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On the Regioselectivity of Pd Catalyzed Intramolecular Carbametalations

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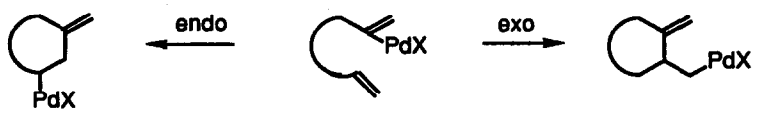
Summary: Whereas 1,6-enynes possessing disubstituted acetylenes cyclize under Pd catalysis via a 5-exo-trig mode, such cyclizations of 1,6-enynes possessing a terminal acetylene favor the equivalent of a 6-endo-trig mode.

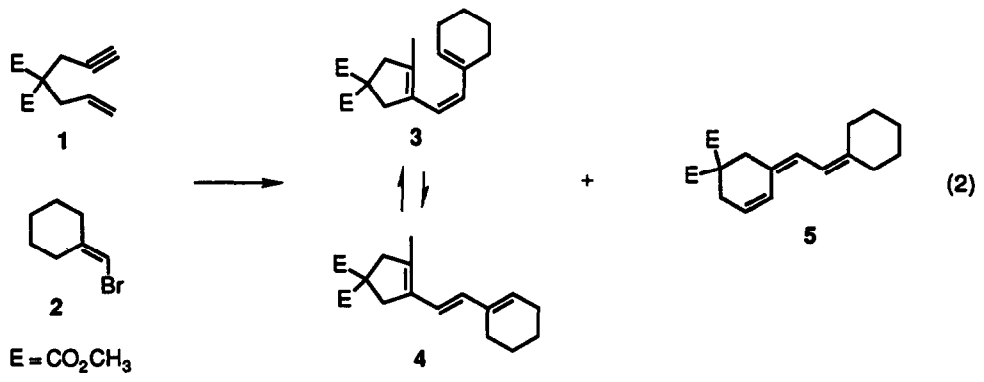
Cyclizations involving intramolecular carbapalladation of olefins and acetylenes as a key step in a catalytic cycle are proving of tremendous value for ring formation.[1-5] The regioselectivity which determines ring size is normally assumed to be determined by the constraints of the ring system to favor an exo type of addition even



(1)

though in unconstrained systems such additions might prefer the opposite regioselectivity such as with monosubstituted olefins (eq 1).[4] We wish to record that in an alkylative cyclization of 1,6-enynes,[5] both pathways may be observed[3] and that the endo addition mode provides a strategy to a novel vitamin D analogue.[6]

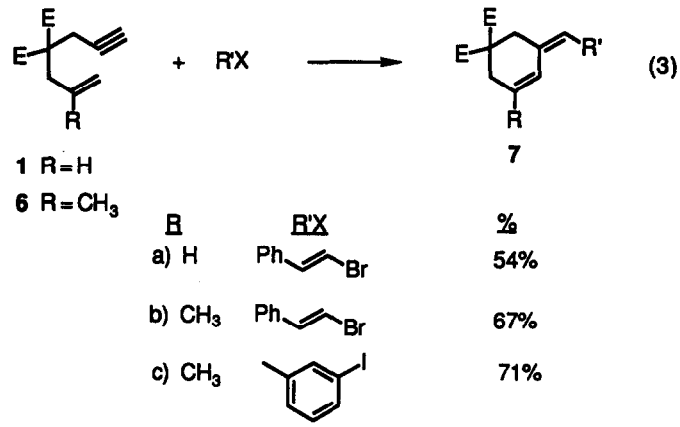
Whereas, 1,6-enynes possessing a disubstituted acetylene cyclized via a 5-exo-trig carbapalladation,[5] the terminal acetylene **1** undergoes alkylative cyclization with vinyl bromide **2** catalyzed by a Pd(0) complex generated from Ph_3P (15 mol%) and $Pd(OAc)_2$ (5 mol%) in 1:1 triethylamine-toluene via both the 5-exo-trig (3 + 4)[7] and 6-



(2)

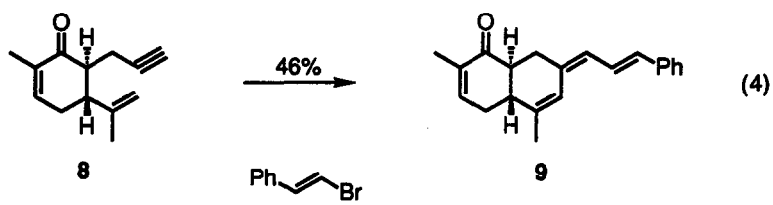
endo-trig (5)[7] mode in a 2.3:1 ratio (eq 2). Switching to a catalyst derived from $(dba)_3Pd_2 \cdot CHCl_3$ (3.4 mol%) and Ph_3P (20 mol%) in 1:1 triethylamine-toluene inverts the selectivity to favor formation of the 6-endo-trig product 5 (3 + 4 : 5 = 1: 2).

