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Incorporation of N_2 and CO into Organic Molecules: Amide Formation by Palladium-Catalyzed Carbonylation and Nitrogenation

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Nitrogen fixation is a very interesting process.[1] NH_3 has been used as a nitrogen source in various fields, and it has been synthesized from N_2 and H_2 under conditions of high pressure and high temperature using a transition metal catalyst. We have developed a novel nitrogen fixation method under very mild conditions (1 atm pressure at room temperature) using a Li−TiX_4−TMSCl system.[2] Recently, we developed a novel method for synthesizing nonsubstituted anilines from aryl halides and titanium−nitrogen complexes using a palladium catalyst.[3] It is thought that the reaction proceeds via transmetaltion of nitrogen from titanium−nitrogen complexes to a palladium complex.

Here we report the synthesis of benzamides from aryl halides, N_2, and CO. Our plan is shown in Scheme 1.

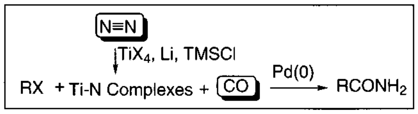
To a THF solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), DPPF (10 mol %), and NaO^tBu (3 equiv) was added a THF solution of titanium−nitrogen complexes[2a] (2 equiv), prepared from $Ti(O^iPr)_4$, Li, TMSCl, and nitrogen (1 atm), and then a THF solution of aryl halide **1a** (1 equiv) was added. The atmosphere of nitrogen was changed to an atmosphere of carbon monoxide (1 atm), and the solution was heated at reflux overnight (Scheme 2). After hydrolysis of the reaction mixture, amide **2a**, imide **3a**, and nitrile **4a**[4] were obtained in 4, 1, and 6% yields, respectively, along with aniline derivative **5a** in 16% yield (Table 1, run 1). Although the combined yields of the products obtained by the carbonylation-nitrogenation process were low (11% yield), gaseous CO and N_2 could be introduced directly into aryl halide under mild conditions.

To try to increase the yield of the desired products, the reaction was carried out under various conditions (Table 1).[5] As a solvent, DMF gave good results, and amide **2a**, imide **3a**, and *N*-formylbenzamide **6a** were obtained in 24, 11, and 26% yields, respectively (run 4). Propionitrile could also used (run 5).

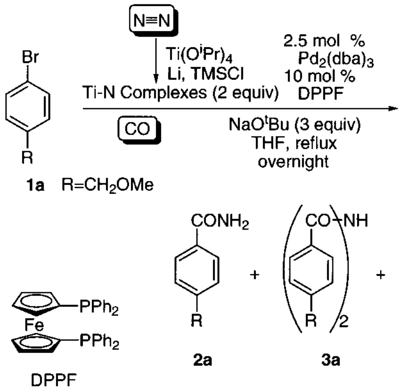
When BINAP was used as a ligand, nitrile **4a** was obtained as the main product (runs 6 and 7). The use of $Pd(OAc)_2$−PPh_3 was less efficient (run 8).

Subsequently, we chose DMF as the solvent, and the base was changed from NaO^tBu to a weak base, such as Li_2CO_3, K_2CO_3, Cs_2CO_3, $NaHCO_3$, $^iPr_2NEt$, or NEt_3. In each case, amide **2a**, *N*-formylbenzamide **6a** or acylamidine **7a**[6] was obtained, but benzimide **3a** was not produced. However, there were no remarkable differences in the combined yields of the products. Interestingly, in the absence of a base, the total yield of the products was 87% (Table 2, run 1, condition A). On the other hand, when propionitrile was used as the solvent in the absence of NaO^tBu, only a low yield of the desired products was obtained (Table 1, run 9). In this case, NaO^tBu might act as a ligand.[7]

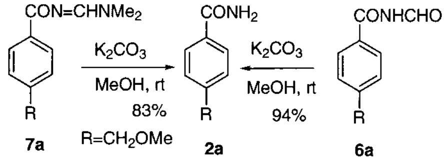
Scheme 1. Plan for Synthesis of Amide



Scheme 2. Reaction of **1a**, CO, and Titanium−Nitrogen Complexes



Scheme 3. Conversion of **6a** and **7a** into **2a**



Compound **6a** or **7a** was treated with K_2CO_3 in MeOH to give amide **2a** in good yield. This indicates that the reaction of an aryl halide with titanium−nitrogen complexes under carbon monoxide (1 atm) in the presence of a palladium catalyst gives amide **2a** and nitrile **4a** in high yields (Scheme 3).

