditions, giving **3f** in 62% yield. No Heck-type reaction was observed with this substrate. A more complex flavone starting material was converted efficiently into the corresponding acid chloride product **3t** in 72% yield. Similar to earlier reports of palladium-catalyzed chlorocarbonylations,[15a,b,16] substrates with *ortho*-substituents resulted in poor conversions. The *ortho*-fluorine-substituted product **3e** was nonetheless obtained in 63% yield.

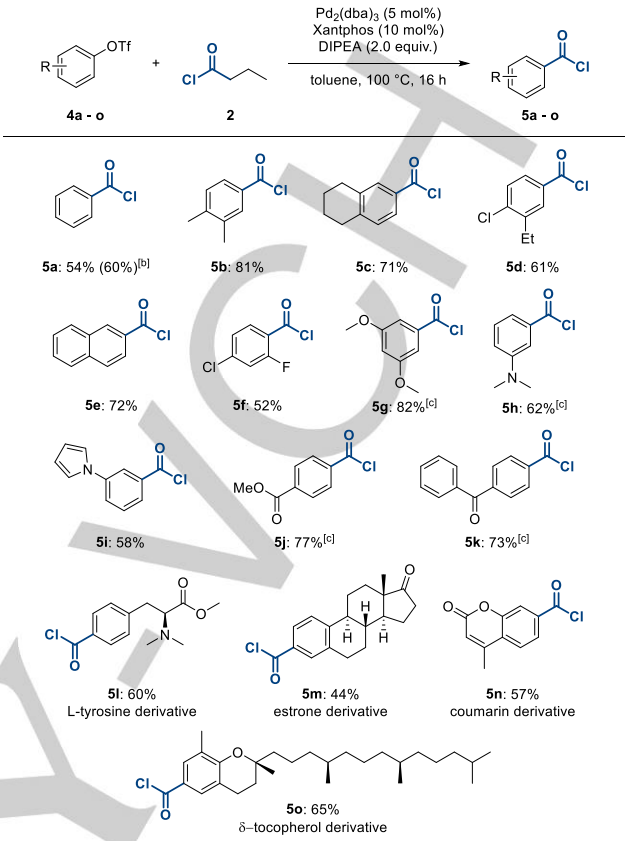
Table 2. Palladium-catalyzed chlorocarbonylation of aryl bromides.[a]
[a] Yields refer to isolated products after *in situ* derivatization of the labile acid chlorides to the corresponding methyl esters. Aryl bromide (3.0 equiv.), butyryl chloride (0.5 mmol), $Pd_2(dba)_3$ (5 mol%), Xantphos (10 mol%), DIPEA (3.0



equiv.), toluene (2.5 mL), 100 °C, 16 h. [b] GC yield using *n*-dodecane as internal standard in parentheses. [c] Isolated with 5% of methyl benzoate.

We next extended the palladium-catalyzed chlorocarbonylation to another important class of electrophiles: aryl triflates. Even though aryl triflates can be easily accessed from phenols, they have rarely been used in carbonylation reactions and, to the best of our knowledge, have never been used in chlorocarbonylation.[8a,22] After a slight re-optimization of the reaction conditions (see Supporting Information, Tables S12-S22), we found that a variety of aryl triflates could successfully undergo the chlorocarbonylation reaction. As shown in Table 3, electron-neutral (**5a** and **5e**), electron-rich (**5b**, **5c**, **5h** and **5i**) and electron-deficient (**5d**, **5g**, **5j** and **5k**) aryl triflates were tolerated under the reaction conditions, giving the corresponding aroyl chlorides in good yields. As in the case of aryl bromides, the presence of *ortho*-substituents remains a limitation. Only a fluorine substituent in the *ortho*-position was tolerated, giving **5f** in a moderate 52% yield, leaving the less hindered chloro-substituent untouched. An *L*-tyrosine derivative, estrone, a coumarin derivative, and δ-tocopherol were converted to their aryl triflate analogs and subjected to the reaction conditions for the chlorocarbonylation. The desired products were obtained in moderate to good yields (**5l**, **5m**, **5n** and **5o**), showing that the reaction can be used on a more complex substrate.

Table 3. Palladium-catalyzed chlorocarbonylation of aryl triflates.[a]



[a] Yields refer to isolated products after *in situ* derivatization of the labile acid chlorides to the corresponding methyl esters. Aryl triflate (3.0 equiv.), butyryl chloride (0.5 mmol), $Pd_2(dba)_3$ (5 mol%), Xantphos (10 mol%), DIPEA (2.0 equiv.), toluene (2.5 mL), 100 °C, 16 h. [b] GC yield using *n*-dodecane as internal standard in parentheses. [c] $[Pd(allyl)Cl]_2$ (5 mol%) used instead of $Pd_2(dba)_3$.

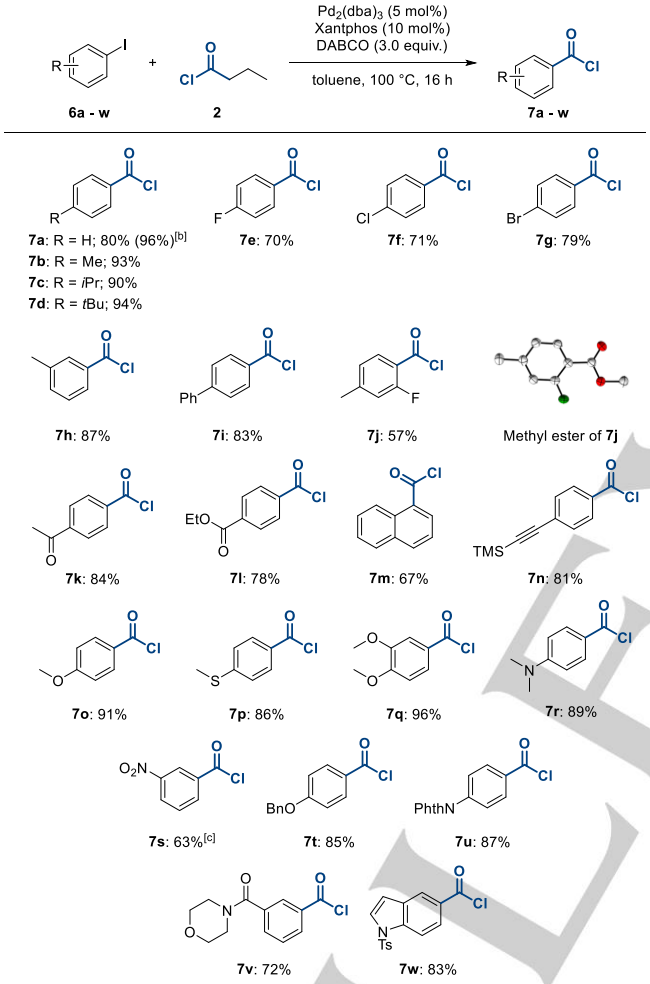
Chlorocarbonylation of Aryl Iodides.

