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Direct Carbamoylation of Alkenyl 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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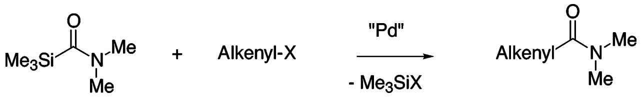
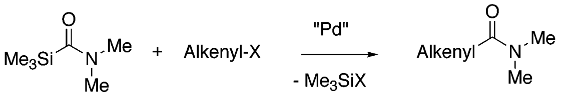
ABSTRACT



Alkenyl chlorides and bromides are converted into tertiary enamides by treatment with a carbamoylsilane in toluene at 110 °C in the presence of phosphine-palladium(0) catalysts.

Ever since the seminal work of Schoenberg and Heck,[1] the aminocarbonylation of aryl and alkenyl halides with carbon monoxide and amines in the presence of palladium-based catalysts has been an important entry to amide functionality.[2] Recently, we[3] and others[4−7] have advanced protocols to obviate the need to employ gaseous carbon monoxide in these transformations. However, only in one instance was any of these approaches shown to apply to alkenyl halides, and that work presented only one such example (a vinylic iodide).[4] Here we report that our previous methodology[3] allows the conversion of alkenyl chlorides and bromides into α,β-unsaturated *N*,*N*-dimethylamides (eq 1).



(1)

1

Reaction conditions consist of heating a toluene solution of carbamoylsilane **1**[8] and alkenyl halide in the presence of a catalytic amount (2−4 mol %) of phosphine-palladium catalyst (Table 1).[9] Two catalysts were investigated: “A”, tetrakis(triphenylphosphine)palladium(0), and “B”, bis(tri-*tert*-butylphosphine)palladium(0), the latter having led to

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[1] Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327−3331.

[2] (a) Skoda-Földes, R.; Kollár, L. *Curr. Org. Chem.* **2002**, *6*, 1097−1119. (b) Beller, M.; Indolese, A. F. *Chimia* **2001**, *55*, 684−687. (c) Yamamoto, A.; Kayaki, Y.; Nagayama, K.; Shimizu, I. *Synlett* **2000**, 925−937. (d) Soderberg, B. C. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 249−251. (e) Tsuji, J. *Palladium Reagents and Catalysis*; Wiley: Chichester, 1995; pp 196−198. (f) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation*; Plenum: New York, 1991; pp 145−149.

[3] Cunico, R. F.; Maity, B. C. *Org. Lett.* **2002**, *4*, 4357−4359.

[4] Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* **2002**, *4*, 2849−2851 (employed DMF−$POCl_3$).

[5] (a) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750−5753 (employed $Mo(CO)_6$−DBU). (b) Kaiser, N.-F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109−111 (employed $Mo(CO)_6$−K_2CO_3).

[6] (a) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Comb. Chem.* **2003**, *5*, 82−84 (employed formamide−KOtBu). (b) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232−6235 (employed DMF−KOtBu).

[7] Morimoto, T.; Fujioka, M.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *Chem. Lett.* **2003**, *32*, 154−155 (employed decarbonylatable aldehydes).

[8] Cunico, R. F.; Chen, J. *Synth. Commun.* **2003**, *33*, 1963−1968.

