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ELECTRONIC EFFECTS ON THE REGIOSELECTIVITY OF NUCLEOPHILIC ATTACKS ON π-ALLYLPALLADIUM COMPLEXES

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Summary: A high regioselectivity has been observed in the palladium catalyzed allylation of "soft" nucleophiles (pentane-2,4-dione and 4-hydroxy-6-methyl-2-pyrone) when both allylic termini have the same steric requirements and different electronic features.

The palladium catalyzed allylation of proton active substrates is a powerful method of carbon-carbon bond formation.[1,2] A common mechanistic feature for nucleophiles based on proton active substrates with pK_a values below 20 ("soft" nucleophiles) is the retention of configuration at the allylic center through a double inversion: one when the palladium(0) displaces the leaving group and another when the nucleophile attacks one of the allylic termini of the cationic π-allylpalladium intermediate.[1,2]

Some attention has been paid to the regioselectivity of the nucleophile attack on cationic π-allylpalladium complexes. It is a general belief that these attacks are very sensitive to steric hindrance caused by the substituents. However, the influence of electronic effects when both allylic termini exhibit the same steric requirements is not clear.

Thus, E. Keinan and coworkers have studied a few examples of the reactions of 1-(4-X-phenyl)-3-phenyl-2-propen-1-ol acetates (X = F, Br, Me) with polymethylhydrosiloxane (hydride donor),[3] alkoxytributylstannanes (alkoxy group donors),[4] and allenyltributylstannane (propargyl group donor).[5] In no case regioselectivity was observed. This lack of regioselectivity is surprising and could induce to believe that electronic effects do not influence the regiochemical outcome of the allylation reactions. However, allylic rearrangements of hydrogen (double bond shifts) under palladium catalysis are well known[2] and allylic rearrangements of groups based on electronegative elements are commonplace. All this cast some doubts on whether the ratios (ca. 50:50) of products found by the group of Keinan are a direct consequence of kinetic control or not.

Allylic migrations of carbon based groups are infrequent and therefore carbon nucleophiles can warrant better that the ratio of formed isomers represents a real kinetic regioselectivity or the lack of it. However, the allenyltributylstannane, the carbon nucleophile studied by Keinan, is a "hard" nucleophile which likely attacks first at the palladium atom in a transmetalation process followed by reductive elimination to form the C-C bond[5] (retention of configuration in the second step of nucleophilic attack at the

allylpalladium complex).

T. Hayashi has also found lack of regioselectivity in the reactions which should be considered as kinetically controlled: those of 1-(4-X-phenyl)-3-phenyl-2-propen-1-ol acetates (X = Cl, Me) with a "soft" nucleophile, sodium pentane-2,4-dionato, under palladium catalysis[6].

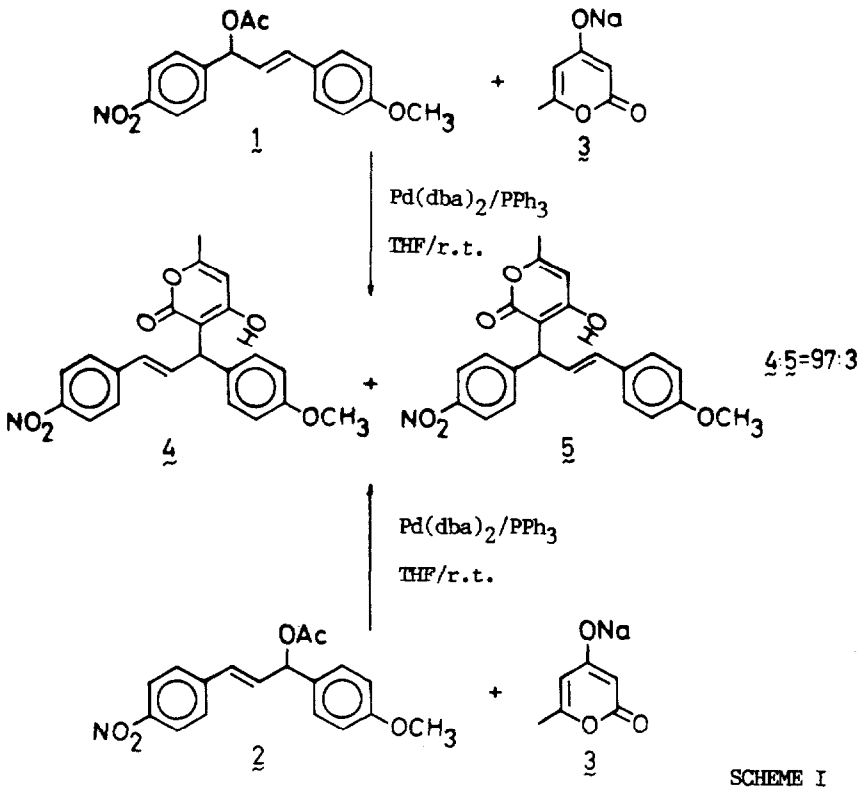
Both groups have worked with systems for which the differences in substituent constants ($\sigma_X - \sigma_H$) range between +0.34 (for Cl) and -0.14 (for Me).

