Double Carbonylation of Aryl Iodides with Primary Amines under Atmospheric Pressure Conditions Using the Pd/PPh_3/DABCO/THF System

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Received April 17, 2001

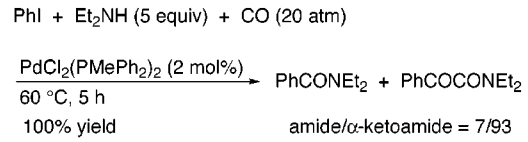
Introduction

The palladium-catalyzed double carbonylation of aryl halides to give α-keto acids, esters, and amides has been extensively studied.[1] However, in contrast to the widespread synthetic use of catalytic single carbonylations,[2,3] catalytic double carbonylations are less convenient to employ.[4] One of the major problems associated with double carbonylations lies in the experimental manipulation where an air-sensitive alkylphosphine ligand and high-pressure conditions are frequently required to promote the double carbonylation selectively. A typical example is shown in Scheme 1. We report herein a new practical protocol for the palladium-catalyzed double carbonylation of aryl halides under atmospheric pressure of carbon monoxide at ambient temperature using triphenylphosphine as a ligand.[5]

Results and Discussion

We have examined several phosphine ligands, solvents, and bases for the double carbonylation of iodobenzene (Scheme 2). Reaction of iodobenzene (**1a**) with *n*-butylamine in the presence of palladium−phosphine complexes and bases under atmospheric pressure of carbon monoxide at 25 °C for 12 h gave a mixture of *N*-butylbenzamide (**2a**) and *N*-butylphenylglyoxamide (**3a**). The selectivity producing the double carbonylation product **3a** was determined by ^{1}H NMR analysis of the crude mixture, and the benzamide **2a** and α-keto amide **3a** were readily isolated by silica gel column chromatography. Representative results are summarized in Table 1. It was found that the combination of triphenylphosphine, tetrahydrofuran, and 1,4-diazabicyclo[2.2.2]octane (DABCO) is essential to construct an efficient catalyst system with much higher selectivity for the double carbonylation product. Thus, when a mixture of **1a**, *n*-butylamine (3 equiv), and DABCO (3 equiv) was stirred at 25 °C under 1 atm of carbon monoxide for 12 h in the presence of 3 mol % of a palladium catalyst generated in situ by mixing di(μ-chloro)bis(η^3-allyl)dipalladium(II) ([PdCl(η^3-C_3H_5)]$_2$) and triphenylphosphine (P/Pd = 2/1), the double carbonylation took place with 92% selectivity to give 7% and 86% isolated yields of **2a** and **3a**, respectively (Table 1, entry 1). The selectivity giving the double carbonylation

Scheme 1



Scheme 2

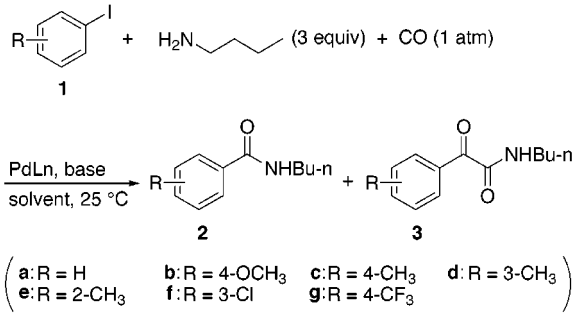


Table 1. Palladium-Catalyzed Carbonylation of PhI (1a) with *n*-$BuNH_2$[a]

entry	ligand	solvent	base	yield[b] (%) 2a	yield[b] (%) 3a	selectivity (%) of 3a
1	PPh_3	THF	DABCO	7	86	92
2[c]	PPh_3	THF	DABCO	21	73	77
3[d]	*n*-Bu_3P	THF	DABCO			
4	dppe	THF	DABCO	16	15	48
5	PPh_3	Et_2O	DABCO	59	39	40
6	PPh_3	DMF	DABCO	51	38	43
7	PPh_3	DMSO	DABCO	62	18	23
8	PPh_3	THF	Et_3N	23	51	69
9	PPh_3	THF	pyridine	36	42	54
10	PPh_3	THF	DBU	72	<1	<1

