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Palladium-Catalyzed Coupling/Cyclization Reactions of Allene-Substituted Lactams

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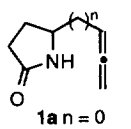
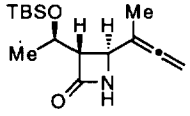
Abstract: ω-(2,3-Butadienyl)lactams react with aryl iodides in the presence of *n*-Bu_4NCl, K_2CO_3 and a catalytic amount of $Pd(PPh_3)_4$ to give bicyclic enamides resulting from attack of nitrogen on the central carbon and transfer of the aryl group to the terminal carbon atom of the allene.

Allenes constitute an interesting class of organic compounds with unusual chemical properties due to their two cumulated double bonds.[1] An interesting example which recently caught our attention, is the palladium-catalyzed reaction of allenes with organic halides (or triflates) in the presence of different nitrogen nucleophiles.[2-4] Several years ago, we reported an efficient synthesis of allene-substituted lactams of type **1a** *via* acid-induced reaction of ω-ethoxylactams with propargyltrimethylsilane.[5] We recently set out to investigate the possibility of palladium-catalyzed cyclizations of γ-lactams **1**. Precedent for this reaction type was found in the work of Prasad and Liebeskind,[2f] who have converted β-lactam **2** into the carbapenem skeleton **3** by reaction with excess allyl bromide and catalytic palladium acetate. In this paper we report our first results, featuring an unprecedented type of allene cyclization with NC-bond formation taking place at the central allene carbon atom.



1a n = 0
1b n = 1



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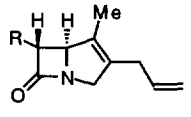

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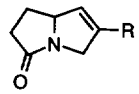

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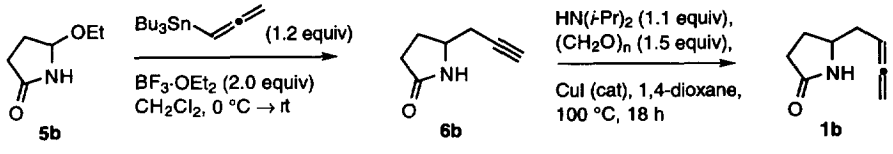
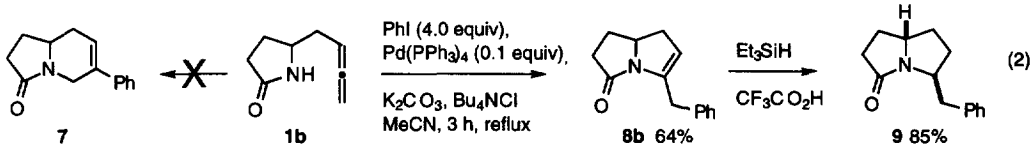
Our first experiments were aimed at the cyclization of **1a**[5] according to the published protocol[2f] to arrive at structures of type **4**. However, we were unable to effect a successful cyclization in this manner. Moreover, the use of the conditions developed by Gallagher and coworkers[2d] for related cyclizations of allenic amides (iodobenzene, catalytic Pd(0), base, DMF, 70 °C) were equally ineffective when applied to **1a**.



5b **6b** **1b** (1)

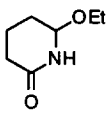
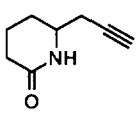
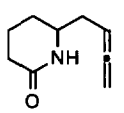
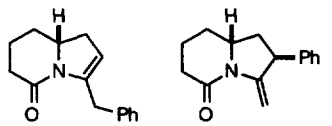
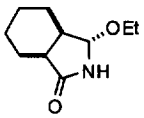
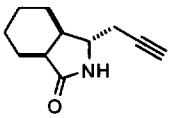
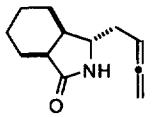
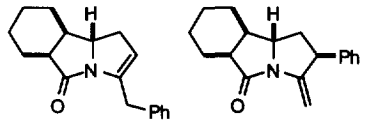
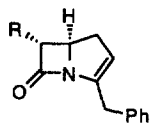
Being unable to achieve a successful cyclization of **1a**, we directed our attention to ring closure reactions of the homologous allene **1b**. Its synthesis (eq 1) involved an *N*-acyliminium coupling of 5-ethoxypyrrolidinone (**5b**) with propadienyltributyltin,[2f] followed by a Crabbé reaction[6] to give **1b** in 53% overall yield.[7] Much to our satisfaction, application of the Gallagher conditions to **1b** gave a clean reaction to produce a major product as a colorless oil in 64% yield (eq 2).



