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Report

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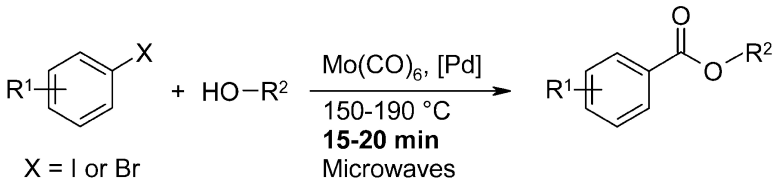

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Rapid Palladium-Catalyzed Synthesis of Esters from Aryl Halides Utilizing $Mo(CO)_6$ as a Solid Carbon Monoxide Source

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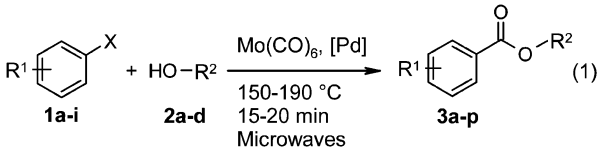
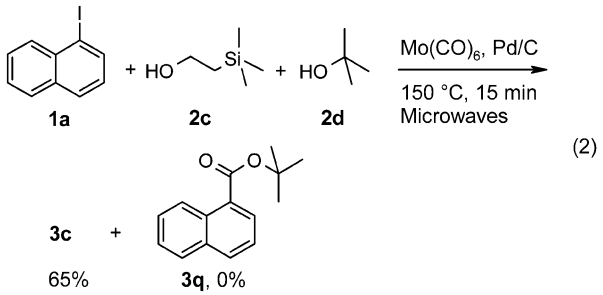
For almost three decades, the palladium-catalyzed carbonylation of aryl halides and pseudohalides (Heck carbonylation) has been utilized as an important method for the synthesis of aromatic esters,[1] amides,[2] and carboxylic acids.[3] Traditionally, this method requires the use of gaseous carbon monoxide to introduce the carbonyl functionality.[4,5] Today, the trend in industrial medicinal chemistry is to move toward high-throughput chemistry, employing small reaction scales and short reaction times.[6−8] Furthermore, the efficiency of microwave flash heating in accelerating metal-catalyzed transformations has recently been proven in many different applications.[9] We recognized that the handling of the toxic CO gas in automated, combinatorial laboratories is clearly inconvenient, and we therefore employed nongaseous CO precursors in microwave-promoted aminocarbonylations.[10,11] Herein, we report a series of examples of fast microwave-mediated ester syntheses successfully conducted with molybdenum hexacarbonyl as a commercially available, stable, and solid carbon monoxide source (eq 1).[12,13]



X=I	R^1	X=Br	R^1		R^2
1a	1-Naphthyl	**1f**	1-Naphthyl	**2a**	-*n*-Bu
1b	4-OMe	**1g**	4-OMe	**2b**	-Bn
1c	2-Me	**1h**	2-Me	**2c**	$-CH_2CH_2Si(CH_3)_3$
1d	$4\text{-}CF_3$	**1i**	$4\text{-}CF_3$	**2d**	-*t*-Bu
1e	3-Br				

Aryl iodide **1a** (2.0 mmol) was mixed with the two solid-phase components $Mo(CO)_6$ (1.0 mmol) and Pd/C (0.1 mmol Pd) together with the additive DMAP (4.0 mmol), the base diisopropylethylamine (DIEA) (4.0 mmol), excess alcohol **2a** (2.0 mL), and 1,4-dioxane (2.0 mL) in a reaction vessel. The vessel was sealed under air and was heated using controlled microwave energy to 150 °C for 15 min to give the ester **3a** in good yield (89%) (Table 1, entry 1). A range of common and valuable ester-protected acids (**3a**−**p**) were synthesized using this noninert protocol. The preparative results starting from electron-poor as well as electron-rich aryl iodides are presented in Table 1. No large difference in the outcome was observed, although the electron-poor substrate **1d** tended to afford slightly lower yields as a result of competing dehalogenation (52−78% yield, entries 10−12). The ester synthesis from naphthyl iodide **1a** proved also to be effective with the homogeneous precatalyst $Pd(OAc)_2$ (63% yield, entry 1). Furthermore, no selectivity issue was encountered with the bromo-substituted aryl iodide **1e**, and only the iodine was prone to undergo displacement with subsequent carbonylation (entries 13−15). The sterically hindered *tert*-butanol, **2d**, provided low or no yields. Thus, **3p** was isolated in 33% yield after massive dehalogenation and incomplete consumption of **1b** (entry 16), while the corresponding naphthalene ester **3q** was not formed as deduced from GC/MS. Despite prolonged heating of the reaction system in entry 16 to investigate if the poor yield of **3p** was a consequence of ester hydrolysis, no free carboxylic acid was detected. In contrast, boosting of the reaction cocktail above 150 °C afforded a complex reaction mixture. In a competitive experiment with an equal amount of the alcohols **2c** and **2d**, only the product **3c** was formed (65% isolated yield) (eq 2), and no *tert*-butyl ester (**3q**) was observed.



