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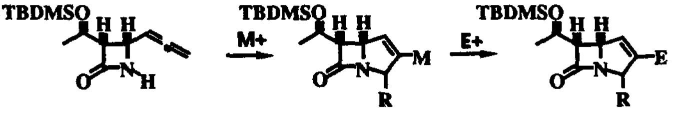
Palladium Mediated Formation of Δ^1- and Δ^2-Carbapenems by Cyclofunctionalization of 4-Allenylazetidinones and 4-(2-Propynyl)azetidinones.

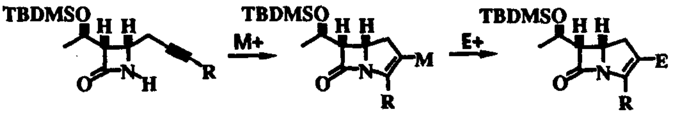
*by J. Siva Prasad and Lanny S. Liebeskind**[1]
Department of Chemistry
Emory University
Atlanta, Georgia 30322

Abstract: A palladium catalyzed cyclofunctionalization of a 4-allenylazetidinone to Δ^1-carbapenems and of 4-(2-propynyl)-azetidinones to Δ^2-carbapenems is described. A palladium(+2) catalyst induces nucleophilic closure of the azetidinone nitrogen on a pendant allene or alkyne, and the resulting vinyl palladium intermediate reacts in a subsequent step with allyl halides or activated alkenes (CH_2=CH-E, E = COOEt, COMe, CHO, CN) to provide 2-functionalized carbapenems. The allylation is catalytic in palladium, while the reaction with CH_2=CH-E, as currently performed, is stoichiometric in palladium.

In the preceding paper we showed that 4-allenylazetidinones and 4-(2-propynyl)azetidinones would undergo Ag^+ catalyzed cyclization to Δ^1-carbapenems and Δ^2-carbapenems, respectively (eqs. 1 and 2, $M^+ = Ag^+$, $E^+ = H^+$).[2] In this reaction, the presumed intermediate vinylsilver species suffers rapid protonation by acid generated under the conditions of the reaction. The ability to intercept the intermediate vinylmetal with reagents other than H^+ might allow a novel method of carbapenem synthesis by cyclofunctionalization. To achieve this goal we have explored a palladium mediated variant of the reactions shown in equations 1 and 2 (M^+ = Pd+2).[3]

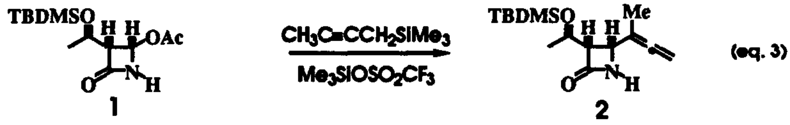


(eq. 1)



(eq. 2)

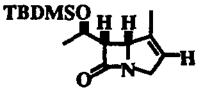
The palladium induced intramolecular addition of nitrogen and oxygen nucleophiles to allenes and alkynes has been used effectively for the synthesis of a variety of heterocycles.[4] To apply this chemistry to the synthesis of carbapenems, 4-allenylazetidinone **2** was prepared by the $Me_3SiOSO_2CF_3$ facilitated addition of $Me_3SiCH_2C{\equiv}CCH_3$ to 4-acetoxyazetidinone **1**[5] (eq. 3).[6,7]



1

2

Treatment of allene **2** with a variety of palladium(+2) reagents gave only traces of the Δ^1–carbapenem **3**, in contrast to the use of $AgBF_4$ which produced **3** in 70% yield.[2] However, in the presence of excess allyl bromide (5 equiv), **2** was transformed into **4** (60%) by the action of catalytic amounts (10%) of either $PdCl_2$ or $Pd(OAc)_2$ at rt in CH_2Cl_2 under argon. In a similar fashion, treatment with 1-chloro-2-methyl-2-propene gave carbapenem **5** in 40% yield. It is presumed that these transformations occur by initial palladium induced N–C3 bond formation to form **6**, followed by insertion of the allyl halide into the intermediate vinyl palladium complex to give **7**, which undergoes β-elimination producing the observed products and regenerating an electrophilic palladium(+2) catalyst.