Subsequently, we turned our focus to the chlorocarbonylation of aryl iodides. Recently, the CO-free synthesis of aroyl chlorides from aryl iodides *via* a single-bond metathesis with sacrificial aromatic acid chlorides had been reported (Scheme 1b),[16] but the purification of the desired product proved to be challenging in several cases due to the high-boiling point and similar polarity of the by-products generated. We envisioned that extension of the reaction developed in this study to aryl iodides could overcome such purification issues by only generating volatile propene as the sole by-product. Careful optimization of the reaction parameters revealed that butyryl chloride could be used in excess to drive the reaction to high conversions in the case of aryl iodide substrates (see Supporting Information, Tables S23-S34). This indicates that the oxidative addition of the Pd-catalyst into the C(aryl)-I bond of the aryl iodide starting material is more facile than the oxidative addition into the C-Cl bond of the acid chloride product. Indeed, with 65 kcal/mol, the bond energy of C(aryl)-I is weaker than the bond energy of C-Cl (74 kcal/mol) in acyl chlorides.[15b,21b,23] Even though DIPEA as base showed good results in the chlorocarbonylation, 1,4-diazabicyclo[2.2.2]octane (DABCO) proved to be superior in this case.[20]

We next examined the substrate scope for the chlorocarbonylation of aryl iodides (Table 4). Similar to aryl bromides and aryl triflates, a broad spectrum of functional groups

was tolerated under the reaction conditions. Electron-neutral (**7a**, **7i**, and **7m**), electron-rich (**7b–d**, **7h**, **7o**, **7p**, **7q**, **7r**, **7t**, and **7u**) and electron-deficient (**7e**, **7f**, **7k**, **7l**, **7s**, and **7v**) substrates were converted to the corresponding aroyl chlorides in good to excellent yields. The substrate 1-bromo-4-iodobenzene (**6g**), bearing both a bromide and iodide substituent, exclusively provided product **7g** in 79% yield, leaving the bromide substituent unreacted. Therefore, this methodology should allow for a sequential, orthogonal installation of multiple groups through chemoselective chlorocarbonylation followed by cross-coupling reactions.

Table 4. Palladium-catalyzed chlorocarbonylation of aryl iodides.[a]



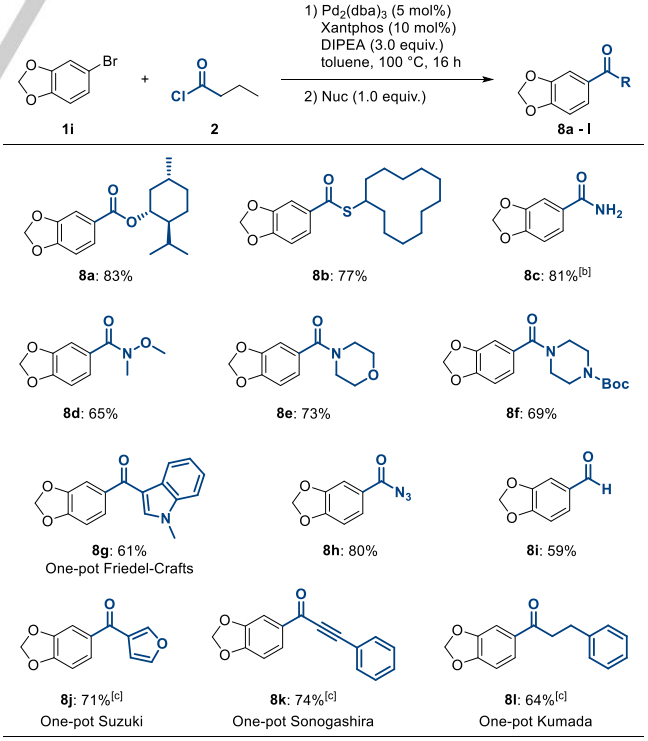
[a] Yields refer to isolated products after *in situ* derivatization of the labile acid chlorides to the corresponding methyl esters. Aryl iodide (0.5 mmol), butyryl chloride (10 equiv.), $Pd_2(dba)_3$ (5 mol%), Xantphos (10 mol%), DABCO (3.0 equiv), toluene (2.5 mL), 100 °C, 16 h. [b] GC yield using *n*-dodecane as internal standard in parentheses. [c] *o*-xylene at 125 °C.

TMS-protected alkynes were left untouched in our reaction, possibly because of steric hindrance (**7n**). Heterocycles were well tolerated in the chlorocarbonylation of aryl iodides (**7w**). Product **7j** with a fluorine substituent in *ortho*-position was isolated in moderate yield (57%). The identity of **7j** could be further confirmed by single crystal X-ray analysis of the corresponding methyl ester.[24]

One-Pot Synthesis of Carbonyl-Containing Products.