An exchange of precatalyst to a reactive palladacycle,[14] combined with an increased reaction temperature (180−190 °C), furnished the possibility to exploit cheaper and more accessible aryl bromides as starting materials. Under these conditions, aryl esters **3a**, **3d**, **3g**, and **3j** were prepared in useful yields after 15−20 min of microwave heating (Table 1).

The above-described fast carbonylation protocol was highly reproducible, and full conversions of the aryl halides were obtained (except for the incomplete conversion of **1b** in entry 16). Impressively, only 0.5 equiv of $Mo(CO)_6$ was used in the general procedure, despite the air atmosphere in the reaction vessel. Problems with solubility ruled out the use of pure alcohol as solvent, and hence, dioxane was exploited as the cosolvent. The reactions could also be conducted in diglyme, a less toxic alternative to dioxane, but because of the tedious downstream work-up procedure, this cosolvent is not recommended for high-throughput chemistry. All attempts to reduce the excess of alcohol below 10 equiv or to reduce the amount of Pd below 5% resulted in incomplete reactions or required the use of more specific protocols. The use of DMAP as an additive was able to slightly enhance the yield of product formed. Thus, with

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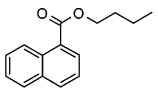
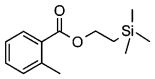
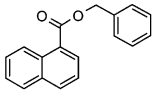
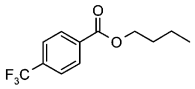
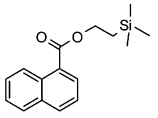
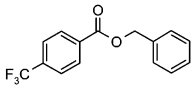
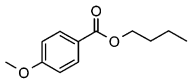
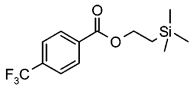
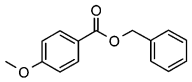
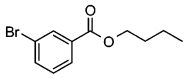
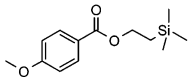
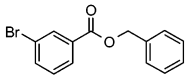
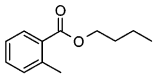
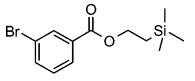
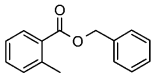
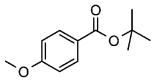
Table 1. Rapid Palladium-Catalyzed Carbonylation of Aryl Iodides and Bromides with Alcohols Using $Mo(CO)_6$ as the CO Source[a]

entry	starting materials	product	yield[b] (%)	entry	starting materials	product	yield[b] (%)
1	**1a** **2a** **1a** **2a** **1a** **2a** **1f** **2a**		**3a** 89 **3a** 72[c] **3a** 63[d] **3a** 64[e]	9	**1c** **2c**		**3i** 68
2	**1a** **2b**		**3b** 76	10	**1d** **2a** **1i** **2a**		**3j** 78 **3j** 67[e]
3	**1a** **2c**		**3c** 86	11	**1d** **2b**		**3k** 60
4	**1b** **2a** **1g** **2a**		**3d** 63 **3d** 72[f]	12	**1d** **2c**		**3l** 52
5	**1b** **2b**		**3e** 74	13	**1e** **2a**		**3m** 73
6	**1b** **2c**		**3f** 74	14	**1e** **2b**		**3n** 66
7	**1c** **2a** **1c** **2a** **1h** **2a**		**3g** 75 **3g** 63[g] **3g** 66[f]	15	**1e** **2c**		**3o** 67
8	**1c** **2b**		**3h** 69	16	**1b** **2d**		**3p** 33

