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ELECTRONIC EFFECTS IN THE REGIOSELECTIVITY OF NUCLEOPHILIC ATTACKS ON CATIONIC 1,3-DIARYL-π-ALLYLPALLADIUM COMPLEXES[1]

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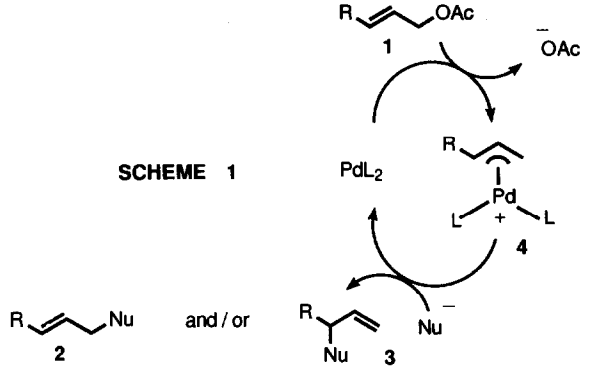
Abstract.- Nucleophilic attacks on π-allylpalladium complexes derived from O_2N-Ph-(CH-CH-CH)-Ph-X systems (X = 4-OMe and 4-Cl) occur preferentially at the allylic terminus remote from the electron-withdrawing group (NO_2).

INTRODUCTION

Palladium(0)-catalyzed allylation of nucleophiles is a well established methodology.[2] Allylic systems bearing a leaving group, generally acetates, **1**, or mixed carbonates, are treated with a nucleophile in the presence of palladium(0) species to afford products **2** and/or **3** (Scheme 1).

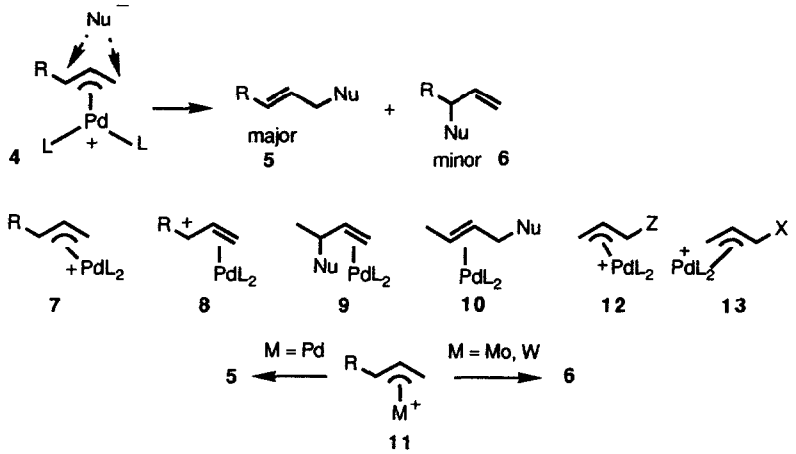
SCHEME 1



The interaction of the allyl compound with a ligand-stabilized palladium(0) species affords a cationic π-allylpalladium complex, **4**, which is attacked by the nucleophile to afford **2** and/or **3**, thus regenerating the catalytic species PdL_2.

However, when both allylic ends are differently substituted, two regioisomers can be obtained. It is generally accepted that, when both substituents are hydrocarbon

radicals or hydrogen, steric effects play an important role on the outcome of the reaction, the compound from attack at the less hindered side being predominantly formed (5>6) (Scheme 2. For the sake of simplicity, all drawings in the schemes are made in the plane of the paper. However, π-allylpalladium complexes contain the Pd atom below the plane defined by the three carbon atoms). Nevertheless, many exceptions are known and some explanations have been offered. Thus, Trost and coworkers[3] found that the regiochemistry of the allylation of stabilized carbanions depends on the ligand. Tri-o-tolylphosphine, being a poor ligand, makes electron donation from the π-allyl system to the metal more important relative to other ligands. This implies that the cationic intermediate is asymmetric with the palladium more bound to the less substituted terminus. This situation is described by formula **7**. Formula **8** represents the extreme case when the metal is practically bound only to the less substituted terminus in a η^2 manner, the more substituted one having carbocationic character. In such a case the nucleophilic attack is governed by charge control and occurs at the most stable cationic center, the most substituted carbon atom. This argument has been used by other authors (Åkermark and coworkers) to explain observed preferential attacks by nucleophiles at the most substituted allylic terminus.[4]



