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Microwave-assisted, $Mo(CO)_6$-mediated, palladium-catalyzed amino-carbonylation of aryl halides using allylamine: from exploration to scale-up

Prasad Appukkuttan [a], Linda Axelsson [a], Erik Van der Eycken [b], Mats Larhed [a,*]

[a] Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala Biomedical Center, Uppsala University, PO Box 574, SE-751 23 Uppsala, Sweden
[b] Laboratory for Organic and Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

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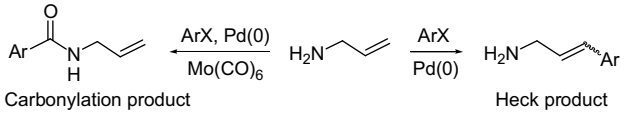
ABSTRACT

Palladium-catalyzed aminocarbonylations of various (hetero)aryl halides with allylamine using $Mo(CO)_6$ as a solid, in situ CO source, were explored. Microwave-enhanced conditions proved to be highly useful in promoting the conversions in a mere 10–20 min with various (hetero)aryl iodides, bromides and chlorides. The scale-up of a microwave-enhanced aminocarbonylation to 25 mmol scale was performed successfully.

Transition metal-mediated carbonylation protocols are a relatively under-explored area of research for the functionalization of aryl halides, in comparison with other transition metal-mediated protocols such as cross-couplings and Heck and Sonogashira reactions.[1–6] The traditional drawbacks of using gaseous reagents and high-pressure reaction conditions have limited the scope of these valuable reactions to a considerable extent. However, gas-free carbonylative protocols[7] using solid CO-sources such as $Mo(CO)_6$[8–11] have paved swift and straightforward routes to small-scale carbonylations under conventional conditions or under high-density microwave irradiation.

We have previously explored $Mo(CO)_6$-based carbonylative transformations for the functionalization of various aryl- and heteroaryl halides using a variety of nucleophiles under microwave-enhanced conditions.[12–14] As a part of our research towards the development of new HIV-protease inhibitors,[10,15,16] we were interested in carrying out aminocarbonylations of various P1 and P3 aryl halide side chains using allylamine as the nucleophile,[17] aimed at the generation of viable handles for macrocyclizations using Ring-Closing Metathesis (RCM).[18] However, we envisaged that the presence of a terminal double bond together with a free amino group could lead potentially to competition between Heck reaction[19,20] and aminocarbonylation under Pd(0)-catalyzed conditions (Scheme 1).



Scheme 1. Aminocarbonylation versus Heck reaction.

Depending on the competing reactions, the arylpalladium(II) intermediate can thus lead to an *N*-allylbenzamide via a 1,1-insertion process with CO, or a styrene derivative as a consequence of a 1,2-insertion-β-elimination sequence. In this contribution, we disclose the development of a completely chemoselective microwave-enhanced protocol for the in situ aminocarbonylation of (hetero)aryl halides using allylamine as the nucleophile. The method was applied successfully to a number of diversely functionalized aryl iodides, bromides and chlorides. Furthermore, we report the first successful scale-up of a $Mo(CO)_6$-mediated, microwave-enhanced aminocarbonylation reaction.

We began our investigations by choosing 2-iodotoluene (**1a**) as the model aryl iodide for reactions with allylamine (**2**), using a modified version of a microwave protocol reported by Wannberg and Larhed.[21] Due to the high reactivity of aryl iodides in palladium(0)-catalyzed transformations, we explored a completely phosphine-free strategy. A number of experiments were conducted

* Corresponding author. Tel.: +46 18 471 46 67; fax: +46 18 471 44 74.
E-mail address: Mats.Larhed@orgfarm.uu.se (M. Larhed).

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altering the temperature and irradiation time, using a slight excess of **2** (1.5 equiv). It quickly became apparent that the aminocarbonylations clearly dominated over the competing Heck reactions. This strong chemoselectivity can be explained in terms of a rapid CO-insertion followed by a subsequent attack of the nucleophile, compared to the much slower 1,2-alkene insertion in the Heck reaction.[22] Appropriate conditions were found to be $Pd(OAc)_2$ as precatalyst and DBU as base in 1,4-dioxane with microwave-heating at 125 °C for 10 min. The use of an inert atmosphere was found to be unnecessary. In fact, the applied conditions were not ideal for Heck reactions, as an experiment run under these conditions, but without $Mo(CO)_6$, furnished essentially no Heck product. Based on the success of initial explorations, we decided to investigate the aminocarbonylation of a variety of aryl iodides **1a–f** with allylamine **2** (see Table 1) under microwave conditions.

As can be seen from Table 1, all the reactions proceeded smoothly under microwave irradiation using a standard single-mode reactor, providing moderate to good isolated yields (72–81%) of the corresponding *N*-allyl benzamides **3**.[23] The electronic nature of the aryl ring did not influence the course of the reaction in any substantial manner, with electron-donating (Table 1, entries 1 and 4) and electron-withdrawing substituents on the aryl ring (entry 3) providing comparable yields. Heterocyclic iodides **1e**, **f** were carbonylated smoothly, generating the 2-thienyl- (entry 5) and 3-furoyl derivatives (entry 6) in good yields. None of the aryl iodides generated the corresponding Heck reaction or dehalogenation products in more than trace amounts as was indicated by LC–MS and NMR.