[a] The reactions were performed in 2.0 mmol scale. A vial was charged with 1.0 equiv Ar−I, 0.05 equiv [Pd] (Pd/C), 0.5 equiv $Mo(CO)_6$, 2.0 equiv DMAP, 2.0 equiv DIEA, 2.0 mL alcohol, and 2.0 mL dioxane. The vial was sealed under air and microwave-irradiated to 150 °C for 15 min. [b] Isolated yields, >95% pure according to ^{1}H NMR. [c] Classic heating (metal heating block, 150 °C for 15 min). [d] 0.05 equiv $Pd(OAc)_2$ instead of Pd/C. [e] Synthezised from the corresponding Ar−Br and microwave-irradiated to 180 °C for 15 min with 0.025 equiv palladacycle instead of Pd/C. [f] Synthezised from corresponding Ar−Br and microwave-irradiated to 190 °C for 20 min with 0.025 equiv palladacycle instead of Pd/C. [g] Synthesized without DMAP.

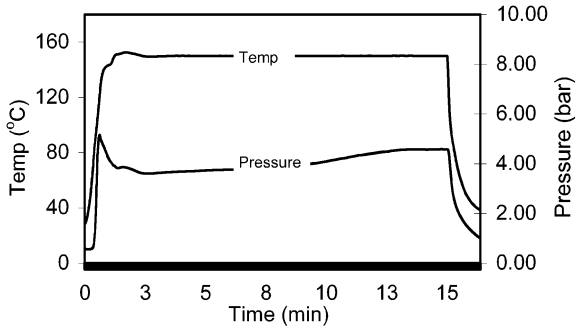
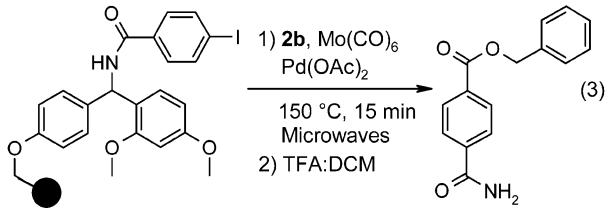


Figure 1. Temperature and pressure profiles for the microwave-heated synthesis of **3a** from **1a** with Pd/C (Table 1, entry 1).

DMAP, the yield of **3g** was 75%, and without DMAP, 63% was isolated (entry 7). This result indicates that the reaction probably proceeds via the activated amide formed with DMAP,[15] promoting the nucleophilic attack from the alcohol. Exclusion of DIEA delivered product but in lower yield.

The synthesis of **3a** was also performed with classic heating (preheated metal block) at 150 °C. Not surprisingly, the reaction could be conducted with the same reaction time (15 min) as with microwave heating, although in a slightly lower yield (72% vs 89%, entry 1). However, the computer-controlled microwave synthesizer was primarily used not because of the positive effect on the yields, but mainly for the automation and experimental convenience. The microwave system also allowed monitoring of both the temperature and the pressure in the reaction vessel (Figure 1),[16] which is otherwise difficult when conventional heating and sealed glassware are employed. The microwave power reached and bypassed the boiling point of dioxane (100−102 °C) in <1 min, despite the very low polarity of dioxane.[17] The pressure never exceeded 5 bar.

To show the generality of the in-situ carbonylation approach, the reaction was also performed with an aryl iodide attached to a solid support (eq 3). In this example $Pd(OAc)_2$ was used as the palladium-source to guarantee that the true catalyst was in solution during the reaction. After acidic cleavage we obtained an isolated yield of 71% of ester **5**. Surprisingly, palladium on charcoal also produced the ester **5**, but was rejected due to incomplete conversion of **4**.



4 **5**, 71% (3)

In summary, we have presented a noninert palladium-catalyzed method for the synthesis of ester-protected carboxylic acids from aryl iodides and bromides, employing $Mo(CO)_6$ as a convenient solid carbon monoxide source. Thus, butyl-, benzyl-, and trimethylsilylethyl esters were smoothly prepared after only 15−20 min of heating. This in-situ carbonylation route couples a facile experimental procedure to handle "carbon monoxide gas" in a high-throughput manner, with the rapid reaction speed associated with single-mode microwave irradiation. The methodology is quite applicable to today's modern synthetic techniques, both in solution and in solid-phase organic chemistry.

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Supporting Information Available. Experimental procedures; ^1H, ^{13}C NMR, MS, IR, and elemental analysis data of all new compounds are available as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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