[a] All reactions were carried out at 25 °C for 12 h under 1 atm of CO. The catalyst was generated in situ by mixing [PdCl(η^3-C_3H_5)]$_2$ and a phosphine ligand. The ratio of **1a** (mol)/*n*-$BuNH_2$ (mol)/[Pd] (mol)/ligand (mol)/base (mol)/solvent (L) = 1.0/3.0/0.03/0.06/3.0/10. [b] Isolated yield. [c] $Pd(PPh_3)_4$ (5 mol %) was used. [d] No reaction.

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(1) (a) Ozawa, F.; Soyama, H.; Yamamoto, T.; Yamamoto, A. *Tetrahedron Lett.* **1982**, *23*, 3383. (b) Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1982**, *233*, C64. (c) Ozawa, F.; Yamamoto, T.; Yamamoto, A. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 442. (d) Ozawa, F.; Sugimoto, T.; Yuasa, Y.; Santra, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1984**, *3*, 683. (e) Ozawa, F.; Yanagihara, H.; Yamamoto, A. *J. Org. Chem.* **1986**, *51*, 415. (f) Sakakura, T.; Yamashita, H.; Kobayashi, T.-A.; Hayashi, T.; Tanaka, M. *J. Org. Chem.* **1987**, *52*, 5733. (g) Son, T.-I.; Yanagihara, H.; Ozawa, F.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1251−1258. (h) Ozawa, F.; Yamagami, I.; Nakano, M.; Fujiwara, F.; Yamamoto, A. *Chem. Lett.* **1989**, 125. (i) Urata, H.; Ishii, Y.; Fuchikami, T. *Tetrahedron Lett.* **1989**, *30*, 4407. (j) Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 433. (k) Lin, Y.-S.; Yamamoto, A. *Organometallics* **1998**, *17*, 3466.

(2) For reviews, see: (a) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley and Sons: Chichester, 1995. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (c) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation*; Plenum Press: New York, 1991.

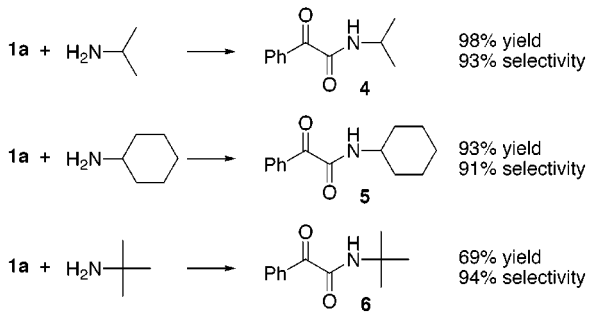
(3) For some examples reported by the author's group, see: (a) Mori, M.; Uozumi, Y.; Ban, Y. *Tetrahedron Lett.* **1985**, *26*, 5947. (b) Mori, M.; Uozumi, Y.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1986**, *7*, 841. (c) Mori, M.; Uozumi, Y.; Ban, Y. *Heterocycles* **1986**, *24*, 1257. (d) Uozumi, Y.; Kawasaki, N.; Mori, E.; Mori, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 3725. (e) Suzuki, T.; Uozumi, Y.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1593−1595.

(4) Recent examples, see: (a) Couve-Bonnaire, S.; Carpentier, J.-F.; Castanet, Y.; Mortreux, A. *Tetrahedron Lett.* **1999**, *40*, 3717−3718. (b) Lin, Y.-S.; Alper, H. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 779−781.

