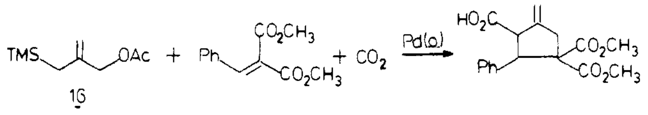
= CO_2^-) may accept the second trimethylsilyl group to generate the substituted TMM–Pd species **4** E = CO_2SiMe_3. Desilylation of the silyl esters anticipated as the initial products during workup accounts for the ultimate products. The regioselectivity of the cycloaddition is anticipated based upon our earlier observations[9] as well as the recent work of Tsuji.[2a] Since Tsuji has shown that the carbomethoxy-substituted TMM–Pd species could be generated by deprotonation compared to desilylation,[2a] we briefly examined the reaction of the parent acetate **16** in the presence of carbon dioxide. However, yields of carboxylated cycloadduct according to eq 6 were only 10% or less. Apparently, the silyl-substituted TMM–Pd precursor **1** favorably balances the reactivity of **2** toward carbon dioxide vis-à-vis electron-deficient olefins. The stereospecificity of this reaction reopens the question of the concertedness of this Pd-catalyzed cycloaddition. Synthetically, the opportunity to functionalize the TMM–Pd intermediate in concert with the cycloaddition expands the scope of this approach to cyclopentanoids.[10]



(6)

Acknowledgment. We thank the National Science Foundation, the National Institutes of Health, and Rhone-Poulenc for their generous support of our programs.

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[9] Trost, B. M.; Nanninga, T. N.; Satoh, T. *J. Am. Chem. Soc.* **1985**, *107*, 721.

[10] For a recent overview, see: Paquette, L. A. *Recent Synthetic Developments in Polyquinane Chemistry*; Springer-Verlag: Berlin, 1984. Ramaiah, M. *Synthesis* **1984**, 529.

A Synthesis of Substituted Pyrrolidines via a Palladium(2+)-Catalyzed Cyclization. An Unusual Approach to a Carbapenem

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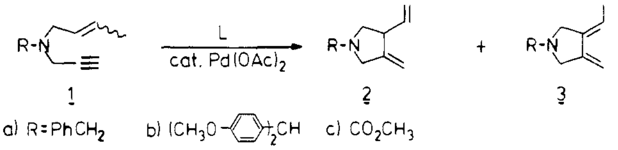
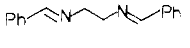
Five-member ring nitrogen heterocycles represent a highly common structural unit of many natural products including such diverse types as the pyrrolizidine alkaloids[1] and the carbapenems[2] (e.g., thienamycin[3]). While the presence of a basic nitrogen frequently inhibits reactions catalyzed by higher oxidation states of transition metals, we wish to report that palladium acetate efficiently cyclizes nitrogen-substituted 1,6-enynes to form substituted pyrrolidines including the very sensitive carbapenem nucleus.[4]

In order to explore the feasibility of the reaction as a function of the substituent on nitrogen, we reacted the crotyl propargyl amine derivatives **1a–c** with 5 mol % of palladium acetate and 10 mol % of triphenylphosphine in benzene-d_6 (~0.5 M) at 65 °C for approximately 1 h. The initial substrate **1a** gave a 75% yield of a mixture of **2a**[5] and **3a**[5] in a 2:1 ratio which is invarient with reaction time, indicating no interconversion by isomerization. The formation of the 1,3-diene stands in contradistinction to our earlier observations[4a] in the carbocyclic case which led us to predict formation of only the 1,4-diene **2a**. Increasing the effective steric bulk (i.e., **1b**) or planarizing nitrogen (i.e., **1c**) has no effect on this ratio (1b gave 2b/3b in 2.8:1 ratio; **1c** gave **2c**/**3c** in 2:1 ratio). Variation of phosphine ligands among tri-*o*-tolyphosphine, triphenylphosphine, and dppb[6] gave a slight increase in **2a** vs. **3a** from 1.6:1 to 2.5:1. A major improvement arose in switching to the nitrogen ligand **4**[7] which produces a 9:1 ratio of **2a**/**3a**. Trisubstituted olefin **5a** gave only the 1,4-diene **6**[5] even with the phosphine ligands.





