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REACTIVITY OF (3-CHLORO-2-METHYLENECYCLOALKYL)PALLADIUM CHLORIDE DIMERS: NUCLEOPHILIC ATTACK BY ONE OR TWO EQUIVALENTS OF MALONATE ANION.

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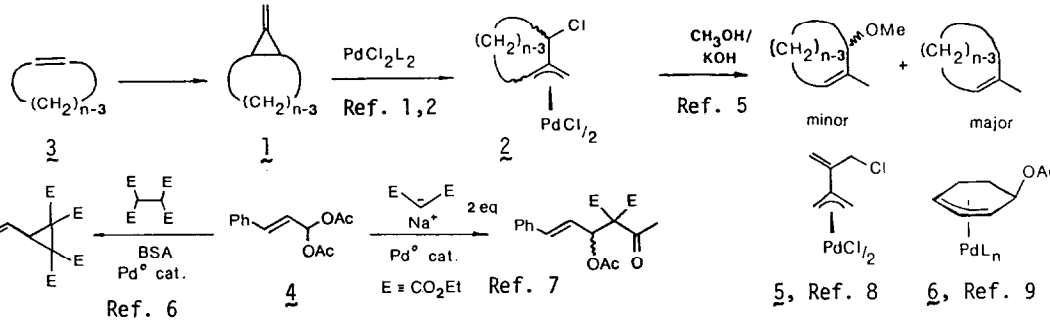
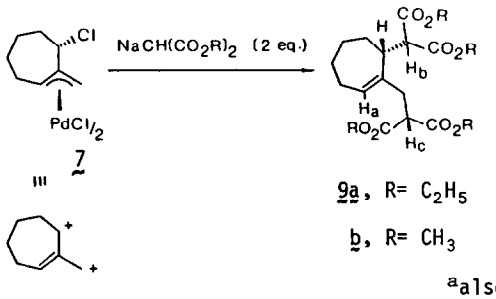
SUMMARY: The title compounds undergo reaction with one and two equivalents of malonate anion in the presence of phosphine ligands to afford mono- and di-substituted products. A mechanism for the formation of both products is presented.

We[1] and others[2] have recently shown that the chloropalladation of ω-methylenebicyclo[n.1.0]-alkanes 1 affords (3-chloro-2-methylenecycloalkyl)palladium chloride dimers 2 in high yields. Since compounds 1 may be prepared from the corresponding cyclic olefins (3)[1,3] these two steps constitute a formal ring homologation methodology. Because of the great potential for elaboration of the π-allyl moiety,[4] we investigated the reactivity of compounds 2 as the final step in an overall ring homologation-functionalization methodology. Our initial results on the basic cleavage of compounds 2 indicates that they react as "1,3-doubly activated" π-allyls.[5] Recent conflicting accounts of the reactivity of "1,1-diactivated" π-allyls[6,7] with carbon nucleophiles as well as the reactivity of other "1,4-diactivated" π-allyls systems (5 and 6)[8,9] have been reported.



3 1 2 4 5, Ref. 8 6, Ref. 9

The reaction of 7 with two equivalents of malonate anion 8 (xs. phosphine, THF, 1h @ RT, 24h @ x°C) afforded the tetraester 9[10,11] as the major product (Table I). *Thus, the title compounds may react as a "trimethylenemethane dication" synthon in the presence of two equivalents of nucleophile.* This may be considered as a complementary system to the zwitterionic trimethylenemethane synthons generated from the reaction of 2-trimethylsilylmethyl-allyl acetates with $Pd(PPh_3)_4$.[13]



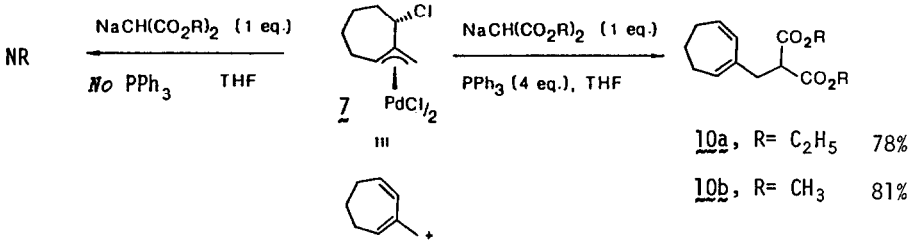
7 9a, R= C_2H_5 b, R= CH_3

TABLE I.