(5) It has been reported that palladium-catalyzed carbonylation of PhI with $HNEt_2$ gives *N*,*N*-diethyl phenylglyoxamide with high selectivity under atmospheric pressure conditions in the presence of copper iodide as a cocatalyst at 50 °C, see: Satoh, T.; Kokubo, K.; Miura, M.; Nomura, M. *Organometallics* **1994**, *13*, 4431.

10.1021/jo0156924 CCC: $20.00
Published on Web 06/27/2001

Scheme 3



product was lowered to 77% by use of tetrakis(triphenylphosphine)palladium (P/Pd = 4/1) (entry 2). A palladium complex coordinated with tributylphosphine did not catalyze carbonylation at all under otherwise similar conditions (entry 3). A bidentate phosphine, 1,2-bis(diphenylphosphino)ethane, decreased the catalytic activity and the selectivity to give 31% of the carbonylation products with 48% of the double carbonylation products (entry 4).

It was found that use of DABCO as a base is critical for the high selectivity of double carbonylation. Thus, carbonylation of **1a** in the presence of triethylamine or pyridine gave single and double carbonylation products in high yields where the selectivity decreased to 69% or 54% (entries 8 and 9) and the reaction with DBU gave the single carbonylation product **2a** exclusively (entry 10), whereas DABCO promotes double carbonylation with 92% selectivity. Use of THF as a solvent is also essential to perform double carbonylation selectively. Single carbonylation giving **2a** preferentially proceeded in ether, DMF, or DMSO (entries 5−7).

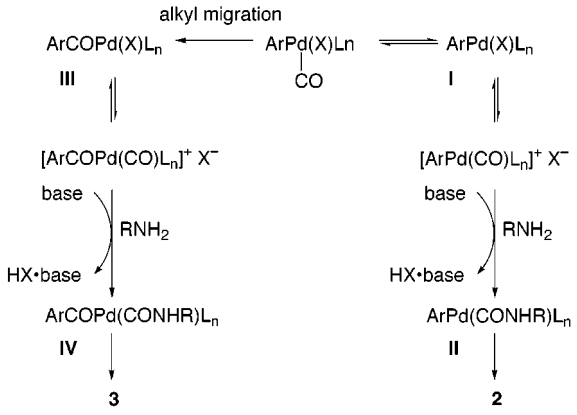
Using the double carbonylation selective catalyst system identified above, several amines as well as aryl halides were examined for the carbonylation reaction. The carbonylation of iodobenzene with isopropylamine, cyclohexylamine, and *tert*-butylamine under the double carbonylation conditions (Pd/PPh_3/DABCO/THF) gave the corresponding α-keto amides **4** (98% isolated yield), **5** (93%), and **6** (69%) with selectivity of 93%, 91%, and 94%, respectively (Scheme 3). It is noteworthy that the selectivity is strongly affected by the substituents of the aromatic ring. Aryl halides bearing electron-donating substituents **1b**, **1c**, and **1d** underwent double carbonylation with high selectivity to give *p*-anisyl, *p*-tolyl, and *m*-tolyl keto amides with 94%, 92%, and 89% selectivity, respectively (Table 2, entries 2−4). Sterically hindered *o*-iodotoluene (**1e**) exhibited lower reactivity and selectivity to give 46% yield of **3e** with 78% selectivity (entry 5). Electron-deficient *m*-chlorophenyl iodide (**1f**) and *p*-(trifluoromethyl)phenyl iodide (**1g**) afforded the single carbonylation products **2f** and **2g** overwhelmingly (entries 6 and 7). It has been reported that the palladium-catalyzed single and double carbonylation of an aryl halide proceeds by way of an aryl(carbamoyl)palladium intermediate (**II** in Scheme 4) and an aroylpalladium intermediate (**III**), respectively,[6] where the irreversible