SCHEME 2

A different way of looking at the same problem is represented by formulae **9** and **10** (Scheme 2). According to Trost and coworkers[3] the real final products of the catalytic cycle are the η^2 complexes **9** and **10**, the former, having the palladium atom linked to the less substituted double bond, being more stable because it is less sterically hindered and also because there is on it more back donation from the metal to the olefin. This argument requires, as pointed out by Trost, that the transition states leading to both possible regioisomers are product like.

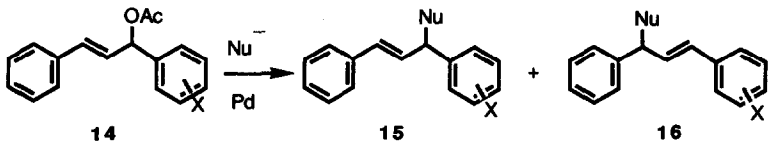
The subtle electronic factors deciding the regioselectivity can also be governed from the metal. Thus, Trost and coworkers have observed a change in regioselectivity depending on the use of palladium or tungsten as metal bound to the same allylic framework.[5] This is represented by the transformations of **11** into **5** and **6**.

A frequent situation is that in which strong electron-withdrawing or electron-donating groups are directly bound to the allylic skeleton. This is represented by formulae **12** and **13**. As a matter of fact, nucleophilic attacks by stabilized carbanions and amines on complexes **12** occur at the allylic end most remote from Z (Z = CN, COOMe),[6] (Z = CN),[7] (Z = COOEt, CH_2OAc)[8] and (Z = COOR).[9] For the case of **12** (substituents of type Z), strong asymmetry of the complex, as indicated in formula **12**, has been invoked.[8,10] The contrary case has been studied by Cazes and coworkers[11] in a complex of type **13** (X = OMe). In this case strong preference of attack by nucleophiles at the terminus bearing the methoxy group has been observed.

A further complication has been reported by Keinan's group.[7,10,12] The regiochemistry in front of a particular cationic π-allylpalladium complex depends also on the nucleophile. Thus, stabilized carbanions have strong tendency to attack at the less substituted end whereas non-stabilized carbanions exhibit propensity to attack first to the palladium atom to be later transferred from it to the most substituted terminus.

Julia and coworkers have also studied the factors governing the regioselectivity[13] and have found that copper species added to the reaction mixtures favour the attack at the most substituted end of the allylic system.[13b]

We speculated with the possibility of preparing systems that could have the difference between both allylic termini concentrated in a unique factor. Thus, we planned to study the regioselectivity in species such as **14** (Table 1) that should give rise to π-allylpalladium systems with equal or very similar steric requirements but different electronic requirements at both allylic ends. Indeed, the influence of electronic effects when both allylic termini exhibit the same steric requirements is not clear. From our bibliographic search we found that Keinan and coworkers had studied a few examples of the reactions of 3-phenyl-1-(4-X-phenyl)-2-propen-1-ol acetates (X = F, Br, Me), **14**, (Table 1), with polymethylhydrosiloxane (hydride donor),[14] alkoxytributylstannanes (alkoxy group donors),[15] and allenyltributylstannane (propargyl group donor).[10] 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 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.



