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Report

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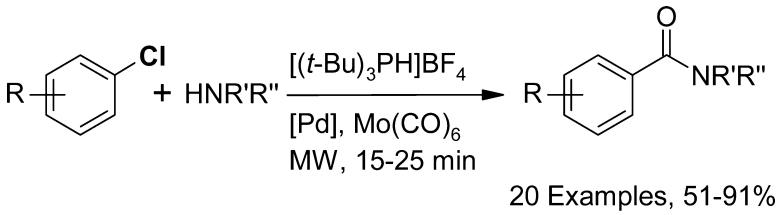

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Microwave-Promoted Aminocarbonylations of Aryl Chlorides Using $Mo(CO)_6$ as a Solid Carbon Monoxide Source

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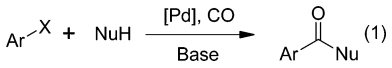
Palladium(0)-catalyzed carbonylation of aryl halides with various nucleophiles is a versatile method for the formation of a wide range of aromatic carboxylic acid derivatives, including benzamides (eq 1).[1−3] The scope of this reaction

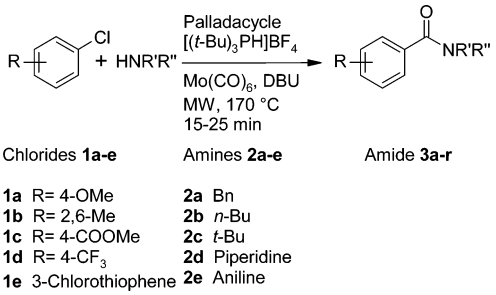


is broad, and the tolerance for different functional groups is high. Even though there are many advantages with classical carbonylation protocols, there are also some detractions. In particular, the low reactivity of aryl chlorides,[4] the problems associated with the use of toxic and gaseous carbon monoxide,[5] and the long reaction times (ranging from hours to days)[1−3] severely limit the usefulness of carbonylative transformation in drug discovery and other small-scale applications.[6]

Although aryl iodides, bromides, and triflates are commonly used as arylpalladium precursors in carbonylation reactions,[1−3] aryl chlorides, which are the least expensive and most accessible coupling partners, have rarely been utilized.[7−9] In fact, except for two reactions with chlorobenzene,[9,10] only examples with electron-poor or metal−carbonyl activated aryl chlorides are reported in the scientific literature.[11−18] However, progress in the identification of catalytic systems for activation of reluctant aryl chlorides in related Heck and cross-coupling reactions[4] encouraged us to revisit the aminocarbonylation reaction using the commercially available preligand $[(t\text{-Bu})_3PH]BF_4$[19−21] as the key component in combination with Herrmann's palladacycle[22] as Pd source.[23] The primary advantages of this catalytic cocktail are the high stability, enabling noninert handling, and the high activity of the in situ-released electron-rich $(t\text{-Bu})_3P$ in oxidative addition of aryl chlorides.[24,25]

In recent years, noteworthy progress has been made in the development of convenient and CO(g)-free metal-mediated carbonylative transformations.[5] Thus, the recent finding that $Mo(CO)_6$ can act as a carbon monoxide releasing reagent,[26−28] together with the use of controlled microwave (MW) irradiation as the energy source,[29−32] has overcome the problems of introducing a gaseous reactant in small-scale high-speed protocols. In this Report, we establish for the first time that both electron-rich and electron-poor aryl chlorides

Scheme 1



serve as useful substrates in microwave-heated in situ aminocarbonylation reactions under noninert conditions. Both aliphatic amines and anilines provide benzamide products in good yields after only 15−25 min of irradiation.

Initially, 0.80 mmol of 4-trifluoromethylphenyl chloride (**1d**) was reacted with benzylic amine (**2a**, 2.4 mmol), $Mo(CO)_6$ (0.80 mmol), Herrmann's palladacycle (trans-di-(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II)) (0.020 mmol), $[(t\text{-Bu})_3PH]BF_4$ (0.040 mmol), and the amine base DBU (2.4 mmol) in 2 mL of dry THF under noninert conditions (Scheme 1). The test reactions were performed at different temperatures and with alternative heating periods using septa-sealed vessels and high-density microwave heating.

