

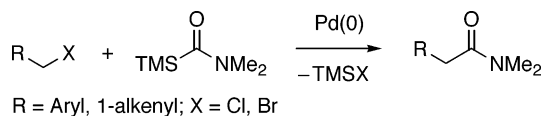
## Palladium-Catalyzed Conversion of Benzylic and Allylic Halides into $\alpha$ -Aryl and $\beta,\gamma$ -Unsaturated Tertiary Amides by the Use of a Carbamoylsilane

Robert F. Cunico\* and Rajesh K. Pandey

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

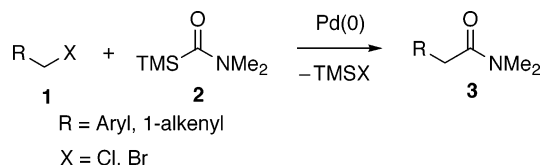
rfc@marilyn.chem.niu.edu

Received June 16, 2005



Treatment of allylic and benzylic halides with *N,N*-dimethylcarbamoyl(trimethyl)silane in the presence of tetrakis(triphenylphosphine)palladium(0) affords tertiary amides, which arise from the replacement of the halogen by the *N,N*-dimethylcarbamoyl group.

Although benzylpalladium halides are known and can be aminocarbonylated with CO and amines,<sup>1</sup> the palladium-catalyzed aminocarbonylation of benzyl or allyl halides is not a generally useful methodology because of concomitant production of allylamines and double carbonylation products.<sup>2</sup> In addition, the necessity of manipulating carbon monoxide in aminocarbonylations<sup>3</sup> is a disadvantage that we have previously addressed in other contexts by using a carbamoylsilane to convert aryl and alkenyl halides directly into tertiary amides under catalysis by palladium(0) complexes.<sup>4,5</sup> This approach has now been extended to benzyl and allyl halides and offers an entry into  $\beta,\gamma$ -unsaturated amides. These are compounds of synthetic utility,<sup>6</sup> but only a few examples of their preparation from the halides exist.<sup>7</sup>

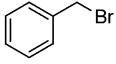
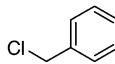
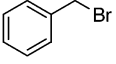
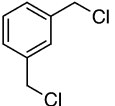
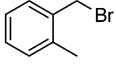
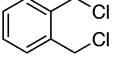
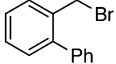
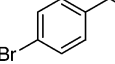
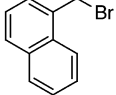

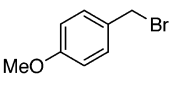

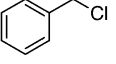

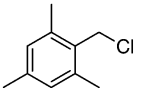
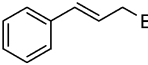
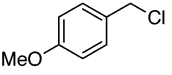
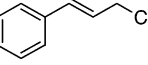
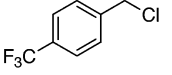



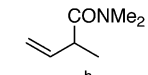
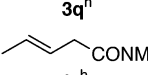
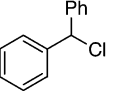



- (1) Lin, Y.-S.; Yamamoto, A. *Organometallics* **1998**, *17*, 3466–3478.  
 (2) Yamamoto, A. *Bull. Soc. Chem. Jpn.* **1995**, *68*, 433–446.  
 (3) For a review of carbon monoxide-free carbonylations, see: Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580–5588.  
 (4) Cunico, R. F.; Maity, B. C. *Org. Lett.* **2002**, *4*, 4357–4359.  
 (5) Cunico, R. F.; Maity, B. C. *Org. Lett.* **2003**, *5*, 4947–4949.  
 (6) For a summary of entries to this compound class from nonhalides and references to applications, see: Luo, F.-T.; Lu, T.-Y.; Xue, C. *Tetrahedron Lett.* **2003**, *44*, 7249–7251. A Pd-catalyzed aminocarbonylation of an allylic carbonate has been reported: Tsuji, J.; Sato, K.; Okumoto, H. *J. Org. Chem.* **1984**, *49*, 1341–1344.  
 (7) (a) From allyl and benzyl magnesiumcuprates and carbamoyl chloride: Lemoucheux, L.; Seitz, T.; Rouden, J.; Lasne, M.-C. *Org. Lett.* **2004**, *6*, 3703–3706. (b) From benzyl chloride, metallic (stoichiometric) nickel, and carbamoyl chloride: Inaba, S.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 1373–1381.