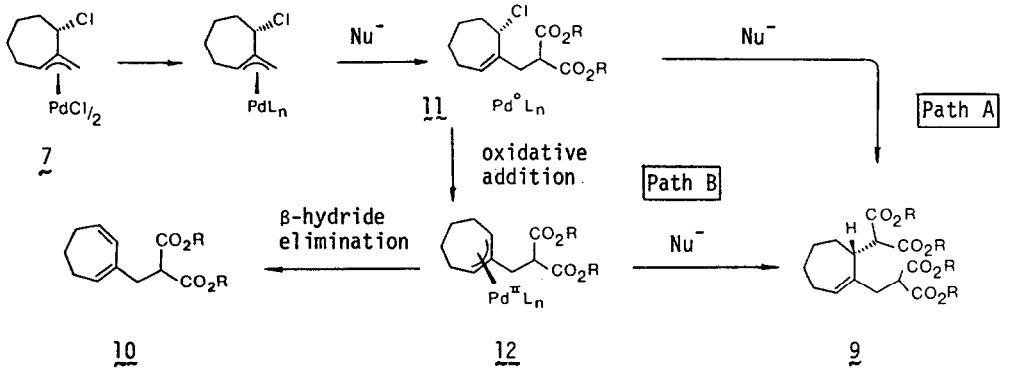
isolated yield	temp.(°C)	R	Ligand (equiv.)
90%	23	CH_3	PPh_3 (4)
75%	67	C_2H_5	PPh_3 (4)
75%	23	C_2H_5	PPh_3 (4)
73%[a]	67	C_2H_5	DIPHOS (2)
48%[b]	23	C_2H_5	$[(Ph_2P)Cp]_2Fe$ (2)
35%[c]	23	C_2H_5	(PS)–PPh_3 (2)

[a]also 19% 10a isolated, [b]30% 10a, [c]21% 10a

Exposure of complex 7 to sodio diethylmalonate (1 eq., THF, 24h, reflux) in the absence of triphenylphosphine ligand led to quantitative recovery of starting material.[14] Furthermore, reaction of 7 with one equivalent of malonate anion in the presence of excess phosphine gave the diene 10[10,15] as the major product. These two results clearly indicate that initial nucleophilic attack occurs on the coordinated allylic functionality.[16]



We propose that both products 9 and 10 are generated along similar pathways (Scheme 1). Initial attack at the unsubstituted allylic terminus affords the allylic halide 11 and a Pd(0) species. Oxidative addition of Pd(0) into the allylic halide bond provides the symmetrical π-allyl intermediate 12.[17] In the absence of additional malonate nucleophile, 12 undergoes β-hydride elimination to afford the diene product 10.[18] The tetraester product 9 might arise via either nucleophilic displacement of allylic chloride of 11 (Path A) or nucleophilic attack on the symmetrical π-allyl 12 (Path B).



Scheme 1.

In an effort to explore the two possibilities (Path A or B), complex 7 was reacted with two equivalents of sodio dimethylmalonate in the presence of chiral phosphine ligands[19] (Table II). Surprisingly, the only isolable product was the achiral diene 10. *In sharp contrast*, the reaction of

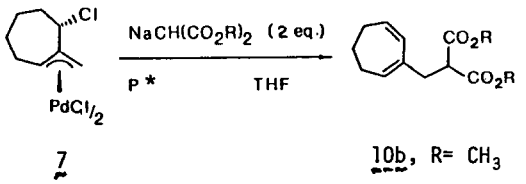
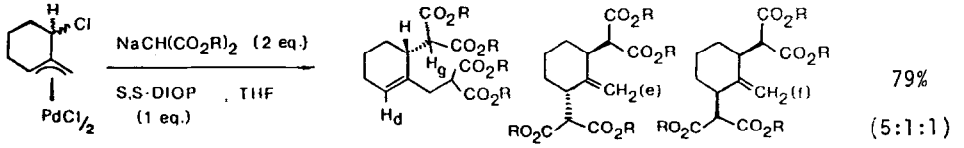


TABLE II.

