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Convenient Method for the Preparation of Weinreb Amides via Pd-Catalyzed Aminocarbonylation of Aryl Bromides at Atmospheric Pressure

Joseph R. Martinelli, Dominique M. M. Freckmann, and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

sbuchwal@mit.edu

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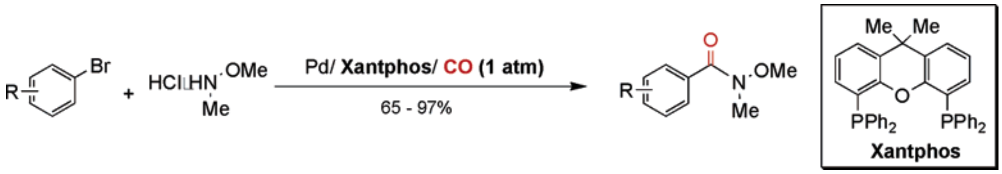
ABSTRACT



The direct transformation of aryl bromides into the corresponding Weinreb amides via Pd-catalyzed aminocarbonylation at atmospheric pressure is reported.

N-Methoxy-*N*-methyl amides (Weinreb amides) are well-established acylating agents.[1] Since the original report by Nahm and Weinreb in 1981,[2] significant effort has been devoted toward the development of mild and general methods for their preparation. The ability of Weinreb amides to undergo selective addition of one equivalent of a variety of organometallic reagents is key to their utility. The importance of these amides as reliable and general acylating agents is reinforced by the frequency with which they appear in advanced synthetic intermediates.[1,3]

To access complex structures containing Weinreb amides more readily, new, mild and general means for their preparation are required. The conversion of acid chlorides[1c,2] to Weinreb amides is straightforward. In addition, esters[4] are also commonly employed precursors. Carboxylic acids can also be converted into the corresponding Weinreb amides by a number of one-pot protocols.[5] Furthermore, methods have been reported for the conversion of lactones, amides, and anhydrides to Weinreb amides.[1c] Murakami has also developed a strategy for the synthesis of vinyl and aryl Weinreb amides using a Stille-type cross-coupling of *N*-methoxy-*N*-methylcarbamoyl chloride with vinyl or aryl stannanes.[6]

Since its initial discovery by Heck in 1974,[7] the three-component coupling of an aryl halide, carbon monoxide, and a nucleophile has been developed to allow the selective synthesis of benzannulated heterocycles[8] and aromatic acyl

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(1) For reviews, see: (a) Khlestkin, V. K.; Mazhukin, D. G. *Curr. Org. Chem.* **2003**, *7*, 967. (b) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340. (c) Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15.

(2) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(3) (a) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001. (b) Sha, C.-K.; Huang, S.-J.; Zhan, Z.-P. *J. Org. Chem.* **2002**, *67*, 831.

(4) (a) Colobert, F. C.; Des Mazery, R.; Solladié, G.; Carreño, M. C. *Org. Lett.* **2002**, *4*, 1723. (b) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

(5) (a) Woo, J. C. S.; Fenster, E.; Dake, G. R. *J. Org. Chem.* **2004**, *69*, 8984. (b) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534. (c) Banwell, M.; Smith, J. *Synth. Commun.* **2001**, *31*, 2011. (d) Tunoori, A. R.; White, J. M.; Georg, G. I. *Org. Lett.* **2000**, *2*, 4091. (e) Gibson, C. L.; Hanada, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1281. (f) Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synth. Commun.* **1990**, *20*, 1105.

(6) Murakami, M.; Hoshino, Y.; Ito, H.; Ito, Y. *Chem. Lett.* **1998**, 163.

(7) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

(8) (a) Perry, R. J.; Wilson, B. D. *Organometallics* **1994**, *13*, 3346. (b) Perry, R. J.; Wilson, B. D. *J. Org. Chem.* **1993**, *58*, 7016. (c) Perry, R. J.; Wilson, B. D.; Miller, R. J. *J. Org. Chem.* **1992**, *57*, 2883.