7 **1b** **8b** 64% **9** 85% (2)

Surprisingly, the obtained product was not the anticipated compound **7**, but the 5,5-bicyclic system **8b**. Strong indications for the formation of the five-membered ring were the position of the olefinic proton in the ^{1}H NMR spectrum at remarkably high field (br s, δ ($CDCl_3$) = 4.79 ppm) and the presence of a clear AB-system for the benzylic protons (δ ($CDCl_3$) = 3.87, 3.97 ppm, J = 16.1 Hz).[8] Additional evidence was obtained by smooth reduction of the enamide double bond (Et_3SiH, CF_3CO_2H) to give the pyrrolizidine derivative **9** in 85% yield. Evidently, opposite to the previously observed reactivity of allenes, the amide nitrogen reacts at the central carbon atom of the allenic moiety, while the phenyl group is transferred to the terminal position. To the best of our knowledge, this represents the first example of a nitrogen atom reacting with the central carbon atom of an allene under palladium-catalyzed conditions.

Table 1. Precursors and cyclizations of ω-(2,3-butadienyl)lactams.

Entry	Ethoxy lactam	Propargyl lactam (yield)	ω-(2,3-butadienyl) lactam (yield)	Cyclization products Ratio **8/10**[c]	Yield (8+10)
1	 **5c**	 **6c** (94%)	 **1c** (73%)	 **8c/10c** 88/12	46%
2	 **5d**	 **6d** 93%	 **1d** 90%	 **8d/10d**[d] 93/7	72%
3	**5e** R = H, X = OBz	**6e** 63%[a]	**1e** 65%	 **8e**[e]	73%
4	**5f** R = (*R*)-CH(OTBS)CH_3, X = OAc	**6f** 85%[a,b]	**1f** 24%	**8f**[e]	79%

[a]TMSOTf was used as the Lewis acid. [b]See: reference 2f. [c]Based on ^{1}H NMR data of the crude reaction mixture. [d]Stereochemistry tentatively assigned as shown, based on **10c**. [e]Only one isomer observed by ^{1}H NMR.

In order to investigate the scope of this reaction, a number of cyclization precursors were prepared following the reaction sequence shown in eq 1. The starting ethoxy lactams were either prepared *via* known

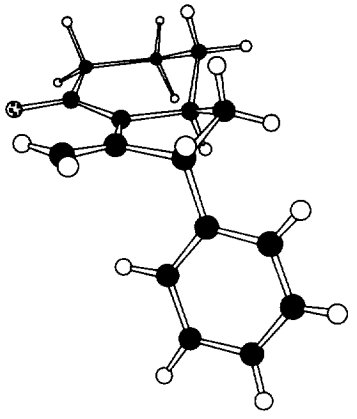
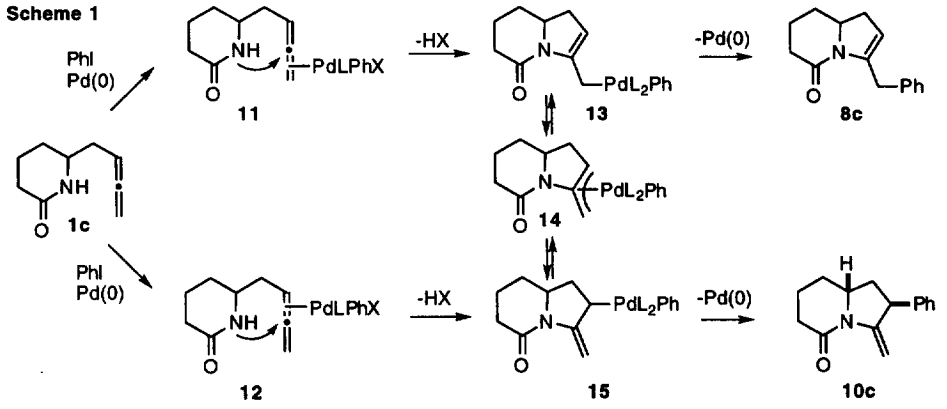