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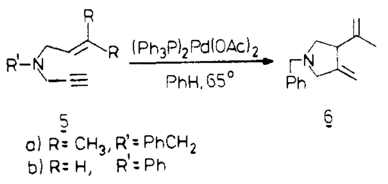
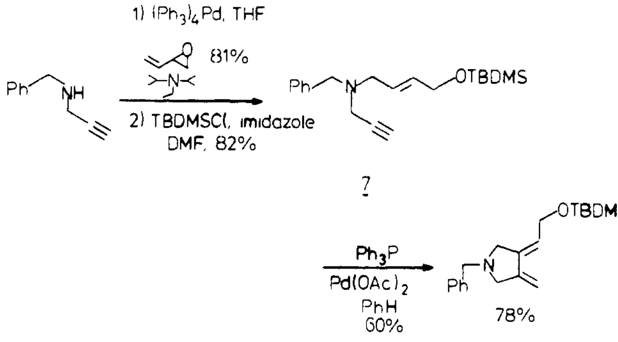


Allylic oxygen substituents have a strong directive effect. A Pd(0)-catalyzed alkylation readily provided the enyne **7**. Its cyclization produced exclusively the 1,3-diene **8**.[5] We tentatively attribute this regioselectivity to the electron-withdrawing inductive effect of oxygen which inhibits the β-H insertion by an extremely electrophilic palladium.[8] The parent 2,3-dimethylenepyrrolidine (**9**)[5] was also readily available by a similar cyclization of **5b**.



The ease of availability of the requisite enyne combined with the ability to generate both 1,3- and 1,4-dienes as products enhances the utility of this process. Equations 1–4 (Scheme I) illustrate the ability to annulate a pyrrolidine ring onto either a carbocyclic or heterocyclic ring. In these examples, many of the ring systems created have relevance to alkaloids. For example,

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[1] Warren, F. L. *Fortschr. Chem. Org. Naturst.* **1966**, *24*, 239. Robins, D. J. *Ibid.* **1982**, *41*, 115.

[2] Southgate, R.; Elson, S. *Progr. Chem. Org. Nat. Prod.* **1985**, *47*, 1.

[3] Albers-Schonberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E. Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491.

[4] For carbocycle formation by cyclization of 1,6-enynes, see: (a) Pd: Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. (b) Zr: Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *Ibid.* **1985**, *107*, 2568. (c) For cyclopentenone formation in reactions of enynes and cobalt, see: Billington, D. C.; Pauson, P. L. *Organometallics* **1982**, *1*, 1560.

[5] Full spectral characterization has been obtained on all new compounds. Unless otherwise noted elemental composition has been determined by high-resolution mass spectroscopy or combustion analysis.

[6] dppb = 1,4-bis(diphenylphosphino)butane.

[7] The efficacy of this ligand in these reactions has been established by Mr. David Jebaratnam in these laboratories and will be discussed in a future publication.

[8] Trost, B. M.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1985**, *107*, 4586. For the effect of phosphines on β-hydrogen insertion in the Heck reaction, see: Chalk, A. J.; Magennis, S. A. *Catal. Org. Synth.* **1977**, *6th*, 139.