Acid chlorides exhibit high reactivity towards a great variety of nucleophiles. Taking advantage of this property, the chlorocarbonylation of aryl (*pseudo*)halides can be exploited to give access to a broad spectrum of carbonyl-containing products. The acyl chloride product can be used as a platform for further *in situ* derivatization, thus enabling the one-pot synthesis of diverse carbonyl products starting from aryl (*pseudo*)halides (Table 5). 1-Bromo-3,4-methylenedioxobenzene (**1i**) was selected as substrate of choice to exemplify the derivatization, since it showed good conversion to the corresponding acid chloride (Table 2). A structurally more complex alcohol, (–)-menthol, and a cycloalkanethiol were first employed as nucleophiles and afforded the desired ester **8a** and thioester **8b** in good yield. Reacting the formed acyl chloride *in situ* with ammonia gave the corresponding primary amide **8c**. Weinreb-amide **8d** could be obtained in 65% yield, starting from aryl bromide **1i** and reacting the *in situ* formed acyl chloride with *N*,*O*-dimethylhydroxylamine. Derivatization with other amines, such as morpholine and *N*-Boc-protected piperazine gave amides **8e** and **8f** in good yields. Friedel-Crafts acylation with *N*-Me-indole gave ketone **8g** in 61% yield. Interestingly, when sodium azide was added after the chlorocarbonylation reaction, acyl azide **8h** was obtained in 80% yield.[25] To the best of our knowledge, this represents the first azidocarbonylation starting from aryl bromides.[26] The combination of our chlorocarbonylation with further catalytic transformations in a one-pot process turned out to be feasible. Aldehyde **8i** was obtained in 59% yield after reacting the *in situ* formed aroyl chloride with Bu_3SnH in the presence of catalytic amounts of indium trichloride.[27] Finally, one-pot Suzuki, Sonogashira, and Kumada couplings with *sp*, sp^2 and sp^3 carbon nucleophiles, respectively, enabled us to access the corresponding ketones in good yields (**8j**, **8k** and **8l**).[28] Overall, these results demonstrate the potential of this new protocol to provide a unified strategy to access several important carbonyl products without using exogeneous carbon monoxide.

Table 5. One-pot Synthesis of carbonyl-containing products.[a]



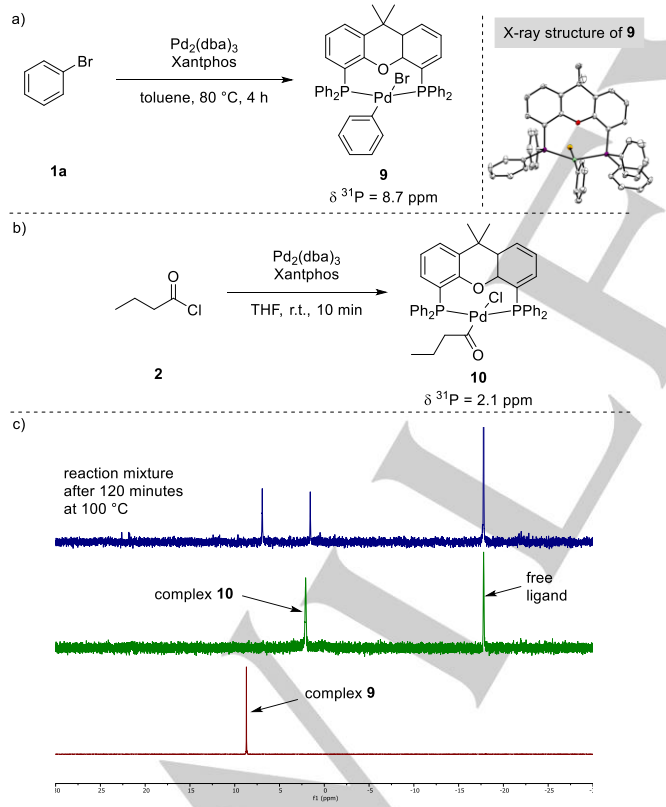
[a] Yield of isolated products. For further information see SI. [b] Isolated with 10% benzamide. [c] $[Pd(allyl)Cl]_2$ (5 mol%) used instead of $Pd_2(dba)_3$.

Mechanistic Studies

In contrast to traditional carbonylation protocols, where a conventional mechanism involving an electrophile and a nucleophile is assumed,[3a,i] our system relies on a reaction between two electrophiles, butyryl chloride and an aryl halide. Because such reactions are much less common, there are only few mechanistic studies available.[19f,g,h,i] The attractive possibility to contribute to this understudied area motivated us to study our reaction using a combined experimental and theoretical approach.

We started our investigation by performing a stoichiometric experiment between bromobenzene, $Pd_2(dba)_3$, and Xantphos. After four hours at 80 °C, it was possible to isolate a complex which was confirmed to be the oxidative addition product **9** by X-ray and NMR analysis (Scheme 2a).[20,29,30] The NMR resonances of the complex are in accordance with literature values for similar complexes.[29]

Next, we turned our attention on the reaction of butyryl chloride and Pd(0). Pioneering work on the oxidative addition of Pd(0) complexes into aliphatic acid chlorides was reported by Skrydstrup using P(*t*-Bu)$_3$ as ligand.[10b,31] Gratifyingly, we could synthesize the related oxidative addition complex **10** bearing a Xantphos ligand. A singlet peak at 2.1 ppm was observed by $^{31}P\{^1H\}$ NMR spectroscopy, which is in accordance to shifts previously reported for other acyl complexes of Xantphos-ligated palladium(II).[5a,32] Furthermore, a very deshielded carbon (δ = 225.8 ppm) was observed as a triplet peak in the $^{13}C\{^1H\}$ spectrum.

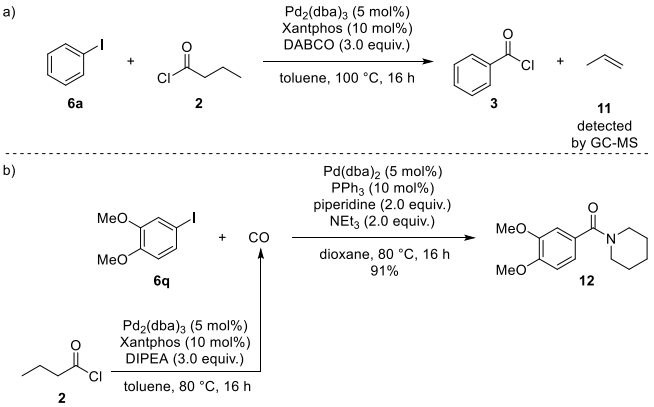


Scheme 2. a) Reaction of bromobenzene with $Pd_2(dba)_3$ and Xantphos. Crystal structure of the oxidative addition complex **9**. b) Reaction of butyryl chloride with with $Pd_2(dba)_3$ and Xantphos. c) $^{31}P\{^1H\}$ NMR spectra of both oxidative addition complexes **9** and **10** (room temperature) in comparison with a $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture (100 °C).