[9] **General Procedure.** A Schlenk tube fitted with a Teflon vacuum stopcock and micro stirbar was flame-heated under vacuum and refilled with argon. Freshly distilled haloalkene (1.0 mmol) and **1** (1.2 mmol) were added, and a threefold evacuation−Ar refill was carried out (at −78 for volatile halides). Then, catalyst A or B (2−4 mol %) was added, followed by deoxygenated toluene (1 mL). The sealed reaction mixture was stirred at 110 °C until no carbamoylsilane could be seen in the ^{1}H NMR of an aliquot. Volatiles were then removed under vacuum, and the residue chromatographed (flash silica gel) using 10−20% acetone−hexane as eluent. All alkenyl halides and amide products exhibited spectral and melting point data in agreement with literature values. New amides were obtained from runs 5 and 18. ***N*,*N*-Dimethyl-2-hexylpropenamide.** ^{1}H NMR ($CDCl_3$): δ 5.59 (d, $J = 1$ Hz), 1H; 5.42 (d, $J = 1$ Hz); 2.45 (t, $J = 7$ Hz), 2H; 1.59 (m), 2H; 1.35 (m), 6H; 0.93 (t, $J = 7$ Hz). ^{13}C NMR: δ 172.1, 145.2, 113.7, 38.5, 34.3, 34.1, 31.4, 28.8, 27.3, 22.4, 13.8. IR: 1642, 1626 cm^{-1} Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.09; H, 11.63; N, 7.61. ***N*,*N*,*N*′,*N*′-Tetramethyl-2-phenyl-3-(trimethylsilyl)-butenediamide** (*E*/*Z* undetermined). ^{1}H NMR: δ 7.53 (m), 2H; 7.32 (m), 3H; 2.97 (s), 3H; 2.88 (s), 3H; 2.75 (s), 3H; 2.61 (s), 3H; 0.25 (s), 9H. ^{13}C NMR: δ 171.4, 169.5, 146.4, 139.7, 136.8, 128.4, 127.8, 127.3, 38.0, 37.4, 34.3, 34.1, −0.9. IR: 1633, 1617 cm^{-1}. Anal. Calcd for $C_{17}H_{26}N_2O_2Si$: C, 64.11; H, 8.23; N, 8.80. Found: C, 64.30; H, 8.48; N, 8.71. Mp: 155−157 °C.

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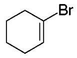
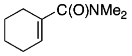
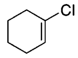
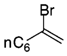
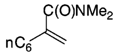
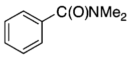
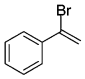
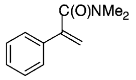
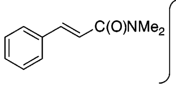
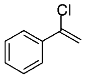
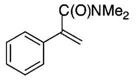
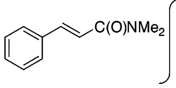
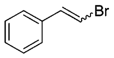
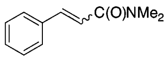
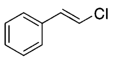
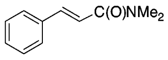
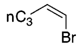
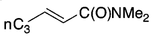
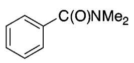
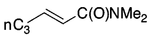
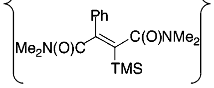
Table 1. Carbamoylation of Alkenyl Halides

entry	substrate	catalyst^a	time(h)^b	product(s)	yield (%)^c
1		A	10		71
2	"	B	8	"	74
3		A	10		0
4	"	B	8	"	79
5		A	22 (10)^d	 	44 (40) 8 (14)
6	"	B	10^d		0
7		A	10^d	 	80 (α:β = 82:18)
8		B	10^d		82 (α:β = 68:32)
9		A	9^d	 	92 (α:β = 100:0)
10	"	B	8^d		88 (α:β = 82:18)
11	 (E:Z = 85:15)	A^d	10		60 (E:Z = 86:14)
12	"	B^d	10	"	82 (E:Z = 91:9)
13		A^d	9		89
14	"	B^d	9	"	88
15		A^d	8^e	 	25 25
16	"	B^d	7^e		48
17	Ph—≡—Br	A	7	Ph—≡—C(O)NMe$_2$ 	69 (80:20)
18		A	10^e		62 (96:4)

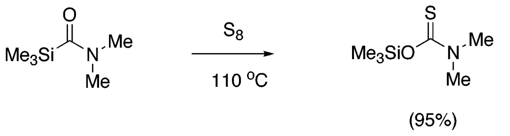
[a] Employed 2 mol % of catalyst A, tetrakis(triphenylphosphine)palladium(0), or B, bis(tri-*tert*-butylphosphine)palladium(0), as indicated. [b] At 110 °C in toluene. [c] Isolated yield. [d] Employed 4 mol %. [e] At 90 °C.

enhanced reactivity in the similar carbamoylation of less-reactive aryl halides.[3] Both catalysts were equally effective at promoting the carbamoylation of cyclohexenyl bromide; however, catalyst A was totally ineffective with cyclohexenyl chloride, whereas B afforded amide product in even higher yield than in the bromide case. However, these results did not fully extend to the open-chain secondary bromide of entry 5. The reaction using A was sluggish, affording only a 40−44% yield of expected product, and thus allowing small amounts of the catalyst-exchange[10] amide to form. Surprisingly, it was now catalyst B that proved to be completely ineffective at the conversion. Replacing the alkyl residue with a phenyl group (entries 7 and 8) restored the reactivity of the alkenyl bromide but introduced a new variant into the results. Whether by use of catalyst A or B, a mixture of unrearranged (ipso) and rearranged (cine) amide was obtained,[11] with B producing more of the cine product. In contrast to the results of entry 3, the phenyl-substituted secondary alkenyl chloride of entries 9 and 10 underwent high conversion with either A or B. However, A now afforded only unrearranged amide, while B gave a mixture of ipso and cine product, with the former more predominant than in the bromide example of run 8.

