Addition–Cyclization catalysed by Palladium(II)

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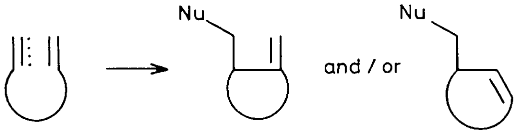
Palladium catalysed nucleophilic additions to 1,6-dienes and a 1,6-enyne lead to cyclization in preference to β-hydrogen insertion; a novel cyclization of a 1,6-enyne to a 1,2-dimethylenecyclopentane is also reported.

Metal catalysed additions to alkenes, highlighted by the Wacker oxidation[1,2] and the Heck reaction,[2,3] create a new carbon–metal bond which normally reacts by β-hydrogen insertion. Trapping of such a species by CO in the case of Wacker-type reactions has been successful[4] but not in the Heck reaction since the CO scavenges the aryl (or vinyl) palladium before addition to the alkene.[5] The possibility that intramolecular trapping by a second unsaturation could compete with β-hydrogen insertion could lead to a valuable cyclization approach, equation (1). Recent work has illustrated the participation of a neighbouring double bond in a Wacker reaction[6] and in a reaction invoking hydropalladation as an initial step.[7]† We report a study of a variety of palladium initiated additions to alkenes and alkynes that could cyclize onto a second proximal double bond as an approach for cyclization.



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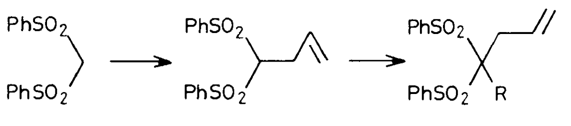

(2)

(1); a, R = $CH_2CH{=}CH_2$
b, R = $CH_2C(Me){=}CH_2$
c, R = $CH_2C{\equiv}CH$
d, R = $CH_2CH{=}CHPh$

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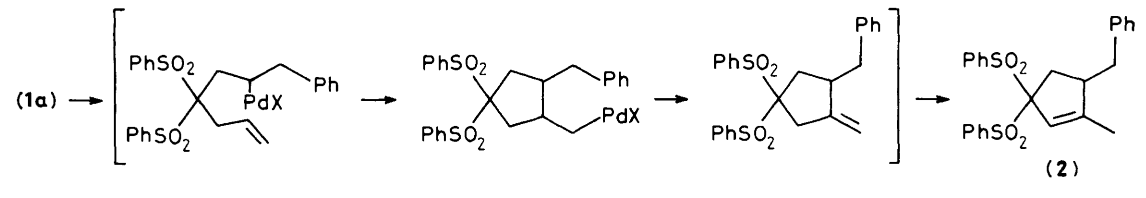
† In contrast to reactions of the type illustrated in equation (1), intramolecular variants of Heck, Wacker, and related reactions are known. See references 1—3.



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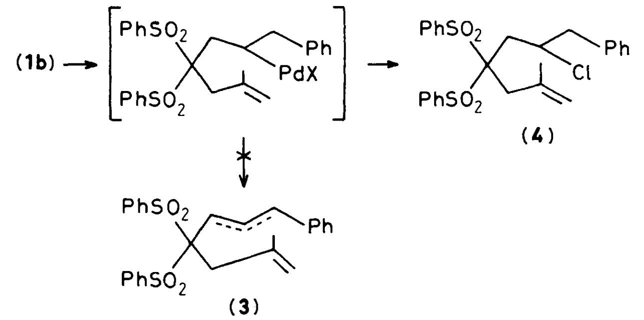

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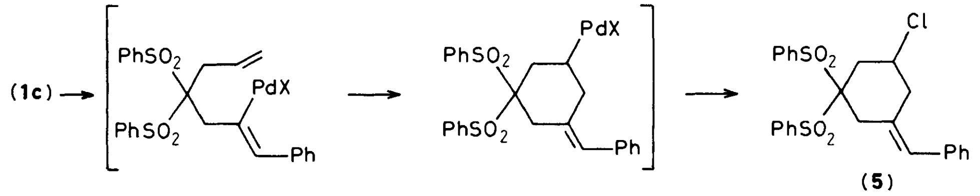

