ORGANIC
LETTERS

2001
Vol. 3, No. 4
511−514

Palladium(0)-Catalyzed Carbonylation–Coupling–Cyclization of Allenic Sulfonamides with Aryl Iodides and Carbon Monoxide

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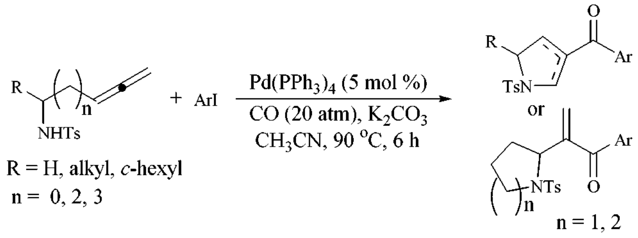
Received October 30, 2000

ABSTRACT



α-Allenic sulfonamides undergo carbonylation–coupling–*endo*-cyclization with aryl iodides in the presence of $Pd(PPh_3)_4$ (5 mol %), K_2CO_3, and CO (20 atm) to form 3-aroyl-2- or 3-pyrrolines. Alternatively the carbonylation–coupling–*exo*-cyclization of γ- and δ-substituted sulfonamides under the same conditions afforded pyrrolidine- or piperidine-substituted enones.

The palladium-catalyzed reaction of allene-substituted amine derivatives to form highly regio- and stereoselective five- and six-membered azacycles has received much attention in recent years.[1] Palladium has been reported to be an effective catalyst for the cyclization of allenes bearing a protected amino group separated from the carbon atom of the allene moiety by one to four carbon atoms.[2] Although the palladium-catalyzed cyclization of various allenic sulfonamides to yield azacycles has been well-documented, the palladium-catalyzed carbonylative cyclization of allenic sulfonamides to form heterocycles is rare. Only the palladium(II)-catalyzed cyclization of allenic amine derivatives by carbomethoxylation in the presence of carbon monoxide and methanol to form pyrrolidine or piperidine carboxylic esters is known.[3] Alternatively the acylation−cyclization of γ-allenic *p*-toluenesulfonamide by treatment of a stoichiometric amount of acyltetracarbonyl cobalt complexes from alkyl halides, carbon monoxide, and $NaCo(CO)_4$ to form the pyrrolidine-substituted enones is known.[4] Herein we wish to report the palladium(0)-catalyzed three-component carbonylation−

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(1) Review: Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3257−3282.

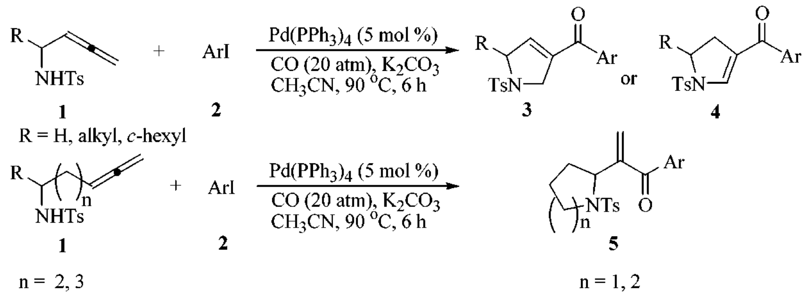
(2) (a) Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421−5424. (b) Davis, I. W.; Scopes, D. I. C.; Gallagher, T. *Synlett* **1993**, 85−87. (c) Karstens, W. F. J.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron Lett.* **1997**, *38*, 6275−6278. (d) Karstens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Hiemstra, H. *Synlett* **1998**, 1126−1128. (e) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 425 7−4260. (f) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64*, 2992−2993. (g) Rutjes, F. P. J. T.; Tjen, K. C. M. F.; Wolf, L. B.; Karstens, W. F. J.; Schoemaker, H. E.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 717−720. (h) Anzai, M.; Toda, A.; Ohno, H.; Takemoto, Y.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 7393−7397. (I) Kang, S.-K.; Baik, T.-G.; Kulak, A. N. *Synlett* **1999**, 324−326.

