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PII:	S0040-4039(18)30223-5
DOI:	https://doi.org/10.1016/j.tetlet.2018.02.035
Reference:	TETL 49720
To appear in:	Tetrahedron Letters
Received Date:	20 December 2017
Revised Date:	31 January 2018
Accepted Date:	14 February 2018



Please cite this article as: Roy, T., Rydfjord, J., Sävmarker, J., Nordeman, P., Palladium-catalyzed carbonylation of aryl bromides using microwave heating and bis[CP-Fe(II)-(CO)<sub>2</sub>] as a carbon monoxide source, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.02.035

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Tetrahedron Letters

journal homepage: www.elsevier.com

# Palladium-catalyzed carbonylation of aryl bromides using microwave heating and bis[CP-Fe(II)-(CO)<sub>2</sub>] as a carbon monoxide source

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#### ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online

Keywords: Palladium Carbon monoxide Carbonylation CORM Microwaves

#### Introduction

Carbonylation reactions, including the carbamoylation of aryl halides using catalytic palladium, has undoubtedly become an integral part of modern organic synthetic chemistry.<sup>1</sup> These three component reactions provide access to a range of products including carboxylic acids, esters and amides, ketones and aldehydes and also serves as intermediates for further transformations of the carbonylative product.<sup>1</sup> In recent years, safer methods for using carbon monoxide (CO) in the form of CO surrogates or CO releasing molecules (CORMs) has been developed.<sup>2,3</sup> By utilizing such methodologies, stoichiometric amounts of the CO source can be accessed in millimolar scale reactions without the potential harm and danger of using gaseous CO.

Oshima and co-workers have previously reported the carbonylative coupling of aryl iodides into various products using bis(cyclopentadienyldicarbonyliron) as the source of CO (Scheme 1, A).<sup>4</sup> This solid CO source is comparatively inexpensive as well as easy to handle.<sup>5</sup>

(A) Literature method<sup>4</sup>



Scheme 1. Carbonylation reactions using bis[CP-Fe(II)-(CO)<sub>2</sub>] as the CO source. (A) Literature procedure with Ar-I. (B) Current method with  $\mu$ -wave irradiation and Ar-Br.

A palladium-catalyzed, microwave assisted carbonylative reaction is described for the synthesis of benzamides from aryl bromides and primary or secondary amines. The developed method uses bis(cyclopentadienyldicarbonyliron) as a solid source of carbon monoxide to produce a diverse set of secondary and tertiary amides in 42-82% yield.

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We envisioned that using microwave ( $\mu$ -wave) irradiation, aryl bromides could be used as substrates in the rapid carbonylative synthesis of amides (Scheme 1, **B**). Herein, we describe the use of bis[CP-Fe(II)-(CO)<sub>2</sub>] as the CO source in the palladium-catalyzed carbonylation of aryl bromides using  $\mu$ -wave irradiation.

### **Results and Discussion**

We initiated our survey by evaluating different ligands using a model reaction with 2-bromotoluene and *n*-hexylamine as reagents (Table 1). Initially, Xphos was employed together with palladium acetate and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) using  $\mu$ -wave irradiation in 1,4-dioxane at 130 °C for 20 min. This reaction resulted in the formation of **2a** in 17% yield (Table 1, entry 1).<sup>67</sup>

**Table 1.** Impact of the ligand in the Pd-catalyzed carbonylation.<sup>6</sup>

Br +	H <sub>2</sub> N H <sub>2</sub> N	
Entry	Ligand	Yield <b>2a</b> (%) <sup><i>a</i></sup>
1	Xphos	17
2	Sphos	35
3	P(t-Bu) <sub>3</sub> HBF <sub>4</sub>	95 (82 <sup>b</sup> )
4	dppf	44
5	CataXium A	26
6	Xantphos	45

<sup>a</sup>Reagents and conditions: *o*-Tol-Br (0.5 mmol), *n*-hexylamine (1.0 mmol), **1** (0.5 mmol), Pd(OAc)<sub>2</sub> (5 mol%), ligand (monodentate 10 mol%, bidentate 5 mol%),  $\mu$ -wave irradiation (130 °C, 20 min), 1,4-dioxane (2 mL). <sup>a</sup>Determined by GC-MS using a standard curve of **2a**. <sup>b</sup>Isolated yield.

Changing the ligand to Sphos slightly increased the yield to 35% (Table 1, entry 2).<sup>8</sup> When the ligand was changed to tri-*tert*butylphosphonium tetrafluoroborate an almost quantitative yield (95% from GC-MS and 82% isolated) was obtained (Table 1, entry 3). Changing to the bidentate ligands dppf, CataXium A or Xantphos gave **2a** in 44%, 26% and 45% yield, respectively (Table 1, entries 4-6).