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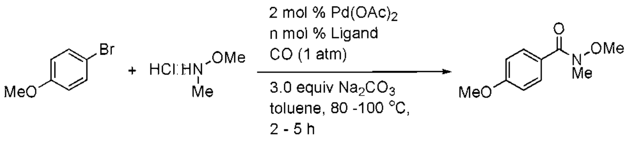
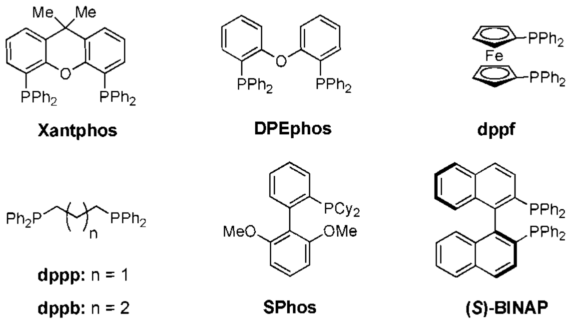
derivatives such as esters,[7a,9a] β-ketoesters,[9b] amides,[7b,9c,d] α-ketoamides,[9e] ketones,[9f] aldehydes,[9g] and anhydrides.[9h] Despite the considerable attention that aminocarbonylation reactions have received, there is, to our knowledge, only one example of a Weinreb amide synthesized in such a way. This reaction was reported, but not highlighted in the main text, by Zhuang and co-workers at Merck.[10] Herein, we report a general Pd-catalyzed process for the conversion of aryl bromides to Weinreb amides that can be carried out at 1 atm of carbon monoxide.

Table 1. Aminocarbonylation of 4-Bromoanisole Using Various Ligands[a]



entry	n mol %	Ligand	Bite Angle	T (°C)	time	% Conversion[b]	% Yield[b]
1	8	PPh$_3$	145[c]	100	2 h	< 1	0
2	5	SPhos	217[c,d]	100	2 h	< 1	0
3	2.2	(*S*)-BINAP	92	100	2 h	< 1	0
4	2.2	dppp	95	100	2 h	< 1	0
5	2.2	dppb	99	100	2 h	< 1	0
6	2.2	dppf	106	100	2 h	< 1	0
7	2.2	DPEphos	108	100	2 h	< 1	0
8	2	Xantphos	110	100	2 h	36	30
9	2	Xantphos	110	100	5 h	90	87
10[e]	2	Xantphos	110	80	5 h	100	89[f]



[a] Reaction conditions: 2 mol % of Pd(OAc)$_2$, *n* mol % of ligand, 1 mmol of 4-bromoanisole, 1.5 mmol of amine, and 3 mmol of base in toluene (2 mL) at 100 °C. [b] Determined by GC; average of two runs. [c] Cone angles. [d] See ref 10c. [e] Reaction was run at 80 °C for 5 h. [f] Isolated yield; average of two runs.

Guided by the literature and our own results, we expected the most efficient ligands for the aminocarbonylation process to be bidentate phosphines possessing a large bite angle.[9a] Thus, we began our studies by examining the reaction shown in Table 1 using a series of bidentate phosphines as ligands. In addition, on the basis of our success using biaryl monophosphines in a variety of Pd-catalyzed processes,[11] we also included SPhos as a representative of this ligand class. Despite the success of PPh$_3$ at higher pressures, reactions that employed PPh$_3$ or SPhos (Table 1, entries 1 and 2) were both ineffective under the atmospheric aminocarbonylation reaction conditions examined. A number of bidentate ligands that have been shown to be useful for other Pd-catalyzed processes were completely ineffective as supporting ligands as well. These included (*S*)-BINAP,[9a,12a] dppp,[12b] dppb,[12c] dppf,[9c,f] and DPEphos.[12d] These are ligands whose bite angles span a range from 92° to 108°.[13] Only van Leeuwen's Xantphos ligand,[14] with the largest bite angle (110°), was effective for the synthesis of Weinreb amides from the corresponding aryl bromides. We began our work using a Pd/Xantphos ratio of 1:1 based on previous work in our laboratory that showed excess Xantphos to be deleterious in Pd-catalyzed C−N bond forming reactions.[15] Using Xantphos as the supporting ligand, the reaction at 100 °C resulted in 36% conversion and 30% of the desired product after only 2 h. Unfortunately, allowing the reaction to run for 5 h at 100 °C resulted in only 90% conversion and 87% of the desired product. Surprisingly, lowering the temperature to 80 °C and allowing the reaction to run for 5 h led to the complete consumption of the aryl bromide and 89% isolated yield of the desired product. This unexpected result may be attributed to enhanced catalyst stability at lower temperatures. With these conditions in hand, we explored the range of this method.