To effect the desired transformation, a 1:1.2<sup>8</sup> mixture of organic halide (**1**) and carbamoylsilane (**2**)<sup>9</sup> and 4 mol % of tetrakis(triphenylphosphine)palladium(0) was heated in toluene (65 or 100 °C) until the disappearance of **1** was observed. Conditions and results for the preparation of individual tertiary amides (**3**) are shown in Table 1. As expected, benzylic bromides exhibited faster reaction rates than benzylic chlorides (compare entries 2 and 7, 6 and 9). Either electron-donating or electron-withdrawing groups are tolerated on the ring without significant change in rate at 100 °C, although the former is somewhat more reactive (compare entry 9 vs entry 10). Entries 3–5 and 8 indicate that steric effects introduced by ortho substituents in the aryl ring (including those of the mesityl group) may be significant but can be easily overcome by slightly longer reaction times or use of the higher reaction temperature. The addition of a third phenyl substituent at the benzylic chloride reaction center (entries 11 and 12) does slow the reaction considerably, but the anticipated products are still obtained, albeit in low yield in the case of chlorotriphenylmethane. However, when the corresponding bromides were employed, carbamoylsilane was consumed but none of the expected amide was obtained. NMR examination of the products indicated that they were a mixture of aromatic compounds showing no TMS or dimethylamide absorptions. Both *p*- and *m*-bis(chloromethyl)benzene proceeded to the diamide product, but the ortho isomer gave only the dibenzylallyl coupled “dimer”, dibenzo-1,5-cyclooctadiene (**4**). Again the para and meta dibromides (at 65 °C) were anomalous, in that no diamide was formed; instead, a white insoluble solid precipitated that appeared to be polymeric in nature.<sup>10</sup> 4-Bromobenzyl chloride was investigated (entry 16) in the hope that the method could be made chemoselective, since aryl bromides are known to undergo carbamoylation under the higher temperature (100 °C) conditions.<sup>4</sup> At 65 °C, only the amide having been introduced at the benzylic position was obtained, and that in 92% yield. The behavior of terminal allylic halides involved in entries 19–21 was regioselective, only affording the terminal amide and none of the allylicly transposed internal product. However, when either the internal halide of entry 22 was employed or its terminal isomer (entry 23), approximately equivalent amounts of amides **3q** and **3r** were obtained in each instance (entry 22, 51:49; entry 24, 46:54). Small amounts of the  $\alpha,\beta$ -unsaturated (conjugated) isomer were detected only in the amide product derived from runs 17 (10%) and 19 (trace). Since a Pd(II)-catalyzed reaction between allylic trifluoroacetates and *acylsilanes* has been reported to afford  $\beta,\gamma$ -unsaturated ketones,<sup>11</sup> we investigated the behavior of both allyl trifluoroacetate and benzyl trifluoroacetate under our conditions. In either instance, no reaction occurred. However, since the conditions described<sup>11</sup> involved phosphine-free Pd(II) complexes as

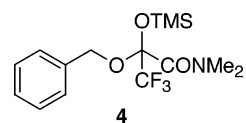
- (8) Some adventitious protonolysis of **2** invariably occurs to give DMF and hexamethyldisiloxane.  
 (9) Cunico, R. F.; Chen, J. *Synth. Commun.* **2003**, *33*, 1963–1968.  
 (10) The noncrystalline, tacky solid was insoluble in, separately, hot toluene, methanol, chloroform, and DMF.

TABLE 1. Formation of Amides **3** from Halides **1** and Carbamoylsilane **2**<sup>a</sup>

entry	<b>1</b>	temp	hours	<b>3</b>	yield, % <sup>b</sup>	entry	<b>1</b>	temp	hours	<b>3</b>	yield, %				
1.		100	15	---	0 <sup>c</sup>	13.		100	4	<b>3j</b> <sup>d</sup>	69				
2.		65	0.5	<b>3a</b>	90	14.		100	1	<b>3k</b> <sup>d</sup>	90				
3.		65	0.25	<b>3b</b>	97	15.		100	11	---	0 <sup>e</sup>				
4.		65	0.75	<b>3c</b>	90	16.		65	20	<b>3l</b>	92				
5.		65	0.75	<b>3d</b>	95	17.		65	0.5	<b>3m</b>	97 <sup>f</sup>				
6.		65	0.10	<b>3e</b>	97	18.		65	0.3	<b>3n</b>	95				
7.		65	7	<b>3a</b>	89	19.		65	5	<b>3o</b>	89 <sup>g</sup>				
8.		100	1.5	<b>3f</b>	90	20.		65	1.5	<b>3p</b>	88				
9.		100	0.5	<b>3e</b>	92	21.		100	0.25	<b>3p</b>	95				
10.		100	1.0	<b>3g</b>	87	22.	  	65	0.3	 <b>3q</b> <sup>h</sup>  <b>3r</b> <sup>h</sup>	99				
11.		100	12	<b>3h</b>	92	23.							65	0.3	98
12.	Ph <sub>3</sub> CCl	100	8	<b>3i</b>	25										

