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Increasing Rates and Scope of Reactions: Sluggish Amines in Microwave-Heated Aminocarbonylation Reactions under Air

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Abstract: Commercially available molybdenum hexacarbonyl serves as a convenient and solid carbon monoxide source in palladium-catalyzed aminocarbonylations of aryl bromides and iodides. This improved microwave protocol, relying on DBU as base and THF as solvent, enables rapid couplings using otherwise sluggish anilines, *tert*-butylamine, and free amino acids. In addition, $Cr(CO)_6$ and $W(CO)_6$ were found to be useful alternative CO-releasing reagents. Altogether, 16 different aromatic amides were synthesized under air in 35−95% yield after only 15 min of controlled microwave irradiation.

Today, a future view of combinatorial synthesis emerges where solid- and liquid-phase methods complement each other.[1] In particular, the recent utilization of novel solid-supported reagents and scavengers in multistep synthesis demonstrates this powerful direction.[2,3] Still, significant limitations remain in the combinatorial chemistry arena, one of which is often reaction speed.[4,5] A second limitation concerns the efficient utilization of reactive gases. Specifically, the difficult handling of toxic carbon monoxide in high-throughput or parallel chemistry has created interest in exploring alternative sources of CO.[6−8] The desire to eliminate the use of gases has resulted in the development of modified gas-free aminocarbonylation protocols,[9−12] especially in the preparation of *N*,*N*-dimethylbenzamides.[13,14]

A recent report from our laboratory describes a palladium-catalyzed amidation protocol employing in situ generation of carbon monoxide from easily handled molybdenum hexacarbonyl ($Mo(CO)_6$).[15] This aminocarbonylation[16−18] procedure affords good yields of benzamides from aryl iodides and bromides provided nonhindered primary and secondary aliphatic amines are employed. Herein, we report an improved tandem carbon monoxide release/amidation methodology relying on the use of DBU as base and THF as solvent. With this new and more general method, successful palladium-catalyzed aminocarbonylations can be accomplished also with anilines, the sterically hindered *tert*-butylamine, and amino acids. The reactions are performed under air in sealed vessels without external carbon monoxide gas, giving moderate to high yields after only 15 min of microwave irradiation.[19−21]

In a lead optimization program,[22] we needed access to certain aspartic protease inhibitors with aromatic amides in the ortho position of the benzylic P1/P1′ side chains. A basic study on high-speed aminocarbonylations using anilines and other sluggish amines was therefore commenced.

Initial experiments to convert aryl halides into benzanilides, using the previously reported conditions for molybdenum hexacarbonyl mediated couplings,[15] met with little success. The low reactivity encountered with anilines encouraged us to improve the methodology with the ultimate goal to extend the scope of the process to include weakly nucleophilic amines as well. To circumvent precipitation of molybdenum metal on the wall of the borosilicate vessel (avoiding subsequent microwave-induced thermal cracking and vessel rupture), the previously reported in situ aminocarbonylations were conducted with diglyme as a coordinating solvent. The high-boiling and water-soluble diglyme was, however, difficult to remove and complicated the isolation of the carbonylated products.

2-Iodotoluene (**1d**) and aniline (**2b**) were selected as model substrates for a series of optimization experiments. Different solvents, palladium precatalysts, and bases were examined. We aimed to obtain full conversion of **1d** in less than 15 min and adjusted the reaction temperature accordingly. All carbonylations were conducted under air with controlled microwave heating in sealed borosilicate vessels. After some experimentation,[23] it was discovered that THF served as a convenient solvent in

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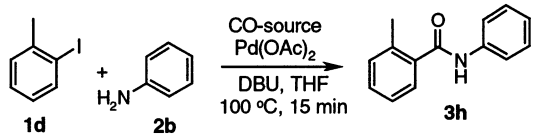
TABLE 1. Examination of Different Solid−CO Sources in the Aminocarbonylation Reaction



entry[a]	CO source	isolated yield of **3h** (%)
1	$Cr(CO)_6$	80
2	$Mo(CO)_6$	84
3	$W(CO)_6$	77
4	$Fe(CO)_5$	0[b]
5	$Fe_3(CO)_{12}$	0[b]
6	$Co_2(CO)_8$	28

[a] Reactions performed according to general procedure A, but with different metal−CO complexes. [b] Less than 5% conversion of **1d**.

