Synthesis of Amides and Esters by Palladium(0)-Catalyzed Carbonylative C(sp³)–H Activation

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Abstract: The 1,4-palladium shift strategy allows the functionalization of remote C–H bonds that are difficult to reach directly. Reported here is a domino reaction proceeding by C(sp³)–H activation, 1,4-palladium shift, and amino- or alkoxy-carbonylation, which generates a variety of amides and esters bearing a quaternary β-carbon atom. Mechanistic studies showed that the aminocarbonylation of the σ-alkylpalladium intermediate arising from the palladium shift is fast using PPh₃ as the ligand, and leads to the amide rather than the previously reported indanone product.

In the past two decades, the palladium(0)-catalyzed activation of C(sp³)–H bonds has proven to be a powerful tool to construct C(sp²)–C(sp³) bonds.^[1,2] These methods rely on the generation of a diorganopalladacycle such as **A** via oxidative addition of a C(sp²)–X bond to palladium(0) and base-mediated C(sp³)–H activation (Scheme 1a). The reductive elimination from such palladacycles leads to a variety of useful carbo- and heterocycles.^[2] Alternatively, trapping the diorganopalladacycle intermediate leads to interesting ring-expansion products. First, the reaction of aryl bromides with diazo compounds furnishes tetrasubstituted indanes via carbene insertion.^[3] Indanes can be also generated upon trapping of **A** with dibromomethane.^[4] More recently, the carbonylative C(sp³)–H arylation of aryl bromides, giving rise to indanones via CO insertion was reported (Scheme 1b).^[5] Alternative to direct trapping, the ring-opening of palladacycle **A** by protonation or oxidative addition/reductive elimination provides a σ-alkylpalladium complex **B** (Scheme 1a), hence leading to an overall 1,4-Pd shift,^[6] as initially observed by Dyker.^[7] This alkylpalladium complex was shown to undergo various reactions. First, β-H elimination furnishes olefins, hence resulting in net alkyl desaturation.^[8] Besides, trapping by boronic acids and anilines leads to arylation and amination products (Scheme 1c).^[9] Moreover, intramolecular dearomatizing carbopalladation (**B**, R = naphthol) provides spiroannulation products.^[10] The alkylpalladium intermediate **B** was also shown to be a competent intermediate to perform

Scheme 1. Examples of Pd⁰-catalyzed C(sp³)–H activation and trapping through various reactions. The ligand is omitted for clarity.

a second intramolecular C(sp³)–H activation, thus generating fused heterocycles^[11] and cyclopropanes (Scheme 1d).^[12] In this paper, we show that the trapping of this σ-alkylpalladium complex by carbon monoxide is feasible, and developed a carbonylative coupling of aryl bromides and amines or alcohols to generate amides and esters containing a β-quaternary center (Scheme 1e).^[13,14] Tuning the reaction conditions favors the 1,4-Pd shift and disfavors the insertion on palladacycle **A** leading to indanones (Scheme 1b).

We started out by exploring the reactivity of *tert*-butylbromobenzene **1a** under conditions similar to those developed for the cyclopropanation reaction (see Scheme 1d),^[12] that is, using Pd(PPh₃)₄ as the catalyst and stoichiometric cesium pivalate as the base (Scheme 2). Under 1 atm of CO and using 2 equiv of water at 140 °C, carboxylic acid **2**, presumably arising from σ-alkylpalladium complex **B** (see Scheme 1a) by CO insertion and hydrolysis of the corresponding acylpalladium intermediate, was formed in high yield.^[15] Remarkably, the protodehalogenated product was not formed despite the presence of water. The reaction was successfully scaled up to 1 mmol without significant loss of yield (82 %).

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Scheme 2. Formation of carboxylic acid **2** by hydroxycarbonylation of **1a**. [a] NMR yield using trichloroethylene as internal standard. [b] Yield of the isolated product. [c] Performed on a 1 mmol scale.

