ORGANIC
LETTERS

2007
Vol. 9, No. 2
275−278

Palladium-Catalyzed Cross-Coupling between Vinyl Halides and *tert*-Butyl Carbazate: First General Synthesis of the Unusual *N*-Boc-*N*-alkenylhydrazines

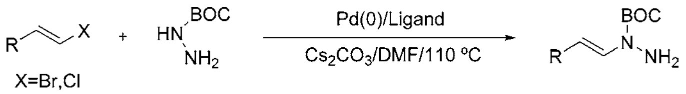
José Barluenga,* Patricia Moriel, Fernando Aznar, and Carlos Valdés*

Instituto Universitario de Química Organometálica "Enrique Moles",
Universidad de Oviedo, Julián Clavería 8, Oviedo 33006, Spain

barluenga@uniovi.es; acvg@uniovi.es

Received November 7, 2006

ABSTRACT



***N*-Boc-*N*-alkenylhydrazines, an almost unknown type of compounds, have been prepared with high to moderate yields via palladium-catalyzed cross-coupling between alkenyl halides and *tert*-butyl carbazate. The present methodology represents the first general way to access this highly functionalized and unusual type of hydrazines.**

Hydrazine derivatives are versatile intermediates in the preparation of heterocyclic compounds containing N−N bonds, such as pyrazoles,[1] indazoles,[2] cinnolines,[3] and 1-aminopyrroles.[4] Moreover, they are used in the preparation of a wide variety of biologically and industrially valuable organic compounds.[5] There are many protocols for the synthesis of aryl- and alkylhydrazines in the literature.[5a,6] However, a general method for the synthesis of *N*-alkenylhydrazines has not been developed. To the best of our knowledge, only two particular examples of the preparation of an alkenylhydrazine, based on the reaction of an alkenyl boronic acid with *tert*-butyl carbazate[7] and azodicarboxylate,[8] respectively, have been previously reported in the literature.[9]

tert-Butyl carbazate **1** is a popular reagent to prepare substituted hydrazines.[6e−g] This simple molecule contains two different nitrogen atoms, a free NH_2, and a Boc-protected NH. When **1** is reacted with a carbonyl, it provides the corresponding hydrazone: the reaction occurs through the more nucleophilic NH_2.[6g] Interestingly, palladium- or copper-catalyzed cross-coupling reactions with aryl halides afford the product derived from the reaction through the NHBoc.[10]

---

(1) (a) Haunert, F.; Bolli, M. H.; Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. I* **1998**, 2235. (b) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V.; Steel, P. J. *J. Org. Chem.* **2001**, *66*, 6787. (c) Staufer, S. R.; Huang, Y. R.; Aron, Z. D.; Coletta, C. J.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2001**, *9*, 151.

(2) (a) Boudreault, N; Leblanc, Y. *Org. Synth.* **1996**, *74*, 241. (b) Pabba, C.; Wang, H. J.; Mulligan, S. R.; Chen, Z. J.; Stark, T. M.; Gregg, B. T. *Tetrahedron Lett.* **2005**, *46*, 7553.

(3) (a) Barber, H. J.; Washbourne, K.; Wragg, W. R.; Lunt, E. *J. Chem. Soc.* **1961**, 2828. (b) Wunsch, B.; Nerdinger, S.; Hofner, G. *Liebigs Ann.* **1995**, 1303. (c) Gomaa, M. A. M. *Tetrahedron Lett.* **2003**, *44*, 3493.

(4) McLeod, M.; Boudreault, N.; Leblanc, Y. *J. Org. Chem.* **1996**, *61*, 1180.

(5) For a review, see: (a) Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205. (b) Zerga, A. *Curr. Med. Chem.* **2005**, *12*, 589. (c) Wagaw, D.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.

