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TO WHAT EXTENT IS A Π-ALLYLIC INTERMEDIATE INVOLVED IN SOME PALLADIUM-CATALYZED ALKYLATIONS ?

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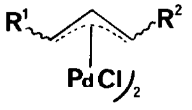
Summary : Comparison of polarimetric data in the asymmetric palladium-catalyzed addition of sodium dimethyl malonate on optically active and racemic 2-cyclohexenyl and carveyl acetates suggests that the reaction does not got - at least totally - through a symmetric π-allylic cationic intermediate.

The alkylation of π-allylic palladium complexes 1 and the palladium-catalyzed alkylation of allylic acetates 2 and 3 with soft nucleophiles is taking an increasing importance in synthetic chemistry[1,2].

Both reactions have been described[2] to proceed via a π-allylic cationic intermediate[3] type 4, even though only few alkylations have been carried out on such preformed species, to be compared with the analogous reaction performed on the parent allylic acetate .



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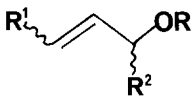

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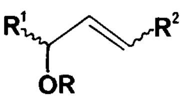

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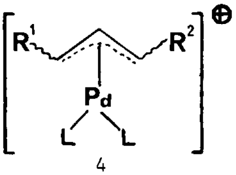

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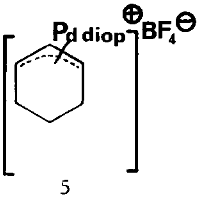


5

R = OAc

We found that the reaction of sodium dimethyl malonate with the (-)diop-tetrafluoroborate cationic complex of di-μ chloro bis(η^3-cyclohexenyl)palladium(II) 5 gives the alkylation product with a lower e.e. than the palladium-catalyzed alkylation of the corresponding allylic acetate 6a (table, entries 1 and 3). This result is not consistent with the involvement of a π-allylic cationic intermediate for the catalyzed reaction.

In order to investigate further this point, we studied the alkylation of suitable substrates (cyclohexenyl acetates 6a, 6b, and carveyl acetates 6c, 7), which also should go through a stereodefined π-allylic cationic intermediate 10[4] . Additions of nucleophiles (sodium dimethyl malonate and cyclopentadienide[5]) on the suggested intermediate complex 10 (where L is chiral) should be considered as enantiopos differentiating reactions[6] at the terminii of the π-allylic ligand. This consideration allow the following predictions :

a) the e.e. of the product obtained from either optically active or racemic 6a or 6b should be identical for a reaction catalyzed by a chiral phosphine, and zero if one uses an achiral ligand.

b) the e.e. of the products obtained with enantiomeric catalysts would be of same magnitude, but of opposite sign, regardless the optical purity of the substrate.

The results collected in Table 1 do not support these predictions :

- similar experiments carried out with optically active allylic acetate 6a (entry 4) and its racemic mixture (entry 1) lead to products of different e.e. (same observations from entries 5 and 6). Moreover the products obtained from the optically active substrates 6c and 7 with an achiral catalyst are optically active (entries 9, 12, 14).
- enantiomeric excesses measured for the compounds produced by enantiomeric catalysts (entries 1 and 2, 7 and 8, 11 and 10) are of opposite sign, but of different magnitude. The e.e. are also higher than those obtained from an achiral catalytic system (entries 9 and 12).

TABLE 1

Palladium-catalyzed addition of sodium dimethyl malonate and sodium cyclopentadienide on allylic substrates in THF[a].