Table 2. Palladium-Catalyzed Carbonylation of Aryl Iodides (1a−g) with *n*-$BuNH_2$[a]

entry	aryl iodide	yield[b] (%) **2**	yield[b] (%) **3**	selectivity (%) of **3**
1	**1a** (R = H)	7	86	92
2	**1b** (R = 4-OCH_3)	6	87	94
3	**1c** (R = 4-CH_3)	8	90	92
4	**1d** (R = 3-CH_3)	10	85	89
5	**1e** (R = 2-CH_3)	13	46	78
6	**1f** (R = 3-Cl)	77	13	14
7	**1g** (R = 4-CF_3)	98	<1	<1

[a] All reactions were carried out in THF at 25 °C for 12 h under 1 atm of CO in the presence of 3 equiv of DABCO and 3 mol % of a Pd−PPh_3 catalyst that was generated in situ by mixing [PdCl(η^3-C_3H_5)]$_2$ and 2 equiv of Pd to PPh_3. The ratio of **1a** (mol)/*n*-$BuNH_2$ (mol)/[Pd] (mol)/ligand (mol)/base (mol)/solvent (L) = 1.0/3.0/0.03/0.06/3.0/10. [b] Isolated yield.

Scheme 4



alkyl migration step forming **III**[7] is the divergence of the reaction pathways. The reactivity of arylpalladium **I** giving aroylpalladium **III** decreases as electron density of the aryl moiety of **I** decreases,[8] thus rationalizing the trend of selectivity observed for **1a**−**g** (Table 2).

In summary, an effective catalyst system, Pd/PPh_3/DABCO/THF, has been developed for the double carbonylation of aryl halides under very mild conditions (CO 1 atm, 25 °C). This catalyst system provides a practical method for the preparation of α-keto acid derivatives.[9] Currently, we are studying the scope of this catalyst system utilizing a broad variety of secondary amines and alcohols. Further mechanistic study, particularly on the role of DABCO, is also currently underway and will be reported in due course.

Experimental Section

Double Carbonylation of Aryl Iodides.[10] A typical procedure is given for the reaction of iodobenzene (**1a**) and *n*-butylamine (Table 1, entry 1). To a solution of [PdCl(η^3-C_3H_5)]$_2$

(6) (a) Ozawa, F.; Soyama, H.; Yanagihara, H.; Aoyama, I.; Takino, H.; Izawa, K.; Yamamoto, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1985**, *107*, 3235. (b) Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1987**, *6*, 1640. (c) Carpentier, J,-F.; Castanet, Y.; Mortreux, A.; Petit, F. *J. Organomet. Chem.* **1994**, *482*, 31. (d) Yamamoto, A.; Ozawa, F.; Osakada, K.; Huang, L.; Son, T.-I.; Kawasaki, N.; Doh, M.-K. *Pure. Appl. Chem.* **1991**, *63*, 687.

(7) (a) Calderazzo, F. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 299. (b) Wijicki, A. *Adv. Organomet. Chem.* **1973**, *11*, 87. (c) Flood, T. C. *Top. Stereochem.* **1981**, *12*, 37.

(8) (a) Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4115. (b) Sugita, N.; Minkiewicz, J. V.; Heck, R. F. *Inorg. Chem.* **1978**, *17*, 2809.

(9) The transformation of α-keto acid derivatives has attracted considerable attention in recent years. For some examples, see: (a) Aldea, R.; Alper, H. *J. Org. Chem.* **1998**, *63*, 9425. (b) Blaser, H.-U.; Jalett, H.-P.; Garland, M.; Studer, M.; Thies, H.; Wirthtijani, A. *J. Catal.* **1998**, *173*, 282. (c) Wang, G.-Z.; Mallet, T.; Baiker, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2133.

(10) Chemical Abstracts Registry numbers have been provided by the author: **2a**, 2782-40-3; **2e**, 5448-58-8; **2f**, 35306-53-7; **3a**, 5070-32-6; **4**, 78523-79-2; **5**, 724-92-5; and **6**, 21020-60-6.