<sup>a</sup> **1**:**2** ratio 1:1.2; **1** 1 M in toluene, 4 mol % Pd. <sup>b</sup> Isolated yield. <sup>c</sup> Without catalyst. <sup>d</sup> The diamide was formed. <sup>e</sup> A 60% yield of dibenzo-1,3-cycloctadiene was obtained. <sup>f</sup> Contained 10% of the  $\alpha,\beta$ -unsaturated isomer. <sup>g</sup> Contained a trace of the  $\alpha,\beta$ -unsaturated isomer. <sup>h</sup> 1:1 ratio of **3q**:**3r**.

catalysts, we also examined the behavior of benzyl trifluoroacetate with **2** in the presence of only Pd(TFA)<sub>2</sub>. Although reactivity was high (completion in 1 h, 25 °C), no **3a** was formed. The product present in the reaction mixture was spectrally consistent with the addition of **2** to the carbonyl group of the TFA ester (see **4**), behavior we have previously seen in the reaction of **2** with electrophilically substituted esters in the absence of Pd catalysts.<sup>12</sup>



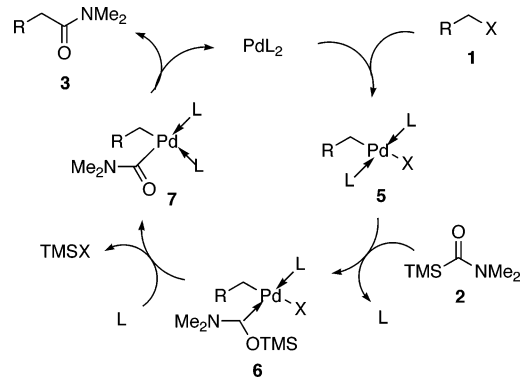
A possible reaction pathway is illustrated by Scheme 1.<sup>13</sup> After oxidative addition of palladium(0) to **1**, the

(12) Cunico, R. F.; Motta, A. R. *Org. Lett.* **2005**, *7*, 771–774.

(13) For simplicity, only  $\eta^1$  bonding to Pd is shown (benzylic substrates), although the scheme is also meant to apply to  $\eta^3$  bonded (allylic) species.

(11) Obora, Y.; Ogawa, Y.; Imai, Y.; Kawamura, T.; Tsuji, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10489–10493.

SCHEME 1



resulting complex **5** is envisioned to undergo ligand exchange ( $L = \text{Ph}_3\text{P}$ ) with a nucleophilic carbene arising from a  $\text{C} \rightarrow \text{O}$  silyl group rearrangement within **2**.<sup>14</sup> The resulting **6** then undergoes dehalosilylation to afford **7**, which suffers reductive elimination to amide **3**.

The regiochemistry of nucleophilic substitution reactions that proceed by way of  $\pi$ -allyl-Pd(II) complexes has been extensively investigated,<sup>15</sup> but only scattered reports address the regiochemistry of allylic halide (or other allylic-X) carbonylations that proceed through these species. Where available, such results largely favor the

formation of the least hindered carbonylation product from either internal or terminal allylic starting materials.<sup>16</sup> The present results leading to a 1:1 ratio of **3q** to **3r** seem to be unique in this regard, but examination of extant mechanistic studies<sup>17</sup> on the carbonylation of allylic substrates sheds little light on this observation.

## Experimental Section

**General Procedure.** A Schlenk tube fitted with a fused Teflon vacuum stopcock and micro stirbar was flame-heated under vacuum and refilled with Ar. The benzylic or allylic halide (0.5 mmol) and carbamoylsilane (0.6 mmol) were added and a 3-fold evacuation–Ar refill was carried out. Catalyst (4 mol % relative to organic halide) was then added, followed by dry toluene (0.5 mL). The sealed reaction mixture was stirred at the indicated temperature and monitored by <sup>1</sup>H NMR using periodic aliquots. After disappearance of starting material, volatiles were removed under vacuum, and the residue was chromatographed on flash silica gel (EtOAc–hexane) and/or Kugelrohr distilled.

**Acknowledgment.** This work was supported by National Institutes of Health grant R15 GM065864.

**Supporting Information Available:** General experimental information, characterization data for new compounds, and references for known **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO0512406

(14) Rationales in support of this possibility are presented in refs 5 and 12.

(15) (a) van Haaren, R. J.; Goubitz, K.; Fraanje, J.; vanStrijdonck, G. P. F.; Oevering, H.; Coussens, B.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Inorg. Chem.* **2001**, *40*, 3363–3372. (b) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995. (c) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1975**, *97*, 2534–2535.

(16) (a) Mandai, T. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishin, E.-I., Ed.; Wiley: New York, 2002. (b) Tsuji, J.; Sato, K.; Okumoto, H. *J. Org. Chem.* **1984**, *49*, 1341–1344. (c) Dent, W. T.; Long, R.; Whitfield, G. H. *J. Chem. Soc.* **1964**, 1588–1594.

(17) van Haaren, R. J.; Oevering, H.; Kamer, P. C. J.; Goubitz, K.; Fraanje, J.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *J. Organomet. Chem.* **2004**, *689*, 3800–3805.