

## Direct Carbamoylation of Aryl Halides

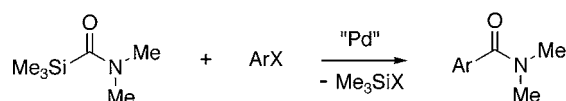
Robert F. Cunico\* and Bikash C. Maity

Department of Chemistry and Biochemistry, Northern Illinois University,  
DeKalb, Illinois 60115

rfc@marilyn.chem.niu.edu

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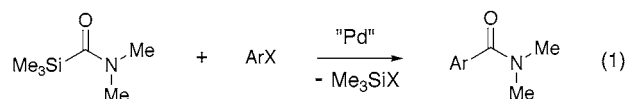
## ABSTRACT



A carbamoylsilane is shown to carry out the direct carbamoylation of aryl chlorides, bromides, and iodides under catalysis by phosphinepalladium(0) complexes.

The carbonylation of aryl halides in the presence of CO, amines, and palladium catalysts to form amides of arenecarboxylic acids is an extremely useful area within the broad scope of metal-catalyzed coupling reactions.<sup>1,2</sup> Modifications of this process continue to appear because of the desire to eliminate the use of gaseous carbon monoxide,<sup>3</sup> or extend the reaction to less reactive aryl halides.<sup>4</sup> As one possible alternative to the above process, direct aromatic carbamoylation has been demonstrated by treating aryl halides with carbamoylstannanes under catalysis by tetrakis(triphenylphosphine)palladium(0).<sup>5</sup> However, these reagents were themselves obtained via carbonylation–stannylation of lithium amides. In addition, issues of stannane stability, low reactivity of even bromobenzene, and the toxicity of organotin compounds<sup>6</sup> constitute practical limits to this approach.<sup>7</sup>

We now report that direct carbamoylation of aryl iodides, bromides, and chlorides can be carried out by employing carbamoylsilane **1**<sup>8</sup> and one of several palladium catalysts (eq 1). A series of haloarenes have been examined under



standard conditions involving a 1.0:1.1:0.02 molar ratio of ArX:1: Pd catalyst in toluene at 100 °C and results for aryl bromides are shown in Table 1.<sup>9</sup> Under catalysis by tetrakis(triphenylphosphine)palladium(0) (**A**), all unhindered bromides afforded good yields of the corresponding amides,

(1) (a) Beller, M.; Indolese, A. F. *Chimia* **2001**, *55*, 684–687. (b) Malleron, J.-L.; Fiaud, J.-C.; Legros, J.-Y. *Handbook of Palladium-Catalyzed Organic Reactions*; Academic Press: San Diego, 1997; p 250. (c) Soderberg, B. C. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, UK, 1995; Vol. 12, pp 249–251. (d) Tsuji, J. *Palladium Reagents and Catalysis*; Wiley: Chichester, 1995; pp 196–198. (e) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation*; Plenum: New York, 1991; pp 145–149. (f) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.

(2) Double carbonylation competes under conditions of high CO pressure: (a) Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1982**, *233*, C64–C66. (b) Ozawa, F.; Soyama, H.; Yamamoto, T.; Yamamoto, A. *Tetrahedron Lett.* **1982**, *23*, 3383–3386.

(3) (a) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232–6235. (b) Kaiser, N.-F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109–111. (c) Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* **2002**, *4*, 2849–2851.

(4) (a) Perry, R. J.; Wilson, B. D. *J. Org. Chem.* **1996**, *61*, 7482–7485. (b) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047–1062.

(5) Lindsay, C. M.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 569–573.



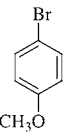
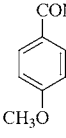
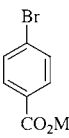
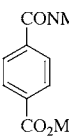
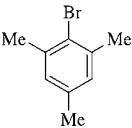
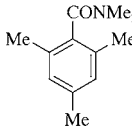
(6) (a) *Chemistry of Tin*, 2nd ed.; Smith, P. J., Ed.; Blakie Academic & Professional; London, UK, 1998; pp 338–441. (b) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, UK, 1987; pp 6–7.

(7) We are unaware of any subsequent application of this methodology.

(8) Prepared from DMF as in: Cunico, R. *Tetrahedron Lett.* **2001**, *42*, 1423–1425. At this scale, an addition period of 8 h, achieved by motorized syringe injection of LDA, was critical to obtaining a synthetically useful yield (70%) of **1**, bp 37–41 °C (0.9 mmHg); <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>) δ 2.76 (3H, s), 2.54 (3H, s), 0.30 (9H, s); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>) δ 185.3, 36.1, 32.0, –1.2. Anal. Calcd for C<sub>6</sub>H<sub>15</sub>NOSi: C, 49.61; H, 10.41; N, 9.64. Found: C, 49.45; H, 10.45; N, 9.50. In contrast to original expectations, **1** and other *N,N*-disubstituted carbamoylsilanes can be prepared by this method.

(9) **General Procedure:** A Schlenk tube fitted with a Teflon vacuum stopcock and a micro stirbar was flame-heated under vacuum and refilled with Ar. Aryl halide (0.50 mmol) and **1** (0.55 mmol) were then added and two evacuations and Ar refills carried out. Catalyst and toluene (0.5 mL, from benzophenone ketyl) were added under Ar purge, and the reaction was held at temperature for the indicated time. Initial runs were monitored by <sup>1</sup>H NMR. Upon total consumption of **1**, volatiles were removed under vacuum and the residue subjected to flash chromatography (silica gel, 1:4 acetone–hexane). All products were characterized by IR, NMR, and mp data comparison to literature values.