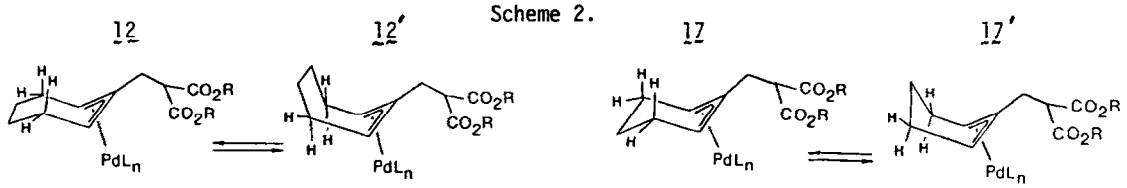
isolated yield	P*
75%	(Neomenthyl)PPh_2
53%	*S,S*-DIOP
13%	*R*-PROPHOS

complex 13[20] with two equivalents of malonate anion in the presence of S,S-DIOP (1 eq.) gave disubstituted products 14, 15, and 16 (79% isolated yield, 5:1:1 ratio by ^{1}H NMR integration).[21] This remarkable difference in reactivity might be rationalized by looking at the structures of the π-allyl intermediates 12 and 17(Scheme 2). Only in the boat conformer of each is the proper orientation for β-hydride elimination achieved. By analogy to the corresponding hydrocarbons,[21] the barrier for chair-boat interconversion should be lower for 12 than for 17. In addition, molecular models indicate that the axial β-hydrogens of 12′ are closer to the Pd metal than the axial β-hydrogens of 17′. Thus, the relative rate of β-hydride elimination versus nucleophilic attack should be considerably greater for 12 than for 17.



13 14 15 16

Scheme 2.



In summary, we have shown that (3-chloro-2-methylenecycloalkyl)palladium chloride dimers may react with *one* equivalent of nucleophile to generate *monosubstituted-diene products* (10). Alternatively reaction of 2 with *two* equivalents of nucleophile results in the *sequential* formation of two new C-C bonds. The use of this reactivity in natural product synthesis as well as the reactivity of the 1,3-diactivated complexes 2 with one equivalent of a dinucleophile will be reported in due course.

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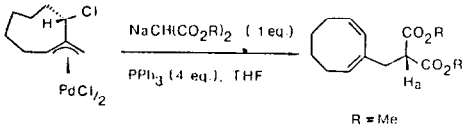
10. Satisfactory elemental analysis was obtained for this compound.
11. A typical experimental procedure follows: To a solution of (3-chloro-2-methylenecycloheptyl)-palladium chloride dimer (250 mg, 0.875 mmoles) and triphenylphosphine (918 mg, 3.50 mmoles) in dry THF (25 mL) under N_2, was added a solution of sodio diethylmalonate (1.75 mmoles, freshly prepared from xs. NaH and diethylmalonate) in dry THF (10 mL). The pale yellow solution turned orange-yellow upon addition. After 24h the solvent was removed, the residue taken up in CH_2Cl_2, washed 1X with H_2O, and the solvent removed to afford the crude product. Purification by "flash" chromatography[12] (elution with hexanes, followed by elution with hexanes: ethyl acetate/28:1) and distillation (kugelrohr) afforded the product as a clear oil.
    9a: bp 115-120°C/ 0.07 mm Hg; IR (neat, cm^{-1}) 1750 s; 60 MHz ^1H NMR ($CDCl_3$) δ 5.75 (t, J=6.8 Hz, 1H, H_a), 4.15 (q, J=7.0 Hz, 8H, OCH_2CH_3), 3.50 (dd, J=9.0, 12.9 Hz, 1H, H_e), 3.2-1.0 (m, 12H), 1.25 (t, 12H, OCH_2CH_3); 15 MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 168,7, 168.1 (C=O), 139.6, 131.5 (C=C), 61.2, 60.9 (OCH_2CH_3), 51.9, 51.2 ($CH(CO_2Et)_2$), 41.8, 39.2, 28.5, 27.2, 26.1 (ring C), 14.0, 13.9 (OCH_2CH_3).
    9b: bp 140-152°C/ 0.21 mm Hg; IR (neat cm^{-1}) 1720 s; 250 MHz ^1H NMR ($CDCl_3$) δ 5.67 (dd, J=6.1, 7.8, H_a), 4.05 (d, J=11.7, H_b), 3.72, 3.71, 3.69, 3.68 (OCH_3 singlets), 3.55 (dd, J=5.6, 10.2, H_e), 2.93 (broad d), 2.5 (m), 1.7-1.5 (m); 15 MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 169.4, 168.6 (C=O), 139.6, 131.9 (C=C), 52.6, 52.2 (OCH_3), 51.9, 51.1 ($CH(CO_2CH_3)_2$), 42.2, 39.4, 28.7, 27.0, 26.2 (ring C).
12. W.C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.* (1978) *43*, 2923.
13. B.M. Trost and D.M.T. Chan, *J. Am. Chem. Soc.* (1979) *101*, 6429, 6432; *Ibid.* (1980) *102*, 6359.
14. Identified by ^1H NMR spectroscopy (Ref. 2).
15. The experimental procedure is essentially as above (Ref. 11) except that only one equivalent of malonate anion is added.
    10a: bp 90-95°C/ 0.07 mm Hg; IR (neat, cm^{-1}) 1750 s; 60 MHz ^1H NMR ($CDCl_3$) δ 5.8-5.4 (m, 3H, vinyl H), 4.15 (q, J=7.0 Hz, 4H, OCH_2CH_3), 3.44 (t, J=8.0 Hz, 1H, H_a), 2.7-1.5 (m, 8H), 1.25 (t, J=7.0 Hz, 6H, OCH_2CH_3); 15 MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 169.1 (C=O), 134.1, 133.1, 131.5, 127.8 (C=C-C=C), 61.3 (OCH_2CH_3), 52.3 (CH_a), 38.3, 31.3, 30.9, 29.8, 14.1 (CH_3).
    10b: bp 85-90°C/ 0.07 mm Hg; IR (neat, cm^{-1}) 1725 s; 60 MHz ^1H NMR ($CDCl_3$) δ 5.8-5.6 (m, 3H, vinyl H), 3.69 (s, 6H, OCH_3), 2.7-1.2 (m, 9H); 15 MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 169.3 (C=O), 139.4, 134.8, 131.6, 127.5 (C=C-C=C), 52.3, 51.4 (CH_a and OCH_3), 38.4, 31.3, 29.7, 27.8.
    Reaction of (3-chloro-2-methylenecyclooctyl)palladium chloride dimer[1b] gave the corresponding 2-substituted-1,3-cyclooctadiene. 71% yield
    bp 65°C/ 0.07 mm Hg; IR (neat, cm^{-1}) 1750s; 60 MHz ^1H NMR ($CDCl_3$) δ 5.8-5.3 (m, 3H, vinyl H), 3.70 (s, 6H, OCH_3), 2.7-1.5 (m, 10H); 15 MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 169.6 (C=O), 133.3, 133.2, 129.2, 126.5 (vinyl C), 52.4, 51.4 (CH_a and OCH_3), 36.7, 29.7, 28.6, 27.8, 24.1.