To determine the scope of this process, a set of aryl bromides were examined as substrates with which the method demonstrated good generality. This was exemplified by the high-yield transformation of 3-bromonitrobenzene, 3-bromobenzonitrile, and 4-bromo-2-fluorobenzonitrile to the corresponding Weinreb amides (Table 2, entries 1−3). Similarly, a *tert*-butyl carbamate group was untouched during the aminocarbonylation of *tert*-butyl *N*-(4-bromophenyl)-carbamate (Table 2, entry 6). The high yield realized with a methyl ester-containing substrate was surprising (Table 2,

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(9) (a) Albaneze-Walker, J.; Bazaral, C.; Leavey, T.; Dormer, P. G.; Murry, J. A. *Org. Lett.* **2004**, *6*, 2097. (b) Lapidus, A. L.; Eliseev, O. L.; Bondarenko, T. N.; Sizan, O. E.; Ostapenko, A. G.; Beletskaya, I. P. *Synthesis* **2002**, *3*, 317. (c) Kumar, K.; Zapf, A.; Michalik, D.; Tillack, A.; Heinrich, T.; Böttcher, H.; Arlt, M.; Beller, M. *Org. Lett.* **2004**, *6*, 7. (d) Atkins, R. J.; Banks, A.; Bellingham, R. K.; Breen, G. F.; Carey, J. S.; Etridge, S. K.; Hayes, J. F.; Hussain, N.; Morgan, D. O.; Oxley, P.; Passey, S. C.; Walsgrove, T. C.; Wells, A. S. *Org. Process Res. Dev.* **2003**, *7*, 663. (e) Iizuka, M.; Kondo, Y. *Chem. Commun.* **2006**, *16*, 1739. (f) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726. (g) Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riermeier, T.; Groβ, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 154. (h) Pri-Bar, I.; Alper, H. *J. Org. Chem.* **1989**, *54*, 36.

(10) Zhuang, L.; Wai, J. S.; Embrey, M. W.; Fisher, T. E.; Egbertson, M. S.; Payne, L. S.; Guare, J. P., Jr.; Vacca, J. P.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Witmer, M. V.; Moyer, G.; Schleif, W. A.; Gabryelski, L. J.; Leonard, Y. M.; Lynch, J. J., Jr.; Michelson, S. R.; Young, S. D. *J. Med. Chem.* **2003**, *46*, 453.

(11) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978. (c) Barder, T. E.; Buchwald, S. L. unpublished results.

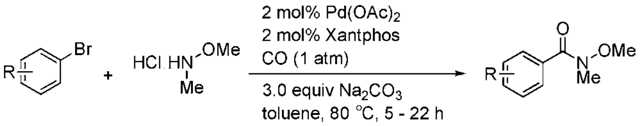
(12) (a) Sadighi, J. P.; Singer, R. A.; Buchwald, S. B. *J. Am. Chem. Soc.* **1998**, *120*, 4960. (b) Scalone, M.; Vogt, P. (Hoffmann−La Roche) EP 385210 A2, 1990. (c) Beller, M.; Mägerlein, W.; Indolese, A. F.; Fischer, C. *Synthesis* **2001**, 1098. (d) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327.

(13) (a) Casey, C. P.; Whiteker, G. T. *Isr. J. Chem.* **1990**, *30*, 299. (b) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

(14) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.

(15) Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, *25*, 82.