(3) The palladium-catalyzed methoxycarbonylation of allene-substituted amines to form pyrrolidine or piperidine carboxylic esters was known by Gallagher et al. See: (a) Gallagher, T.; Davies, I. W.; Jones, S. W.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Shaw, R. W.; Vernon, P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 433−440. (b) Fox, D. N. A.; Gallagher, T. *Tetrahedron* **1990**, *46*, 4697−4710. (c) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652−2656. (e) Lathbury, D.; Vernon, P.; Gallagher, T. *Tetrahedron Lett.* **1986**, *27*, 6009−6012.

(4) Bates, R. W.; Rama-Devi, T.; Ko, H.-H. *Tetrahedron* **1995**, *51*, 12939−12954.

10.1021/ol006796o CCC: $20.00

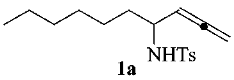
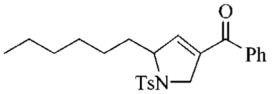
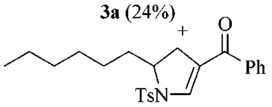
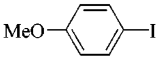
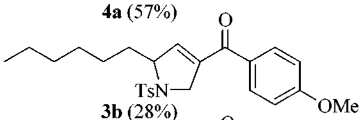
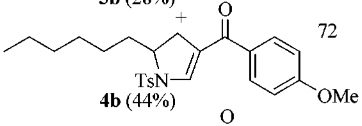
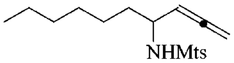
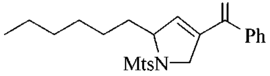
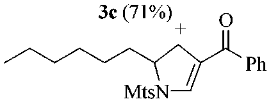
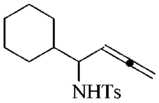
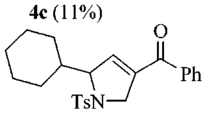
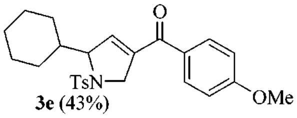
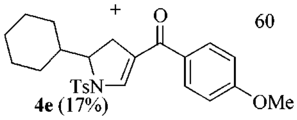
Scheme 1



coupling–cyclization reaction of α-, γ-, and δ-allene substituted *p*-toluenesulfonamide with aryl iodides and carbon monoxide to form pyrrolines, pyrrolidine, and/or piperidine heterocycles (Scheme 1).[5]

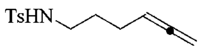
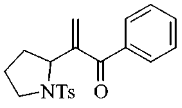
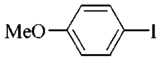
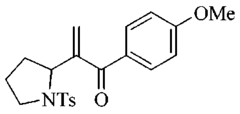
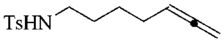
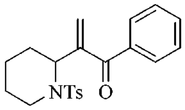
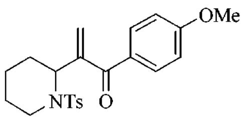
Our initial work began with α-allenic *p*-toluenesulfonamide **1a**[6] with iodobenzene under CO (atmospheric pressure) at 90 °C in CH_3CN to obtain the carbonylative cyclization product without success. After a series of experiments we found that the reaction of α-allenic *p*-toluenesulfonamide **1a** with iodobenzene at 90 °C under CO (20 atm) in CH_3CN for 6 h afforded two easily separable compounds, 3-benzoyl-3-pyrroline **3a** (24%) and 3-benzoyl-

Table 1. Pd(0)-Catalyzed Carbonylative Cyclization of α-Allenic Sulfonamide Derivatives

entry	substrate	aryl iodide	product	isolated yield (%)
1	 **1a**	PhI **2a**	 **3a** (24%) +  **4a** (57%)	81
2	**1a**	 **2b**	 **3b** (28%) +  **4b** (44%)	72
3	 **1b**[a]	**2a**	 **3c** (71%) +  **4c** (11%)	82
4	 **1c**	**2a**	 **3d**	72
5	**1c**	**2b**	 **3e** (43%) +  **4e** (17%)	60

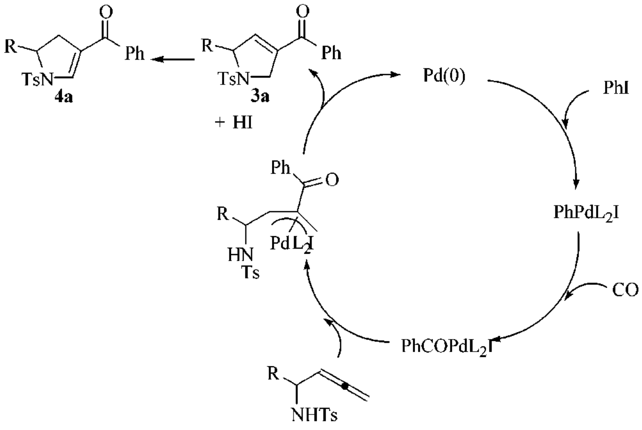
[a] The abbreviation Mts represents 2,4,6-trimethylbenzenesulfonyl.