Encouraged by the good results with aryl iodides, we decided to extend the scope of our investigation by incorporating a diverse array of (hetero)aryl bromides as the carbonylation substrates. Based on our previous experience with the aminocarbonylation of aryl bromides,[24] we envisaged the need for a more reactive catalytic system to conduct the transformation efficiently. Thus, the pre-ligand $[(t\text{-Bu})_3PH]BF_4$[25,26] in combination with Herrmann's palladacycle[27] was chosen as the catalytic combination to promote the reactions reliably.

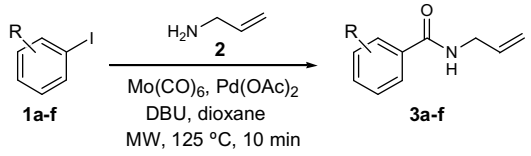
Carbonylations of selected aryl bromides are summarized in Table 2. The dibromoaryls **1g–i** furnished the corresponding di-*N*-allyl benzamides **3g–i** in good yields only after 15 min (Table 2, entries 1–3), and the presence of side products arising from mono-carbonylation or dehalogenation was negligible. Benzophenone **3j** was obtained in a disappointing 43% yield. The ester functionality of **1k** remained intact in product **3k**.

Heterocyclic bromides **1l–n** were found to react promptly, generating the corresponding furoyl- (**3l** and **3f**, entries 6 and 7) and thienyl- (**3e**, entry 8) derivatives in good yields of 66–76%. In all cases, only >5% of the Heck arylation products were detected.

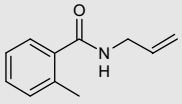
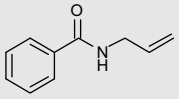
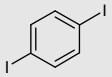
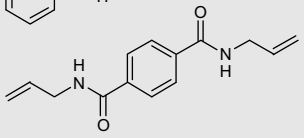
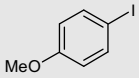
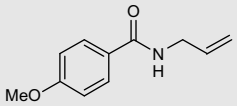
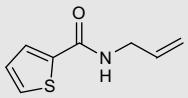
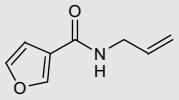
At this stage, we decided to investigate aryl- and heteroaryl chlorides as the arylpalladium precursors with **2**. From previous experiences with other nucleophiles, we knew that the aminocarbonylation of aryl chlorides would benefit from elevated reaction temperatures, and thus conditions of 160 °C for 20 min were employed.[28–34]

As can be seen from Table 2, good yields of amide products **3** were obtained quickly. Aryl chloride **1o** reacted in a straightfor-

Table 1
Aminocarbonylation of aryl iodides **1a–f** with allylamine **2**



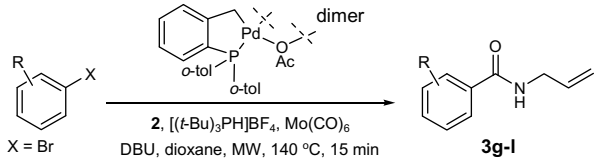
1a-f **3a-f**

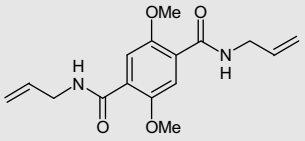
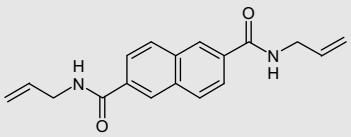
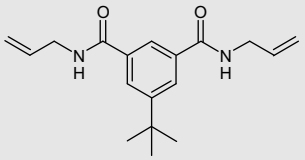
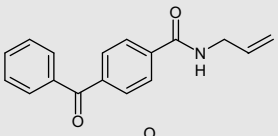
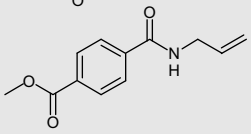
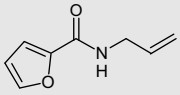
No.	Ar–I		Product		Yield (%)
1		**1a**		**3a**	76
2		**1b**		**3b**	73
3		**1c**		**3c**	76
4		**1d**		**3d**	81 78[a]
5		**1e**		**3e**	76
6		**1f**		**3f**	72

All reactions were performed in a sealed-vial on a 0.4 mmol scale with 1.5 equiv of **2**, 1.0 equiv of $Mo(CO)_6$, 3.0 equiv of DBU and 7.0 mol % of $Pd(OAc)_2$ in 3.0 mL of 1,4-dioxane at 125 °C for 10 min under microwave irradiation. All yields are isolated yields.

[a] Reaction was performed at 130 °C on a 2.0 mmol scale.