(6) (a) Huddleston, P. R.; Coutts, I. G. C. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 2, pp 371−383. (b) Barluenga, J.; Merino, I.; Viña, S.; Palacios, F. *Synthesis* **1990**, 398. (c) Grehn, L.; Lönn, H.; Ragnarsson, U. *Chem. Commun.* **1997**, 1381. (d) Loog, O.; Mäeorg, U.; Ragnarsson, U. *Synthesis* **2000**, 1591. (e) Tsubrik, O.; Mäeorg, U. *Org. Lett.* **2001**, *3*, 2297. (f) Kabalka, G. W.; Guchhait, S. K. *Org. Lett.* **2003**, *5*, 4129. (g) Meyer, K. G. *Synlett* **2004**, 2355.

(7) Kabalka, G. W.; Guchhait, S. K. *Org. Lett.* **2003**, *5*, 4129.

(8) Uemura, T.; Chatani, N. *J. Org. Chem.* **2005**, *70*, 8631.

(9) While preparing this manuscript, Buchwald et al. reported the employment of bis(*tert*-butyloxycarbonyl)hydrazine in a tandem Cu amidation/hydroamination sequence leading to pyrazoles: Martín, R.; Rodríguez Rivero, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079.

(10) Palladium-catalyzed cross-coupling: (a) Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, *40*, 3543. (b) Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351. (c) Lim, Y.-K.; Lee, K-S.; Cho, C.-G. *Org. Lett.* **2003**, *5*, 979. (d) Lim, Y.-K.; Jung, J.-W.; Lee, H.; Cho, C.-G. *J. Org. Chem.* **2004**, *69*, 5778. Copper-catalyzed cross-coupling: (e) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (f) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.

10.1021/ol062726r CCC: $37.00

We have recently disclosed the palladium-catalyzed amination of alkenyl bromides and chlorides.[11] This methodology, which is an extension of the well-developed Buchwald−Hartwig amination of aryl halides,[12] allows for the preparation of enamines and imines with high regio- and stereoselectivity. Continuing with our interest in the application of cross-coupling reactions of alkenyl halides with nitrogen nucleophiles,[13] we decided to focus on the preparation of *N*-alkenylhydrazines. In this communication, we report our progress in the development and optimization of a general and stereoselective method for the synthesis of this almost unknown class of hydrazines.

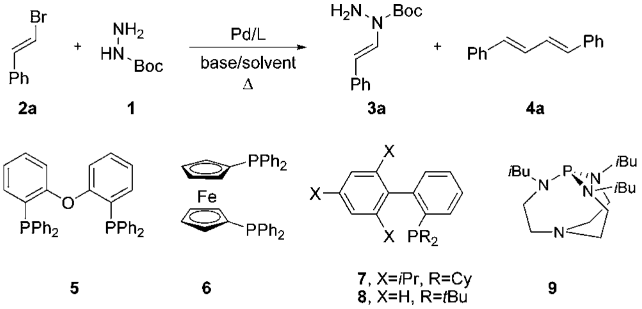
In a preliminary study we investigated the coupling between β-bromostyrene **2a** and *tert*-butyl carbazate **1** under different catalytic combinations using $Pd_2(dba)_3$ as a metal source and different supporting ligands and reaction conditions. The set of ligands included in our study consisted of P^tBu_3, chelating diphosphines, Dpephos **5** and DPPF **6**, electron-rich bulky biphenyls, Xphos **7**[14] and Johnphos **8**,[15] and Verkade's proazaphosphatrane **9**.[16]

Most of the catalytic combinations promoted the formation of the hydrazine **3a** to some extent; however, to our surprise, in some examples, apart from the desired coupling product, relatively high amounts of the Ullmann-type[17] homocoupling product **4a** were also detected (Table 1).