Figure 1. Chem3D™ representation of the crystal structure of **10c**.

procedures (**5c** and **d**),[9] or were commercially available (**5e** and **f**). The yields of the conversions into the cyclization precursors **1c-f** and the results from application of the aforementioned conditions (Pd(0), PhI) are summarized in Table 1. In contrast with the pyrrolidinone-derived allene **1b**, allenes **1c** and **d** did not only lead to the expected enamides **8c** and **d**, but also to small amounts of isomeric products **10c** and **d**, in which the phenyl group was transferred to the internal sp^2-carbon of the allene and an exocyclic double bond was formed (entries 1 and 2). The structure of the minor isomer **10c** was proven unambiguously by X-ray crystallography (Fig. 1), thereby confirming the formation of the NC-bond at the central carbon atom of the allene.[10] The cyclization of the β-lactams **1e** and **f** (entries 3 and 4) proceeded cleanly to give the carbapenems **8e** and **f**, without formation of the other isomer. The slightly higher yields in these cases might be attributed to the higher nucleophilicity of the β-lactam nitrogen atom. Although other aryl iodides (such as 1-iodonaphthalene) behaved in a similar manner as iodobenzene, extension of this methodology to vinyl halides appeared to be troublesome. Vinyl bromides sofar proved to be virtually ineffective under the standard conditions and use of 2-iodo-1-heptene led to the desired product in only 23% yield.

A rationale for this unprecedented behavior of allenes is detailed in Scheme 1 starting from **1c**. The phenylpalladium(II) halide (formed *in situ* from iodobenzene and Pd(0)) complexes to the terminal double bond of the allene, rendering the olefin sufficiently electrophilic to undergo nucleophilic attack[11] by the tethered amide nitrogen atom (*viz.* **11**) leading to intermediate **13**. Reductive elimination of Pd(0) then leads to the major isomer **8c**. Formation of **10c** can be explained likewise through activation of the internal allene double bond. Alternatively, it is conceivable that the shown π-allylpalladium complex **14** (formed *via* isomerization of one of the σ-allylpalladium complexes) plays a role in this mechanism.

Scheme 1



Walkup[4] and Gallagher[2d] have previously suggested this type of activation of an allenic double bond by an *in situ* formed organopalladium(II) halide. The formation of their products could also be explained by a different mechanism, which proceeds *via* a π-allylpalladium intermediate as proposed by Tsuji[2g] and Cazes.[3] In our case, however, it is clear that the latter mechanism does not take place because this would lead to products of type **7**.

In summary, we have shown that ω-(2,3-butadienyl)lactams readily cyclize under the influence of an *in situ* formed organopalladium(II) species with the lactam nitrogen reacting at the central allene carbon atom,

thus giving rise to several pyrrolizidine, indolizidine and carbapenem derivatives. We are currently working to further elucidate the mechanistic details and establish the synthetic possibilities of this type of reaction.

