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CATALYTIC INTRAMOLECULAR 2-(4-ALKENYL)ALLYLPALLADIUM INSERTIONS 1)

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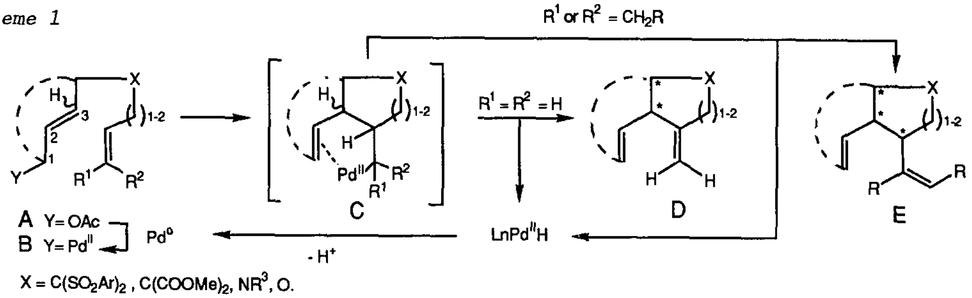
Abstract: Pd(0)-catalyzed cyclizations of 1-acetoxy-2-methylene-6-heptenes(3 → 4 , 18 → 19) are consistent with a allylpalladium/olefin insertion involving a metal-transfer to the distal alkene terminal. Cyclization 7 → 8 exemplifies a new stereocontrolled access to exocyclic trisubstituted alkenes which indicates a C,C-bond formation at the less substituted allylpalladium terminal thus showing a regio- and stereochemistry opposite to the type-II-magnesium-ene process 12 → 14.

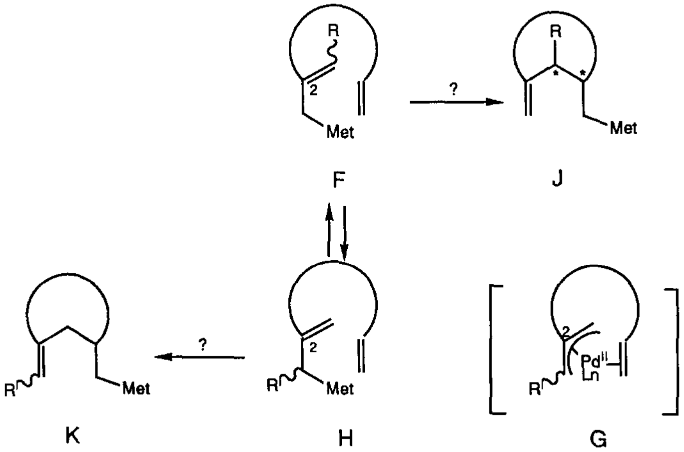
As part of a program directed towards the exploration of intramolecular transition-metal-allyl/alkene(alkyne) insertions 2) we have described the smooth, palladium(0)-catalyzed conversions of allylacetates to carbo- 1,2a,b,c) and heterocyclic 1,2d) systems (A → D and A → E, Scheme 1).

Scheme 1



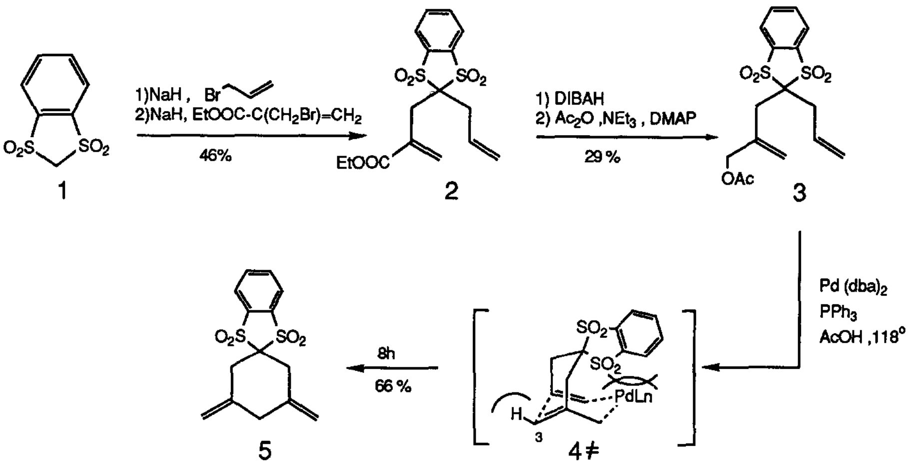
These transformations, where the olefinic bridge is tied to the terminal (C3) of the allyl unit, are consistent with the operation of a type-I-palladium-ene step 3) (B → C). We also considered the feasibility of an analogous type-II-cyclization 3) *i.e.* the insertion of an allyl-Pd species 4) (G or F or H) into an alkene, attached by a tether to C(2) (Scheme 2).