14 15 16

TABLE 1.- Pd-Catalyzed Nucleophilic Attacks on Systems **14** Reported in the Literature

X	$\sigma_X^+ - \sigma_H^+$	Nucleophile	15:16	Reference
4-F	-0.07	CH_2=C=CHSnBu$_3$	56:44	10
4-Br	0.15	"	53:47	10
4-Me	-0.3	"	50:50	10
3-Me	-0.07	Na(acac), **28**	44:56	16
4-Cl	0.11	"	46:54	16
4-Me	-0.3	"	45:55	16

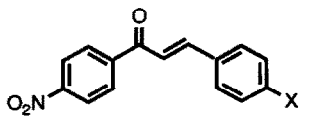
Allylic migrations of carbon-based groups are infrequent and therefore carbon nucleophiles can warrant better that the ratio of formed isomers represents a real kinetic regioselectivity or the lack of it. However, the allenyltributylstannane, the carbon nucleophile studied by Keinan, is a non-stabilized nucleophile which likely attacks first at the palladium atom in a transmetallation process followed by reductive elimination to form a C-C bond[10] (retention of configuration in the second step of the nucleophilic attack at the allylpalladium complex). Hayashi has also found lack of selectivity in reactions which should be considered as kinetically controlled: those of acetates **14** (X = Cl, Me) with a stabilized carbanion, Na(acac), under palladium catalysis.[16] The significant work with carbon nucleophiles by Keinan and Hayashi is collected in Table 1. Both groups have worked with systems for which the differences in substituent constants ($\sigma_X^+ - \sigma_H^+$) range between +0.15 (for 4-Br) and -0.3 (for 4-Me).

RESULTS

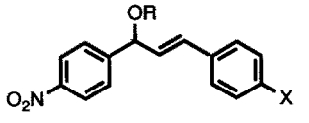
The allylic systems selected for this work are represented by acetates **20a,b** and **22a,b**. They were prepared (Scheme 3) from chalcones **17** and **18** by sequential reduction with lithium aluminium hydride and acetylation. The differences $\Delta\sigma^+$ are 1.53 for **20a** and **22a** and 0.64 for **20b** and **22b**. The chosen nucleophiles were the sodium salt of triacetic acid lactone, **23**, and the sodium salt of acetylacetone, **28**. Triacetic acid lactone is an acidic product (pK_a = 4.94) affording a stable anion. We have reported its behaviour in palladium-catalyzed allylations. This pyrone reacts by double inversion (overall retention) manner.[17] Na(acac) is an example of "stabilized anion" nucleophile.

Treatment of both **20a** and **22a** with the sodium salt of triacetic acid lactone, **23**,

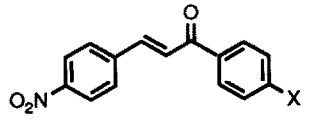
under the conditions specified in Table 2, led to the same mixture of allylated pyrones **24a** and **25a** (ratio 3:97), in isolated yields higher than 80% (Scheme 4). The experiments were run in duplicate giving exactly the same results. In the absence of the catalytic system no reaction took place. The ratio of regioisomers was determined by reductive ozonolysis of the mixture to afford a mixture of 4-nitrobenzaldehyde and 4-methoxybenzaldehyde in the same 97:3 ratio. Thus, for $\Delta\sigma^{+} = 1.53$, $\Delta\Delta G^{\neq}$ is about 7.9 kJ/mol (1.9 Kcal/mol) at room temperature defining a high regioselectivity.



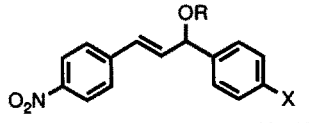
17a; X = OMe
17b; X = Cl



19a: R = H; X = OMe; **19b**: R = H; X = Cl
20a: R = OAc; X = OMe; **20b**: R = OAc; X = Cl



