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Palladium-Catalyzed Approach to Primary Amides Using Nongaseous Precursors

Dennis U. Nielsen, Rolf H. Taaning, Anders T. Lindhardt,* Thomas M. Gøgsig, and Troels Skrydstrup*

Center for Insoluble Protein Structure (inSPIN), Department of Chemistry, Interdisciplinary Nanoscience Center, Aarhus University, Langelandsgade 140, 8000 Aarhus C, Denmark

ts@chem.au.dk

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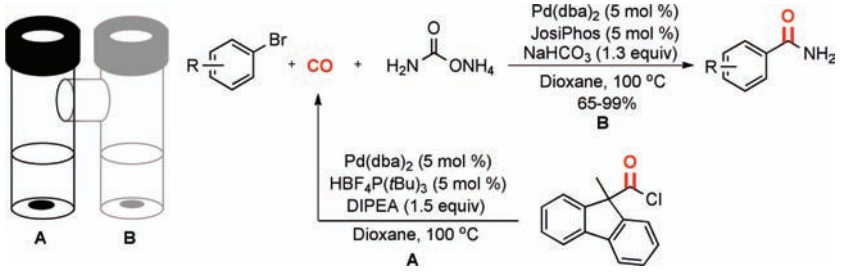
ABSTRACT



A simple protocol is reported for the preparation of primary aryl amides under Pd-catalyzed carbonylation chemistry applying a two-chamber system with crystalline and nontransition metal based sources of carbon monoxide and ammonia. The method is suitable for the synthesis of a number of primary amides with good functional group tolerance. Incorporation of ^{13}CO into the primary amide group was also found to be effective making this approach useful for accessing carbon isotope labeled derivatives.

Improved methods for the formation of amides are of key value for the pharmaceutical industry due to the high occurrence of this functional group in a plethora of biologically important compounds.[1] Direct functionalization of aromatic halides using transition metal catalyzed carbonylation chemistry selecting an amine as the nucleophile is a very useful approach for accessing amides. Such methodology typically offers mild conditions allowing the introduction of the amide to be performed at almost any intermediate in a linear synthesis and in the presence of a wide variety of functional groups.

The application of carbonylation chemistry for the synthesis of primary amides has not received similar attention as that for the preparation of secondary and tertiary amides. This reluctance is hardly due to the chemical insignificance of this functionality being an important fragment of plastics, detergents, and lubricants, as well as representing a structural motif in many bioactive compounds. Furthermore, primary amides act as synthetic platforms to primary amines upon reduction, or nitriles by dehydration.[2] However, the required handling of two gases, explicitly carbon monoxide (CO) and ammonia, which are toxic, flammable, or corrosive could potentially explain this reluctance.[2] To avoid the handling of ammonia gas in the palladium-catalyzed synthesis of primary amides, several groups have successfully applied ammonia surrogates such as hexamethyldisilazane,[3]

(1) Bernard, C. F. J. *Organometallics* **2008**, *27*, 5402.

(2) For a few examples of the use of CO and ammonia in palladium-catalyzed carbonylation of aryl halides, see: (a) Wu, X.-F.; Neumann, H.; Beller, M. *Chem.—Asian. J.* **2010**, *5*, 2168. (b) Wu, X.-F.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2010**, *16*, 9750.

(3) Morera, E.; Ortar, G. *Tetrahedron Lett.* **1998**, *39*, 2835.

(4) (a) Takács, A.; Abreu, A. R.; Peixoto, A. F.; Pereira, M.; Kollár, L. *Synth. Commun.* **2009**, *39*, 1534. (b) Csajági, C.; Borcsek, B.; Niesz, K.; Kovács, I.; Székelhidi, Z.; Bajko, Z.; Urge, L.; Darvas, F. *Org. Lett.* **2008**, *10*, 1589. (c) Neumann, H.; Brennführer, A.; Groβ, P.; Reirmeier, T.; Almena, J.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 1255. (d) Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327. (e) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750.