Then, the same conditions were applied using benzylamine (2 equiv) instead of water, which provided the corresponding aminocarbonylation product **3a** in 62% yield (Scheme 3). To test the generality of the current method, cyclic and acyclic primary amines (benzylamine, cyclohexylamine, *n*-butylamine, *tert*-butylamine), secondary amines (morpholine, piperidine, diethylamine) and aniline were screened as nucleophiles. The corresponding amide products **3a–h**, bearing a quaternary β carbon, were obtained in 45–71% yields, with an efficiency mirroring the nucleophilicity of the amine.^[16] For instance, the weakly nucleophilic aniline delivered a 45% yield (**3e**), whereas morpholine provided a 71% yield (**3h**). Of note, performing the reaction on a fivefold (1 mmol) scale furnished a comparable yield for

amide **3b**. Replacing one methyl group on the aryl bromide substrate with various functional groups such as sulfonamides (**3i–l**), a Boc-carbamate (**3m**) or a TIPS-protected alcohol (**3n**) did not affect the efficiency of the reaction to a great extent, to the exception of **3m** for which degradation was observed. It is interesting to note that the reaction furnishing amide **3j** could be conducted in a two-chamber (COware) system using 3 equiv of COgen (COgen = 9-methylfluorene-9-carbonyl chloride)^[17] with a similar efficiency. In addition, electron-donating (methoxy, methylene-dioxy, **3o–t**) and electron-withdrawing (fluoro, trifluoromethyl, **3u–x**) substituents in *meta* or *para* position to the bromine atom were well tolerated although reduced yields were often observed. The reaction providing amide **3p** was also conducted on a 7.5 $\times$ scale without affecting the yield. For selected examples (**3j**, **3r**, **3s**, **3u**, **3w**), using AdCO_2Cs as the base, formed in situ from Cs_2CO_3 and catalytic AdCO_2H , provided better results than CsOPiv . Of note, direct amidation was observed for some other substrates (see Table S6 in the Supporting Information).

The synthesis of esters by alkoxycarbonylation required further optimization of the reaction conditions, and potassium benzoate was found to be a more efficient base (Scheme 4).^[15] Prolonging the reaction time to 27 h was also found necessary

Scheme 3. Synthesis of amides by carbonylative $\text{C(sp}^3\text{)}\text{–H}$ activation. Reaction conditions: aryl bromide (0.2 mmol), amine (2 equiv), $\text{Pd(PPh}_3)_4$ (10 mol%), CsOPiv (2 equiv), *o*-xylene (*c* 0.05 mol L^{−1}), CO balloon, 140 °C, 18 h. [a] Performed on a 1 mmol scale. [b] Using Cs_2CO_3 (1 equiv) and AdCO_2H (0.3 equiv) instead of CsOPiv . [c] Using COgen (3 equiv) and a two-chamber system instead of CO balloon (NMR yield). [d] Performed on a 1.5 mmol scale. Ts = *p*-toluenesulfonyl, Boc = *tert*-butoxycarbonyl, TIPS = triisopropylsilyl.

Scheme 4. Synthesis of esters by carbonylative C(sp³)–H activation. Reaction conditions: aryl bromide (0.2 mmol), alcohol (2.0 equiv), Pd(PPh₃)₄ (10 mol%), PhCO₂K (1.5 equiv), *o*-xylene (*c* 0.05 mol L⁻¹), CO balloon, 140 °C, 27 h. [a] Performed on a 1 mmol scale.

to increase the yield, presumably due to the reduced nucleophilicity of alcohols compared to amines.^[18] For the same reason, the reaction was more limited than the preceding aminocarbonylation. Nevertheless, benzylic (**4a–c**), primary (**4d**), secondary (**4e,f**) alcohols as well as phenol (**4g**) were found to be competent coupling partners, delivering the corresponding esters in 43–64% yield. The reaction with cyclohexanol was scaled up to 1 mmol, furnishing ester **4e** in 53% yield.

Two of the products synthesized with the current method were converted to γ - and δ -lactams (Scheme 5). First, amide **3p** underwent intramolecular C–H amidation to provide δ -lactam **5a** upon treatment with NIS in 1,2-dichloroethane.^[19] In addition, ester **4e** underwent cyclization to γ -lactam **5b** upon cleavage of the tosyl group with Li/napthalene.