It is worth noting that in a way similar to the reactions with aryl halides the coupling proceeds regioselectively through the N-Boc nitrogen. Thereby, it seems that the Pd-catalyzed C−N bond forming reaction occurs upon deprotonation of the more acidic N*H*Boc proton. The requirement of an initial deprotonation step might account for the strong dependence of the reaction on the base and the solvent employed.[18]

As represented in Table 1, the best results were obtained using Cs_2CO_3 as base, DMF as solvent, and the Pd(0)/**8** catalytic combination (entries 9−11), which provided the amidation product **3a** with high selectivity and yield. A catalyst loading of 1 mol % of Pd can be used, even though the reaction rate decreases substantially (entry 11).

Table 1. Reaction of β-Bromostyrene **2a** with *tert*-Butyl Carbazate **1**[a−c]



	$Pd_2(dba)_3$ (mol % of Pd)	ligand	base	solvent	*T* (°C)	*t* (h)	**3a/4a**[d]
1	2	P^tBu_3[e]	Cs_2CO_3	toluene[f]	110	17	22:88
2	4	**5**	Cs_2CO_3	DMF	110	18	77:23
3	4	**6**	Cs_2CO_3	DMF	110	18	79:21
4	4	**7**	Cs_2CO_3	toluene	100	22	87:13
5	4	**7**	Cs_2CO_3	DMF	110	18	93:7
6	4	**7**	K_3PO_4	DMF	110	22	89:11
7	4	**7**	NaO^tBu	DMF	110	17	0:100 (36%)
8	4	**7**	NaO^tBu	DMF	110	17	0:100 (26%)[g]
9	4	**8**	Cs_2CO_3	DMF	110	10	100:0
10	2	**8**	Cs_2CO_3	DMF	110	14	100:0
11	1	**8**	Cs_2CO_3	DMF	110	21	100:0 (82%)
12	4	**9**	Cs_2CO_3	DMF	110	19	27:63
13	4	**9**	Cs_2CO_3	DMF[h,i]	110	19	0:100 (58%)[g]
14	4	−	Cs_2CO_3	DMF	110	22	0:100 (45%)

[a] Selected data from the optimization of the reaction conditions. [b] All the reactions were conducted until complete conversion of β-bromostyrene as judged by GC. [c] General reaction conditions: 0.5 mmol of β-bromostyrene; 0.6 mmol of *tert*-butyl carbazate; $Pd_2(dba)_3$ as the metal source; 2:1 molar relationship Pd/ligand; 1.4 equiv of base, 1 mL of solvent. [d] Determined by analysis of the ^1H NMR spectra of the reaction. Isolated yields are shown in brackets. [e] 1:1 molar relationship Pd/Ligand was used. [f] 2 mL of solvent was used. [g] Without *tert*-butyl carbazate in the reaction media. [h] 0.7 equiv of base was used. [i] 0.5 mL of solvent was used.

With regard to the homocoupling product **4a**, the best conditions were obtained employing Pd(0)/**9** as the catalytic combination (entry 13). Interestingly, **4a** was obtained as a unique coupling product under several different reaction conditions (entries 7, 8, 13, and 14); however, only under the conditions of entry 13, the yield was preparatively acceptable.

The scope of the reaction to synthesize *N*-alkenylhydrazines was studied using different alkenyl bromides and chlorides. Under the optimized reaction conditions, a wide variety of *N*-alkenylhydrazines were synthesized with high to moderate yields. The results are shown in Table 2.

The coupling reaction provides good results for electron-rich, electron-neutral, and electron-poor substituted β-bro-

---

(11) (a) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Chem. Commun*. **2002**, 2362. (b) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Chem. Commun*. **2004**, 1400. (c) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Chem.*−*Eur. J.* **2004**, *10*, 494. (d) Barluenga, J.; Aznar, F.; Moriel, P.; Valdés, C. *Adv. Synth. Catal.* **2004**, *346*, 1697.

(12) For recent revisions of palladium-catalyzed C−N bond forming reactions, see: (a) de Meijere, A., Diederich, F., Eds. *Metal-Catalyzed Cross Coupling Reactions*; VCH: Weinheim, 2004; Vol. 2, pp 699−760. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (c) Hartwig, J. F. *Handbook of Organopalladium Chemistry of Organic Synthesis*; Wiley-Interscience: New York, 2002; Vol. 1, pp 1051−1096. (d) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.