(5) (a) Salvadori, J.; Balducci, E.; Zaza, S.; Petricci, E.; Taddei, M. *J. Org. Chem.* **2010**, *75*, 1841. (b) Cardullo, F.; Donati, D.; Merlo, G.; Paio, A.; Petricci, E.; Taddei, M. *Synlett* **2009**, *1*, 47. (c) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102. (d) Tambade, P. J.; Patil, Y. P.; Bhanushali, M. J.; Bhanage, B. M. *Synthesis* **2008**, *15*, 2347. (e) Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460.

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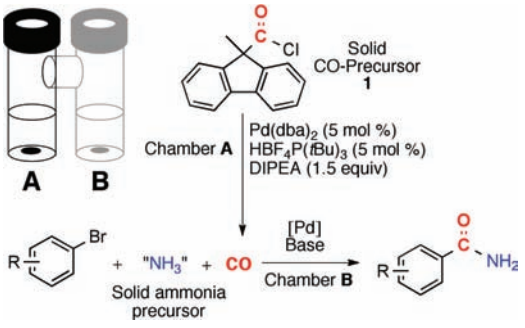
tert-butyl amine,[4] benzyl amine,[4e,5] allyl amine,[6] and others,[7] which upon workup or simple deprotection would release the primary amide functionality. Alternatively, the groups of Bernard and Skoda-Földes utilized the *in situ* release of ammonia from solid precursors such as NH_4Cl and ammonium carbamate.[1,8] Especially, the method developed by Larhed et al. deserves attention, whereby $Mo(CO)_6$ acts as the source of CO while simultaneously performing the *in situ* reduction of hydroxylamine to ammonia during the palladium-catalyzed formation of primary amides under microwave irradiation.[9] Other methods utilize the decomposition of formamides into CO and ammonia/amines; however, this decomposition only occurs at high temperatures in the presence of strong bases.[10]

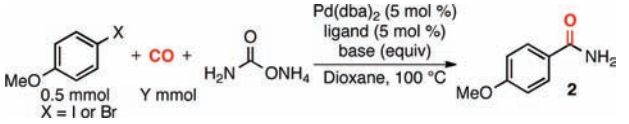
Scheme 1. *Ex situ* Generation of CO for the Synthesis of Primary Amides in a Two-Chamber System



Recently we reported on a novel approach to the safe release, handling, and incorporation of CO from a solid acid chloride precursor such as **1** in a sealed two-chamber system.[11] CO is produced *ex situ*, which avoids the complication of having the CO-precursor or CO-synthon mixed in with the reagents and thereby retaining a high chemical scope in CO-chemistry (Scheme 1). Already having established the method in carbonylative Mizoroki–Heck couplings[12] as well as alkoxy- and aminocarbonylations and inspired by the above-mentioned ammonia synthons, we set forth to investigate its application for the synthesis of primary amides.

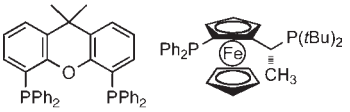
In this paper, we wish to report a protocol for the formation of primary amides based on palladium-catalyzed aminocarbonylation of aromatic bromides using solid nongaseous precursors for both CO and ammonia. CO was successfully applied in near-stoichiometric and substoichiometric quantities making this approach suitable for ^{13}C-isotope labeling using a ^{13}C-labeled acid chloride as the CO-source.

Table 1. Optimization of the Aminocarbonylation[a]