Table 2. Pd(0)-Catalyzed Carbonylative Cyclization of γ- and δ-Allenic Sulfonamide Derivatives

entry	substrate	aryl iodide	product	isolated yield (%)
1	 **1d**	PhI **2a**	 **5a**	83
2	**1d**	 **2b**	 **5b**	91
3	 **1e**	**2a**	 **5c**	61
4	**1e**	**2b**	 **5d**	65

2-pyrroline **4a** (57%) in 81% combined yield (entry 1 in Table 1).[7-8] Presumably under the conditions with palladium the compound **3a** was isomerized to the thermodynamically more stable compound **4a**. For the formation of **3a** the plausible mechanism is shown in Scheme 2.

Scheme 2



It is presumed that oxidative addition of Pd(0) to ArI is followed by carbonylation to give PhCOPdI, which adds to the central carbon of allene moiety to provide π-allylpalladium complex. Cyclization of this intermediate by the *endo*-mode would give the pyrroline enone **3a** (Scheme 2).[9] Under the same conditions with *p*-iodoanisole the coupling and cyclization gave the two pyrrolines **3b** and **4b** in 72% combined yield (entry 2). When alkyl-substituted α-allenic mesitylsulfonyl amide **1b** was reacted with iodobenzene, 3-pyrroline derivative **3c** and 2-pyrroline derivative **4c** were afforded in 71% and 11% (total 82%) yields, respectively

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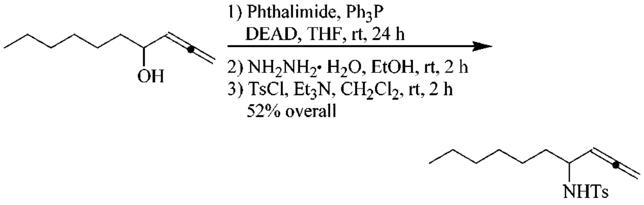
(5) The palladium(0)-catalyzed cyclization−carbonylation−coupling of aryl halides and γ-hydroxyallenes to form aryl(tetrafuran-2-yl)vinyl ketones is known. See: Walkup, R. D.; Guan, L.; Kim, Y. S.; Kim, S. W. *Tetrahedron Lett.* **1995**, *36*, 3805−3808.

(6) The α-allenic *p*-toluenesulfonamide **1a** was prepared from deca-1,2-diene-4-ol by Mitsunobu reaction followed by deprotection and tosylation in 52% yield.



(7) The same reactions and conditions under CO (10 atm) at 90 °C in CH$_3$CN for 18 h gave **3a** and **4a** in 42% yield. As the solvent, DMF can be used to ovtain the similar products and yields.

(8) **Typical Procedure.** A stainless autoclave was charged with α-allenic *p*-toluenesulfonamide **1a** (100 mg, 0.33 mmol), CH$_3$CN (3 mL), iodobenzene (99.4 mg, 0.49 mmol), K$_2$CO$_3$ (179 mg, 1.30 mmol), and Pd(PPh$_3$)$_4$ (18.7 mg, 5 mol %) and flushed with 20 atm of CO three times. It was then pressurized to 20 atm, and the reaction mixture was stirred at 90 °C for 6 h. The mixture was cooled and then quenched with saturated NH$_4$Cl solution. The reaction mixture was extracted with ether (20 mL × 3), and the organic layer was dried over anhydrous MgSO$_4$ and evaporated in vacuo. The crude product was separated by SiO$_2$ column chromatography (hexanes/EtOAc, 6:1) to give 3-pyrroline **3a** (32 mg, 24%) and 2-pyrroline **4a** (76 mg, 57%). Walkup et al. suggested two possible mechanisms for cyclization−coupling between aryl halides and γ-hydroxyallenes (ref 4).