(13) (a) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973. (b) Barluenga, J.; Valdés, C. *Chem. Commun.* **2005**, 4891.

(14) Huang, X.; Anderson, W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

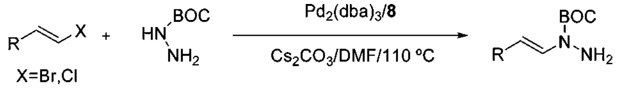
(15) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

(16) Reddy, C.; Reddy, V.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2005**, *7*, 4427.

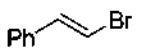
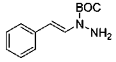
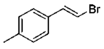
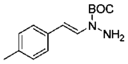
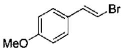
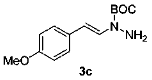
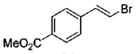
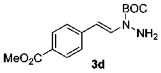
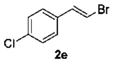
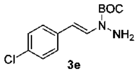
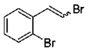
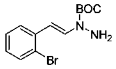
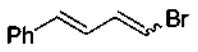
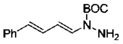
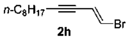
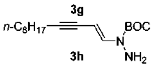
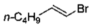
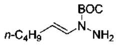
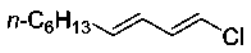
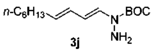
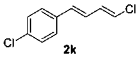
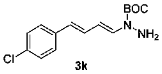
(17) For leading reviews, see: (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265.

(18) Pd-catalyzed arylations and vinylations of amides and related systems are usually best achieved employing inorganic bases such as Cs_2CO_3 and K_3PO_4: (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (b) Klapars, A.; Campos, K. R.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185 and references cited therein.

Table 2. *N-tert*-Butoxycarbonyl-*N*-alkenylhydrazines Prepared[a]



2a-k **1** **3a-k**

	alkenyl halide	*N*-alkenylhydrazine	t(h)	yield (%)[b]
1	 2a	 3a	21	82[c]
2	 2b	 3b	14	62
3	 2c	 3c	17	75
4	 2d	 3d	15	52[d]
5	 2e	 3e	15	50
6	 E/Z 94:6 2f	 3f	16	53[e]
7	 E/Z 2:1 2g	 3g	23	64[e]
8	 2h	 3h	15	62
9	 2i	 3i	15	66
10	 2j	 3j	16	60
11	 2k	 3k	14	62

[a] General reaction conditions: 0.5 mmol of haloalkene, 0.6 mmol of *tert*-butyl carbazate, 2 mol % of $Pd_2(dba)_3$; 8 mol % of Johnphos, 1.4 equiv of cesium carbonate, 1 mL of DMF, 110 °C. [b]Isolated yields, after flash chromatography. [c]Used 1 mol % of Pd for catalyst loading. [d]Reaction conducted at 90 °C. [e]Synthesized as a pure stereoisomer *E*.

mostyrenes (entries 1−6). Moreover, the reaction can be carried out in the presence of an aryl chloride (entries 5 and 11) and an aryl bromide (entry 6), given the higher reactivity of vinyl bromides over aryl halides toward oxidative addition reactions.[19] Besides, 1-bromodienes (entry 7), 4-bromoenynes (entry 8), and bromoolefins with an aliphatic group (entry 9) can be used in the same way, providing a large variety of *N*-alkenylhydrazines.

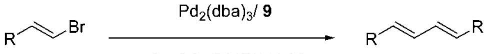
We also examined the participation of less-reactive 1-chlorodienes **2j** and **2k**. As indicated in Table 2 (entries 10 and 11), using the optimized reaction conditions for alkenyl bromides, the corresponding *N*-alkenylhydrazines were obtained with good yield. It is worth noting that the coupling reaction with chloroalkenes did not require harsher conditions or a longer reaction time.