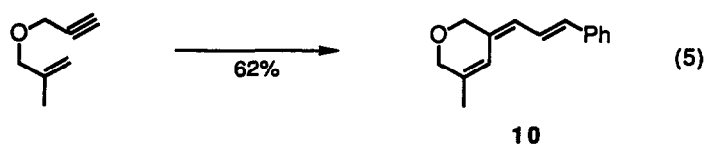
Using the latter conditions, alkylative cyclization of 1 with styryl bromide gives the 6-endo-trig product 7a[7] as the only cyclization product. Introduction of a vinylic methyl group in the enyne as in 6 does not inhibit the 6-



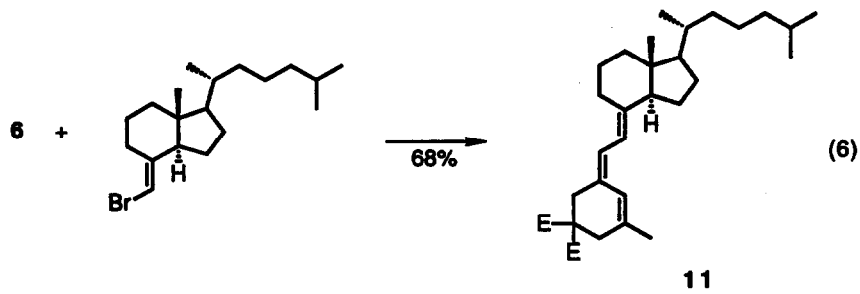
endo-trig mode as shown in the cyclizations with both styryl bromide and 3-iodotoluene to give the 6-endo-trig products 7b[7] and 7c.[7]

Excellent chemoselectivity is observed as shown in the above examples and by the formation of the hexalone 9[7] derived from the propargylated carvone enyne 8 (eq 4). An oxygen heterocycle 10[7] can also be synthesized

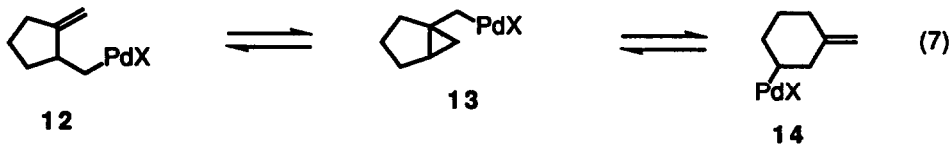




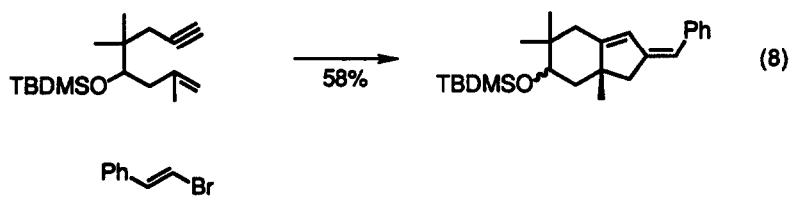
by this method (eq 5). The 6-endo-trig path provides access to potentially interesting Vitamin D analogues. The vinyl bromide[8] obtained from Grundmann's ketone gives the triene 11[7] in 68% isolated yield (eq 6). In all cases, the exocyclic double bond possesses a single geometry assigned as Z based upon nmr chemical shifts.



Two mechanisms can be envisioned for the formation of these 6-endo products. The simplest invokes a direct carbapalladation to the six membered ring. The differential formation of the 5-exo vs. 6-endo product then derives from variation of ligands on palladium. Based upon the effect of the catalyst choice on the 5-exo vs. 6-endo mode, it would appear that pre-coordination of the internal double bond to palladium favors 5-exo attack; whereas, direct carbapalladation favors 6-endo attack. On the other hand, the 6- endo product may derive by



isomerization of the organopalladium intermediate first formed upon 5-exo addition (i.e. 12) as depicted in eq 7 via a cyclopropane 13 to give the complex 14 which then becomes the precursor of the 6-endo product. This suggestion appears attractive in light of several reports of isolating cyclopropane containing products derived in such fashion.[2,3] Normally β-hydrogen elimination had been precluded in such cases but need not be precluded in our alkylative cyclization (cf enyne 1). Furthermore, there is no a priori reason not to isolate cyclopropyl products in our cases nor to expect exclusive geometrical control of the exocyclic double bond. The fact that 1,7-enynes only undergo exo-type addition to give ultimately a novel bicyclization (eq 8)[9] rather than an isomerization analogous to that depicted in eq 7 would require the inability of the six membered analogue to undergo a



similar isomerization - a conclusion for which there is no obvious explanation. While additional studies are required to resolve the mechanistic details of the 6-endo process, synthetically it provides a new dimension to our alkylative cyclization.

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9. Dumas, J. unpublished observations in these laboratories. This reaction represents a convenient bicyclization to perhydroindanes.

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