Entry	Substrate	phosphine ligand	nucleophile	(%) yield	Product $[\alpha]_D(CHCl_3)$	α/γ[b]
1	dl - 6a[c]	(-) diop	sodium dimethyl malonate	56	+ 2.40°	
2	dl - 6a[c]	(+) diop	"	88	- 3.89°	
3	5	(-) diop	"	40	+ 1.20°	
4	(+)- 6a[c]	(-) diop	"	52	+ 4.10°[j]	
5	dl - 6b[d]	(-) diop	"	66	+ 0.69°	
6	(+)- 6b[d]	(-) diop	"	76	+ 2.1°	
7	(+)- 6c[e]	(-) diop	"	89	+ 1.69°	
8	(+)- 6c[e]	(+) diop	"	58	- 2.86°	
9	(+)- 6c[e]	dppb[h]	"	72	- 0.15°	
10	7[f]	(-) diop	"	68	+ 1.31°	0.78
11	7[f]	(+) diop	"	84	- 2.66°	1.56
12	7	dppb[h]	"	83	- 0.32°	1.04
13	(+)- 6c	(-) diop	sodium cyclopentadienide	58	-16.1°	
14	(+)- 6c	dppe[i]	"	69	- 1.6°	

[a] 48 hr at room temperature : catalyst Pd(dba)$_2$(2.6 x 10^{-5}mole) ; phosphine (2.6 x 10^{-5}mole allylic acetate (2.6 x 10^{-3} mole) ;

[b] α/γ ratio for overall substitution was determined by integration of the cyclic vinyl and methine protons in the ^{1}H n.m.r. spectra of 8;

[c] $[\alpha]_D^{20}$ + 105.4° (c = 10, hexane) ;

[d] $[\alpha]_D^{20}$ + 40.7° (c = 10.5, hexane) ;

[e] Obtained from LAH reduction of (-)-carvone in ether at 0°C and successive acetylation : $[\alpha]_D^{22}$ - 50.2° (c= 5.8,hexane)

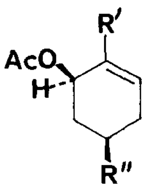
[f] Obtained from LAD reduction of (-)-carvone in ether at 0°C and successive acetylation ; $[\alpha]_D^{22}$ - 50.2° (c = 8, hexane) ;

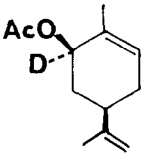
[g] Diop is 2,3-isopropylidenedioxy-1,4-bis(diphenylphosphino)-butane, (-)-diop $[\alpha]_D^{22}$ - 12.4° (c = 2, benzene) ; (+)-diop $[\alpha]_D^{22}$ + 12.5° (c = 2, benzene)[7];

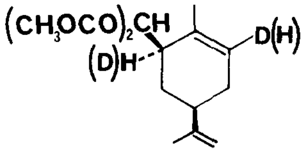
[h] dppb stands for 1,2-bis(diphenylphosphino)butane ;

[i] dppe stands for 1,2-bis diphenylphosphino)ethane ;

[j] the configuration of this compound has been shown to be R by chemical correlation to (+)-(S)-3-(2-hydroxyethyl)cyclohexene[8].