Analysis of the resulting product mixture after 15 min of heating at 170 °C revealed both full conversion of aryl chloride **1d** and formation of the desired benzamide product **3d**, indicating that the bulky $(t\text{-Bu})_3P$ ligand does not inhibit the essential CO insertion process. After purification, **3d** was isolated in 89% yield. Attempted reactions at temperatures above 190 °C afforded lower productivity due to extensive palladium-black formation. Inspired by the positive outcome with **1d** and **2a**, we next extended the study to include five electronically and sterically diverse aryl chlorides (**1a**−**e**) and five selected amines (**2a**−**e**). The preparative results employing the selected standard method with both primary and secondary amines are summarized in Table 1. In all cases, the formation of benzamide products **3a**−**r** was strongly favored, providing 51−91% isolated yields after only 15−25 min of heating. From the presented results, it is clear that this is a general method that tolerates both electron-rich and electron-poor aryl chlorides, including sensitive esters. Impressively, sterically congested 2,6-dimethylated **1b** provided useful yields of products **3b**, **3l**, and **3p** according to the standard protocol (entries 2, 12, and 16). Disappointingly, **1b** in combination with nonhindered *n*-butylamine (**2b**) rendered a mixture of the target amide and the corresponding symmetrical urea (*N*,*N*′-dibutylurea).[33,34] Aminocarbonylations with *tert*-butylamine **2c** were slower, and full conversions of the investigated arylpalladium precursors were never realized, although 66 and 53% isolated yields of products **3i** and **3j** were obtained. Accordingly, the weakly nucleophilic aniline furnished 54−65% isolated yields (Table 1, entries 15−18).

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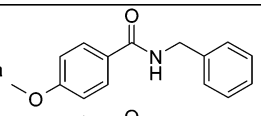
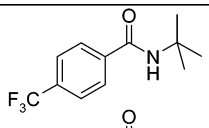
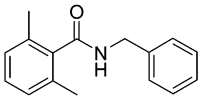
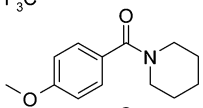
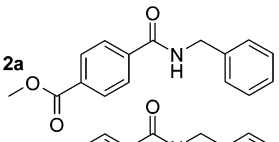
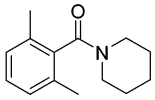
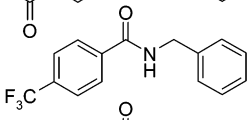
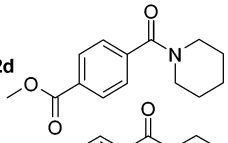
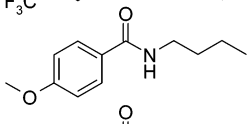
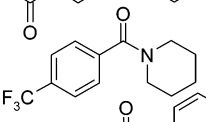
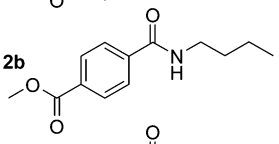
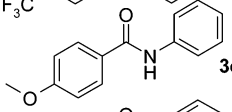
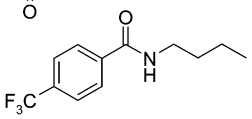
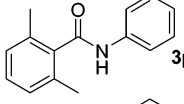
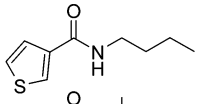
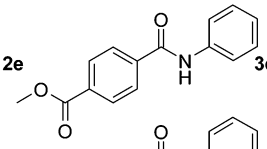
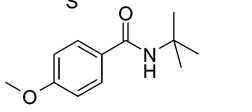
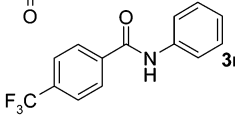
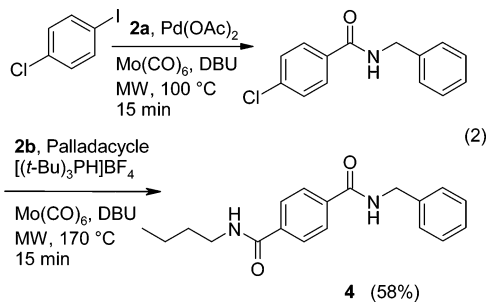
Table 1. Microwave-Promoted Aminocarbonylations of Aryl Chlorides Using $Mo(CO)_6$ as a Solid Carbon Monoxide Source[a]