18a; X = OMe
18b; X = Cl

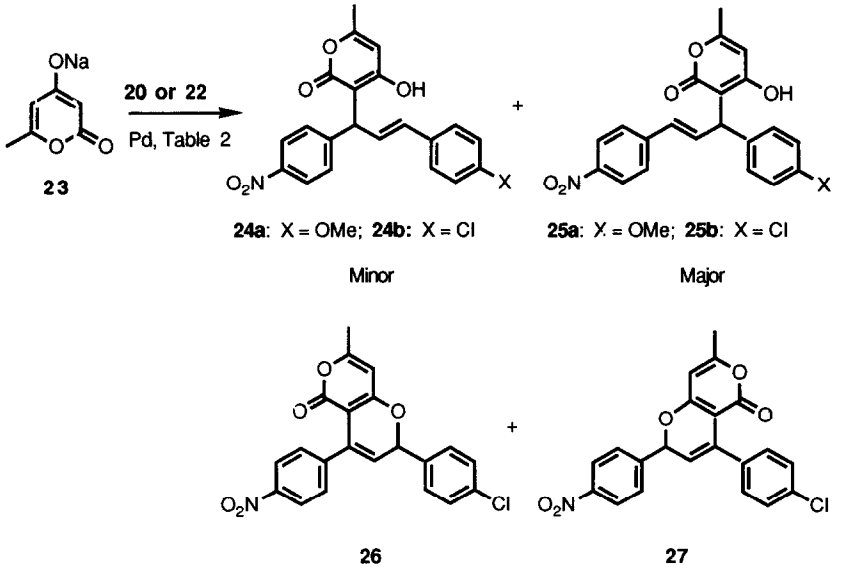


21a; R = H; X = OMe; **21b**; R = H; X = Cl
22a; R = OAc; X = OMe; **22b**; R = OAc; X = Cl

SCHEME 3

Next, we reduced the $\Delta\sigma^{+}$ value to 0.64 by using acetates **20b** and **22b**. Treatment of **20b** with the sodium salt **23** (Table 2 and Scheme 4) produced a mixture of regioisomers **24b** and **25b** in a ratio 15:85 (56%). The same result was obtained starting from the isomeric acetate **22b** (ratio **24b:25b** = 16:84 and 82% yield). The analysis of the mixtures was made by a combination of 1H-NMR at 400 MHz and ozonolysis. Thus, the 1H-NMR spectra of the mixtures showed two doublets at δ = 5.11 and 5.16 ppm with relative intensities 85:15 assigned to the CH(sp^3) protons. Ozonolyses of the same mixtures afforded mixtures of 4-nitrobenzaldehyde and 4-chlorobenzaldehyde in a ratio 84:16. In both reactions minor amounts (13% from **20b** and 4% from **22b**) of a mixture of pyranopyrones **26** and **27** were isolated in a ratio 67:33. These isomeric pyranopyrones probably arise from oxidation of **24b** and **25b**. They could not be separated, but a purified mixture gave correct elemental analysis. The IR spectrum did not exhibit O-H absorption and showed a CO stretching at 1705 cm^{-1} indicating that the oxygen atom at C-4 of the pyrone ring belongs to an ether function. The mass spectrum showed the molecular peak at m/e 395(100). The 1H-NMR spectrum of the mixture presented two set of equal intensity doublets, the first at δ 5.55 and 6.06 (J = 4.5 Hz) assigned to **26** and the second set, of lower intensity, at δ 5.64 and 6.00 (J = 4.5 Hz) assigned to **27**. The doublets at

higher fields are assigned to the benzylic protons and those at lower fields to the olefinic protons. The relative positions of the olefinic absortions are consonant with the electronic effects of the nitro and chloro groups. We conclude that the percentage of attack at the allylic end more remote from the electron-withdrawing nitro group is 75-82%. Therefore, for a $\Delta\sigma^{+} = 0.64$, still the regioselectivity of attack is important with a value of $\Delta\Delta G^{\ddagger}$ about 3.1 kJ/mol (0.7 Kcal/mol) at room temperature.



SCHEME 4

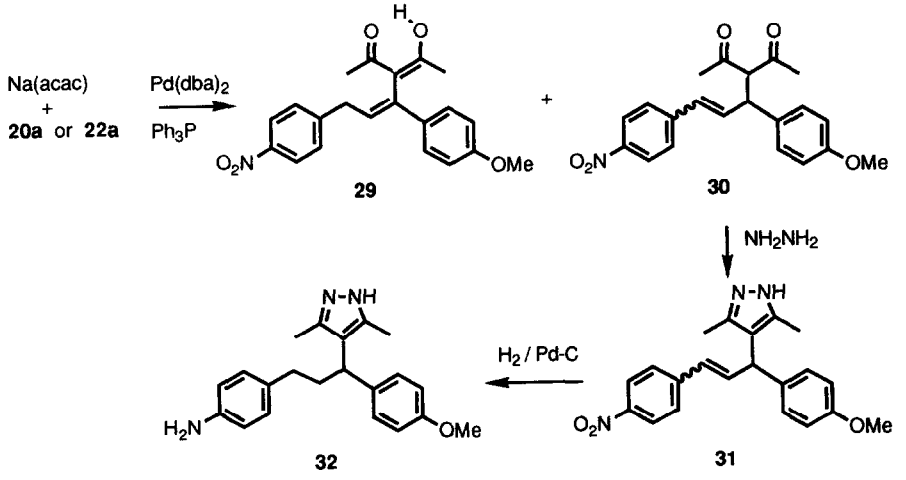
TABLE 2.- Regioselectivity of the Pd-Catalyzed Reactions of Scheme 4