We assigned this peak to the carbonyl carbon of **10** that couples to the ligand phosphorous atoms. Its chemical shift is very similar to related acyl complexes of Xantphos-ligated palladium(II).[32] Long range correlation in the ^1H-^{13}C HMBC spectrum between the carbon peak at δ = 225.8 ppm and a proton signal, identified as a CH_2 group, confirms the identity of this deshielded carbon signal as the carbonyl group of acyl complex **10**. Unfortunately, this complex was found to be less stable than the related complex reported by Skrydstrup[31] and rapidly decomposed at room temperature. We could identify the decomposition product of **10** as (Xantphos)$PdCl_2$ by comparing the spectroscopic data to the data of an authentic sample.

In order to further investigate our chlorocarbonylation reaction, we performed *in situ* NMR analysis under catalytic conditions. Within the first 30 minutes, two new resonances appeared in the $^{31}P\{^1H\}$ NMR spectrum which had very similar shifts when compared to the shifts of complexes **9** and **10**. These two peaks remained visible over the course of the reaction and therefore possibly correspond to the resting states of the catalytic cycle.[20] Taking into account the difference in temperature at which the spectra were recorded, these two complexes could correspond to compounds **9** and **10**. DFT calculations of the reaction mechanism (Figure 1; *vide infra*) support the assignment of complex **10** as a resting state of the reaction and propose (Xantphos)Pd(benzoyl)(Br) (complex **J**) instead of (Xantphos)Pd(Ph)(Br) (**9**) as the second resting state. Considering that (Xantphos)Pd(benzoyl)(X) (X= Cl or Br) and complex **9** have very similar $^{31}P\{^1H\}$ NMR shifts,[5a,32] no definite conclusions can be drawn about the identity of the complexes observed by $^{31}P\{^1H\}$ NMR spectroscopy of the catalytic reaction (Scheme 2c).

Similar to previous reports,[10b,31] we envisaged that carbon monoxide release from complex **10** and subsequent β-hydride elimination of the propyl fragment could lead to formation of a (Xantphos)Pd(H)(Cl) species. The latter could be readily transformed to an active Pd(0) species by reductive elimination in the presence of DIPEA. This Pd(0) species could then undergo oxidative addition with the aryl halide. As the time scale of these steps limited an *in situ* spectroscopic investigation, we decided to test our hypothesis of CO release and β-hydride elimination by other means. By using a gas-tight syringe, the gases present in the headspace of the reaction could be analyzed by GC-MS. Propene was unambiguously identified by comparison of the mass spectrum with an independent reference spectrum (Scheme 3a).[20] The formation of propene was further confirmed by ^1H-NMR spectroscopy with signals at δ = 5.67, 4.96, and 4.90 ppm, matching data reported in literature.[20,31]



Scheme 3. a) Detection of propene by GC-MS headspace analysis. b) Detection of carbon monoxide by two-chamber aminocarbonylation.

Since carbon monoxide cannot be detected by our GC-MS detector, we investigated the potential formation of free carbon monoxide by other means. When running the reaction of bromobenzene in an open system, the yield of benzoyl chloride drops to 38%, compared to 83% yield in a closed system.[20] This indicates that *in situ* generated free, unbound CO might escape the reaction medium during the process. To further support our hypothesis of carbon monoxide release, the reaction depicted in Scheme 3b was conducted in a sealed two-chamber system.[10b] One chamber was loaded with the optimized conditions for the chlorocarbonylation of aryl bromides discussed earlier, omitting bromobenzene. The other chamber was loaded with 4-iodo-1,2-dimethoxybenzene (**6q**) and conditions developed for the aminocarbonylation of aryl halides.[10b] The expected aminocarbonylation product **12** was isolated in 91% yield, confirming that CO is generated *in situ* from our catalytic conditions.

Computational Studies

In order to study the feasibility of different mechanistic pathways, we performed extensive computational studies based on density functional theory (DFT). The transformation of bromobenzene to benzoyl chloride was used as a model for the reaction of aryl bromide substrates. All calculations were conducted using the Gaussian09 suite of programs.[20,33] The keyword integral(grid=ultrafine) was used in all calculations to limit grid-based errors.[34] Geometries were optimized at the PBE level of theory[35,36] including Grimme dispersion correction (D3) with Becke-Johnson damping[37,38] and the SMD solvent model for toluene.[39] Palladium was modelled with the def2tzvp basis set and ECP.[40,41] All other atoms were modelled with the def2svp basis set. Single point energies and thermochemical corrections were calculated with the PBE0 functional[35,36,42,43] including Grimme dispersion correction (D3) with Becke-Johnson damping,[37,38] the SMD solvent model for toluene,[39] and thermal correction to 373 K. The PBE0 functional was chosen due to its excellent performance in benchmarking studies.[44] All atoms were modelled with the def2tzvp basis set.[40,41] The corresponding ECP was used for palladium. Structures were visualized with CYLview.[45]

We began our investigation by analyzing the activation of butyryl chloride (**2**) by Pd(Xantphos) (**A**) (Figure 1). Based on our experimental results and previous reports, it is likely that the reaction commences by the oxidative addition of the palladium(0) complex **A** into the C-Cl bond of butyryl chloride (**2**).[10b,31] This process has a low computed energy barrier of 4.8 kcal/mol (**TS1**). The resulting complex **B** is 12.1 kcal/mol more stable than the combination of Pd(Xantphos) (**A**) and butyryl chloride (**2**). Next, as suggested by experimental evidence, the energy pathway for the de-insertion of carbon monoxide and subsequent propene formation was investigated. The CO de-insertion step is predicted to have an energy barrier of 22.4 kcal/mol (**TS2**). From complex **C**, in which a propyl, chloride, and carbonyl ligand are bound to Pd(Xantphos), two possible pathways for the extrusion of propene were analyzed. The first option is the direct β-hydride elimination from complex **C** to give rise to a carbonylated palladium hydride species. This pathway could be ruled out by the high-energy transition state (30.1 kcal/mol, **TS3**) compared to alternative pathways. This high activation barrier presumably arises from the coordinatively saturated nature of the palladium species. In contrast, CO loss from **C** is only 1.7 kcal/mol uphill, and the subsequent β-hydride elimination from the square-planar complex **D** is more easily accessible with a lower energy barrier of 17.9 kcal/mol (**TS4**). Loss of propene gives rise to Pd(Xantphos)(H)(Cl) (**E**), which undergoes reductive elimination of HCl in the presence of base (**TS5**).