Turning to terminal alkenyl halides, both catalysts converted styrenyl bromide or chloride into the cinnamyl amides in good yields and in a high degree of stereoretention (runs 11−14). As before, however, the use of an open-chain aliphatic bromide (runs 15 and 16) led to lower yields and cogeneration of the catalyst-exchange amide with A. In this instance, catalyst B was effective, but only the *trans*-amide was formed (complete inversion of configuration).[11]

Brief examination of an alkynyl halide (entries 17 and 18) under conditions of catalyst A resulted in the formation of the expected alkynylamide but was accompanied by smaller amounts of a bis-amidoalkene resulting from the addition of a second molecule of **1** to the initially produced alkynylamide.[12] The amount of this byproduct could be significantly lowered by a reduction in operating temperature. We are unaware of any previous report concerning the aminocarbonylation of a haloacetylene.[13]

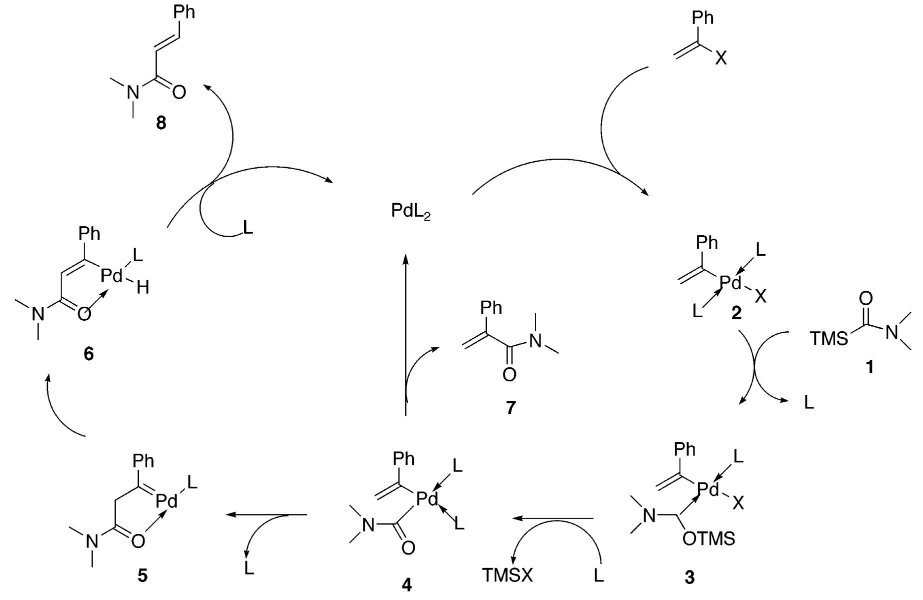
A possible rationalization of the process leading to observed products is given in Scheme 1. After oxidative addition of Pd(0) to the alkenyl halide affords **2**, ligand exchange between phosphine and a nucleophilic carbene arising from rearrangement of the carbamoylsilane is envisioned (**3**).[14] That the carbamoylsilane may exhibit carbenic behavior under these conditions was confirmed by the results of eq 2.



(2)

Heating **1** and elemental sulfur in toluene gave, in less than 1 h, a high yield of the thiocarbamate capture product[15] derived formally from the carbene that would arise from C

Scheme 1



to O silyl group migration within **1**.[16] In Scheme 1, complexation of the carbene with the electrophilic Pd atom is seen as the driving force for this rearrangement. Loss of trimethylsilyl halide from this complex then leads to a carbamoylpalladium intermediate (**4**), which may partition between reductive elimination to ipso product (**7**) or undergo an unprecedented 1,3 migration of the carbamoyl group[17] to form an internally complexed palladium carbene species (**5**).[18] Evidence for the involvement of Pd(0) carbenes leading to cine products of the Stille reaction has been presented by several authors,[19] following an explanation offered by Busacca, et al.[20] However, the present chemistry follows a different sequence of events up to the formation of **5**. Once formed, the rearranged structure may proceed to product (**8**) by 1,3-H migration to **6** followed by reductive elimination, as suggested by Busacca, or by 1,2-H migration to the carbene formed by loss of Pd.[21] We note that the exclusive trans stereochemistry of the cine product obtained is consistent with the intramolecularly complexed Pd(0) precursor.