Acetate	23:acetate	Conditions[a]	24:25 (%)
20a	2.5:1.0	$Pd(dba)_2$ (2%), Ph_3P (14%), 1h	**24a:25a** = 3:97 (83%)
20a	2.5:1.0	No catalysis, 47h	-------
22a	2.5:1.0	$Pd(dba)_2$ (2%), Ph_3P (14%), 50m	**24a:25a** = 3:97 (87%)
22a	2.5:1.0	No catalysis, 47h	-------
20b	1.7:1.0	$Pd(dba)_2$ (7%), Ph_3P (25%), 1h	**24b:25b** = 15:85 (56%)
			26:27 = 67:33 (13%)
22b	1.7:1.0	$Pd(dba)_2$ (7%), Ph_3P (25%), 1h	**24b:25b** = 16:84 (82%)
			26:27 = 67:33 (4%)

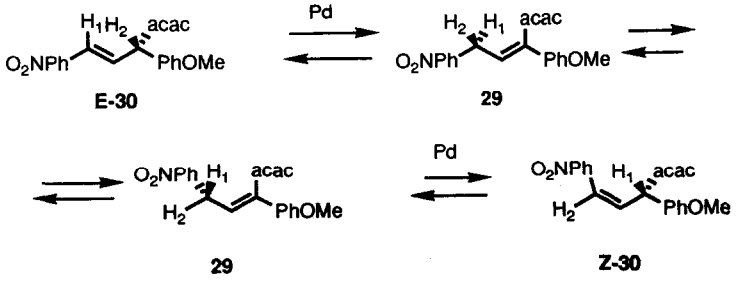
[a]All reactions were carried out at room temperature in THF

In conclusion, the stable anion **23** shows a high degree of regioselectivity in the nucleophilic attack, the allylic terminus remote from the electron-withdrawing group (NO_2) being preferentially attacked.

Na(acac), **28**, exhibited even a higher degree of regioselectivity in the palladium-catalyzed reactions with acetates **20a** and **22a** (Scheme 5). No products from attack at the end bearing the 4-nitrophenyl ring were detected in spite of having performed seven reactions under slightly different conditions (See Table in our preliminary letter[1]). Mixtures of Z and E isomers **30** were produced in all studied cases. Frequently the mixtures contained product **29**, in which a double bond shift has occurred. Compounds **30** could not be separated. Their ratio was determined by integration of the 1H-NMR spectra of the mixtures of isomeric pyrazoles **31**. Hydrogenation under palladium catalysis of both E-**31** and a 40:60 E:Z mixture afforded a unique compound, **32**, thus indicating that the mixtures **30** and **31** were made of geometric isomers. Again, ozonolysis of **31** afforded only 4-nitrobenzaldehyde, no 4-methoxybenzaldehyde being detected. It is remarkable that ozonolysis of Z-**31** is much slower than that of its E isomer. Therefore, by controlling the ozonolysis conditions we could isolate a sample of nearly pure Z-**31**.



