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Microwave-promoted aminocarbonylation of aryl triflates using $Mo(CO)_6$ as a solid CO source

Luke R. Odell, Jonas Sävmarker, Mats Larhed *

Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala Biomedical Center, Uppsala University, PO Box 574, SE-751 23 Uppsala, Sweden

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ABSTRACT

Palladium-catalyzed carbonylations of aryl triflates with a range of nucleophiles using $Mo(CO)_6$ as a solid CO source were explored. The reactions proceeded smoothly providing moderate to good yields of the corresponding aryl amides, esters, or acylsulfonamides after only 20 min of microwave irradiation. The acyl transfer reagent 4-dimethylaminopyridine was found to promote some of the more difficult transformations.

The Heck carbonylation is a well established method for the regioselective preparation of carbonyl compounds from an organic electrophile, carbon monoxide (CO), and a nucleophile.[1,2] Depending on the choice of nucleophile, ketones, carboxylic acids, esters, or amides can be readily obtained from the corresponding aryl or vinyl halide (or halide surrogate).[3,4] However, the drawbacks of handling toxic CO gas and the requirement for high-pressure reaction conditions have limited the scope of these reactions, especially on a laboratory scale. The recent development of CO gas-free carbonylative conditions,[5] using formamides[6–8] or solid metal carbonyls[9,10] as CO sources, have overcome the problems of using gaseous reagents in small-scale reactions.

We have previously reported on the palladium-catalyzed $Mo(CO)_6$-mediated carbonylative coupling of numerous aryl and heteroaryl halides using a variety of nucleophiles under microwave-assisted conditions.[11–19] Aryl triflates are a valuable class of starting materials that are easily prepared from the corresponding phenols, and they have been widely utilized as coupling partners in various metal-catalyzed transformations,[20–24] including Heck carbonylations.[25–29] However, to date there has been only one paper describing the $Mo(CO)_6$-mediated hydroxycarbonylation of aryl and vinyl triflates to yield the corresponding benzoic acids.[30] Thus, the scope of nucleophiles explored in this transformation is limited to water, which encouraged our investigations in this area.

Herein, we report a general palladium(0)-catalyzed protocol for the $Mo(CO)_6$-mediated carbonylation of diversely substituted aryl triflates with various nucleophiles. This process proceeds smoothly under microwave irradiation, and the addition of the acyl transfer reagent 4-dimethylaminopyridine (DMAP) was shown to be beneficial for some of the more challenging transformations.

As the starting point for our investigations, we decided to explore the carbonylation of aryl triflates using organic amines as the nucleophiles. We chose 4-methoxyphenyl triflate (**1a**) as the model aryl triflate and piperidine (**2a**) as the amine nucleophile. Initially, we employed the microwave-assisted protocol reported by one of us, which was shown to be effective in promoting the aminocarbonylation of aryl bromides and chlorides.[16] This aqueous protocol, using Herrmann's palladacycle[31] (5%) as a thermostable palladium source and the pre-ligand $[(t\text{-Bu})_3PH]BF_4$ (10%) with Na_2CO_3 (3 equiv) as base was found to be ineffective in promoting the desired transformation and, after 30 min of microwave heating at 170 °C, yielded only starting material and the hydrolyzed triflate, 4-methoxyphenol. Exchanging the pre-ligand for the bulky and electron-rich Xphos ligand[32] proved to be beneficial, providing small amounts of the desired aryl amide product. However, GC–MS analysis showed that the major product was still 4-methoxyphenol and thus, dioxane was chosen as a solvent to minimize hydrolysis of the triflate starting material. Fine tuning of the reaction conditions (base, time, temperature, and catalyst loading) led to a reliable protocol, which furnished full conversion of **1a** to the desired aryl amide product **3a**. This procedure was then further evaluated for its scope and general applicability.