With regard to the stereoselectivity of the process, the reactions with pure (*E*)-haloalkenes afforded the (*E*)-*N*-alkenylhydrazines as pure isomers as deduced by the ^1H NMR spectra. Interestingly, when the coupling reactions were carried out with bromodiene **2g**, which consisted of a 2:1 mixture of *E*/*Z* bromoalkenes, respectively, we observed double bond isomerization to obtain the corresponding (*E*)-*N*-alkenylhydrazine as a pure stereoisomer. Clearly, the less stable (*Z*)-isomer undergoes isomerization into the more stable (*E*)-isomer.

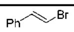
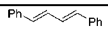
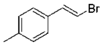
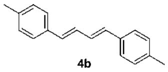
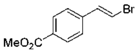
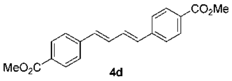
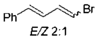
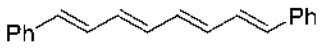
Next, we turned our attention to the homocoupling reaction. The Ullmann coupling is one of the most important tools to prepare symmetrical biaryls;[17] however, its application to the preparation of polyenes has been scarce.[20] Noteworthy is that although in most Pd-catalyzed Ullmann couplings a reducing agent is required to facilitate the regeneration of Pd(0) species, only in some particular examples the catalytic coupling takes place in the absence of an external reducing agent.[17a,21] It is believed that the solvent, in most cases DMF, plays that role. Taking into account these precedents, we decided to investigate this novel homocoupling reaction.

At this point of development, the process shows limited scope, probably due to the harsh conditions and long reaction times required, which provoked the decomposition of the alkenyl bromides in several cases. Nevertheless, several dienes could be synthesized with moderate yields (Table 3).

Table 3. Homocoupling Products Prepared through the Ullman-Type Reaction[a]



2 **4**

	alkenyl bromide	homocoupling product	t(h)	yield (%)[b]
1	 2a	 4a	22	58
2	 2b	 4b	16	56
3	 2d	 4d	22	44[c]
4	 E/Z 2:1 2g	 4g	18	68[d]

[a] See Supporting Information for reaction conditions. [b]Isolated yields, after flash chromatography. [c]Reaction conducted at 90 °C. [d]Obtained as a unique stereoisomer.

In all cases, the (*E*,*E*)-dienes were obtained as pure isomers as deduced by the ^1H NMR spectra. It is worth noting that when the homocoupling reaction was carried out with bromodiene **2g**, which is formed by a 2:1 mixture of *E*/*Z* bromoalkenes, we noticed double bond isomerization to obtain the corresponding (*E*,*E*,*E*,*E*)-tetraene as a pure stereoisomer.

---

(19) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdes, C. *Chem.*−*Eur. J.* **2005**, *11*, 2276.

(20) (a) Lee, P. H.; Seomoon, D.; Lee, K. *Org. Lett.* **2005**, *7*, 343. (b) Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W. *Org. Lett.* **2003**, *5*, 2497. (c) Banwell, M. G.; Lupton, D. W.; Ma, X.; Renner, J.; Sydnes, M. O. *Org. Lett.* **2004**, *6*, 2741.

(21) Hassan, J.; Penalva, V.; Laverot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793.

In conclusion, we have reported a new and simple methodology for the synthesis of *N*-alkenylhydrazines from readily available substrates, alkenyl bromides, and chlorides. This report establishes the first general route for the synthesis of this particular class of hydrazines, which were almost unknown in the literature. Given the usefulness of hydrazines in heterocyclic synthesis, we believe that the reaction presented herein may be of great applicability in synthetic organic chemistry.

Acknowledgment. Financial support of this work by Fundación Ramón Areces and DGI (Grant MCT-04-CTQ2004-08077-C02-01) is acknowledged. P.M. wishes to thank MEC of Spain for a predoctoral fellowship.

Supporting Information Available: Full experimental details and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062726R