Table 2. Conversion of Aryl Bromides to Weinreb Amides via Pd-Catalyzed Aminocarbonylation at 1 atm[a]



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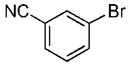
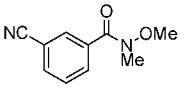
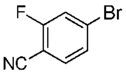
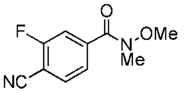
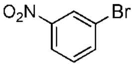
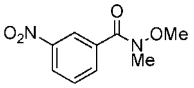
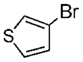
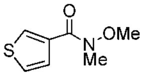
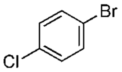
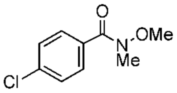
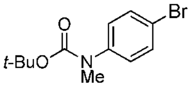
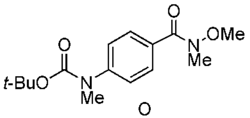
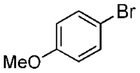
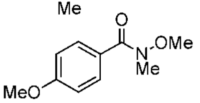
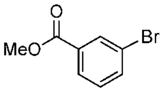
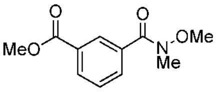
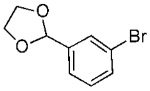
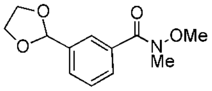
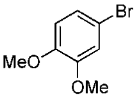
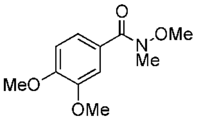
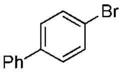
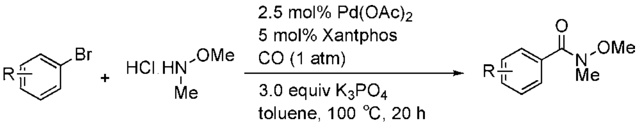
1			88
2			90
3			87
4			91
5			87
6			95
7			89
8			88
9			93[c]
10			89[c]
11			94[c]

[a] Reaction conditions: 2 mol % of Pd(OAc)$_2$, 2 mol % of Xantphos, 1 mmol of aryl bromide, 1.5 mmol of amine, and 3 mmol of Na$_2$CO$_3$ in toluene (2 mL) at 80 °C. [b] Yields are an average of two runs. [c] 3 mmol of Et$_3$N was used as base.

Table 3. Conversion of Ortho-Substituted Aryl Bromides to Weinreb Amides via Pd-Catalyzed Aminocarbonylation at 1 atm[a]



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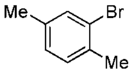
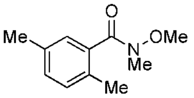
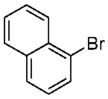
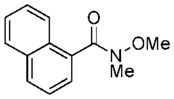
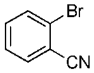
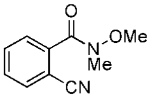
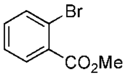
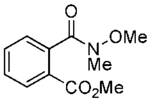
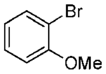
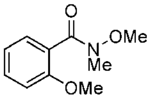
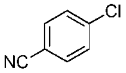
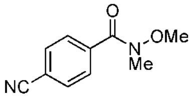
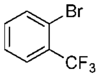
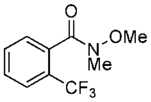
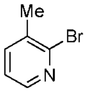
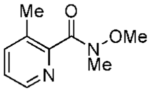
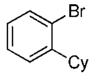
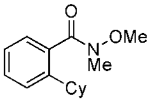
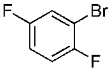
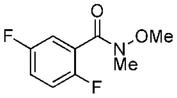
1			87
2			97
3			84
4			80[c]
5			81[c]
6			74[d]
7			94[e]
8			78[e]
9			90[f]
10			65[g]

[a] Reaction conditions: 2.5 mol of % Pd(OAc)$_2$, 5 mol % of Xantphos, 1 mmol of aryl bromide, 1.5 mmol of amine, and 3 mmol of K$_3$PO$_4$ in toluene (2 mL) at 100 °C. [b] Yields are an average of two runs. [c] 3 mol % of Pd(OAc)$_2$ was used. [d] 3 mol % of Pd(OAc)$_2$ was used at 105 °C. [e] 3 mol % of Pd(OAc)$_2$ was used in *m*-xylene (2 mL) at 110 °C. [f] 3 mol % of Pd(OAc)$_2$ was used in *m*-xylene (2 mL) at 120 °C. [g] 2.5 mol % of Pd(OAc)$_2$ was used in *m*-xylene (2 mL) at 110 °C.