**Table 1.** Carbamoylation of Aryl Bromides

entry	substrate	catalyst <sup>a</sup>	time <sup>b</sup>	product	yield (%) <sup>c</sup>
1		A	6 h		88
2	"	B	6 h	"	82
3	"	C	6 h	"	78
4		A	8 h		66 + 11 <sup>d</sup>
5	"	A <sup>e</sup>	20 h	"	71 + 8 <sup>d</sup>
6	"	B	10 h	"	76
7	"	C	8 h	"	70 + 7 <sup>d</sup>
8		A	4 h		71 + 9 <sup>d</sup>
9	"	B	10 h	"	74
10		A			0
11	"	B	11 h	"	92

<sup>a</sup> 2 mol % of **A** = tetrakis(triphenylphosphine)palladium(0); **B** = bis(*tert*-butylphosphine)palladium(0); **C** = bis(triphenylphosphine)palladium dichloride. <sup>b</sup> At 100 °C in toluene. <sup>c</sup> Isolated yield. <sup>d</sup> Exchange product: *N,N*-dimethylbenzamide. <sup>e</sup> 1 mol %.

while the hindered bromomesitylene (entry 10) was found to be totally unreactive. The introduction of groups known<sup>10</sup> to enhance (entry 8) or to retard (entry 4) the rate of oxidative addition to aryl bromides resulted in expected variances in time to completion, but mattered little to the yield obtained. The latter two reactions displayed the typical aryl group exchange exhibited by coupling reactions catalyzed by triphenylphosphinepalladium complexes,<sup>11</sup> leading to small amounts of *N,N*-dimethylbenzamide. Reducing the catalyst loading by half (entry 5) lengthened the time to completion, but afforded a slightly better result in terms of both yield and exchange product formation. The air-stable bis(triphenylphosphine)palladium(II) dichloride (**C**) was briefly



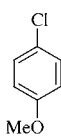
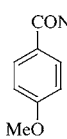
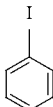
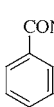

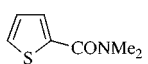

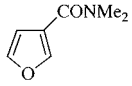

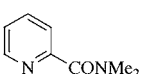
(10) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998.

(11) Goodson, F. E.; Wallow, T. I.; Novak, B. N. *J. Am. Chem. Soc.* **1997**, *119*, 12441–12453 and references therein.

examined as a catalyst (entries 3 and 7), and was found to closely parallel the behavior to **A**. In recent years, bis(*tert*-butylphosphine)palladium(0) has been shown to exhibit unique catalytic activity in a variety of coupling environments.<sup>12</sup> When this catalyst (**B**) was applied to the transformation of unhindered bromides (entries 2, 6, and 9), no significant improvement in rate or yield relative to the use of **A** occurred, except for the lack of aryl exchange. However, treatment of the hitherto inert bromomesitylene with **B** (entry 11) now afforded an excellent yield of amide.

Table 2 indicates our results with other aryl and heteroaryl halides. Although chlorobenzene was inert when in contact

**Table 2.** Carbamoylation of Aryl and Heteroaryl Halides

entry	substrate	catalyst <sup>a</sup>	time <sup>b</sup>	product	yield (%) <sup>c</sup>
1		A	20 h		0
2	"	B	5 h	"	74
3		B	9 h		78
4		A	14 h		60
5	"	B	14 h <sup>d</sup>	"	8
6		A <sup>e</sup>	9 h		89
7	"	B <sup>e</sup>	8 h	"	87
8		B <sup>e</sup>	11 h		61
10		B <sup>e</sup>	8 h		68

<sup>a</sup> 2 mol % of **A** = tetrakis(triphenylphosphine)palladium(0); **B** = bis(*tert*-butylphosphine)palladium(0). <sup>b</sup> At 100 °C in toluene. <sup>c</sup> Isolated yield. <sup>d</sup> No change after 2 h. <sup>e</sup> 4 mol %.

with **A**, of particular interest is the observation that chlorobenzene, and even 1-chloro-4-methoxybenzene, afford good

(12) (a) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348 and references therein. (b) Nishiyama, M.; Yamamoto, Y.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617–620.

yields of amides under catalysis by **B** (entries 2 and 3). Chlorobenzenes are generally quite unreactive and extensive investigations have been pursued in order to engage these inexpensive halides in a variety of coupling reactions.<sup>12a,13</sup> In a surprising turnabout, **B** was found to be ineffective in catalyzing the conversion of iodobenzene to product.<sup>14</sup> However, the use of **A** led to carbonylation in 60% yield.<sup>15</sup> Thus the general protocol can be adapted to allow the conversion of aryl chlorides, bromides, and iodides into the

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(13) (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047–1062. (b) An effective catalyst for aminocarbonylation of aryl chlorides (using CO) has been reported: Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742–8744.

(14) The pinkish solution quickly turned brown upon heating. Several authors have commented on the lower reactivity of aryl iodides vs bromides when using tri-*tert*-butylphosphinepalladium(0) complexes in coupling reactions: (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028. (b) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225.

(15) These reactions were anomolous in that separation of a solid occurred within minutes of heating the initially homogeneous mixture.

corresponding amides. Methyl 4-fluorobenzoate was unreactive under catalysis by **B**. Initial attempts at utilizing 2-bromothiophene and 3-bromofuran as substrates with the standard 2 mol % of catalyst **A** or **B** led to slow rates of conversion (typically less than 50% after 14 h). More acceptable rates were realized by doubling the catalyst load (entries 6–8). Finally, 2-bromopyridine behaved quite normally at a 2 mol % level of **B**. Thus the presence of heteroatom substitution in the aryl moiety does not seem to seriously inhibit the reaction.

Further investigations of this carbamoylation protocol are in progress.

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