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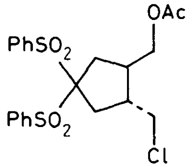

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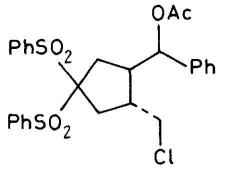

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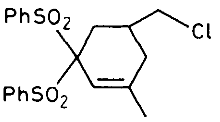

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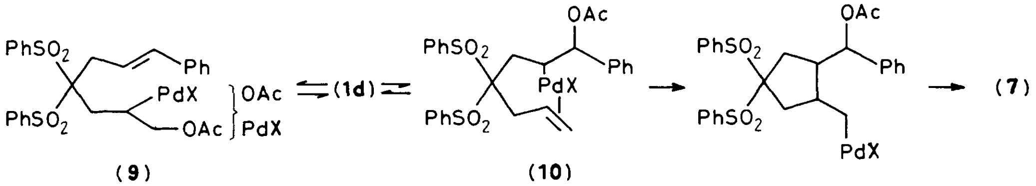

(6)

For ease of preparation and handling, as well as subsequent synthetic flexibility, we chose bis-alkylated sulphones (**1**) as substrates. Phase transfer alkylation [equation (2), Bu_4NOH, CH_2Cl_2, H_2O, allyl bromide, room temp.] gives the crystalline products (**1**) [(**1a**) m.p. 98—98. 5 °C, 80%; (**1b**) m.p. 98.5—99 °C, 86%; (**1c**) m.p. 141—141.5°, 66%; (**1d**), m.p. 124—124.5 °C, 77%].‡

Heck arylation of (**1a**) (PhHgCl, $CuCl_2$, 10 mol% $PdCl_2$, tetrahydrofuran, room temp.) gives a 50% yield of a crystalline cyclized product (**2**), m.p. 155—156 °C.‡ The ^1H n.m.r. spectrum is particularly diagnostic [δ 7.96—7.86 (m, 4H), 7.71—7.48 (m, 6H), 7.29—7.18 (m, 3H), 7.03—7.01 (m, 2H), 5.38 (s, 1H), 2.84 (dd, *J* 14, 2 Hz, 1H), 2.68—2.55 (m, 2H), 2.33—2.24 (m, 1H), 1.96 (dd, *J* 14,11 Hz, 1H), and 1.74 (s, 3H)]. As outlined in equation (3), exactly the desired sequence transpired. The isomerization of the exocyclic double bond under such conditions is expected, but the double bond position, which presumably is thermodynamically controlled, is surprising and may result from relief of non-bonded interactions related to the geminal sulphone grouping.§ More polar solvents which generally improve the Wacker reaction are either detrimental (in dimethylformamide) or have little effect (MeOH, HOAc) here.

Not unexpectedly, the cyclization shows a sensitivity to steric effects such that when (**1b**) is employed, no cyclization occurs, equation (4). The typical Heck product resulting from β-hydrogen insertion (**3**) does not form. Instead, a 66% yield of the product resulting from chlorinolysis, (**4**), m.p. 62—64 °C, results.

With substrate (**1c**) an alkene and an alkyne compete for the initial addition, equation (5). The ^1H and ^{13}C n.m.r. spectra establish (**5**), m.p. 141.5—142 °C, as the structure of the

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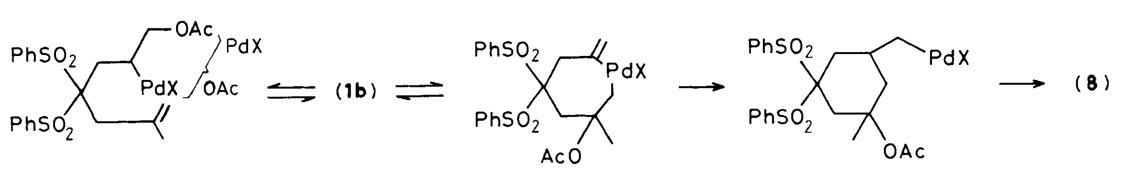
‡ All new compounds have been fully characterized spectrally and elemental composition established by combustion analysis and/or high resolution mass spectroscopy.