Scheme 2



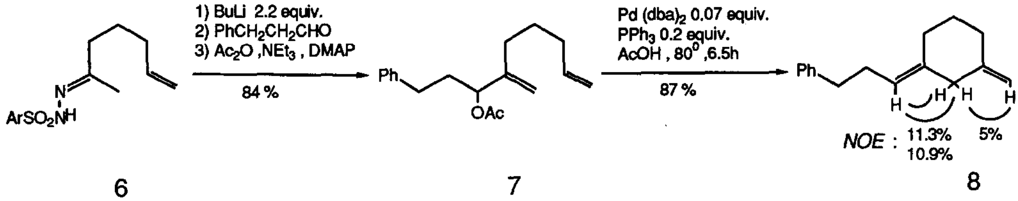
Employing disulfone 1 as a convenient CH_2^{2-} building block 5) successive alkylations [1) NaH, DMF, 20°, 40 min; 2) allylbromide, 5°, 30 min, 88%, m.p. 130 - 132°; 3) ethyl 2-bromomethylacrylate (1.25 equiv), NaH (1.0 equiv), THF, 20°, 30 min] gave dienylester 2 6) (m.p. 86.5 - 87°, 52%) which on reduction and acetylation [1) DIBAL (3 equiv), THF, -78°, 2h, -20° 5h, +20° 12h, 51%, m.p. 121-122°; 2) Ac_2O (1 equiv), NEt_3 (1 equiv), DMAP (0.12 equiv), THF, +20°, 30 min] afforded dienyl acetate 3 6) (56%, m.p. 85.5 - 87°).

Scheme 3



Heating 3 with $Pd(dba)_2$ (0.07 equiv) and PPh_3 (0.2 equiv) in AcOH at 118° for 8h furnished the expected "palladium-ene" / β-elimination product 5 6). The excellent regioselectivity of the "ene" process with regard to the "enophile" (*i.e.* C,C-bond formation with the nearer and metal transfer to the distal enophile terminal) parallels the corresponding type-II-magnesium-ene cyclization (F → J, Met = MgCl, R = H) 7). However, the reaction conditions, required for the conversion 3 → 5 were relatively harsh which we attribute to a steric repulsion between the PdL_n (or 3-CH_2) and sulfone groups in transition state $4^{\#}$ 8). Accordingly, it should be of advantage to minimize the steric demand of the bridge which links the two reaction partners.

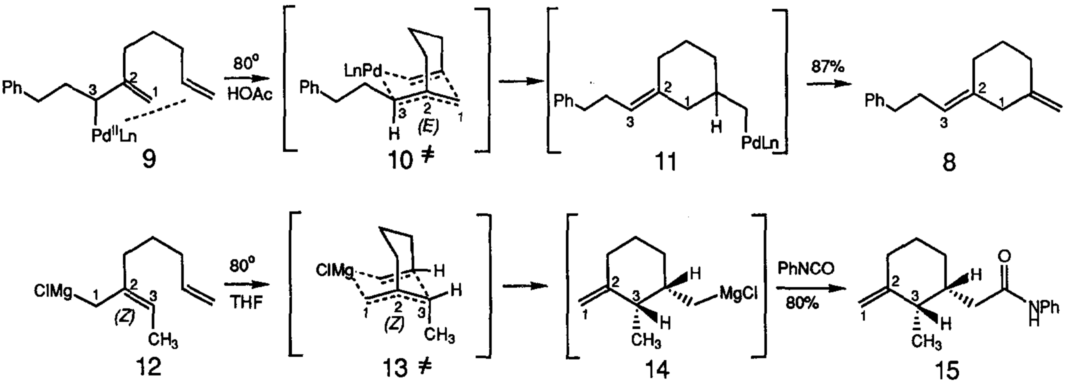
Scheme 4



*B*amford-Stevens-Shapiro reaction of trisylhydrazone 6 6) trapping of the non-isolated vinyllithium intermediate 9) with 3-phenylpropanal and acetylation [1) *n*-BuLi (2.2 equiv), THF, -78°, 45 min, 0°, 15 min; addition of 3-phenylpropanal (1.25 equiv), 20 min 0°, 88%; 2) Ac_2O (1.5 equiv), NEt_3(1.5 equiv), DMAP (0.05 equiv), 4h 20°] gave dienylacetate 7 6) (84% from 6) where the potential ene- and enophile units are linked by three simple methylene groups.