(9) The mechanistic path via an η^3-allylpalladium(II) complex is considered to be operative for intermolecular coupling nucleophilic reaction with amines. See: (a) Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233−236. (b) Cazes, B. *Pure Appl. Chem.* **1990,** *62*, 1867−1878. (c) Larock, R. C.; Berrios-Pena, N. G.; Fried, C. A. *J. Org. Chem.* **1991,** *56*, 2615−2617. Alper et al. suggested that the initial addition of aroylpalladium to allene is followed by nucleophilic attack of the hydroxy group in the carbonylation of *o*-iodophenol with allenes. See: Okuro, K.; Alper, H. *J. Org. Chem.* **1997**, *62*, 1566−1567.

(entry 3). In the case of cyclohexyl-substituted α-allenic sulfonamide **1c**, the same coupling and cyclization with iodobenzene under CO (20 atm) at 90 °C in CH_3CN for 6 h provided 3-benzoyl-2-pyrroline **3d** in 72% as the sole product (entry 4). However, with *p*-iodoanisole as an electrophile two products, **3d** and **4d**, were obtained in 43% and 17% yields, respectively (entry 5). The results of carbonylation−coupling−cyclization of α-allenic sulfonamide derivatives are summarized in Table 1.

Our carbonylation−coupling−cyclization method was extended to γ- and δ-allenic *p*-toluenesulfonamides **1d** and **1e,** and the results are summarized in Table 2. When γ-allenyl *p*-toluenesulfonamide **1d** was treated with iodobenzene under CO, the pyrrolidine-substituted enone **5a** was provided in 83% yield (entry 1). The structure of **5a** was unambiguously confirmed by X-ray crystallography (Figure 1). When *p*-iodoanisole was utilized under the same conditions, the pyrrolidine **5b** was obtained (entry 2). Alternatively, when δ-allenyl *p*-toluenesulfonamide **1e** was reacted with iodobenzene, the piperidine-substituted enone **5c** was afforded (entry 3). Finally, for the *p*-iodoanisole, carbonylation gave the *p*-anisole-substituted enone **5d** (entry 4). A plausible mechanism for the formation of **5a** is that this reaction may occur by addition of an aroylpalladium intermediate to the allene unit of the allenic *p*-toluenesulfonamide **1e** to produce a η^3-allylpalladium species, which undergoes nucleophilic attack via the *exo*-mode by *p*-toluenesulfonamide group to produce the cyclized product **5a** (Scheme 3).

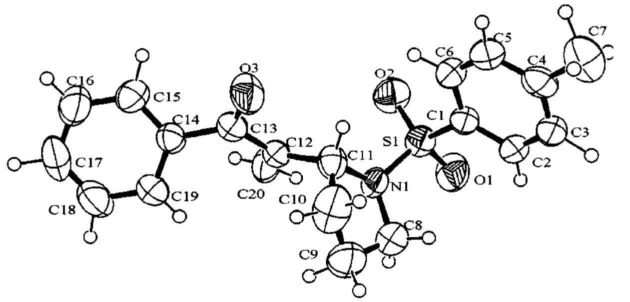
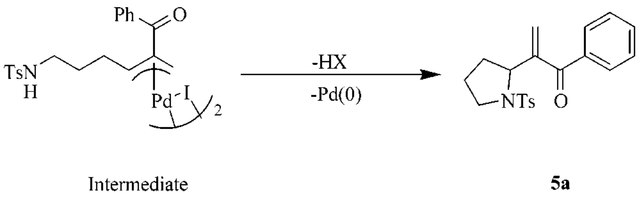


Figure 1. ORTEP drawing of **5a**.

Scheme 3



In conclusion, the palladium(0)-catalyzed carbonylation−coupling−cyclization of allenic *p*-toluenesulfonamides with aryl iodides under CO (20 atm) to give substituted pyrrolines and pyrrolidine or piperidine enones was accomplished.

Acknowledgment. Generous financial support from KOSEF-CMDS (Center for Molecular Design and Synthesis) is gratefully acknowledged.

Supporting Information Available: Typical experimental procedures and characterization for **3a−4e** and **5a−d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006796O