Various aryl bromides were treated in a similar manner, and the corresponding products were obtained in good to high yields (Table 2).[8] Both the electron-donating and electron-withdrawing groups on the aromatic ring can be used.

The reaction is presumed to proceed by transmetalation of nitrogen from titanium−nitrogen complexes to acylpalladium complex **8** (Figure 1), because the reaction proceeded in the absence of a base. Then **9** is converted into amide−titanium

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[1] (a) Hidai, M.; Mizobe, Y. *Chem. Rev.* **1995**, *95*, 1115. (b) Vol'pin, M. E.; Shur, V. B. *Dokl. Akad. Nauk SSSR* **1964**, *156*, 1102. (c) Vol'pin, M. E.; Ilatovskaya, M. A.; Kosyakova, L. V.; Shur, V. B. *J. Chem. Soc., Chem. Commun.* **1968**, 1074. (d) van Tamelen, E. E.; Seeley, D.; Schneller, S.; Rudler, H.; Cretney, W. *J. Am. Chem. Soc.* **1970**, *92*, 5251. (e) van Tamelen, E. E. *Acc. Chem. Res.* **1970**, *3*, 361. (f) Yamamoto, A.; Ookawa, M.; Ikeda, S. *J. Chem. Soc., Chem. Commun.* **1969**, 841. (g) Shiina, K. *J. Am. Chem. Soc.* **1972**, *94*, 9266. (h) Mori, M.; Uozumi, Y.; Shibasaki, M.; *Tetrahedron Lett.* **1987**, *28*, 6187. (i) Uozumi, Y.; Kawasaki, N.; Mori, E.; Mori, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 3725. (j) Uozumi, Y.; Mori, M.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1991**, 81.

[2] (a) Kawaguchi, M.; Hamaoka, S.; Mori, M. *Tetrahedron Lett.* **1993**, *34*, 6907. (b) Hori, M.; Mori, M. *J. Org. Chem.*, **1995**, *60*, 1480. (c) Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Sato, Y.; Nishida M. *Angew. Chem., Int. Ed.* **1998**, *37*, 636.

[3] Hori, K.; Mori, M. *J. Am. Chem. Soc.* **1998**, *120*, 7651.

[4] Synthesis of nitrile from benzoyl chloride and N_2 has been reported. van Tamelen, E. E.; Rudler, H. *J. Am. Chem. Soc.* **1970**, *92*, 5253.

[5] Titanium−nitrogen complexes were prepared in THF. If it is desirable that the solvent be changed from THF to another solvent, an appropriate solvent is added to the THF solution of titanium−nitrogen complexes, and THF is removed upon heating.

[6] Compound **7a** would be formed from acylpalladium complex **8**, titanium−nitrogen complex and DMF as shown in Figure 1. The structure of **7a** was determined by X-ray crystallography.

[7] (a) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

[8] Typical procedure for carbonylation−nitrogenation: A solution of $Ti(O^iPr)_4$ (0.3 mL, 1 mmol), Li (69.8 mg), and TMSCl (1.27 mL, 10 mmol) in THF (15 mL) was stirred under nitrogen (1 atm) at room temperature overnight. To this solution was added DMF (5 mL), and then the excess amount of TMSCl was removed upon heating with THF. To this DMF solution was added $Pd_2(dba)_3{\cdot}CHCl_3$ (12.9 mg, 0.0125 mmol) and DPPF (28.8 mg, 0.05 mmol) and then a solution of aryl halide **1a** (100 mg, 0.5 mmol) in DMF (5 mL), and then the nitrogen atmosphere was changed to a carbon monoxide atmosphere (1 atm). The solution was warmed at 90 °C for 14 h. After hydrolysis of the reaction mixture, **2a** (12 mg, 14%), **4a** (20 mg, 27%), **6a** (5 mg, 5%), and **7a** (45 mg, 41%) were obtained.