entry	$[NH_3]$/ equiv	CO/ mmol	L	base/ equiv	conv [%][b]/ (yield) [%]
1[c,d]	1	0.5	**3**	NaOAc (1.3)	81 (62)
2[c,d]	1.1	0.5	**3**	NaOAc (1.4)	71
3[c,d]	1.1	0.75	**3**	$NaHCO_3$ (1.4)	100 (62)[e]
4[c,d]	1	0.33	**4**	$NaHCO_3$ (1.4)	29[e]
5[d]	1	0.33	**4**	$NaHCO_3$ (1.3)	51[e]
6	2	0.33	**4**	$NaHCO_3$ (1.3)	88[e]
7[d]	2	0.33	**4**	$NaHCO_3$ (1.3)	68[e]
8	2	0.33	**4**	$NaHCO_3$ (2.2)	74[e]
9	2	0.33	**4**	Na_2CO_3 (2.2)	61[e]
10	1.1	0.33	**4**	$NaHCO_3$ (1.4)	86[e]
11	1.3	0.65	**4**	$NaHCO_3$ (1.3)	95 (93)
12[f]	1.3	0.65	**4**	$NaHCO_3$ (1.3)	93
13[g]	1.3	0.65	**4**	$NaHCO_3$ (1.3)	38

[a] Chamber A: **1** (0.Y mmol), $Pd(dba)_2$ (5 mol %), $HBF_4P(tBu)_3$ (5 mol %), DIPEA (1.5 equiv) in dioxane (3 mL). Chamber B: Iodoanisole or bromoanisole (0.5 mmol), $Pd(dba)_2$ (5 mol %), L (5 mol %) in dioxane (3 mL). [b] Determined by ^1H NMR analysis. [c] Iodoanisole used as the electrophile. [d] Reaction performed at 80 °C. [e] Based on limiting CO. [f] $Pd(dba)_2$ (3 mol %), **4** (3 mol %) [g] $Pd(dba)_2$ (1 mol %), **4** (1 mol %).



Xantphos **3** Josiphos **4**

The conditions required for the palladium-catalyzed CO-production in chamber A by decarbonylation of **1** were taken directly from our previous reports (Scheme 1 and Table 1).[11,12] Initial screenings were performed using iodoanisole as the electrophile applying NH_4Cl and ammonium carbonate[13] as the ammonia precursors. Testing PPh_3 and DPPF as ligands in combination with bases such as triethylamine, diisopropylethylamine (DIPEA), or potassium carbonate at 80 °C did lead to the desired amide albeit in low yields (results not shown). Changing the ammonia precursor to ammonium carbamate as reported

(6) Appukkuttan, P.; Axelsson, L.; Eycken, E.; Van der.; Larhed, M. *Tetrahedron Lett.* **2008**, *49*, 5625.
(7) Ueda, K.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 10722.
(8) Balogh, J.; Mahó, S.; Háda, V.; Kollár, L.; Skoda-Földes, R. *Synthesis* **2008**, *19*, 3040.
(9) Wu, X.; Wannberg, J.; Larhed, M. *Tetrahedron* **2006**, *62*, 4665.
(10) (a) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Comb. Chem.* **2003**, *5*, 82. (b) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232. (c) Schnyder, A.; Beller, M.; Mehltretter, G.; Nsenda, T.; Studer, M.; Indolese, A. F. *J. Org. Chem.* **2001**, *66*, 4311.
(11) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061.
(12) Hermange, P.; Gøgsig, T. M.; Lindhardt, A. T.; Taaning, R. H.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 2444.

(13) Ammonium carbonate can either liberate 1 equiv of ammonia by reaction with base or two from the thermal decomposition of this salt.[8] In any case, all reactions were performed behind a blast shield (see Supporting Information). It should be noted though that no amide formation from the reaction of acid chloride **1** with ammonia was observed in the CO producing chamber in any of the reactions studied, suggesting that the release of CO is significantly faster than the nucleophilic acyl substitution reaction.

by the group of Sköda-Foldes and applying the ligand Xantphos (**3**) did, however, provide an 81% conversion and an isolated yield of 62% of amide **2** using NaOAc as the base (Table 1, entry 1). Changing the base to $NaHCO_3$ and increasing the loading of CO led to full conversion, but still only a 62% isolated yield was obtained (entry 3). ^1H NMR analysis of the crude reaction mixtures displayed the formation of several undesired byproducts, which was the case for all the entries applying Xantphos as the ligand.