In summary, we have shown that cyclohexenyl and both α- and β-styrenyl bromides and chlorides can be aminocarbonylated to tertiary amides in good yields under neutral conditions using a carbamoylsilane instead of the usual protocol (CO + amine). Open-chain bromides can also be employed, although they afford somewhat lower yields. A bromoacetylene was also shown to undergo the reaction. Although a number of questions remain to be answered with regard to scope, catalyst choice, and observed rearrangements, results in hand suggest that a wider application of this methodology can be achieved.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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[10] Goodson, F. E.; Wallow, T. I.; Novak, B. N. *J. Am. Chem. Soc.* **1997**, *119*, 12441−12453.

[11] Blank run omitting **1** showed no isomerization of the bromide under these conditions.

[12] Bis-amide is the expected result of silycarbamoylation of an electrophilically substituted acetylene; see: Cunico, R. F. *Tetrahedron Lett.* **2001**, *42*, 2931−2932.

[13] For the aminocarbonylation of a terminal acetylene, see: Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M. *J. Organomet. Chem.* **2001**, *622*, 84−88.

[14] A carbamoylsilane has previously exhibited carbene-like behavior. See: Cunico, R. F. *Tetrahedron Lett.* **2001**, *42*, 2931−2932.

[15] *O*-Trimethylsilyl *N,N*-dimethylthiocarbamate: (a) Lemire, A. E.; Thompson, J. C. *Can. J. Chem.* **1975**, *53*, 3732−3738. (b) Yoder, C. H.; Komoriya, A.; Kochanowski, J. E.; Suydam, F. H. *J. Am. Chem. Soc.* **1971**, *93*, 6515−6518. ^{13}C NMR (C_6D_6): δ 185.9, 41.6, 37.3, 0.76.

[16] Sulfur has been previously used to capture nucleophilic carbenes. See: (a) Nakayama, J.; Sugiura, H.; Hoshino, M. *Tetrahedron Lett.* **1983**, *24*, 2585−2588. (b) Balli, H.; Grüner, H.; Maul, R.; Schepp, H. *Helv. Chim. Acta* **1981**, *64*, 648−656. (c) Reiffen, M.; Hoffmann, R. W. *Chem. Ber.* **1977**, *110*, 37−48.

[17] No rearranged product is obtained from the terminal halides of runs 11−14, Table 1. Factors that would favor migration in the structures of runs 7−10 are increased steric compression at the acylpalladium stage and retained conjugation in the palladium carbene intermediate.

[18] Although shown as fully L-coordinated in Scheme 1, the Pd in the species undergoing loss of TMSX must to some extent become coordinatively unsaturated during this process. A longer residence time in this state may be a factor in favoring rearrangement to the intramolecularly complexed Pd carbene. In this regard, it would be significant that more cine product results from the use of catalyst B, in which the bulky tris(*tert*-butyl)-phosphine ligand affords a Pd(0) complex of low coordination number.

[19] (a) Quayle, P.; Wang, J.; Xu, J.; Urch, C. J. *Tetrahedron Lett.* **1998**, *39*, 489−492. (b) Farina, V.; Hossain, M. A. *Tetrahedron Lett.* **1996**, *37*, 6997−7000.

[20] (a) Heck addition of RPdX to the vinylstannane to form an α-Pd stannane, (b) loss of SnX to form the Pd(0) carbene, (c) 1,3-migration of H to Pd, and (d) reductive elimination to the cine alkene. Busacca, C. A.; Swestock, J.; Johnson, R. E.; Bailey, T. R.; Musza, L.; Rodger, C. A. *J. Org. Chem.* **1994**, *59*, 7553−7556.

[21] Chen, S.-H. *Tetrahedron Lett.* **1997**, *38*, 4741−4744.