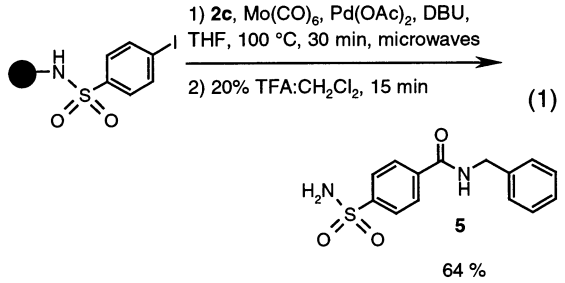
combination with the strong amine base DBU,[24] $Mo(CO)_6$, and palladium acetate. Under these conditions, full conversion of **1d** was obtained within 15 min of irradiation at 100 °C reaction temperature, affording 84% isolated yield of the benzamide **3h** (Table 1, entry 2). The selected conditions (A) were thereafter investigated with other potential solid sources of carbon monoxide (Table 1). Pressure curves from these reactions indicated gas release in all cases, and although $Mo(CO)_6$ produced the highest yield (entry 2), the other metal carbonyls of the same group ($Cr(CO)_6$, $W(CO)_6$) proved almost equally efficient.

Preparative aminocarbonylations with $Mo(CO)_6$ as the source of CO and with a variety of aryl iodides (**1a**, **1b**, **1d,** and **1f**) and amines (**2a**−**h**) are summarized in Table 2. The previously investigated piperidine (**2a**) produced improved yields,[15] and aniline (**2b**) and benzylamine (**2c**) also coupled easily with these aryl iodides (Table 2, entries 1−4, 6, 9, and 11), whereas the sterically hindered *tert*-butylamine and the labile 2-aminothiazole afforded lower yields of products **3i** and **3j** (entries 13 and 15). In addition, protected and nonprotected glycine could conveniently be benzoylated (entries 21 and 22), and importantly, nonprotected L-leucine reacted without racemization under the accelerated conditions.[25] The relatively low yields of acidic products **3o** and **3p** are partly explained by loss of material during preparative RP-LC−MS purification.

To increase the scope of the reaction, we decided to investigate aryl bromides as coupling partners. In these aminocarbonylations, Herrmann's palladacycle (*trans*-di-(*μ*-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium-(II), **4**)[26,27] was an effective palladium(0) source at 150 °C. As shown in Table 2, this precatalyst delivered reaction conditions (B) sufficiently general to tolerate not only the presence of the *o*-methyl substituent on the aryl bromide **1e** but also other electron-donating (entries 5, 7, and 8) as well as electron-withdrawing groups (entries 17, 19, and 20). Thus, upon controlled microwave treatment the transformations of all amines, except the 2-aminothiazole, were completed within 15 min in 35−92% isolated yield. In accordance with the results with aryl iodide **1d**, low yields (35−44%) were obtained with aryl bromides and *tert*-butylamine (**2d**) (entries 8, 14, and 20).

Aminocarbonylations of aryl iodides were also performed with traditional heating in preheated metal blocks (100 °C, 15 min). These reactions resulted in the same high yields as those observed after microwave irradiation (Table 2, entries 9 and 11). Despite this additional possibility of performing the amidation reactions, the microwave protocol was adopted because of practical convenience, excellent reaction control, and safety reasons. With aryl bromides, we did not investigate the 150 °C sealed procedure using conventional heating with standard glass vessels due to the risk of vessel rupture at the relatively high pressures experienced at this temperature (THF, bp 65−67 °C).

The flash heated aminocarbonylation reaction also worked smoothly with resin-bound 4-iodobenzenesulfonamide (Polystyrene-Rink amide) (eq 1).[28−30] Full conversion to the carbonic anhydrase II inhibitor **5**[31] was accomplished within 30 min of heating with an isolated yield of 64% (calculated from the loading of the resin).



The aminocarbonylation pathway utilizing DBU as base is probably very similar to the one proposed with weaker bases, but one obvious difference concerns the release of carbon monoxide from the molybdenum hexacarbonyl complex. Addition of DBU to the reaction mixture at room temperature immediately induces a chemical liberation of carbon monoxide. At higher temperatures, this occurs instantly. This reactivity is clearly demonstrated in the temperature−pressure profiles pro-

(23) Investigation of the reaction parameters showed that the choice of base was crucial in the aminocarbonylation of 2-iodotoluene with aniline. Inorganic carbonate bases and tertiary aliphatic amines were nonproductive at the temperatures investigated here (50−150 °C). The nucleophilic catalysts imidazole and DMAP were effective at high temperatures (150 °C), but the use of DBU as base furnished a dramatically improved reaction rate, which allowed substantially lower temperatures. Palladium acetate afforded a slightly superior catalytic system compared to Pd/C and phosphine containing pre-catalysts. The etherous solvents diglyme, DME, dioxane, and THF were all more efficient than DMF, MeCN, or toluene. THF was the preferred choice because of the easy access to freshly distilled solvent and the simple removal from the reaction mixture.