§ For a related observation with an unexpected thermodynamic bias in enolization of a 3,3-disubstituted cyclopentanone see G. Stork, W. C. Still, and J. Singh, *Tetrahedron Lett.*, 1979, **20**, 5077.



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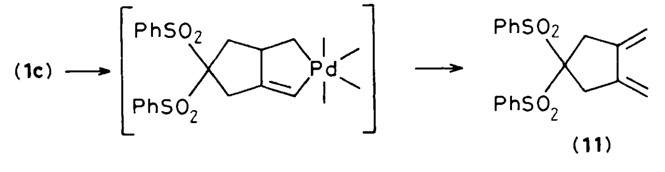

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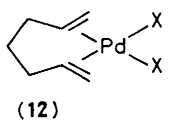

(12)

product except for the alkene geometry which is assigned on mechanistic considerations. This result establishes the higher reactivity of the alkyne.¶ However, a 6-*endo–trig* cyclization now prevails over a 5-*exo–trig*.[9] Again, chlorinolysis of the Pd–C bond dominates over β-hydrogen insertion.

For comparison, Wacker type conditions were also investigated. Treatment with 10 mol% $Pd(OAc)_2$ and 10 fold excess of $CuCl_2$ as reoxidant in acetic acid converts (**1a**) into the chloroacetate (**6**), m.p. 129 °C, in 56% yield. Unexpectedly, (**1d**) gives (**7**), m.p. 171—171.5 °C, rather than the alternative chloroacetate, equation (6). ^1H and ^{13}C N.m.r. spectroscopy establish the structure. For example, (**6**) shows the ^1H and ^{13}C chemical shifts for the CH_2 next to acetate at δ_H 4.05 and δ_C 63.4 compared to δ_H 3.58 and δ_C 44.8 for the CH_2Cl unit. For (**7**), the shifts of δ_H 3.40 and δ_C 44.7 establish the CH_2Cl unit; the CHOAc exhibits the corresponding absorptions at δ_H 5.81 and δ_C 73.5. Previous work suggests that (**9**) should be kinetically favoured. The obtention of products *via* (**10**) may indicate that the initial addition is reversible and the product determining step depends on the rate of cyclization. Intermediate (**10**) invokes addition to the less substituted double bond which should be kinetically faster. Support for such an interpretation derives from reaction of (**1b**) which does cyclize (in contrast to reaction under Heck conditions) but to give the six membered ring chloride (**8**), m.p. 146.5—147 °C (δ_H 3.48, δ_C 48.7) as in equation (7). As in equation (6), initial addition to the less substituted double bond, a preference seen in the Heck arylation (*vide supra*), is followed by product formation arising from rapid cyclization of the adduct to the more substituted alkene.

Exposure of the enyne (**1c**) to Pd^{II} leads to a totally different pathway to give (**11**), m.p. 144 °C (decomp.), as shown in equation (8). Synthetically, the best conditions involve 5 mol% $Pd(OAc)_2$ and 7.5 mol% Ph_3P in benzene.[10]

Except for the special cases of norbornadiene and cycloocta-1,5-diene,[2] Pd-catalysed addition of carbon nucleophiles to α,ω-dienes normally led to β-hydrogen insertion being faster than cyclization.[11] Our results suggest that useful intramolecular trapping by a proximal alkene can occur. The differences may reside in a Thorpe–Ingold effect of the geminal substitution. An attractive alternative is the possibility that the 1,6-dienes serve as bidentate ligands as in (**12**). This templating effect facilitates the intramolecular addition relative to β-hydrogen insertion. The higher reactivity of the alkyne of the enyne may be an exciting solution to the problem of controlling alkene geometry of trisubstituted exocyclic double bonds.

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¶ To our knowledge, the relative reactivity of an alkyne and an alkene in the Heck reaction has not been previously tested. The fact that some alkynes can add to a C–Pd bond has been demonstrated. For examples see reference 8.