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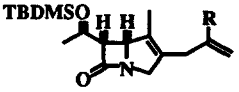
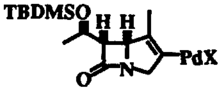


4, R = H
5, R = Me



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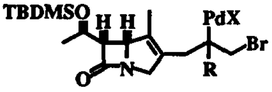
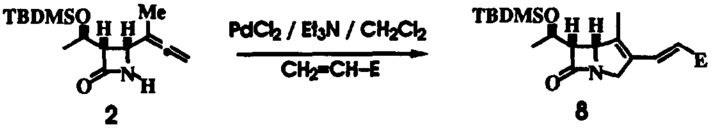


7

Synthetically useful transformations were also observed by trapping the vinyl palladium species **6** in a Heck-type reaction[8] with activated olefins. On treatment with stoichiometric $PdCl_2$, 1.5 equiv of Et_3N, and 5 equiv. CH_2=CH–E in CH_2Cl_2 at rt, allene **2** was transformed into the substituted Δ^1-carbapenems **8** (Table).

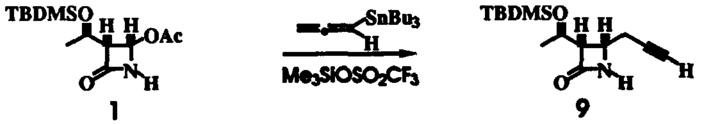
Table. Cyclofunctionalization of Allene 2 to Δ^1-Carbapenems 8.



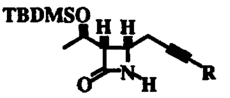
entry	8, E =	yield 8, %
1	COOEt	46
2	$COCH_3$	46
3	CHO	40
4	CN	53[a]

[a] isolated as a 3:1 mixture of *E/Z* double bond stereoisomers

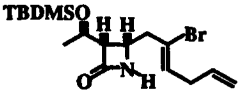
The palladium induced cyclofunctionalization procedure was extended, with only marginal success, to Δ^2-carbapenem formation from 4-(2-propynyl)azetidinones. The parent alkyne **9** was prepared by the $Me_3SiOSO_2CF_3$ catalyzed addition of allenyltri-n-butylstannane to **1** in 85% yield (eq. 4).[9] Terminal alkyne **9**, in turn, was converted into substituted alkynes **10–13**.[10] Reaction of **9** with palladium(+2) reagents and added allyl halides or activated alkenes did not lead to the production of Δ^2-carbapenems. However, compound **14** was isolated from the reaction of **9** with 10% $Pd(OCOCF_3)_2$ and 5 equivalents of allyl bromide in CH_2Cl_2 at rt.[11] No palladium mediated reaction was observed using either azetidinone **10** or **11**. On the other hand, aryl substituted alkynes **12** and **13** behaved according to plan on treatment with 10% $Pd(OAc)_2$ and 5 equiv. of allyl bromide in CH_2Cl_2 at reflux and provided, albeit in very low yields, the unstable Δ^2-carbapenems **15** and **16** (15% and 18%, respectively).



1 **9** (eq. 4)



10, R = Me **12**, R = Ph
11, R = SiMe₃ **13**, R = 4-methoxyphenyl



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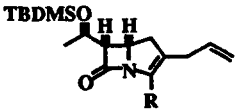

15, R = phenyl
16, R = 4-methoxypheny

Although, as currently constituted, the reactions described in this manuscript require further optimization, the palladium mediated cyclofunctionalization of 4-allenylazetidinones and 4-(2-propynyl)azetidinones provides a novel organotransition metal approach for the synthesis of Δ^1- and Δ^2-carbapenems.

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References and Notes

1 Fellow of the Alfred P. Sloan Foundation, 1983-1987; Camille and Henry Dreyfus Foundation Teacher-Scholar, 1986-1991.

2 Prasad, J. S.; Liebeskind, L. S. Tetrahedron Lett., 1988, preceeding paper in this issue.

3 An alternative palladium catalyzed route to carbapenems can be found in: Trost, B. M.; Chen, S-F. J. Am. Chem. Soc., **1986**, *108*, 6053–6054.