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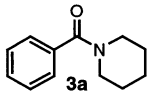
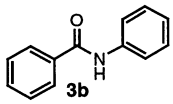
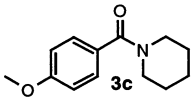
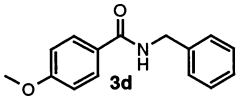
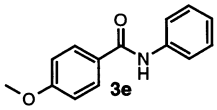
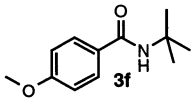
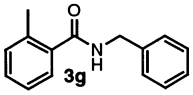
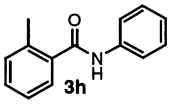
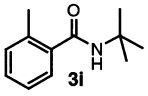
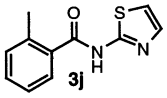
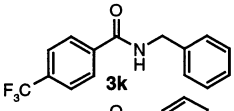
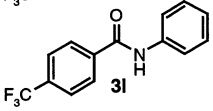
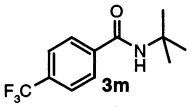
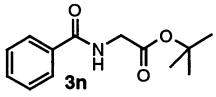
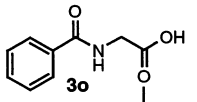
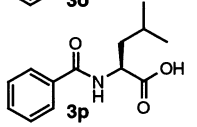
TABLE 2. Rapid Palladium-Catalyzed Aminocarbonylation Reactions with $Mo(CO)_6$ as a CO Source

1a Ph-I
1b 4-MeO-Ph-I
1c 4-MeO-Ph-Br
1d 2-Me-Ph-I
1e 2-Me-Ph-Br
1f 4-CF_3-Ph-I
1g 4-CF_3-Ph-Br

2a Piperidine
2b Aniline
2c Benzylamine
2d *tert*-Butylamine
2e 2-Aminothiazole
2f H-Gly-O*t*Bu · HCl
2g H-Gly-OH
2h H-L-Leu-OH

Entry[a]	Starting material		Product	Method	Yield[b] (%)
1	**1a**	**2a**	 **3a**	A	81
2	**1a**	**2b**	 **3b**	A	84
3	**1b**	**2a**	 **3c**	A	88
4	**1b**	**2c**	 **3d**	A	81
5	**1c**	**2c**		B	92
6	**1b**	**2b**	 **3e**	A	87
7	**1c**	**2b**		B	68
8	**1c**	**2d**	 **3f**	B	44
9	**1d**	**2c**	 **3g**	A	83,87[c]
10	**1e**	**2c**		B	83
11	**1d**	**2b**	 **3h**	A	84,81[c]
12	**1e**	**2b**		B	85
13	**1d**	**2d**	 **3i**	A	53
14	**1e**	**2d**		B	39
15	**1d**	**2e**	 **3j**	A	42
16	**1e**	**2e**		B	<5
17	**1g**	**2c**	 **3k**	B	95
18	**1f**	**2b**	 **3l**	A	86
19	**1g**	**2b**		B	53
20	**1g**	**2d**	 **3m**	B	35
21	**1a**	**2f**	 **3n**	A	64[d]
22	**1a**	**2g**	 **3o**	A	50[d]
23	**1a**	**2h**	 **3p**	A	46[d,e]

[a] The reactions were performed in 0.40 mmol scale. Method A: A reaction vessel was charged with dry THF (1.0 mL), Ar−I (1.0 equiv), amine (3.0 equiv), $Mo(CO)_6$ (1.0 equiv), DBU (3.0 equiv), and $Pd(OAc)_2$ (10 mol %). The reaction mixture was thereafter microwave heated to 100 °C for 15 min. Method B: As method A but with Ar−Br (1.0 equiv), palladacycle **4** (5.0 mol %), and microwave heating to 150 °C for 15 min. [b] Isolated yield, >95% pure according to GC−MS or ^{1}H NMR. [c] Synthesized with conventional heating (metal heating block, 100 °C, 15 min). [d] DBU (6.0 equiv). Acids **3o** and **3p** purified by LC−MS. [e] No racemization detected.

vided in Figure 1. In the presence of both DBU and $Mo(CO)_6$ (A and B), the pressure increases to almost 4 bar upon heating to 100 °C. For the preparative palladium-catalyzed reaction B, the pressure increased extremely rapidly.[32] The decrease in pressure with irradiation time indicates the consumption of CO in the carbonylation reaction (Table 2, entry 11). Control experiments C and D revealed that the pressure without DBU or $Mo(CO)_6$ never exceeded 2.0 bar.