Initially, we decided to investigate the aminocarbonylation of a variety of aryl triflates **1a–j** with piperidine **2a** (see Table 1) under

* 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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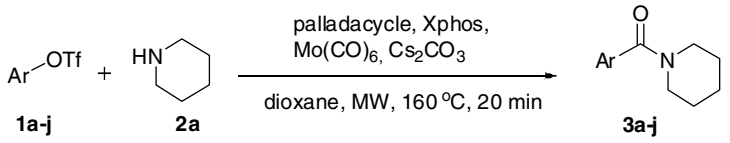
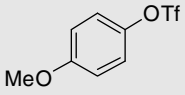
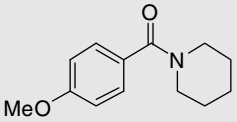
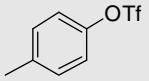
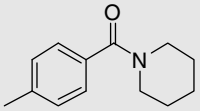
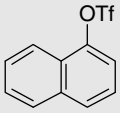
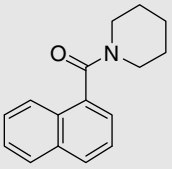
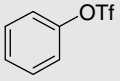
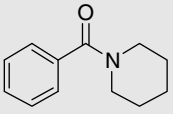
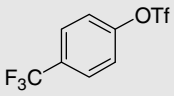
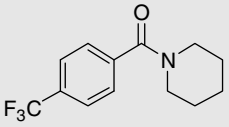
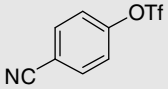
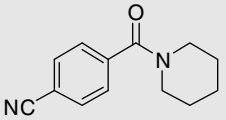
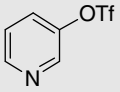
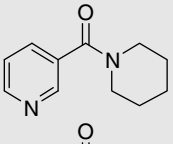
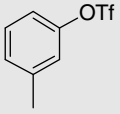
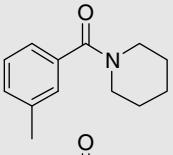
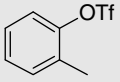
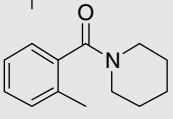
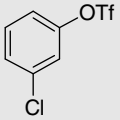
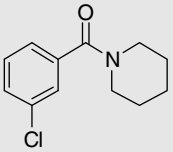
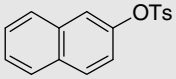
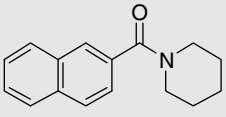
Table 1
Aminocarbonylation of aryl triflates **1a–j** and 2-naphthyl tosylate **1k** with piperidine **2a**



1a-j **2a** **3a-j**

Entry	Ar-OTf		Product		Yield (%)
1		**1a**		**3a**	78
2		**1b**		**3b**	93
3		**1c**		**3c**	84
4		**1d**		**3d**	74
5		**1e**		**3e**	62
6		**1f**		**3f**	68
7		**1g**		**3g**	76
8		**1h**		**3h**	79
9		**1i**		**3i**	49
10		**1j**		**3j**	65
11[a]		**1k**		**3k**	55

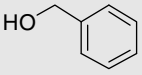
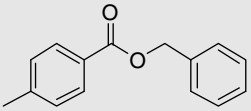
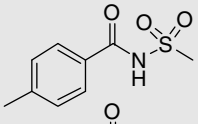
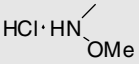
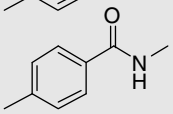
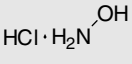
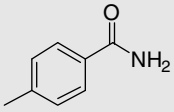
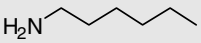
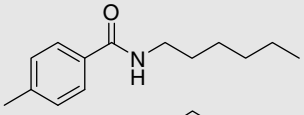
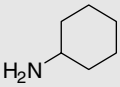
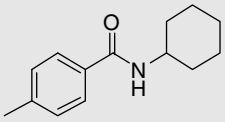
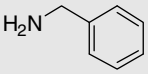
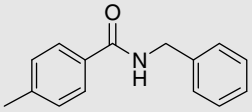
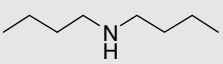
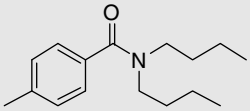
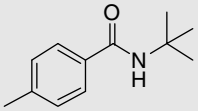
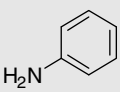
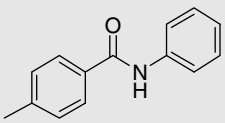
Reactions were performed under microwave irradiation in a sealed vial on a 0.25 mmol scale with 2.0 equiv of **2a**, 1.0 equiv of $Mo(CO)_6$, 3.0 equiv of Cs_2CO_3, 2.5 mol % of palladacycle, and 7.5 mol % of Xphos in 2.5 mL of dioxane at 160 °C for 20 min.