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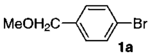
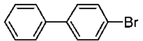
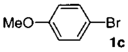
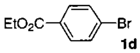
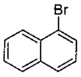
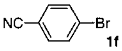
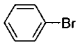
Table 1. Reaction of **1a** with Titanium−Nitrogen Complexes under CO in the Presence of NaO^{t}Bu

run	catalyst	solvent	temp. (°C)	**2a** (%)	**3a** (%)	**4a** (%)	combined yields (%)[a]	**5a** (%)	**1a** (%)
1	$Pd_2(dba)_3$−DPPF	THF	reflux	4	1	6	11	16	62
2	$Pd_2(dba)_3$−DPPF	toluene	90	12	6		18	22	
3	$Pd_2(dba)_3$−DPPF	CH_3CN	reflux	-	-	20	20		50
4	$Pd_2(dba)_3$−DPPF	DMF	90	24	11		61[b]		
5	$Pd_2(dba)_3$−DPPF	CH_3CH_2CN	90	47	11	20	78		
6	$Pd_2(dba)_3$−BINAP	toluene	90	5		56	61	7	27
7	$Pd_2(dba)_3$−BINAP	CH_3CH_2CN	90	23		45	68		20
8	$Pd(OAc)_2$−PPh_3	toluene	90			6	6		89
9	$Pd_2(dba)_3$−DPPF[c]	CH_3CH_2CN	90	7		11	18		46

[a] The combined yields of the products obtained by the carbonylation-nitrogenation process. [b] ArCONHCO (**6a**) was obtained in 26% yield. [c] In the absence of NaO^{t}Bu.

Table 2. Synthesis of Amides from Aryl Halide, CO, and N_2[a]

run	Substrate	Conditions	**2** (%)	**3** (%)	**4** (%)	**6** (%)	**7** (%)	Total[b] (%)
1	 **1a**	A	14	-	27	5	41	87
		B	23	-	45	-	-	68
2	 **1b**	A	47	-	13	9	-	69
		B	42	13	32	-	-	87
3	 **1c**	A	40	-	21	11	10	82
		B	45	13	20	-	-	78
4	 **1d**	A	75	-	8	2	11	96
		B	47	-	4	-	-	51
5	 **1e**	A	52	-	21	5	-	78
		B	64	14	20	-	-	98
6	 **1f**	A	-	-	-	-	55	55
7	 **1g**	A	34	-	-	5	8	47

[a] Reaction conditions: A; $Pd_2(dba)_3 \cdot CHCl_3$−DPPF in DMF at 90 °C overnight. B; $Pd_2(dba)_3 \cdot CHCl_3$−BINAP in CH_3CH_2CN at 90 °C overnight in the presence of NaO^{t}Bu. [b] The total yields of the products obtained by the carbonylation-nitrogenation process.

complex **10** by reductive elimination, which reacts with DMF to give compounds **7** and **6** via **11**. Alternatively, the carbonyl oxygen of **9** coordinates intramolecularly with titanium metal, if nitrile **4** would be produced via **12** (Figure 1).

Usually, N-substituted benzamides are synthesized from aryl halides and primary or secondary amines under carbon monoxide in the presence of a palladium catalyst. However, primary benzamides cannot be synthesized from aryl halides by palladium-catalyzed carbonylation because the nucleophilicity of NH_3 is low and handling of gaseous NH_3 is difficult. The present work is not only interesting for the incorporation of gaseous N_2 and CO into aryl halides but also useful for the synthesis of primary benzamides from aryl halides.

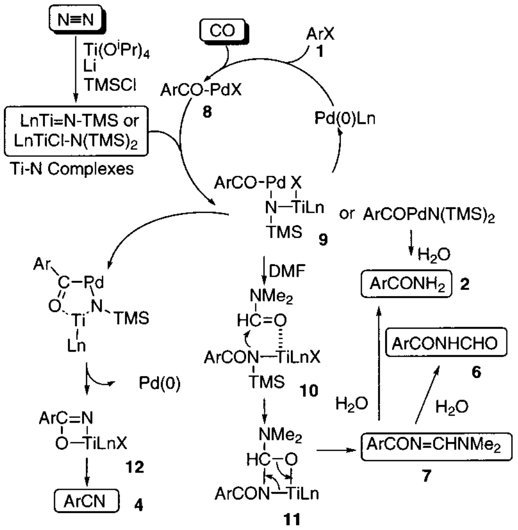


Figure 1. Possible reaction mechanism.

Further studies are in progress.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, IR, and MASS spectral data of compounds **2a**, **3a**, **6a**, **6b**, **6d**, **6e**, **7d**, and **7f**. Experimental procedures (Method A and Method B) for **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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