16. This is in *sharpcontrast* to the reactivity of 1,4-diactiviated π-allyl complex 5 (Ref. 8) which is reported to undergo chloride displacement *prior* to attack at the π-allyl.
17. Oxidative addition of Pd(0) into activated allyls is well precedented. R.D. Rieke, A.V. Kavaliunas, L.D. Rhyne and D.J.J. Fraser, *J. Am. Chem. Soc.* (1979) *101*, 246; Y. Inoue, J. Yamashita and H. Hashimoto, *Synthesis* (1984) 244; also see Ref. 4.
18. Pd-allyl complexes are less susceptible to β-hydride elimination than Pd-alkyls, however the thermal decomposition of certain Pd-allyls to afford dienes is believed to proceed via β-hydride elimination. K. Dunne and F.J. McQuillin, *J. Chem. Soc. (C)* (1970) 2200.
19. Asymmetric alkylation of symmetrical π-allyls has been effected by the use of chiral chelating bisphosphine ligands: B.M. Trost and T.J. Dietsche, *J. Am. Chem. Soc.* (1973) *95* , 8200; B.M. Trost and D.J. Murphy, *Organometallics* (1985) *4*, 1143.
20. This complex is a racemic misture of the *exo* and *endo* Cl diastereomers.[1b]
21. The formation of 15 and 16 requires initial nucleophilic attack at the more substituted endocyclic allylic terminus. Attack at the endocyclic terminus has previously been observed for (methylenecyclohexyl)palladium complexes.[22] The procedure is essentially as in Ref. 11: 79% yield (14:15:16/5:1:1); IR (neat, cm^{-1}) 1725 s, 1410,s, 890 s; 60 MHz H NMR (partial, $CDCl_3$) δ 5.62 (t, J=4.5 Hz, H_d), 4.70 (s, H_e), 4.45 (s, H_f), 3.75 (broad s, OCH_3). A 300 MHz ^1H NMR study of the mixture with Eu(tfc)$_3$ showed no splitting for the H_d or H_g signals of 14, however the H_e signal of the two enantiomers of 15 *did* split under this study[9](3:2 ratio).
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