Acknowledgement: J. Fraanje and K. Goubitz (Laboratory of Crystallography, University of Amsterdam) are gratefully acknowledged for the X-ray structure determination. These investigations were supported (in part) by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

References and Notes

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2. (a) Desarbre, E.; Mérour, J-.Y. *Tetrahedron Lett.* **1996**, *37*, 43; (b) Larock, R.C.; Zenner, J.M. *J. Org. Chem.* **1995**, *60*, 482; (c) Kimura, M.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1995**, *60*, 3764; (d) Davies, I.W.; Scopes, D.I.C.; Gallagher, T. *Synlett* **1993**, 85; (e) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1992**, *60*, 6377; (f) Prasad, J.S.; Liebeskind, L.S. *Tetrahedron Lett.* **1988**, *29*, 4257; (g) Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233.
3. For carbon nucleophiles, see *e.g.*: (a) Vicart, N.; Cazes, B.; Goré, J. *Tetrahedron Lett.* **1995**, *36*, 5015 and references cited therein; (b) Cazes, B. *Pure Appl. Chem.* **1990**, *62*, 1867.
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5. Hiemstra, H.; Fortgens, H.P.; Speckamp, W.N. *Tetrahedron Lett.* **1984**, *25*, 3115
6. Searles, S.; Li, Y.; Nassim, B.; Lopes, M.T.R.; Tran, P.T.; Crabbé, P. *J. Chem. Soc. Perkin Trans 1* **1984**, 747.
7. All new compounds were appropriately characterized with IR, ^{1}H and ^{13}C NMR and HRMS data.
8. Representative procedure for the cyclization of allene **1b**: Under an argon atmosphere, a mixture of **1b** (137 mg, 1.0 mmol), K_2CO_3 (553 mg, 4.0 mmol), PhI (816 mg, 4.0 mmol), Bu_4NCl (416 mg, 1.5 mmol) and $Pd(PPh_3)_4$ (0.1 mmol) in MeCN (20 mL) was refluxed for 2-3 h (TLC showed complete conversion). The mixture was cooled, diluted with water (25 mL) and extracted with ether (3 × 25 mL). The combined ether extracts were washed with water (25 mL) and brine (25 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, EtOAc/hexanes 1:2) afforded 137 mg (64%) of **8b** as a colorless oil. IR (neat) ν_{max} 1639, 1395, 1340 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.29 (m, 5 H), 4.79 (br s, 1 H), 4.38-4.46 (m, 1 H), 3.97 (AB, *J* = 16.1 Hz, 1 H), 3.87 (AB, *J* = 16.1 Hz, 1 H), 2.67-2.76 (m, 1 H), 2.43-2.53 (m, 2 H), 2.24-2.33 (m, 2 H), 1.85-1.94 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 142.1, 138.0, 129.1, 128.2, 126.4, 111.6, 64.0, 37.1, 34.9, 33.8, 29.0; MS (EI, 70 eV) *m/z* (relative intensity) 213 (M^+, 100), 158 (63), 91 (77), 84 (27). HRMS calculated for $C_{14}H_{15}NO$ 213.1154, found 213.1149.
9. Hubert, J.C.; Wijnberg, J.B.P.A.; Speckamp, W.N. *Tetrahedron* **1975**, *31*, 1437.
10. X-ray data for **10c**: $C_{15}H_{17}NO$, M_r = 227.3, monoclinic, Cc, a = 12.994(2), b = 9.907(1), c = 10.371(2) Å, β = 111.36(1)°, V = 1243.4(3) Å^3, Z = 4, D_x = 1.21 gcm^{-3}, λ(CuKα) = 1.5418 Å, μ(CuKα) = 5.57 cm^{-1}, F(000) = 488, -25 °C. Final R = 0.040 for 1064 observed reflections. Further details were deposited by the editor at the Cambridge Crystallographic Data Centre.
11. For electrophilic activation of acetylenes and olefins by organopalladium(II) species, see: (a) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B.R. *J. Org. Chem.* **1992**, *57*, 976. (b) Luo, F.-T.; Schreuder, I.; Wang, R.-T. *J. Org. Chem.* **1992**, *57*, 2213; (c) Bruyère, D.; Gaignard, G.; Bouyssi, D.; Balme, G.; Lancelin, J.-M. *Tetrahedron Lett.* **1997**, *38*, 827 and references cited therein.

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