Before the belief will be universally accepted that electronic effects do not play any role in the regioselectivity of nucleophilic attacks on cationic π-allylpalladium complexes when both allylic termini exhibit the same steric requirements, we want to report completely different results when a) more electronic difference is introduced between both termini of the allylic system; b) "soft" carbon nucleophiles are used and c) both starting regioisomeric allylic acetates are compared. We have chosen the nitro and methoxy groups ($\Delta\sigma$ = 0.93) to differenciate electronically the electrophilic centers and pentane-2,4-dione (pK_a 9) and 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone, pK_a 5) as nucleophiles. We have recently shown that triacetic acid lactone can be allylated under palladium catalysis with overall retention of configuration at the allylic center[7].

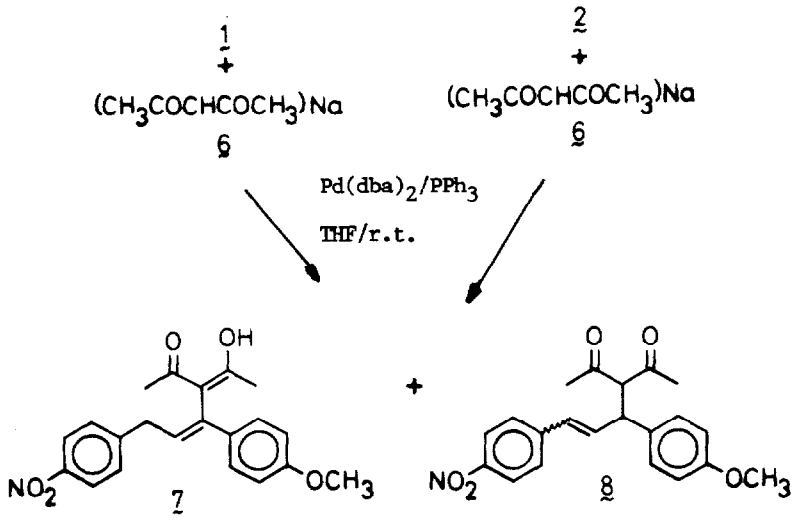
Our results are indicated in Schemes I and II. The reactions of both 3-(4-methoxyphenyl)-1-(4-nitrophenyl)-2-propen-1-ol acetate, **1** (yellow oil[8]), and its regioisomer **2** (yellow oil[8]), with the sodium salt of triacetic acid lactone, **3**, under palladium catalysis gave a mixture of 4-hydroxy-3- 1-(4-methoxyphenyl)-3-(4-nitrophenyl)-2-propen-1-yl -6-methyl-2-pyrone, **4**, and its regioisomer **5** in a ratio 97:3[8] (Scheme I). The experiments were run in duplicate (90 and 83% yields from **1** in 3h 20min and 86 and 87% yields from **2** in 3h 20min and 51min respectively). The ratio was determined by reductive (Me_2S) ozonolysis at -70ºC which afforded 88% yield of a mixture of 4-nitro- and 4-methoxybenzaldehydes in a ratio 97:3. Thus, for a $\Delta\sigma$ of 0.93, $\Delta\Delta G^{\neq}$ is about 1.9 Kcal/mol at room temperature.