(4.6 mg, 0.0125 mmol) and PPh_3 (13.1 mg, 0.05 mmol) in 8.3 mL of THF were added iodobenzene (170 mg, 0.83 mmol), DABCO (280 mg, 2.5 mmol), and *n*-butylamine (183 mg, 2.5 mmol) at 0 °C under a carbon monoxide atmosphere. The reaction mixture was stirred at 25 °C under 1 atm of CO for 12 h and then diluted with EtOAc, washed with dilute HCl and brine, and dried over Na_2SO_4. After removal of the solvent in vacuo, the resulting residue was chromatographed on silica gel (*n*-hexane/EtOAc = 1/10−1/1) to give 12 mg of **2a** (7% yield) and 147 mg of **3a** (86% yield).

***N*-Butyl-4-methoxyphenylglyoxamide (3b):** ^{1}H NMR δ 0.95 (t, J = 7.3 Hz, 3H), 1.40 (septet, J = 7.3 Hz, 2H), 1.58 (quintet, J = 7.3 Hz, 2H), 3.38 (q, J = 7.3 Hz, 2H), 3.88 (s, 3H), 6.94 (d, J = 9.0 Hz, 2H), 7.18 (br s, 1H), 8.41 (d, J = 9.0 Hz, 2H). Anal. Calcd for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.01; H, 6.95; N, 5.98.

***N*-Butyl-4-methylphenylglyoxamide (3c):** ^{1}H NMR δ 0.95 (t, J = 7.3 Hz, 3H), 1.40 (septet, J = 7.3 Hz, 2H), 1.58 (quintet, J = 7.3 Hz, 2H), 3.38 (q, J = 7.3 Hz, 2H), 2.41 (s, 3H), 7.16 (br s, 1H), 7.26 (d, J = 8.2 Hz, 2H), 8.25 (d, J = 8.2 Hz, 2H). Anal. Calcd for $C_{13}H_{17}O_2N$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.92; H, 7.95; N, 6.33.

***N*-Butyl-3-methylphenylglyoxamide (3d):** ^{1}H NMR δ 0.95 (t, J = 7.1 Hz, 3H), 1.40 (septet, J = 7.1 Hz, 2H), 1.58 (quintet, J = 7.1 Hz, 2H), 2.40 (s, 3H), 3.38 (q, J = 7.1 Hz, 2H), 7.12 (br s, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.42 (br d, J = 7.6 Hz, 1H), 8.11−8.13 (overlapped m, 2H). Anal. Calcd for $C_{13}H_{17}O_2N$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.85; H, 8.02; N, 6.62.

***N*-Butyl-2-methylphenylglyoxamide (3e):** ^{1}H NMR δ 0.96 (t, J = 7.1 Hz, 3H), 1.42 (septet, J = 7.1 Hz, 2H), 1.60 (quintet, J = 7.3 Hz, 2H), 2.49 (s, 3H), 3.40 (q, J = 7.3 Hz, 2H), 7.04 (br s, 1H), 7.26−7.29 (overlapped m, 2H), 7.44 (br t, J = 7.6 Hz, 1H), 7.92 (dd, J = 1.7, 7.6 Hz, 1H. Anal. Calcd for $C_{13}H_{17}O_2N$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.98; H, 7.90; N, 6.32.

***N*-Butyl-3-chlorophenylglyoxamide (3f):** ^{1}H NMR δ 0.96 (t, J = 7.3 Hz, 3H), 1.41 (septet, J = 7.3 Hz, 2H), 1.62 (quintet, J = 7.3 Hz, 2H), 3.40 (q, J = 7.3 Hz, 2H), 7.08 (br s, 1H), 7.43 (t, J = 8.2 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.35 (s, 1H). Anal. Calcd for $C_{12}H_{14}O_2NCl$: C, 60.13; H, 5.89; N, 5.84; Cl, 14.79. Found: C, 60.50; H, 6.01; N, 6.02, Cl, 14.99.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research, the Japan Society for the Promotion of Science, and Special Coordination Funds of the Science and Technology Agency of the Japanese Government.

JO0156924