Indeed, 7 cyclized under milder conditions [Pd(dba)$_2$ (0.07 equiv), PPh$_3$ (0.2 equiv), AcOH, 80°, 6.5 h] giving, to our surprise, *(E)*-1,4-diene 8 6) as the exclusive regio- and stereoisomer. This stereocontrolled preparation of an exocyclic trisubstituted alkene apparently involves C,C-bond formation with the less substituted C(1) of an allylpalladium unit 10,11) 9 → 10 # → 11 (Scheme 5). Accounting for a relatively fast 1,3-Pd-shift F ⇌ H, Met = Pd(II) (*via* G, Scheme 2) it appears that only the isomer H, Met = Pd cyclizes to give *(E)*- K, Met = Pd(II).

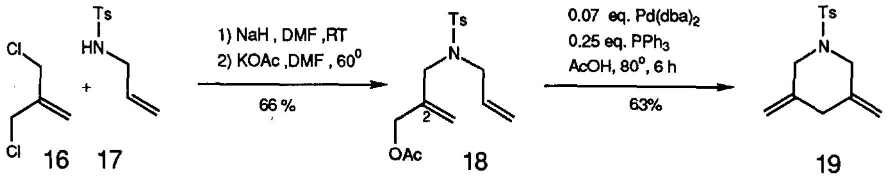
Scheme 5



In contrast, type-II-magnesium-ene processes show the opposite regio- and stereochemistry relative to the metallo-ene unit as illustrated by the conversion 12 → 15. Accordingly, among the rapidly equilibrating allylmagnesium isomers F ⇌ H, Met = MgCl 12) it is the *(Z)*-regioisomer F which forms a carbon bond at the more substituted C(3) to afford *cis*-J (12 → 13# → 14).

This comparison highlights the complementary nature of the type-II-allylmagnesium *versus* allylpalladium / alkene cyclizations which may be put to advantage in organic synthesis.

Scheme 6



Scheme 6 6) exemplifies the compatibility of the palladium catalyzed process with a nitrogen atom as part of the bridge 13) which opens further perspectives in alkaloid synthesis.

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8) Attempted cyclization of the *gem*-bis-phenylsulfone analogue of 3 failed which illustrates the comparatively modest bulk of the 1,3-benzodithiole tetraoxide moiety ref 5).

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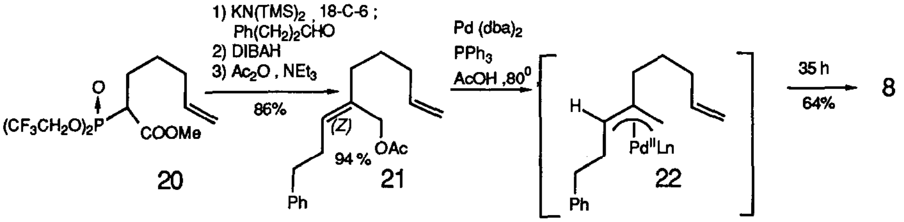
10) Methyl oleate and *(Z)*-1-phenyl-1-heptene did not isomerize to their *(E)*-isomers on heating with Pd(PPh$_3$)$_4$ (0.07 equiv) at 80° in AcOH for 16h which indicates that the *(E)*-configuration of 8 is formed under kinetic control.



21, prepared from 20 *via* a modified Horner olefination (W.C.Still, C.Gennari, *Tetrahedron Lett.* 1983, *24*, 4405) required 35 h to afford only the same *(E)*-product 8. Hence, the initially formed *(Z)*-allylpalladium intermediate 22 did not cyclize to give the *(Z)*-isomer of 8 but rather isomerizes slowly (*e.g. via* 7) to give 8 *via* 10# 11).

11) Direct π-allylpalladium/olefin insertion of *syn*-G cannot be excluded.

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