The re-formed Pd(Xantphos) complex **A** can readily trap the released carbon monoxide. The resulting complex Pd(Xantphos)(CO) (**F**) is predicted to be 18.3 kcal/mol more stable than the combination of Pd(Xantphos) (**A**) and free CO. The activation energy for the oxidative addition of bromobenzene (**1a**) to **F** was calculated to be much higher in energy (**TS7**; 34.1 kcal/mol) than to **A** (**TS6** *via* complex **G**; 12.3 kcal/mol). The oxidative addition of bromobenzene should therefore preferentially occur with the non-carbonylated complex **A**.

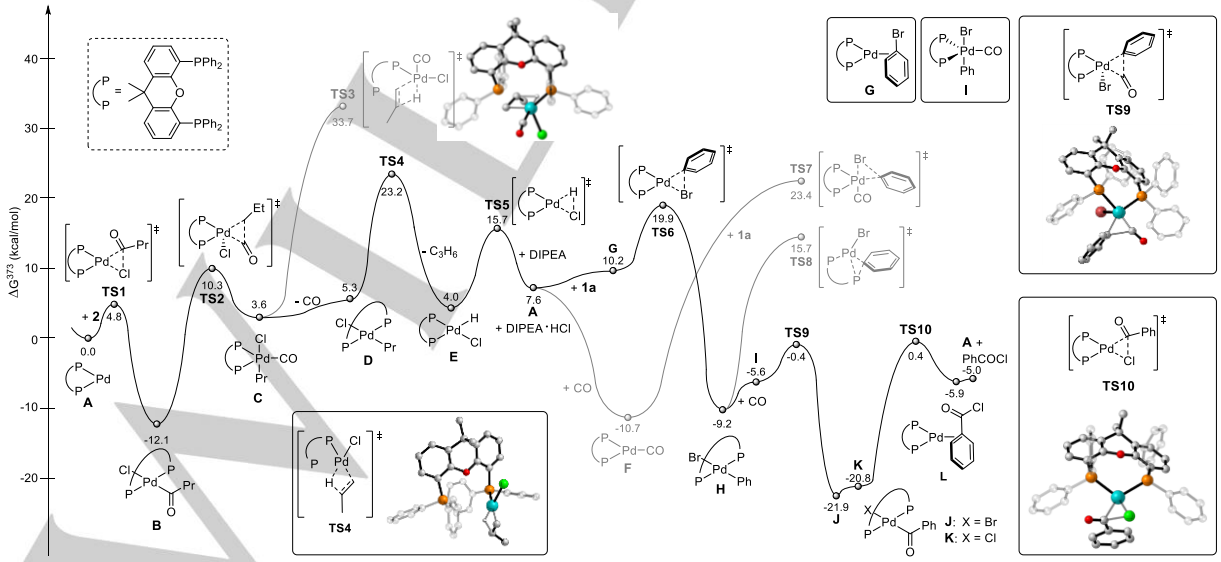


Figure 1. Energy profile for the palladium-catalyzed formation of benzoyl chloride (**3a**) from butyryl chloride (**2**) and bromobenzene (**1a**) at the PBE0-D3(BJ)/SMD(PhMe)-def2tzvp//PBE-D3(BJ)/SMD(PhMe)-def2svp-def2tzvp(Pd) level of theory. The optimized geometries of the transition states **TS3**, **TS4**, **TS9**, and **TS10** are depicted. Hydrogen atoms except for hydrides are omitted for clarity.

Although the carbonyl complex **F** is unlikely to be a productive intermediate in the catalytic reaction, temporary trapping of free CO by Pd(Xantphos) to form complex **F** and potentially [Pd(Xantphos)(CO)$_2$][26b] might explain why the reaction of bromobenzene (**1a**) still gave 38% yield of benzoyl chloride (**3a**) product in an open reaction system (*vide supra*). Complex **H** can trap carbon monoxide to form the penta-coordinate complex **I**. Migratory insertion of CO into the Pd-Ph bond of **I** (**TS9**) has a low energy barrier of 5.2 kcal/mol and is 16.3 kcal/mol downhill (complex **J**). The energy barrier for the subsequent reductive elimination of acyl halide was found to be slightly lower from chlorido complex **K** than bromido complex **J**.[20] This suggests that complex **J** preferentially undergoes halide exchange with the hydrochloride of DIPEA to form complex **K**. The subsequent reductive elimination of benzoyl chloride (**1a**) has an energy barrier of 21.2 kcal/mol and leads to the regeneration of palladium(0) complex **A**, closing the catalytic cycle. The halide exchange from bromide to chloride was also evaluated for earlier (from complex **H**) and later stages (from free benzoyl bromide) of the reaction.[20] The resulting energy profiles for the formation of the acyl chloride product are only slightly less favorable than the pathway described above and also accessible. It is therefore likely that a mixture of these mechanisms is operating in the experiment with the depicted energy profile as the main pathway.

Recently, we reported the synthesis of aroyl chlorides from aryl iodides, through a functional group metathesis pathway, using a similar catalytic system to the one employed in this study (Scheme 2b).[16a] Mechanistic experiments showed that the reaction likely proceeds *via* C-P reductive elimination with the Xantphos ligands to form phosphonium ions. While investigating the scope of the reaction developed in this study, methyl benzoate was indeed observed as a minor side product in the reaction of certain substrates (e. g. **3k**). Its formation could be explained by scrambling of the Xantphos-phenyl groups with the aryl group of the substrate. We therefore investigated if the main mechanistic pathway involves a similar C-P reductive elimination step as in our previous study. If the reaction proceeded through a phosphonium ion, complex **H** would have to undergo C-P reductive elimination (**TS8**). The energy barrier for this process was calculated to be 24.9 kcal/mol (Figure 1). This pathway is therefore accessible, but much less favorable than the one depicted in Figure 1. This makes it very unlikely that the main mechanistic pathway of this new reaction proceeds through a C-P reductive elimination mechanism. We were curious to understand whether the availability of free, unbound CO in the reaction mixture might be the origin of the different pathways that are observed for this reaction and our previously reported single-bond metathesis reaction.[16a] To test whether free CO is generated under the conditions employed in the latter protocol[16a], we used a similar two-chamber system as depicted in Scheme 3b.[20] Only traces of carbonylation were observed in the second reaction chamber. This supports our hypothesis that the availability of free CO in the reaction leads to the difference in reaction pathways observed between this new reaction and our previously-reported single-bond metathesis reaction.[16a] The reason why aroyl chlorides do not generate free CO in their reaction with the Pd(Xantphos) system while aliphatic acyl chlorides do, is unclear at this stage and under further investigation.