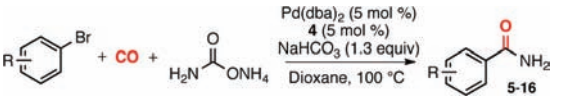
To test the influence of the CO-pressure and to ensure that this protocol would be useful for isotope labeling at all CO-levels, the loading of the acid chloride CO-precursor **1** was changed to 0.33 mmol.[5c,14] Furthermore, reports by Trogler, Bernard, and Larhed suggested that ammonia has a low nucleophilicity in combination with a strong binding to Pd(II) potentially retarding the reaction.[1,9,15] To overcome this possible problem, our attention was turned to a recent report by Hartwig in which ammonia was applied in the synthesis of anilines facilitated by ligands of the Josiphos type.[16] Applying ligand **4** under the conditions in entry 4, Table 1 only afforded a 29% conversion, but changing the electrophile to the bromoanisole led to a reaction free of undesired byproduct with a 51% conversion (entry 5). Changing the temperature to 100 °C and finetuning the loading of the base and ammonium carbamate improved the conversion to 86% (entries 6–10). Finally, increasing the CO-loading to 1.3 equiv, applying $NaHCO_3$ and ammonium carbamate in a 1:1 ratio, afforded an isolated yield of 93% of the desired primary amide **2** (entry 11). Attempts to lower the catalytic loading proved unrewarding (entries 12 and 13 respectively).

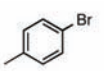
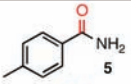
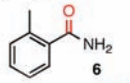
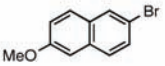
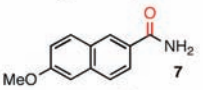
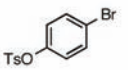
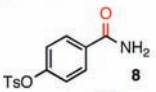
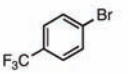
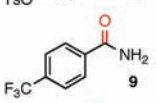
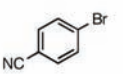
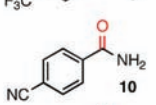
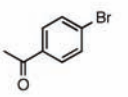
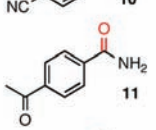
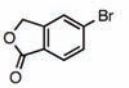
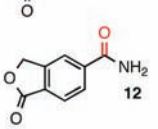
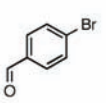
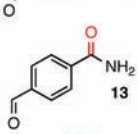
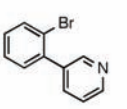
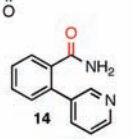
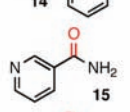
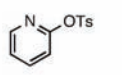
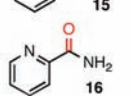
With these conditions in hand, the scope of this transformation was tested using several substituted aryl bromides (Table 2). In general, high yields were obtained in combination with excellent functional group tolerance affording the desired primary amides. Electron-rich arenes coupled well with yields attaining quantitative levels (entries 1–4).[17] Only a small drop in the isolated yield was observed when introducing a methyl group *ortho* to the halide (entry 2 vs 1).

Whereas 4-bromophenol failed in the reaction, simple protection by tosylation of the free alcohol afforded an 88% isolated yield of the desired amide. Placing electron-withdrawing groups in the *para* position did not seem to affect the reactivity as both a trifluoro- and cyano-functionality provided 87% and 90% isolated yields of the desired amides (entries 5 and 6, respectively). Nitro groups on the aryl bromide did however impede the reaction with poor conversion rates (results not shown). In addition, functionalities such as an acetyl, an ester, and even an aldehyde proved compatible with the conditions affording isolated yields of 96%, 72%, and 65% (entries 7–9), respectively

Also, a few heteroaromatic bromides were subjected to the catalytic system leading to identical isolated yields of the amides, including the synthesis of nicotinamide (entries 10 and 11). Finally, 2-pyridyl tosylate proved useful