Similar reactions were performed with sodium pentane-2,4-dionato, **6**, as indicated in Scheme II and in the Table. Again, a high regioselectivity was observed (100%), the attack at the most remote terminus from the electron-withdrawing group being again favoured. The final mixtures were more complicated due to the presence of **7**[8] (m.p. 149-50ºC) and both stereoisomers **8**[8]. Compound **7** exhibited a peak at m/e 231(93) attributed to ($M^+ - O_2N\text{-}Ph\text{-}CH_2$) which is a good evidence for its proposed constitution. Products **8** were converted into the pyrazoles **9** (**9-E**[8], m.p. 146-148ºC) which upon reductive ozonolysis afforded 4-nitrobenzaldehyde (82%), no traces of 4-methoxybenzaldehyde being detected. Hydrogenation of a mixture of pyrazoles **9** afforded only one reduced pyrazole **10**[8] thus giving evidence of the presence of both isomers **8**.

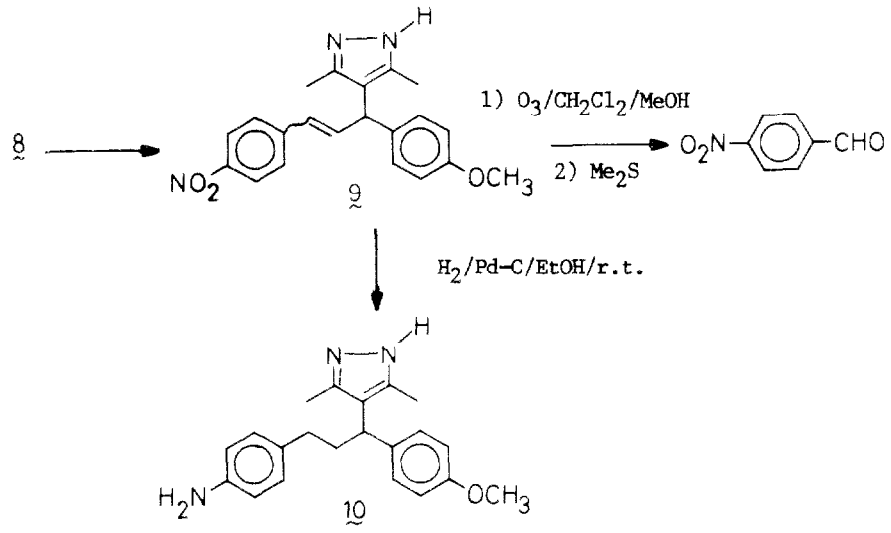
In summary, a high regioselectivity operates in palladium catalyzed allylations of "soft" nucleophiles when both termini of the allylic system have the same steric requirements and are electronically well differentiated.



SCHEME I



SCHEME II



TABLE[a]

	Molar Ratios		Isolated yields[b] (%)		
Acetate	**1** or **2**:**6**:Pd[c]:PPh_3	Time (h)	**7**	**Z-8**	**E-8**
1	2:3:0.1:0.4	4.5	17	4.5	17
1	2:4:0.1:0.3	4.0	7	7	48
1	4:8:0.1:0.3	7.25	8	4	35
1	2:4:0.1:0.3	2.25	0	11	47.5
1	8:16:0.1:0.3	2.25	8	10	53.5
2	2:4:0.1:0.3	2.25	0	23	35
2	4:8:0.1:0.3	1.25	7	15	59

[a] All the reactions were performed in THF at room temperature.
[b] Isomers **8** were not separated. Their ratio was determined by integration of the methyl signals in the 1H-NMR spectrum of the mixture of pyrazoles **9**.
[c] Introduced as $Pd(dba)_2$ but for the first experiment in which $Pd(acac)_2$ was used.

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8) Good elemental analysis and/or spectroscopic behaviour was exhibited by this compound or mixture.

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