SCHEME 5



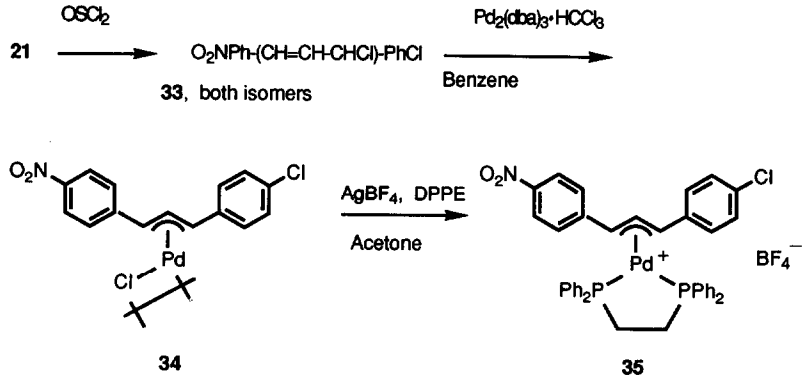
SCHEME 6

The presences of **29** and Z-**30** seem to be connected. The stereochemistry of **29** is probably Z as indicated in Scheme 6. The palladium-catalyzed double bond migration through formation of π-allylhydridopalladium complexes is well documented.[2] This mechanism requires transfer of hydrogen between both termini of the allyl system by the same face, from one carbon atom to the palladium atom, and from it to the other carbon atom. This is represented in Scheme 6. Transfer of hydrogen in E-**30** under palladium catalysis can give Z-**29**. Rotation of the single bond as indicated gives an alternative conformation, from which trasfer of hydrogen back to the original carbon atom would lead finally to Z-**30**.

Our final target was the preparation of the complex salt **35** (Scheme 7) to perform a X-ray study to get information on its geometry. In particular we were interested in the proposed deviation of the palladium atom from the vertical plane perpendicular to the C-C-C plane of the complex passing by the central carbon atom. Also the geometric parameters had to be introduced into theoretical calculations.

Treatment of **21b** with thionyl chloride afforded a mixture of two regioisomeric chlorides, **33**, which without separation was treated with $Pd_2(dba)_3 \cdot HCCl_3$ in benzene. The resulting complex **34** gave correct elemental analysis and was probably a dimer although this was not further studied. Treatment of **34** with silver tetrafluoroborate and DPPE in acetone gave **35**. A pure sample was obtained by preparative thin layer chromatography.

All attempts to perform X-ray diffraction studies failed for the bad quality of the crystals.



SCHEME 7

EXPERIMENTAL

Chalcones **17** and **18** were prepared by aldol condensation of the corresponding aldehydes and acetophenones in water-ethanol under sodium hydroxyde catalysis.
3-(4-Methoxyphenyl)-1-(4-nitrophenyl)-2-propen-1-one, **17a**, mp 178-9ºC (Lit.[18] mp 175-8)
3-(4-Chlorophenyl)-1-(4-nitrophenyl)-2-propen-1-one, **17b**, mp 161-3ºC (Lit.[19] mp 164)
1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-2-propen-1-one, **18a**, mp 173-4ºC (Lit.[20a] mp 173)
1-(4-Chlorophenyl)-3-(4-nitrophenyl)-2-propen-1-one, **18b**, mp 161-3ºC (Lit.[19] mp 164)