Table 2. Synthesis of Primary Amides[a]



entry	Ar-X	product	yield [%][b]
1		 **5**	99
2		 **6**	86
3		 **7**	93
4		 **8**	88
5		 **9**	87
6		 **10**	90
7		 **11**	96
8		 **12**	72
9		 **13**	65
10		 **14**	89
11		 **15**	89
12		 **16**	77

[a] Chamber A: **1** (0.65 mmol), $Pd(dba)_2$ (5 mol %), $HBF_4P(tBu)_3$ (5 mol %), DIPEA (1.5 equiv) in dioxane (3 mL). Chamber B: Aryl bromide or tosylate (0.5 mmol), $Pd(dba)_2$ (5 mol %), **4** (5 mol %), ammonium carbamate (1.3 equiv), $NaHCO_3$ (1.3 equiv) in dioxane (3 mL). [b] Isolated yield after column chromatography.

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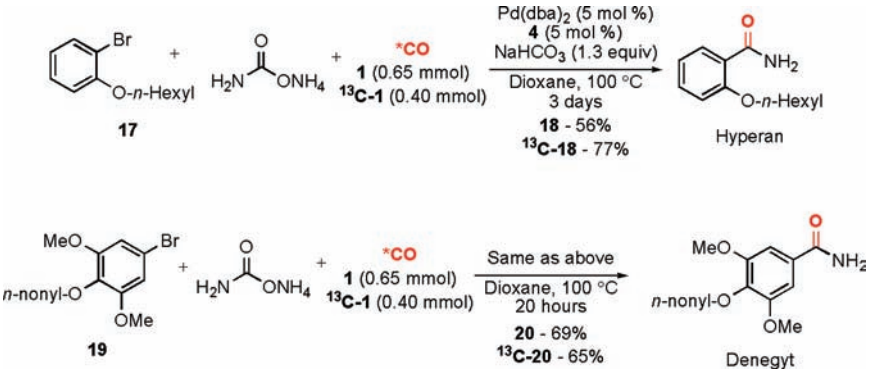
(15) Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 2520.

(16) Vo, G. D; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049.

(17) For references on electron-rich arenes enhancing CO-insertion, see: (a) Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4115. (b) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726.

Scheme 2. Synthesis and ^{13}C-Labeling of Hyperan and Denegyt



affording picolinamide in a 77% isolated yield (entry 12).[18] Placing the tosylate other than at the 2-position of the pyridine ring did not provide useful substrates for this reaction, which corresponds well with the trend seen in entry 4 of Table 2. Furthermore, aryl chlorides proved less reactive with conversion rates lower than 20% (results not shown).

As a final test for this newly developed protocol, we attempted the synthesis of two biologically relevant structures, hyperan (antifungal) and denegyt (anticonvulsant).[19,20] In addition, the technique was exploited for the isotopic labeling of these two compounds using the ^{13}C-carbonyl labeled version of the acid chloride CO-precursor **1**. The results of this work are depicted in Scheme 2. For the synthesis of hyperan (**18**), the carbonylation of the *ortho*-substituted phenyl bromide **17** required a prolonged reaction time to secure a high conversion and a good 56% isolated yield. Applying these reaction conditions to bromide **19** also allowed access to denegyt (**20**) in an isolated yield of 69%. Next, simply substituting the acid chloride CO-precursor **1** for its ^{13}C-isotope labeled derivative (**^{13}C-1**) and applying this as the overall limiting reagent under substoichiometric CO afforded the desired isotopically labeled structures in good yields of 77% and 65%, respectively (Scheme 2).

In conclusion, we have provided a simple setup for the direct formation of primary aryl amides using a two-chamber system with solid precursors for carbon monoxide and ammonia. Good functional group tolerance is also characteristic of this protocol. Our method allows for the synthesis of primary amides using essentially stoichiometric quantities of reagents, and furthermore it can be adapted to isotope labeling of the carbonyl group. Further work is in progress to examine the use of this setup for the introduction of other carbon isotopes, the work of which will be reported in due course.

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Supporting Information Available. Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for all the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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