With the results of our mechanistic experiments and the computational studies, we propose a mechanism for the chlorocarbonylation of aryl halides (Figure 2). In the right cycle of the mechanism, Xantphos-ligated Pd(0) undergoes oxidative addition into the carbon-chlorine bond of butyryl chloride (**2**) to give intermediate **I**. This can then de-insert and subsequently release carbon monoxide to give intermediates **II** and **III**, respectively. A free coordination site at the palladium center is created to facilitate β-hydride elimination and afford (Xantphos)Pd(H)(Cl) complex **IV**. This can then undergo base-induced reductive elimination to regenerate the Pd(0) species. On the left side of the catalytic cycle, aryl bromide **1a** can undergo oxidative addition to (Xantphos)Pd(0) to give literature-known complex **V**.[29] This complex can then bind free carbon monoxide present in the reaction mixture to give complex **VI**. After CO insertion to afford **VII**, nucleophilic displacement of the bromine ligand with chloride takes place to give complex **VIII**. This can then reductively eliminate to give benzoyl chloride (**3**) and close the catalytic cycle.

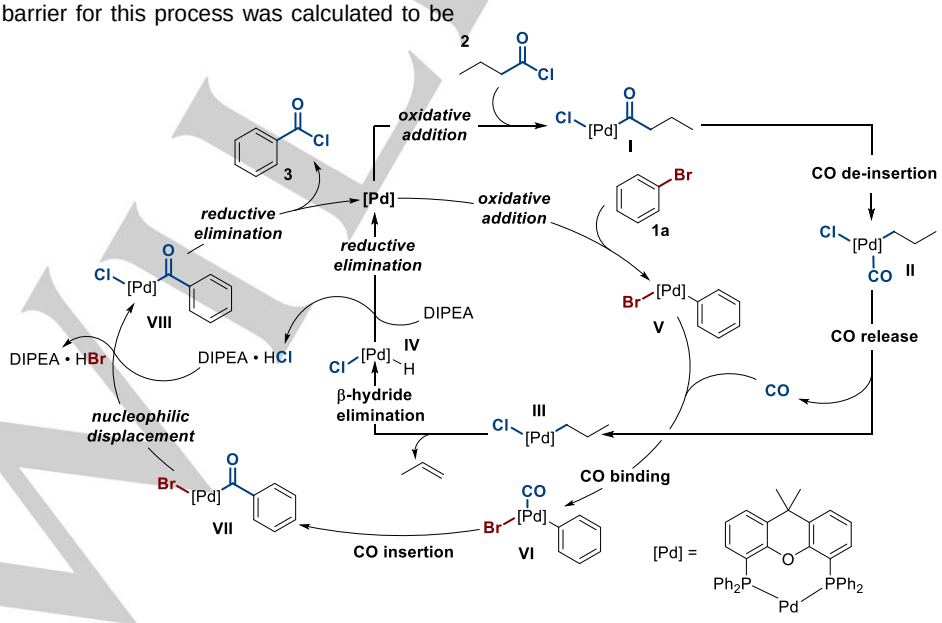


Figure 2. Proposed mechanism for the chlorocarbonylation of aryl halides based on experimental and computational studies.

Conclusion

In summary, we have developed a new palladium-catalyzed chlorocarbonylation of aryl (*pseudo*)halides which uses butyryl chloride as *in situ* source of both CO and Cl. This reaction gives access to a broad variety of acid chlorides, starting from commercially available or easily accessible aryl bromides, iodides, and triflates. Inexpensive butyryl chloride as a donor not only addresses the safety issues encountered with the use of exogenous carbon monoxide, but also overcomes the need for specialized equipment, such as high-pressure or two-chamber reactors. A single catalytic system can be used to synthesize a broad range of carbonyl-containing products in a one-pot two-step procedure which normally requires different catalytic systems and pressurized CO for their synthesis.

In-depth experimental and computational studies of the reaction mechanism point towards *in situ* generation of CO from butyryl chloride and its incorporation into the aryl halide. In contrast to our previously reported functional group metathesis between aryl iodides and aroyl chlorides, the pathway *via* reductive elimination with the Xantphos ligand is kinetically unfavorable when employing aliphatic acid chlorides as reagents.

Experimental Section

Experimental and computational details, full reference 33, and compound characterization are given in the supporting information.

Acknowledgements

This project received funding from the European Research Council under the European Union's Horizon 2020 research and innovation program (Shuttle Cat, Project ID:757608). ETH Zürich is gratefully acknowledged for financial support. We thank the NMR service, the Molecular and Biomolecular Analysis Service (MoBiAS), and the Small Molecule Crystallography Center (Dr. Nils Trapp, SMoCC) of ETH Zürich for technical assistance. P. B. thanks the FCI for a scholarship. We thank Tristan Delcaillau, Yong Ho Lee, Michael Bogdos, and Marius Lutz for fruitful discussions.

Keywords: chlorocarbonylation • palladium • shuttle catalysis • reaction mechanism • computations

[1] a) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed*. **2009**, *48*, 4114–4133.; *Angew. Chem.* **2009**, *121*, 4176–4196. b) H. M. Colquhoun, D. J. Thompson, M. V. Twigg, *Carbonylation: Direct Synthesis of Carbonyl Compounds*, Springer Science+Business Media, New York, **1996**. c) A. Haynes, P. M. Maitlis, G. E. Morris, G. J. Sunley, H. Adams, P. W. Badger, C. M. Bowers, D. B. Cook, P. I. P. Elliott, T. Ghaffar, H. Green, T. R. Griffin, M. Payne, J. M. Pearson, M. J. Taylor, P. W. Vickers, R. J. Watt, *J. Am. Chem. Soc.* **2004**, *126*, 2847–2861.

[2] a) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3318–3326. b) A. Schoenberg, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3327–3331.