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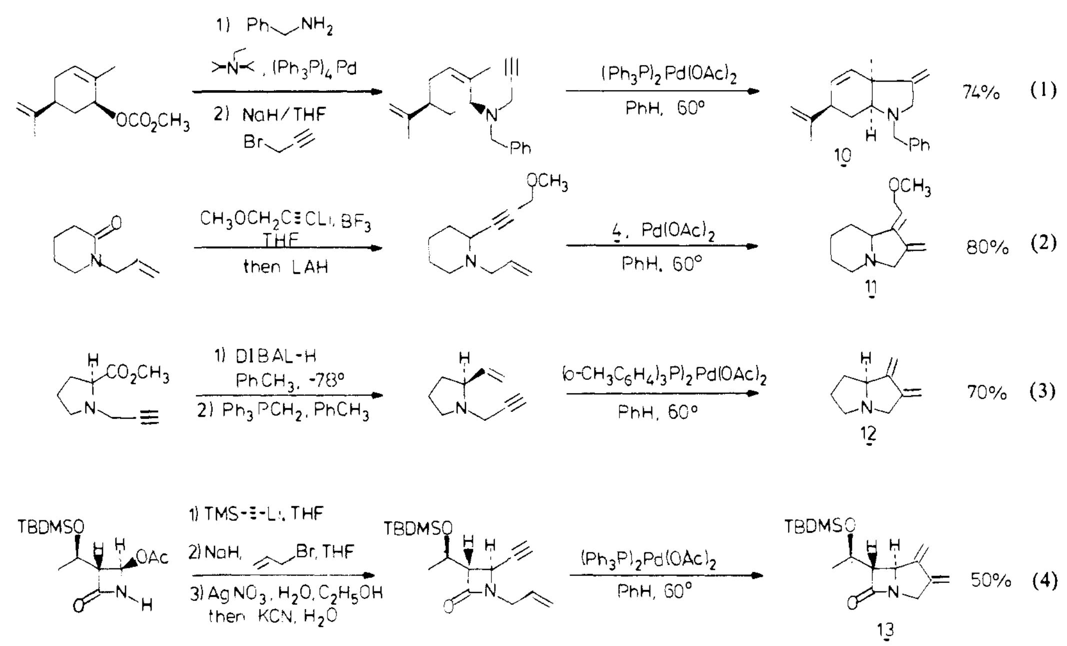
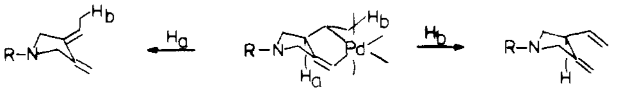
Scheme I



the bicyclic skeleton of **10**[5] corresponds to the core ring of dendrobium alkaloids as represented by dendrobine itself.[9] The indolizidine skeleton of **11**[5] may represent a bicyclic nucleus of diverse alkaloids.[10–13] The pyrrolizidine skeleton of **12** is the ring nucleus of many alkaloids of current interest.[1] The mildness of the reaction conditions is highlighted by the successful formation of the carbapenem nucleus of **13**,[2] eq 4, by formation of the C(3)–C(4) bond.[2,14] This success is even more striking in light of a recent report where an attempt to form a similar carbapenem nucleus via a palladium-catalyzed addition of a vinyl bromide onto an olefin failed.[14]

While the mechanism of this reaction remains unknown, invoking a palladacycle such as **14** as an intermediate allows understanding of the origin of both the 1,3- and 1,4-dienes which control experiments establish as kinetic products.[4a,15,16] Whereas,



14

the allylic hydrogen H_a in **14** represents the weakest bond and therefore the most likely bond for migration, steric hindrance in inserting into a tertiary hydrogen combined with the conformational restraints of the palladacyclopentene disfavor the process leading to the 1,3-diene in favor of inserting into H_b to give the 1,4-diene. The substantial amount of 1,3-diene formed in the case of **1** with phosphine ligands compared to the previously examined carbocycles may reflect more of the intrinsic electronic bias for H_a insertion as a result of greater conformational mobility and less steric hindrance in this heterocyclic system. Nevertheless, it could be controlled by ligand manipulation. As noted, the presence of an oxygen on the carbon bearing H_b as in **7** inhibits insertion into the C–H_b bond.[8] It appears that this electronic effect of oxygen on the regioselectivity is general and may be conveniently exploited as a regiochemical control element. The ability to generate nitrogen heterocycles under such mild conditions greatly expands the applicability of this cyclization to five-membered rings via palladium-catalyzed isomerization especially combined with Pd(0)-catalyzed alkylations to generate the requisite substrates.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, and the National Science Foundation for their generous support of our programs. We thank Drs. Burton Christensen and Frank DiNinno of Merck Sharp and Dohme Research Laboratories for a generous gift of the β-lactam starting material of eq 4.

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(14) For a recent example, see: Knight, J.; Parsons, P. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1986**, 78.

(15) Trost, B. M.; Lautens, M. *Tetrahedron Lett.* **1985**, *26*, 4887.

(16) For palladacyclopentanes, see: Diversi, P.; Ingrosso, G.; Luccherini, A.; Murtas, S. *J. Chem. Soc., Dalton Trans.* **1980**, 1633.

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Asymmetric Synthesis of β-Lactams and the Carbapenem Antibiotic (+)-PS-5

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The condensation of ester enolates with aldimines is an effective method for preparing β-lactams.[1–8] Attempts to obtain optically

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