[a] 5.0 equiv of **2a** at 180 °C for 40 min. All yields are isolated yields with >95% purity by GC–MS.

the identified microwave conditions. In a typical reaction, the aryl triflate (0.25 mmol), Herrmann's palladacycle (2.5 mol %), Xphos (7.5 mol %), $Mo(CO)_6$ (0.25 mmol), Cs_2CO_3 (3 equiv), piperidine (2 equiv), and dioxane (2.5 mL) were microwave heated at 160 °C for 20 min in sealed vessels under an atmosphere of air.[33] As can be seen from Table 1, all the reactions proceeded smoothly, providing moderate to good isolated yields (49–93%) of the corresponding aryl amides. Electron-rich (entries 1–3), electron-poor (entries 5 and 6), and electron-neutral (entry 4) triflates were all well tolerated. Slightly lower yields were observed with electron-poor substrates **1e**,**f**, most probably due to competing reduction of the aryl triflate. Heterocyclic triflate **1g** was also smoothly transformed, providing the nicotinic amide derivative **3g** in a good yield (76%). *ortho*-Substituents were not as well tolerated, most probably due to unfavorable steric interactions (entry 9). Surprisingly, full chemoselectivity was observed for the aminocarbonylation of *meta*-chlorophenyl triflate **1j** and no trace of the corresponding chlorocarbonylation product was detected by GC–MS. Finally, the reaction scope could be extended to include naphthyl tosylate **1k**. Useful yields of the amide product **3k** could be isolated if a larger excess of **2a** was used (5.0 equiv) and if the reaction temperature and time were increased (180 °C and 40 min). This, to the best of our knowledge, is the first reported aminocarbonylation of an aryl tosylate. Unfortunately, this reaction was found to be exclusive for this particular substrate. Attempts with other aryl tosylates, even under more forcing conditions, yielded only unreacted starting material.[34]

To examine further the scope of this protocol, a variety of nucleophiles were employed using *p*-tolyl triflate **1b** as the oxidative addition substrate (Table 2). The use of benzyl alcohol

Table 2
Carbonylation of aryl triflate **1b** with nucleophiles **2b–k**

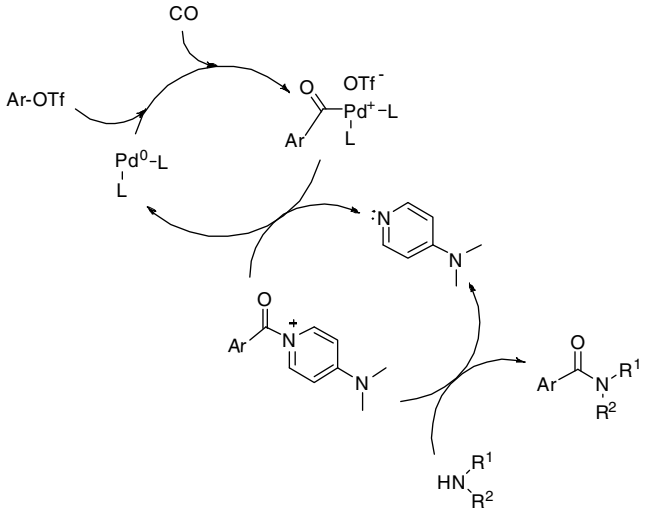
Entry	Nucleophile	Product	Yield (%)
1[a]	 **2b**	 **4a**	71
2	 **2c**	 **4b**	62
3[b]	 **2d**	 **4c**	67
4[b]	 **2e**	 **4d**	55
5	 **2f**	 **4e**	76
6	 **2g**	 **4f**	70
7	 **2h**	 **4g**	75 92[c]
8	 **2i**	 **4h**	38 51[c]
9	 **2j**	 **4i**	45 68[c]
10	 **2k**	 **4j**	21 70[c]

Reactions were performed under microwave irradiation in a sealed vial on a 0.25 mmol scale with 2.0 equiv of **2c–k**, 1.0 equiv of $Mo(CO)_6$, 3.0 equiv of Cs_2CO_3, 2.5 mol % of palladacycle, and 7.5 mol % of Xphos in 2.5 mL of dioxane at 160 °C for 20 min.