With other investigated bases,[33] much lower reaction pressures were observed. Therefore, the higher conversions and yields obtained with poor amino nucleophiles using the DBU-based conditions might partly be explained by an accelerated liberation of carbon monoxide. In particular, the aminocarbonylations performed at 100 °C (condition A) require DBU as base.

In an attempt to study the CO-liberation process, $Mo(CO)_6$ was heated in a large excess of DBU until gas release subsided. With addition of isohexane, a labile yellow molybdenum complex precipitated. Infrared spectroscopy and combustion elemental analysis indicate that structure **6** was formed (eq 2). Unfortunately, the decomposition of the CO-liberating complex **6** in solution prevented a thorough NMR and MS analysis but analytical LC−MS of reaction mixtures from Table 1 display a peak with the same retention time as complex **6**. Furthermore, direct high-resolution FAB-MS of precipitated **6** identifies two ions corresponding to $(\mathbf{6} - \text{DBU})^+$ and $(\mathbf{6} - \text{DBU} - \text{CO})^+$ respectively. Against this background,

(32) Repeated experiments clearly proved that the precatalyst, $Pd(OAc)_2$, was responsible for the immediate CO-release illustrated in Figure 1, profile B. The omission of **1d** or **2b** did not affect the pressure.

(33) Using aqueous potassium carbonate, triethylamine, 1,2,2,6,6-pentamethylpiperidine, or **2c** as base in the aminocarbonylation of **1d** with **2c** at 100 °C, 15 min, afforded less than 10% conversion of **1d** and little or no increase in pressure. DMAP was able to release CO, but the conversion was still low under these conditions.

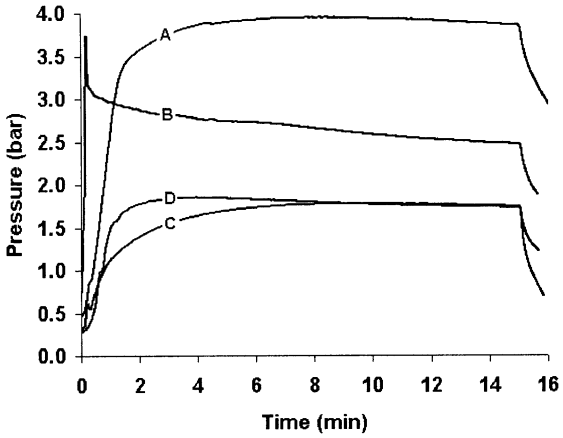


FIGURE 1. Pressure profiles from microwave heating at 100 °C with a power of 0−300 W: (A) $Mo(CO)_6$ (0.40 mmol), DBU (3 equiv) in THF (1 mL); (B) preparative synthesis of **3h**, entry 11 (conditions A); (C) as B but without $Mo(CO)_6$; (D) as B but without DBU.

it seems reasonable that **6** is formed as a labile CO-releasing intermediate in the DBU-promoted aminocarbonylation reaction.

$$Mo(CO)_6 + DBU\ (excess) \xrightarrow{\Delta} \underset{\mathbf{6}}{Mo(DBU)_2(CO)_4} + 2CO \quad (2)$$

The formation of **6**, and its relatively poor stability compared to $Mo(CO)_6$,[34] explains the DBU-accelerated CO release from the reaction cocktail. We have at present no viable theory for the mechanism of the extremely rapid CO-liberation in the presence of both DBU and palladium acetate (Figure 1, profile B).

In reactions with weakly nucleophilic amines and aryl iodides or bromides, this improved high-speed aminocarbonylation method affords useful yields of benzamides after only 15 min reaction time. The base DBU accelerates the CO release from $Mo(CO)_6$ and improves the outcome of the reaction. In addition, a possible explanation for the effect of DBU on the rate of CO liberation from $Mo(CO)_6$ is suggested. Given the experimental convenience by employing a condensed carbon monoxide source and the combination of THF and DBU, this microwave protocol should be of importance for sluggish high-throughput carbonylation applications.