Table 2
Aminocarbonylation of aryl bromides and chlorides **1** with **2**



No.	Ar–Br/Ar–Cl	Product	Yield (%)
1	**1g**[a]	 **3g**	73
2	**1h**[a]	 **3h**	76
3	**1i**[a]	 **3i**	81
4	**1j**[a]	 **3j**	43
5	**1k**[a]	 **3k**	56
6	**1l**[a]	 **3l**	76
7	**1m**[a]	**3f**	66
8	**1n**[a]	**3e**	72
9	**1o**[b]	**3b**	67
10	**1p**[a]	**3e**	69
11	**1q**[a]	**3f**	73

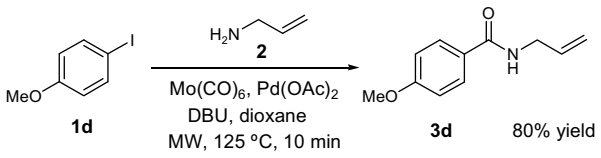
All reactions were performed in a sealed-vial on a 0.4 mmol scale with 1.5 equiv of **2**, 1.0 equiv of $Mo(CO)_6$, 3.0 equiv of DBU.

[a] 2.5 mol % of palladacycle and 7.0 mol % of $[(t\text{-Bu})_3PH]BF_4$ in 3.0 mL of 1,4-dioxane at 140 °C for 15 min.

[b] 3.5 mol % of palladacycle and 9.0 mol % of $[(t\text{-Bu})_3PH]BF_4$ in 3.0 mL of 1,4-dioxane at 160 °C for 20 min. All yields are isolated yields.

ward manner, generating the benzamide **3b** in 67% yield (Table 2, entry 9). The heterocyclic chlorides **1p**, **q** reacted smoothly, providing the corresponding amides **3e**, **f** in good yields of 69–73% (Table 2, entries 10 and 11). Attempts to lower the reaction temperature resulted in incomplete conversion of the aryl chlorides. Compounds containing nitro-substituted aryl halides were reduced to the corresponding anilines during the microwave irradiation under these reaction conditions.[35] Aryl halides with an amine functionality at the *ortho* position provided incomplete conversion, probably due to poisoning of the Pd-catalyst.[36]

Finally, the scale-up of a microwave-enhanced aminocarbonylation was investigated (Scheme 2).[37]



Scheme 2. Aminocarbonylation on a 25 mmol scale.

Due to potential problems in handling the CO-gas released during the process, no in situ carbonylation reaction has been reported previously in a large-scale (>20 mL) microwave reactor. The reaction between **1d** and **2** was chosen as the model reaction. In order to validate the microwave methodology step-wise, the reaction was first scaled-up to a 2.0 mmol scale in 10 mL of 1,4-dioxane in a 20 mL sealed Pyrex vial at 130 °C for 15 min. The reaction was found to proceed smoothly, furnishing **3d** in a good 78% yield (Table 1, entry 4). Encouraged by this result, we further increased the scale of the reaction to 25.0 mmol in 125 mL of 1,4-dioxane, keeping the reaction stoichiometry intact. The reaction was carried out for 15 min at 125 °C in the cavity of a Biotage Advancer batch reactor,[38] equipped with a reaction vessel designed to handle 50–350 mL volumes, a powerful mechanical stirrer, as well as an efficient 'instant' adiabatic cooling system. Once again, the reaction was found to proceed as expected, providing **3d** in a good 80% isolated yield (Scheme 2). The maximum observed pressure during the reaction was 3.0 bar, which was found to decrease to 1.0 bar as the reaction proceeded, indicating the gradual consumption of the liberated CO-gas during the amidation step.

In conclusion, we have successfully demonstrated a microwave-enhanced aminocarbonylation of various (hetero)aryl iodides, bromides and chlorides using allylamine as the nucleophile. The reactions proceeded with complete selectivity, generating no competing Heck-reaction products. The produced benzamides were isolated in good yields and purity. Furthermore, a scale-up of a microwave-enhanced aminocarbonylation reaction was successfully performed. Further scope of the protocol as well as its use in generating valuable allyl handles for macrocyclizations reactions is under current investigation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.053.

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23. *Typical procedure for the synthesis of N-allyl benzamides* **3** *from aryl iodides* **1**: A 5.0 mL process vial was charged with **1d** (94 mg, 0.40 mmol), **2** (34 mg, 0.60 mmol, 1.5 equiv), $Mo(CO)_6$ (106 mg, 0.40 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.3 mg, 7.0 mol %) and 1,4-dioxane (3.0 mL). DBU (183 mg, 1.20 mmol, 3.0 equiv) was added and the vial was immediately sealed. The reaction mixture was then exposed to microwave heating for 10 min at a pre-selected maximum temperature of 125 °C using a Smith single-mode synthesizer from Biotage. The reaction temperature was measured using the built-in, on-line IR-sensor. The reaction was thereafter cooled to rt, and the mixture was filtered through a small plug of Celite® and the plug was washed with EtOAc (5 mL × 3). The combined fractions were evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel) to furnish the corresponding benzamide **3d** in 81% yield.
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