To get further insight into the reaction mechanism, and in line with our previous mechanistic work in the context of cyclopropane synthesis,^[12] we performed experiments with isolated Pd complexes (Scheme 6). The known σ -alkylpalladium complex **6a**^[20] was first heated in *o*-xylene to various temperatures for 18 h in the presence of PPh₃, cyclohexyl-

Scheme 5. Application to the synthesis of lactams. Conditions are unoptimized. NIS = *N*-iodosuccinimide.

Scheme 6. Stoichiometric experiments with Pd complexes. NMR yields using trichloroethylene as internal standard. [a] Without CsOPiv.

amine and CO (Scheme 6a). Amide **3b** was formed in good yield at room temperature, and quantitatively at 60 °C, thereby showing that the aminocarbonylation step occurs with a low energy barrier. Next, the known five-membered palladacycle **6b**^[21] was heated in the presence of PPh₃, CyNH₂, CO, pivalic acid and cesium pivalate (Scheme 6b). The formation of amide **3b**, resulting from palladacycle protonation^[8d,12,22] and aminocarbonylation of the resulting σ -alkylpalladium complex, occurred from 100 °C, and was quantitative at 120 °C. Finally, the oxidative addition complex **6c**, prepared in 88% yield from 2-*tert*-butylbromobenzene (**1a**) and Pd(PPh₃)₄ in toluene at 120 °C,^[12] was mixed with CsOPiv and CyNH₂ (Scheme 6c). The formation of amide **3b** required a higher temperature than from other complexes, with only 27% at 120 °C and 75% at 140 °C. As expected, almost no product was obtained in the absence of CsOPiv. These results indicate that the slowest step in the current reaction is the C(sp³)–H activation leading to the five-membered palladacycle intermediate. In the cyclopropane-forming reaction occurring under similar conditions (see Scheme 1d), similar studies concluded that the oxidative addition was rate-limiting. The only difference in the current work is the presence of CO and the amine, which likely modify the catalyst by ligand displacement and therefore affect the relative energy barriers.

Based on this and previous^[12,22] mechanistic studies, the following reaction mechanism is proposed (Scheme 7). The oxidative addition of aryl bromide **1** leads to complex **A** (corresponding to **6c** in Scheme 6). Ligand exchange of bromide with pivalate provides complex **B**,^[12] which undergoes rate-limiting C(sp³)–H activation by the concerted metallation-deprotonation mechanism^[22,23] to furnish five-membered palladacycle **C**. Protonation of the latter^[8d,22] with PivOH leads to σ -alkylpalladium complex **D**, which undergoes CO insertion and nucleophilic attack by the amine to provide amide **3** via intermediate **E** and close the catalytic cycle. The competence of complexes **C** and **D** as reaction

Scheme 7. Mechanistic proposal. L = PPh₃ or CO.

intermediates is indicated by the experiments shown in Scheme 6b and a, respectively.

Interestingly, Wang and co-workers reported the formation of indanone **7** from similar substrates and under similar conditions except for the use of IMes^{Me}, an *N*-heterocyclic carbene (NHC), as the ligand (Scheme 1b).^[5] Based on stoichiometric studies, they proposed that **7** arises from palladacycle **C** by CO insertion and reductive elimination. These authors also observed regioisomeric products arising from the reversible opening of **C** to **D**. In our case, using PPh₃ as the ligand and in the absence of amine, carboxylic acid **2** (Scheme 2) was formed whereas indanone **7** was not. In the presence of amine, the indanone was also not observed. As shown in Scheme 5a, the CO insertion from **D** and nucleophilic attack of the amine to give the amide product **3** occur at room temperature, and therefore are faster than the pathway leading to the indanone **7** using PPh₃ as the ligand.

In conclusion, the first carbonylative C(sp³)-H activation reaction proceeding by 1,4-Pd shift was developed. A variety of amides and esters bearing a quaternary β carbon was produced by amino- or alkoxy-carbonylation in moderate to good yields.^[24] Mechanistic studies showed that the amino-carbonylation of the σ-alkylpalladium intermediate is fast using PPh₃ as the ligand, thereby leading to the amide product at the expense of the previously described indanone.

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Conflict of interest

The authors declare no conflict of interest.

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