4 (a) Walkup, R. D.; Park, G. Tetrahedron Lett., **1987**, *28*, 1023–1026. (b) Lathbury, D.; Vernon, P.; Gallagher, T. Tetrahedron Lett., **1986**, *27*, 6009–6012. (c) Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H. J. Am. Chem. Soc., **1986**, *108*, 2753–2754. (d) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H.; Tetrahedron, **1985**, *41*, 3655–3661. (e) Sheng, H.; Lin, S.; Huang, Y. Tetrahedron Lett., **1986**, *27*, 4893–4894. (f) Lambert, C.; Utimoto, K.; Nozaki, H. Tetrahedron Lett., **1984**, *25*, 5323–5326. Utimoto, K. Pure & Appl. Chem., **1983**, *55*, 1845–1852.

5 We thank Bristol–Myers, France, for a generous supply of compound **1**.

6 Treatment of 4-acetoxyazetidinone **1** with 3 equiv of 1-trimethylsilyl-2-butyne and 1.9 equiv of trimethylsilyltriflate in CH_2Cl_2 at -5°C gave the allene **2** in 65% yield.

7 All new compounds were fully characterized by IR and high field ^1H NMR spectroscopy and by high resolution mass spectroscopy.

8 Heck, R. F. Acc. Chem. Res., **1979**, *12*, 146–151.

9 Preparation: Treatment of 4-acetoxyazetidinone **1** with 2.1 equiv allenyltri-n-butylstannane and 1.9 equiv of $Me_3SiOSO_2CF_3$ in CH_2Cl_2 at rt gave **9** in 85% yield. Compound **9** was previously prepared by the addition of propargylmagnesium bromide to 4-(phenylsulfonyl)azetidinone: Shibasaki, M.; Nishida, A.; Ikegami, S. J. Chem. Soc., Chem. Commun., **1982**, 1324. This reaction proved problematic in our hands.

10 **10**: Compound **9** was treated with t-butyldimethylsilyl chloride, Et_3N, DMF at rt to give the N-protected azetidinone in 89% yield. Methylation of the terminal alkyne was accomplished by deprotonation with $LiN(SiMe_3)_2$ in THF at -40°C followed by addition of $CH_3OSO_2CF_3$ (90% yield) and then selective desilylation of the protected nitrogen atom ($n\text{-}Bu_4N^+F^-$, THF, rt) gave compound **10** in 60% yield.

11: Treatment of terminal alkyne **9** with 2 equiv of $LiN(SiMe_3)_2$ in THF followed by a $ClSiMe_3$ quench gave the product of trimethylsilylation of both the terminal alkyne and the azetidinone nitrogen. Treatment of this compound with acid washed Al_2O_3 produced the desired trimethylsilylalkyne **11** in 87% yield over two steps.

C-Arylation of the terminal alkyne was accomplished according to the following procedure adapted from Dieck, H. A.; Heck, R. F. J. Organometal. Chem., **1975**, *93*, 259: a mixture of the terminal alkyne (1.0 equiv), aryl halide (0.96 equiv), CuI (0.022 equiv), and $PdCl_2(PPh_3)_2$ (0.022 equiv) were suspended in Et_3N and stirred under argon at rt until starting material disappeared.

12: from **9** and iodobenzene in 94 % yield. **13**: from **9** and p-iodoanisole in 86% yield.

11 This reaction is precedented: Kaneda, K.; Kawamoto, F.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. Tetrahedron Lett., **1974**, 1067; Kaneda, K.; Utchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. J. Org. Chem., **1979**, *44*, 55.

Note Added: After submission of this manuscript, a relevant article describing the palladium catalyzed ring closure and subsequent allylation of 2-alkynylindoles appeared: Iritani, K.; Matsubara, S.; Utimoto, K. Tetrahedron Lett., **1988**, 1799.

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