Alcohols **19** and **21** were prepared by reduction of the chalcones with $LiAlH_4$ in THF.
3-(4-Methoxyphenyl)-1-(4-nitrophenyl)-2-propen-1-ol, **19a**, mp 96-7ºC (Lit.[20] mp 94-5)
3-(4-Chlorophenyl)-1-(4-nitrophenyl)-2-propen-1-ol, **19b**, mp 130-2ºC (Lit.[20] mp 132-3)
1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-2-propen-1-ol, **21a**, mp 78-80ºC (Lit.[20] mp 79-80)
1-(4-Chlorophenyl)-3-(4-nitrophenyl)-2-propen-1-ol, **21b**, mp 103-4ºC (Lit.[20] mp 104-5)
Acetates **20** and **22** were prepared by treatment of the alcohols with acetic anhydride and pyridine in dichloromethane. Compounds **20a** and **22a** had some propensity to allylic isomerization and therefore they were used without further purification.
3-(4-Chlorophenyl)-1-(4-nitrophenyl)-2-propen-1-ol Acetate, **20b**. A mixture of alcohol **19b** (2,30g, 0.008 mole), acetic anhydride (1.9 mL, 0.02 mole), pyridine (1.6 mL, 0.02 mole) and dichloromethane (50 mL) was magnetically stirred for 120h (Tlc monitoring). The mixture was partitioned adding dichloromethane (further 50 mL) and saturated aqueous sodium bicarbonate (4 x 100 mL), the organic layer was washed with 1N HCl (4 x 100 mL), with water (2 x 100 mL), dried and evaporated to afford 2.45 g of **20b** (92%). Bp 240ºC (oven temp.)/0.07 mmHg; Ir (film): 1740, 1602, 1522, 1347, 969 cm^{-1}; 1H-NMR ($CDCl_3$): δ 2.17 (s, 3H), 6.24 (dd, J = 6.4 and 15.3 Hz, 1H), 6.49 (d, J = 6.4 Hz, 1H), 6.66 (d, J = 15.3 Hz, 1H), 7.30 (s, 4H), AA'BB' system centered at 7.58 and 8.25 (4H); 13C-NMR($CDCl_3$): δ 20.7, 74.6, 123.5, 126.6, 127.3, 127.7, 128.5, 132.2, 133.7, 134.0, 146.0, 147.3, 169.3; Ms: m/e 331(M^+, 7), 289(29), 236(44), 189(31), 43(100).
Calcd. for $C_{17}H_{14}ClNO_4$: C, 61.55; H, 4.25; N, 4.22. Found: C, 61.68; H, 4.25; N, 4.20.
1-(4-Chlorophenyl)-3-(4-nitrophenyl)-2-propen-1-ol Acetate, **22b**. Mp 75.5-76.5ºC; Ir(KBr): 1730, 1596, 1517, 1343, 978 cm^{-1}; 1H-NMR ($CDCl_3$): δ 2.17 (s, 3H), 6.31-6.84 (m, 3H), 7.44 (s, 4H), AA'BB' system centered at 7.56 and 8.24 (4H); Ms: m/e 331(M^+, 5), 43(100).
Calcd. for $C_{17}H_{14}ClNO_4$: C, 61.55; H, 4.25; N, 4.22. Found: C, 61.65; H, 4.32; N, 4.10.
3-(4-Methoxyphenyl)-1-(4-nitrophenyl)-2-propen-1-ol Acetate, **20a**. Oil; Ir(film): 1730, 1615, 1515, 1350, 980 cm^{-1}; 1H-NMR ($CDCl_3$): δ 2.17 (s, 3H), 3.81 (s, 3H), 6.10 (dd, J = 7.0 and 16.0 Hz, 1H), 6.47 (d, J = 7.0 Hz, 1H), 6.64 (d, J = 16.0 Hz, 1H), AA'BB' system at 6.874, 6.88, 7.26 and 7.37 (4H), AA'BB' system at 7.50, 7.61, 8.18 and 8.28 (4H); 13C-NMR ($CDCl_3$): δ 21.06, 55.10, 75.37, 114.01, 123.59, 123.74, 127.49, 127.98, 128.24, 133.69, 146.63, 147.47, 159.84, 169.66; Ms: m/e 327(M^+, 49), 284(45), 268(84), 267(100), 252(26), 221(53), 178(61), 150(75), 135(19), 121(40), 43(72).
1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-2-propen-1-ol Acetate, **22a**. Oil; Ir(film): 1735, 1610, 1600, 1515, 1350, 975 cm^{-1}; 1H-NMR ($CDCl_3$): δ 2.15 (s, 3H), 3.85 (s, 3H), 6.43-7.4 (m, 7H), 7.44, 7.56, 8.12, 8.22 (AA'BB' system, 4H); 13C-NMR ($CDCl_3$): δ 21.07, 55.20, 75.15, 114.15, 123.81, 127.10, 128.56, 129.50, 130.46, 132.65, 142.72, 147.18, 159.78, 169.72; Ms: m/e 327(M^+, 43), 284(24), 268(80), 267(100), 221(71), 178(56), 150(25), 137(44), 135(73), 121(33), 43(53).
Reaction of **23** with **20a**. THF (20 mL) was added to a 60% sodium hydride suspension (160 mg, 4 mmole) washed with dry hexane. Triacetic acid lactone (630 mg, 5 mmole) was added to the above mixture. When gaseous evolution ceased, triphenylphosphine (79 mg, 0.7 mmole) and $Pd(dba)_2$ (57 mg, 0.1 mmole) were also added. Finally, **20a**, (654 mg, 2 mmole) in THF (10 mL) was introduced with a syringe. All the operations were performed under argon atmosphere. The mixture was magnetically stirred for 1 hour. 1M HCl (5 mL) and saturated sodium chloride (150 mL) were added to the mixture which was partitioned with ethyl acetate (3 x 50 mL). The organic layer was washed with saturated sodium chloride (4 x 25 mL), dried (Na_2SO_4) and evaporated. The residue was chromatographed through silica-gel to afford a mixture of 4-hydroxy-6-methyl-3-(1-(4-methoxyphenyl)-3-(4-nitrophenyl)-2-propen-1-yl)-2-pyrone, **25a**, and its isomer 4-hydroxy-6-methyl-3-(3-(4-methoxyphenyl)-1-(4-nitrophenyl)-2-propen-1-yl)-2-pyrone, **24a**, (652 mg, 83%) (ratio 97:3) (See below). The major isomer could not be isolated in pure form in spite of the several efforts made. The mixture was a solid foam, mp 105-111ºC; Ir(KBr): 3500-2500 (broad), 1670, 1575, 1510, 1340 cm^{-1}; 1H-NMR ($CDCl_3$) of a 89:11 mixture: δ **25a**: 2.18 (s, 3H), 3.78 (s, 3H), 5.18 (d, J = 8 Hz, 1H), 5.90 (broad s, 1H), 6.55 (d, J = 16 Hz, 1H), 6.95 (dd, J = 8 and 16 Hz, 1H), 6.86, 6.88, 7.28 and 7.30 (AA'BB' system, 4H) 7.48, 7.50, 8.12 and 8.15 (AA'BB' system, 4H), **24a** (only well visible and integrated peaks): 2.15 (s), 3.76 (s), 6.83, 6.85, 7.39, 7.41 (AA'BB' system), 8.09, 8.11 (part of a AA'BB' system); Ms: m/e 393(M^+, 22), 272(36), 257(39), 189(20), 135(22), 134(100), 121(46).
Calcd. for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56. Found: C, 66.59; H, 4.89; N, 3.57.
Reaction of **23** with **22a**. As for **20a** (See Table 2).
Reaction of **23** with **20b**. As for **20a** (See Table 2). The following products were isolated