[a] Reaction performed in 1:1 (2.5 mL) dioxane/benzyl alcohol.

[b] 5.0 equiv of Cs_2CO_3 used.

[c] 2.0 equiv of DMAP added to the reaction. All yields are isolated yields with >95% purity by GC–MS.



Scheme 1. Proposed role of DMAP in promoting the aminocarbonylation reactions.

as a co-solvent afforded the corresponding alkoxycarbonylation product **4a** in good yield (71%). An analogous amidocarbonylation reaction was also performed using methanesulfonylamide as the nucleophile, affording a moderate yield of acyl sulfonamide **4b**. Attempts to access the Weinreb amide gave only the corresponding methyl amide **4c**, resulting from the loss of methanol.[35] Similarly, the use of hydroxylamine hydrochloride, which we have previously utilized as a convenient solid ammonia source,[17] afforded the primary amide **4d** in moderate yield (55%). As expected, primary cyclic and acyclic amines reacted smoothly providing good yields of the desired *p*-tolyl amide products (entries 5–7). In contrast, sterically hindered amines (entries 8 and 9) and the weakly nucleophilic aniline (entry 10) proved to be more problematic, providing only incomplete conversion of the aryl triflate starting material and consequently low isolated product yields. Inspired by our own findings[7,8] and the work of others[36,37] in this field, we decided to explore the use of an acylation catalyst[38,39] to improve these transformations. To our delight, the addition of DMAP to the reaction provided both full conversion and significantly higher yields of the desired products (entries 7–10). We believe that DMAP acts as an acyl transfer reagent, which reacts with the aroylpalladium species generated from the insertion of CO into the arylpalladium oxidative addition complex.[40] The resulting aroylpyridinium intermediate exits the catalytic cycle and is attacked by the amine nucleophile to yield the desired aryl amide products (Scheme 1).

In conclusion, we have successfully developed an efficient and CO-gas free, microwave-enhanced protocol for the carbonylation of various (hetero)aryl triflates with a range of nucleophiles. This robust and general method can be utilized for the transformation of aryl triflates into their corresponding aryl amides, esters, or acylsulfonamides.

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33. *Example synthesis:* Compound **3a**. To a microwave transparent vial (2–5 mL) with a Teflon coated stirring bar was added 4-methoxyphenyl triflate (64 mg, 0.25 mmol), Hermann's palladacycle (5.4 mg, 2.5 mol %), Xphos (8.9 mg, 7.5 mol %), Cs_2CO_3 (244 mg, 0.75 mmol), piperidine (43 mg, 0.5 mmol), and dioxane (2.5 mL). The vial was then sealed under air and heated at 160 °C by microwave irradiation in a Smith Synthesizer™ or Emrys Initiator™ for 20 min using a fixed hold time. After cooling, the mixture was diluted with dichloromethane and filtered. The residue was washed with dichloromethane and the filtrate was concentrated in vacuo. The crude product was thereafter purified by flash chromatography eluting with hexane/ethyl acetate (3:1). Yield: 42.5 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (br s, 4H), 1.55–1.65 (m, 2H), 3.37 (br s, 4H), 3.75 (s, 3H), 6.82 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 26.2 (br), 45.5 (br), 49.0 (br), 55.5, 113.8, 128.7, 129.1, 160.8, 170.0. EI-MS: m/z 219 (M^+).
34. 4-Methyl-, 4-CF_3- and 4-MeO-phenyl tosylates were tried up to temperatures of 220 °C.
35. Lowering of the reaction temperature gave only **1b** and **4c**.
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40. In addition to its function as an acylation catalyst, DMAP might also accelerate the release of CO from $Mo(CO)_6$ by a ligand substitution reaction. See Ref. 10 and Barnard, T. M.; Leadbeater, N. E. *Chem. Commun.* **2006**, *34*, 3615–3616.