Experimental Section

General Procedure A. Aminocarbonylation of Aryl Iodides. A 0.5−2.0 mL process vial was charged with an aryl iodide (0.40 mmol) and $Pd(OAc)_2$ (9.0 mg, 0.040 mmol), $Mo(CO)_6$ (0.106 g, 0.40 mmol), amine (1.2 mmol), DBU (0.180 mL, 1.2 mmol), and dry THF (1.0 mL). The vial was immediately capped with a Teflon septum under air and irradiated with microwaves to 100 °C for 15 min. After cooling, the reaction mixture was filtered through a short Celite pad, and the solvent, excess DBU, and if possible, excess amine were removed under reduced pressure. The residue was purified by silica gel flash chromatography (0−1% MeOH in $CHCl_3$) to give the desired pure amides **3** (>95% by GC−MS or ^1H NMR).

General Procedure B. Aminocarbonylation of Aryl Bromides. A 0.5−2.0 mL process vial was charged with an aryl bromide (0.40 mmol) and palladacycle **4** (18.8 mg, 0.020 mmol), $Mo(CO)_6$ (0.106 g, 0.40 mmol), amine (1.2 mmol), DBU (0.180 mL, 1.2 mmol), and dry THF (1.0 mL). The vial was immediately capped with a Teflon septum under air and irradiated with microwaves to 150 °C for 15 min. After cooling, the reaction mixture was filtered through a short Celite pad, and the solvent, excess DBU, and if possible, excess amine were removed under reduced pressure. The residue was purified by silica gel flash chromatography (0−1% MeOH in $CHCl_3$) to give the desired pure amides **3** (>95% by GC−MS or ^1H NMR).

2-Methyl-*N*-thiazol-2-ylbenzamide (3j). The title compound was obtained as a colorless solid in 42% yield (36.7 mg) from **1d**: MS *m*/*z* (relative intensity, 70 eV) 218 (M^+, 9), 203 (11), 119 (100), 91 (83); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.6 Hz, 1.8 Hz, 1H), 7.47 (dt, J = 7.6 Hz, 1.8 Hz, 1H), 7.28−7.37 (m, 2H), 6.85 (d, J = 3.8 Hz), 6.46 (d, J = 3.8 Hz), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 160.4, 137.4, 135.9, 134.2, 131.4, 131.2, 127.9, 126.1, 113.1, 20.0; IR (KBr, cm^{-1}) 3160, 1685, 1560. Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.5; H, 4.9; N, 12.6.

***N*-Benzyl-4-trifluoromethylbenzamide (3k)** The title compound was obtained as a white solid in 95% yield (106 mg) from **1g**: MS *m*/*z* (relative intensity, 70 eV) 279 (M^+, 65), 173 (100), 145 (61); ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 and 7.67 (AA′BB′ system, 4H), 7.25−7.39 (m, 5H), 6.60 (br s, 1H), 4.64 (d, J = 5.7 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.2, 137.8, 137.7, 133.4 (q, $^2J_{C-F}$ = 33 Hz), 129.0, 128.0, 127.9, 127.6, 125.7 (q, $^3J_{C-F}$ = 4 Hz), 123.7 (q, $^1J_{C-F}$ = 273 Hz), 44.4; IR (neat, cm^{-1}) 3270, 1640. Anal. Calcd for $C_{15}H_{12}F_3NO$: C, 64.51; H, 4.33; N, 5.02. Found: C, 64.5; H, 4.4; N, 5.0.

***N*-Benzyl-4-sulfamoylbenzamide (5)**[31] 4-Iodobenzenesulfonamide Rink amide resin (Novabiochem; 200 mg, loading 0.59 mmol/g, 0.12 mmol), $Mo(CO)_6$ (158 mg, 0.60 mmol), $Pd(OAc)_2$ (13.5 mg, 0.060 mmol), benzylamine (0.47 mL, 3.6 mmol), and 2.0 mL of THF were added to a 2.0−5.0 mL process vial. The vial was capped with a Teflon septum under air, DBU (0.54 mL, 3.6 mmol) was added by syringe through the septum, and the reaction was irradiated with microwaves to 100 °C for 30 min. After cooling, the resin was filtered and washed with DMF (4×) and CH_2Cl_2 (4×). The resin was treated with 20% TFA/CH_2Cl_2 for 15 min and filtered, and the eluent was evaporated under reduced pressure. The crude was washed with a small amount of isohexane to remove traces of the linker and then dried under reduced pressure to give the title compound as a white solid in 64% yield (21.8 mg).

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Supporting Information Available: Experimental details, spectroscopic data and references for compounds **3a**−**i**,**3l**−**p**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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