[3] For reviews on carbonylation of aryl halides see: a) C. F. J. Barnard, *Organometallics*. **2008**, *27*, 5402–5422. b) J. B. Peng, F. P. Wu, X. F. Wu, *Chem. Rev*. **2019**, 119, 2090 – 2127. c) M. Beller, C*atalytic Carbonylation Reactions*, Springer, Berlin, **2006**. d) X. F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986–5009. e) X. F. Wu, *RSC Adv.* **2016**, *6* 83831–83837. f) Y. Li, Y. Hu, X. F. Wu, *Chem. Soc. Rev*. **2018**, *47*, 172–194. g) C. F. J. Barnard, *Org. Process Res. Dev.* **2008**, *12*, 566–574. h) I. Omae, *Coord. Chem. Rev*. **2011**, *255*, 139–160. i) R. Grigg, S. P. Mutton, *Tetrahedron*. **2010**, *66*, 5515–5548. j) X. F. Wu, *RSC Adv*. **2016**, *6*, 83831–83837.

[4] For selected examples see: a) X. F. Wu, H. Neumann, M. Beller, *ChemCatChem* **2010**, *2*, 509–513. b) R. H. Munday, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 2754–2755. c) D. Watson, X. Fan, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7096–7101. d) M. Arthuis, A. Lecup, E. Roulland, *Chem. Commun.* **2010**, *46*, 7810–7812. e) W. Mägerlein, A. F. Indolese, M. Beller, *Angew. Chem. Int. Ed.* **2001**, *40*, 2856–2859. f) J. Albaneze-Walker, C. Bazaral, T. Leavey, P. G. Dormer, J. A. Murry, *Org. Lett.* **2004**, *6*, 2097–2100.

[5] For selected examples see: a) J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7102–7107. b) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 8460–8463.; *Angew. Chem.* **2007**, *119*, 8612–8615. c) Q. Yang, H. Cao, A. Robertson, H. Alper, *J. Org. Chem.* **2010**, *75*, 6297–6299. d) A. C. Tadd, A. Matsuno, M. R. Fielding, M. C. Willis, *Org. Lett.* **2009**, *11*, 583–586. e) H. Cao, H. Alper, H. *Org. Lett.* **2010**, *12*, 4126–4129. f) X. F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 9750–9753.

[6] a) X. F. Wu, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 5284–5288.; *Angew. Chem.* **2010**, *122*, 5412–5416. b) X. Wu, P. Nilsson, M. Larhed, *J. Org. Chem.* **2005**, *70*, 346–349. c) X. F. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 14596–14602.

[7] For selected examples see: a) B. M. O'Keefe, N. Simmons, S. F. Martin, *Org. Lett.* **2008**, *10*, 5301–5304. b) M. V. Khedkar, P. J. Tambade, Z. S. Qureshi, B. M. Bhanage, *Eur. J. Org. Chem.* **2010**, *2010*, 6981–6986. c) C. Pirez, J. Dheur, M. Sauthier, Y. Castanet, A. Mortreux, *Synlett* **2009**, *18*, 1745–1748. d) P. J. Tambade, Y. P. Patil, A. G. Panda, B. M. Bhanage, *Eur. J. Org. Chem.* **2009**, *2009*, 3022–3025. e) E. Maerten, F. Hassouna, S. Couve-Bonnaire, A. Mortreux, J. F. Carpentier, Y. Castanet, *Synlett* **2003**, *12*, 1874–1876. f) P. Larini, A. Guarna, E. G. Occhiato, *Org. Lett.* **2006**, *8*, 781–784. g) X. F. Wu, H. Neumann, M. Beller, *Tetrahedron Lett.* **2010**, *51*, 6146–6149. h) H. Neumann, A. Brennführer, M. Beller, *Chem. Eur. J.* **2008**, *14*, 3645–3652.

[8] For selected examples see: a) X. F. Wu, B. Sundararaju, H. Neumann, P. H. Dixneuf, M. Beller, *Chem. Eur. J.* **2011**, *17*, 106–110. b) A. Fusano, T. Fukuyama, S. Nishitani, T. Inouye, I. Ryu, *Org. Lett.* **2010**, *12*, 2410–2413. c) X. F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 12104–12107. d) M. S. Mohamed Ahmed, A. Mori, *Org. Lett.* **2003**, *5*, 3057–3060. e) M. Iizuka, Y. Kondo, *Eur. J. Org. Chem.* **2007**, *2007*, 5180–5182.

[9] a) T. Morimoto, K. Kakiuchi, *Angew. Chem. Int. Ed*. **2004**, *43*, 5580–5588.; *Angew. Chem.* **2004**, *116*, 5698–5706. b) T. Schareina, A. Zapf, A. Cotté, M. Gotta, M. Beller, *Adv. Synth. Catal.* **2010**, *352*, 1205–1209. c) B. Roberts, D. Liptrot, L. Alcaraz, T. Luker, M. J. Stocks, *Org. Lett.* **2010**, *12*, 4280–4283.

[10] a) S. D. Friis, A. T. Lindhardt, T. Skrydstrup, *Acc. Chem. Res.* **2016**, *49*, 594–605. b) P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp, T. Skrydstrup, *J. Am. Chem. Soc*. **2011**, *133*, 6061–6071.

[11] R. G. Kinney, J. Tjutrins, G. M. Torres, N. J. Liu, O. Kulkarni, B. A. Arndtsen, *Nat. Chem.* **2018**, *10*, 193–199.

[12] R. K. Dieter, *Tetrahedron* **1999**, *55*, 4177–4236.

[13] C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827–10852.

[14] a) S. Patai, *The Chemistry of Acyl Halides.* Interscience, London **1972**. b) D. A. Petrone, J. Ye, M. Lautens, *Chem. Rev.* **2016**, *116*, 8003–8104.

[15] a) J. S. Quesnel, B. A. Arndtsen, *J. Am. Chem. Soc.* **2013**, *135*, 16841–16844. b) J. S. Quesnel, L. V. Kayser, A. Fabrikant, B. A. Arndtsen, *Chem. Eur. J.* **2015**, *21*, 9550–9555. c) M. G. Torres, Y. Liu, B. A. Arndtsen, *Science* **2020**, *368*, 318–323.

[16] a) Y. H. Lee, B. Morandi, *Nat. Chem.* **2018**, *10*, 1016–1022. b) M. De La Higuera Macias, B. A. Arndtsen, *J. Am. Chem. Soc.* **2018**, *140*, 10140–10144.