No	Starting material	Product	Time	Isolated Yield [b] (%)	No	Starting material	Product	Time	Isolated Yield [b] (%)
1	**1a 2a**		**3a**	15	86	10	**1d 2c**		**3j**	15	53
2	**1b 2a**		**3b**	15	81	11	**1a 2d**		**3k**	15	69
3	**1c 2a**		**3c**	25	62	12	**1b 2d**		**3l**	25	51
4	**1d 2a**		**3d**	15	89	13	**1c 2d**		**3m**	15	74
5	**1a 2b**		**3e**	15	70	14	**1d 2d**		**3n**	15	76
6	**1c 2b**		**3f**	25	51	15	**1a 2e**		**3o**	25	64
7	**1d 2b**		**3g**	15	91	16	**1b 2e**		**3p**	25	65
8	**1e 2b**		**3h**	15	78	17	**1c 2e**		**3q**	25	54
9	**1a 2c**		**3i**	25	66	18	**1d 2e**		**3r**	15	64

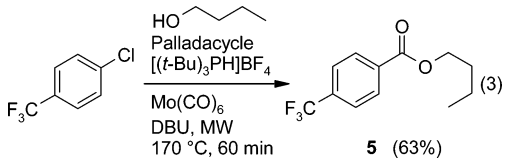
[a] The reactions were carried out in 0.8-mmol scale. A vial was charged with 1 equiv of Ar−Cl, 3 equiv of amine, 3 equiv of DBU, 0.025 equiv of palladacycle, 0.05 equiv of $[(t\text{-Bu})_3PH]BF_4$, 1 equiv of $Mo(CO)_6$, and 2 mL of THF. The vial was sealed under air and was microwave-irradiated to 170 °C for 15−25 min. For safety reasons, no experiments were performed with oil-bath heating. [b] >95% pure according to GC/MS.

Next, a chemoselective two-step protocol to provide a controlled double aminocarbonylation was investigated. The reaction sequence was started by using a phosphine-free $Mo(CO)_6$-induced carbonylation of the iodo functionality.[27] Importantly, no substitution of the chloride group was detected. After a quick purification, a second aminocarbonylation of the intermediate monoamide followed, which gave the bifunctionalized product **4** in a total yield of 58% (eq 2).



(2)

To further investigate the scope of the aryl chloride protocol, an analogous alkoxycarbonylation was performed. In this reaction, it was found that a prolonged reaction time of 60 min and the use of butanol as a combined solvent and nucleophile afforded the best yield of the ester product **5** (63%, eq 3).



(3)

In summary, we have developed a robust and straightforward palladium-catalyzed aminocarbonylation protocol that rapidly transforms aryl chlorides into a variety of benzamides. Noteworthy features of this microwave method include the following: use of commercially available $[(t\text{-Bu})_3PH]BF_4$ to activate the strong Ar−Cl bond, impressive results with sluggish aniline and *tert*-butylamine reactants, tolerance of air, short reaction times, and employment of $Mo(CO)_6$ as a solid carbon monoxide source. This procedure affords a convenient and versatile alternative for small-scale carbonylative applications relative to existing methods starting from aryl bromides or aryl iodides.

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Supporting Information Available. Experimental procedures, spectroscopic data and references for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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