Using the optimized reaction conditions for the palladiumcatalyzed carbonylation we sought to evaluate the scope and limitations of the developed method. Initially the impact of the aryl bromide was evaluated (Table 2). In general, the electronic properties had little effect on the yield of the products. Aryl bromides containing electron-withdrawing or donating groups gave the corresponding amides (2a-2f) in 70-82% isolated yield (Table 2, entries 1-6). Functional groups such as methoxy (2b and 2e) or cyano (2d) did not significantly change the yield. One exception was the 2-phenyl substituted product 2f (Table 2, entry 7). In this case the steric bulk of the phenyl group in close vicinity to the bromide most likely causes the decreased yield (52%). When 1-bromo-4-nitrobenzene was used no amide 2h was formed (Table 2, entry 8). The iron-containing 1 may cause a reduction of the nitro functional group to an amine which could compete with *n*-hexylamine in the carbonylative reaction.

**Table 2.** Influence of the aryl bromide in the  $\mu$ -wave assisted carbonylative reaction.





<sup>a</sup>Reagents and conditions: ArBr (0.5 mmol), *n*-hexylamine (1.0 mmol), **1** (0.5 mmol), Pd(OAc)<sub>2</sub> (5 mol%), P(*t*-Bu)<sub>3</sub>HBF<sub>4</sub> (10 mol-%),  $\mu$ -wave irradiation (130 °C, 20 min), 1,4-dioxane (2 mL). <sup>b</sup>Isolated yield.

Next, the effect of the amine was evaluated (Table 3). Primary amines generally provided the corresponding product in higher yield than secondary amines or aniline. 2-Methylpropan-1-amine provided amide **2i** in 60% yield, whereas when benzylamine was used, a yield of 68% (**2j**) was obtained (Table 3, entries 1-2). The secondary amines 4-phenylpiperidine and morpholine gave amides **2k** and **2l** in 52% and 65% yield, respectively (Table 3, entries 3-4). Changing the amine to aniline provided the corresponding amide **2m** in 42% yield (Table 3, entry 5). Lastly, when diisobutylamine was used no amide **2n** could be identified in the crude mixture (Table 3, entry 6). The flexible and bulky nature of this amine may cause the reaction to be hampered.

**Table 3.** Influence of the amine in the carbonylative reaction.



<sup>a</sup>Reagents and conditions: *p*-Tol-Br (0.5 mmol), amine (1.0 mmol), **1** ( $\overline{0.5}$  mmol), Pd(OAc)<sub>2</sub> (5 mol%), P(*t*-Bu)<sub>3</sub>HBF<sub>4</sub> (10 mol%),  $\mu$ -wave irradiation (130 °C, 20 min), 1,4-dioxane (2 mL). <sup>b</sup>Isolated yield.

#### Conclusion

In conclusion a palladium-catalyzed method was developed for the carbonylation of aryl bromides into amides using  $\mu$ -wave irradiation at 130 °C for 30 min. After optimization of the reaction condition it was shown that tri-*tert*-butylphosphonium tetrafluoroborate (P(*t*-Bu)<sub>3</sub>HBF<sub>4</sub>) was a superior ligand that provided the desired products in up to 82% isolated yield.

#### **References and notes**

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5. Compared to other CORMS such as  $Mo(CO)_6$ . For 1: CAS: 12154-95-9. Saftey classification: GHS07, exlamation mark. Signal word: warning. Hazard statements: H302 + H332. Use dustmask, eyeshields and gloves.

6. Yield determined by GC-MS using a calibration curve of 2a.

7. General procedure for the  $\mu$ -wave assisted carbonylative reaction: In a 5 mL microwave vial, palladium acetate (0.025 mmol) and tri*tert*-butylphosphonium tetrafluoroborate (0.05 mmol) were taken together in 1,4-dioxane (2 mL) and the resulting mixture was stirred for 10 min at room temperature. To this solution, aryl bromide (0.5 mmol), amine (1 mmol), bis[CP-Fe(II)-(CO)<sub>2</sub>] (0.5 mmol) and DBU (1 mmol) were added. The reaction vial was subsequently sealed and heated under  $\mu$ -wave irradiation at 130 °C for 20 min. After cooling to room temperature, the reaction mixture was purified using silica gel column chromatography (10-50% ethyl acetate in isohexane) to obtain the amide products.

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#### **Supplementary Material**

Supplementary data associated with this article can be found, in the online version, at XYZ.

CCE

- A palladium-catalyzed carbonylative reaction to yield benzamides is described.
- Bis(cyclopentadienyldicarbonyliron) is used as solid source of CO.
- Accepter The reaction is enabled by microwave heating •

**Graphical Abstract** To create your abstract, type over the instructions in the template box below.

Palladium-catalyzed carbonylation of aryl	Leave this area blank for abstract info.	
bis[CP-Fe(II)-(CO) <sub>2</sub> ] as a carbon monoxide		
source Tamal Roy, Jonas Rydfjord, Jonas Sävmarker and Patrik Norde	eman <sup>*</sup>	
R         Pd(OAc) <sub>2</sub> , P(t-Bu) <sub>3</sub> HBF <sub>4</sub> bis[CP-Fe(II)-(CO) <sub>2</sub> ]           μ-wave, NHR'R''           130 °C, 20 min	42-82% yield	
<sup>2</sup> onts or abstract dimensions should not be changed or altered.	59	