6a R' = R'' = H

6b R' = CH_3 ; R'' = H

6c R' = CH_3 ; R'' = $-\underset{CH_3}{C}=CH_2$

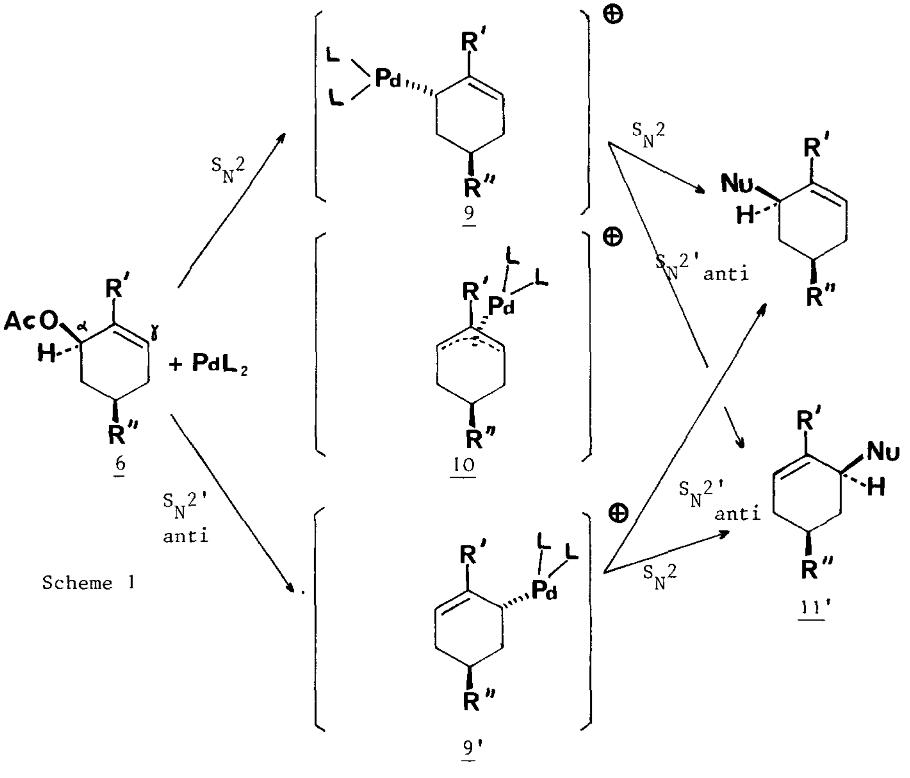
7

8

These features are inconsistent with the sole occurence of a symmetric cationic π-allylic ligand as intermediate.

A more compatible mechanism for the present alkylation could involve a π-complexation of the palladium by the allylic substrate, followed by the expulsion of the acetoxy group to form a discrete σ metal-carbon bond (through either a S_N2 or S_N2' anti reaction of the palladium onto the allylic acetate) (scheme 1). Then, at least to some extent, S_N2 or S_N2' anti attack of the nucleophile upon these organometal intermediates 9 and 9' would produce enantiomeric compounds 11 and 11', corresponding to α or γ substitution of the acetoxy group by the nucleophilic, with overall retention of configuration.

The involvement of 9 and 9' as diastereomeric intermediates (when L is chiral) could explain the differences in regioselectivity observed in the alkylation of a chiral substrate



Scheme 1

(carveyl acetate 6c) with two enantiomeric forms of the catalyst, based on (+) or (-) diop. The nucleophile should react with different S_N2/S_N2' rates (or α/γ ratio) on the two stereomeric intermediates 9, to produce different enantiomeric compositions for the product. Further support is brought by the results obtained for the reaction carried out with dl-6a (entries 1 and 2). Throughout this latter reaction, the optical rotation of the product 11a remains constant, and the recovered starting material 6a keeps racemic. Hence, the optical activity in the product cannot be rationalized by a partial resolution of the allylic acetate 6a. Additional experiments demonstrate the stability of 6a under the reaction conditions(both 6a and (+)-6b show optical stability in the absence of nucleophile), and the invariance of the asymmetric induction versus Pd/phosphine ratios in the range 0.5-1.

The polarimetric data discussed above were confirmed - within experimental errors - by the analysis of the products of alkylation of labelled compound (-) cis-carveyl-2d$_1$ acetate 7, (see Table).

Unlike some reactions of allylic acetates with lithium dialkyl cuprates, which have been shown to proceed via a symmetrical intermediate (π-allyl complex or allyl radical)[9,10], the palladium-catalyzed alkylation of cyclohexenyl acetates by sodium dimethyl malonate does not proceed - at least totally- through a symmetrical cationic π-allylic intermediate. One must however keep in mind that, at the moment, this conclusion may strictly refer to the systems studied in the experimental conditions above-described (especially smooth temperature conditions).

Work is in progress to clarify the role of the nucleophile, of the leaving group and the phosphine on both the α/γ substitution ratio and on the asymmetric induction. Search for consequences brought up this observation in the stereochemistry of the palladium-catalyzed allylation are under investigation.

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