entry 8); no product resulting from addition of the hydroxylamine to the ester group was detected. It is also important to note that the selective aminocarbonylation of aryl bromides can be achieved in the presence of aromatic fluoride and chloride groups (Table 2, entries 2 and 5). Electron-rich aryl bromides were also cleanly converted into the corresponding Weinreb amides (Table 2, entries 4, 6, 7, and 10). The reaction of 3-bromothiophene was of particular interest due to the common occurrence of the thiophene moiety in organic electronic materials.[16] Though sodium carbonate was employed as the base in most reactions shown in Table 2, it is also possible to use organic bases such as triethylamine (Table 2, entries 9−11).

Despite the wide scope indicated by the results described in Table 2, there were several substrates that were not successfully converted to the corresponding Weinreb amides using this procedure. Specifically, *ortho*-substituted aryl

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(16) Wong, K.-T.; Hwu, T.-Y.; Balaiah, A.; Chao, T.-C.; Fang, F.-C.; Lee, C.-T.; Peng, Y.-C. *Org. Lett.* **2006**, *8*, 1415.

bromides were not satisfactorily converted to product. Given that (Xantphos)Pd-based catalyst systems can be used to transform *ortho*-substituted aryl bromides in C−N coupling reactions,[17] it is likely that the problematic step in this reaction involves the nucleophilic addition of the amine to the Pd−acyl intermediate.[18] If this process is sluggish, the Pd−acyl intermediate could be vulnerable to putative decomposition processes leading to an inefficient overall transformation.

In an effort to overcome this limitation, the reaction conditions were reevaluated. During optimization of the transformation of the test substrate, 2-bromo-*p*-xylene (Table 3, entry 1), it was found that use of potassium phosphate as the base with a Pd/Xantphos ratio of 1:2 at 100 °C led to complete conversion of the starting aryl bromide with formation of a high yield of the desired product. This new procedure was also effective for a variety of other *ortho*-substituted substrates. Both 1-bromonaphthalene and 2-bromobenzonitrile were efficiently converted to the corresponding Weinreb amides (Table 3, entries 2 and 3). A slightly higher quantity of catalyst (3 mol % of Pd, 6 mol % of Xantphos) was required to achieve full conversion in the case of (2-bromo)methylbenzoate and 2-bromoanisole (Table 3, entries 4 and 5). In the former case, the lower reactivity may possibly be attributed to the ability of the *ortho*-substituent to coordinate to the Pd center. The same quantity of catalyst at a slightly higher temperature (105 °C) was also effective for the aminocarbonylation of the electron-poor aryl chloride, 4-chlorobenzonitrile (Table 3, entry 6).

Although these conditions were effective for most *ortho*-substituted aryl bromides, substrates with large *ortho*-substituents and/or certain functional groups remained unreactive. The simplest way to overcome this lack of reactivity was to use *m*-xylene as solvent and increase the reaction temperature to 110 or 120 °C. In this way, substrates such as 2-bromobenzotrifluoride, 2-bromo-3-methylpyridine, 2-cyclohexylbromobenzene and 2,5-difluorobromobenzene were successfully transformed into the corresponding Weinreb amides (Table 3, entries 7−10).

In conclusion, a protocol for the direct transformation of aryl bromides into the corresponding Weinreb amides via an aminocarbonylation protocol at atmospheric pressure has been developed. Electron-deficient, -neutral, and -rich aryl bromides were all efficiently transformed to product. Furthermore, the process tolerates a wide variety of functional groups, is mild, and is operationally simple.

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Supporting Information Available: Detailed experimental procedures and characterization data of each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061902T

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[17] Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.

[18] (a) Milstein, D. *Acc. Chem. Res.* **1988**, *21*, 428. (b) Ozawa, F.; Sugimoto, T.; Yuasa, Y.; Santra, M.; Yamamoto, T.; Tamamoto, A. *Organometallics* **1984**, *3*, 683. (c) Ozawa, F.; Suglmoto, T.; Yamamoto, T.; Tamamoto, A. *Organometallics* **1984**, *3*, 692.