[17] a) X. Fang, P. Yu, B. Morandi, *Science* **2016**, *351*, 832–836. b) B. N. Bhawal, B. Morandi, *Angew. Chem. Int. Ed*. **2019**, *58*, 10074–10103.; *Angew. Chem.* **2019**, *131*, 10178–10209.

[18] X. Fang, B. Cacherat, B. Morandi, *Nat. Chem.* **2017**, *9*, 1105–1109.

[19] a) P. Yu, B. Morandi, *Angew. Chem. Int. Ed.* **2017**, *56*, 15693–15697.; *Angew. Chem.* **2017**, *129*, 15899–15903. b) D. A. Everson, B. A. Jones, D. J. Weix, *J. Am. Chem. Soc.* **2012**, *134*, 6146–6159. c) L. K. G. Ackerman, M. M. Lovell, D. J. Weix, *Nature* **2015**, *524*, 454–457. d) X. Yu, T. Yang, S. Wang, H. Xu, H. Gong, *Org. Lett.* **2011**, *13*, 2138–2141. e) R. T. Smith, X. Zhang, J. A. Rincón, J. Agejas, C. Mateos, M. Barberis, S. García-Cerrada, O. De Frutos, D. W. C. Macmillan, *J. Am. Chem. Soc.* **2018**, *140*, 17433–17438. f) S. Biswas, D. J. Weix, *J. Am. Chem. Soc.* **2013**, *135*, 16192–16197. g) D. J. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767–1775. h) T. T. Tsou, J. K. Kochi, *J. Am. Chem. Soc.* **1979**, *101*, 7547–7560. i) C. Amatore, A. Jutand, *Organometallics* **1988**, *7*, 2203–2214.

[20] See Supporting Information for details.

[21] a) R. J. Kominar, M. J. Krech, S. J. W. Price, *Can. J. Chem.* **1978**, *56*, 1589–1592. b) M. Szwarc, J. Watson Taylor, *J. Chem. Phys.* **1954**, *22*, 2078.

[22] a) A. Brennfuhrer, H. Neumann, M. Beller, *Synlett* **2007**, 16, 2537–2540. b) G. Lesma, A. Sacchetti, A. Silvani, *Synthesis* **2006**, *4*, 594–596. c) S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Lett.* **2003**, *5*, 4269–4272. d) S. Cacchi, A. Lupi, *Tetrahedron Lett.* **1992**, *33*, 3939–3942.

[23] R. J. Kominar, M. J. Krech, S. J. W. Price, *Can. J. Chem.* **1976**, *54*, 2981–2984.

[24] The structure of the methyl ester of **7j** was confirmed by X-ray analysis. The data are available free of charge from the Cambridge Crystallographic Data Center (CCDC number 1998513).

[25] a) E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, *88*, 297–368. b) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240.; *Angew. Chem.* **2005**, *117*, 5320–5374.

[26] a) F. M. Miloserdov, V. V. Grushin, *Angew. Chem. Int. Ed.* **2012**, *51*, 3668–3672.; *Angew. Chem.* **2012**, *124*, 3728–3732. b) F. M. Miloserdov, C. L. McMullin, M. M. Belmonte, J. Benet-Buchholz, V. I. Bakhmutov, S. A. Macgregor, V. V. Grushin, *Organometallics* **2014**, *33*, 736–752.

[27] K. Inoue, M. Yasuda, I. Shibata, A. Baba, *Tetrahedron Lett.* **2000**, *41*, 113–116.

[28] a) Y. Urawa, K. Nishiura, S. Souda, K. Ogura, *Synthesis* **2003**, *2003*, 2882–2885. b) J. P. Waldo, S. Mehta, R. C. Larock, *J. Org. Chem.* **2008**, *73*, 6666–6670. c) B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943–3949.

[29] a) K. I. Fujita, M. Yamashita, F. Puschmann, M. M. Alvarez-Falcon, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 9044–9045. b) T. L. Andersen, S. D. Friis, H. Audrain, P. Nordeman, G. Antoni, T. Skrydstrup, *J. Am. Chem. Soc.* **2015**, *137*, 1548–1555.

[30] The structure of complex **9** was confirmed by X-ray analysis. The data are available free of charge from the Cambridge Crystallographic Data Center (CCDC number 1998512).

[31] D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard, T. Skrydstrup, *J. Am. Chem. Soc.* **2010**, *132*, 7998–8009.

[32] a) P. L. Lagueux-Tremblay, A. Fabrikant, B. A. Arndtsen, *ACS Catal.* **2018**, *8*, 5350–5354. b) K. Domino, M. B. Johansen, K. Daasbjerg, T. Skrydstrup, *Organometallics* **2020**, *39*, 688–697.

[33] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, *et al.*, Gaussian09, Revision D.01; Gaussian Inc.: Wallington, CT, **2016**.

[34] A. N. Bootsma, S. Wheeler, “Popular Integration Grids Can Result in Large Errros in DFT-Computed Free Energies.,” *ChemRxiv*. Preprint. https://doi.org/10.26434/chemrxiv.8864204.v5, **2019**.

[35] J. P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **1996**, *77*, 3865–3868.

[36] J. P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **1997**, *78*, 1396–1396.

[37] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.

[38] S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, *32*, 1456–1465.

[39] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

[40] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.

[41] F. Weigend, *Phys. Chem. Chem. Phys.* **2006**, *8*, 1057.

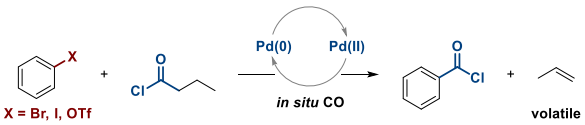
[42] C. Adamo, V. Barone, *J. Chem. Phys.* **1999**, *110*, 6158–6170.

[43] M. Ernzerhof, G. E. Scuseria, *J. Chem. Phys.* **1999**, *110*, 5029–5036.

[44] T. Weymuth, E. P. A. Couzijn, P. Chen, M. Reiher, *J. Chem. Theory Comput.* **2014**, *10*, 3092–3103.

[45] C. Y. Legault , CYLview, 1.0b, Université de Sherbrooke, **2009** (http://cylview.org).

Entry for the Table of Contents



- Safe reaction set-up
- High functional group tolerance
- Broad scope (> 50 examples)
- One-pot syntheses
- Mechanistic experiments
- Computational studies