after chromatography in the indicated order:
A mixture of 4-(4-chlorophenyl)-7-methyl-2-(4-nitrophenyl)-2H,5H-pyrano[3,2-c]pyran-5-one, **27**, and its isomer 2-(4-chlorophenyl)-7-methyl-4-(4-nitrophenyl)-2H,5H-pyrano[3,2-c]pyran-2-one, **26**. Mp 204-6ºC; Ir(KBr): 1705, 1641, 1547, 1520, 1348 cm^{-1}; 1H-NMR($CDCl_3$) of a 75:25 mixture of **26** and **27**: δ for **26** 2.27 (s, 3H), 5.55 (d, J = 4.5 Hz, 1H), 5.97 (s, 1H), 6.06 (d, J = 4.5 Hz, 1H), AA'BB' system centered at 7.20 and 7.33 (4H), AA'BB' system centered at 7.66 and 8.28 (4H), δ for **27** (only well defined and integrated peaks) 2.25 (s, 3H), 5.64 (d, J = 4.5 Hz, 1H), 5.93 (s, 1H), 6.00 (d, J = 4.5 Hz, 1H), 7.43 (s, 4H), AA'BB' system centered at 7.45 and 8.20 (4H); Ms: m/e 397 (M^++2, 35), 395(M^+, 100), 43(42).
Calcd. for $C_{21}H_{14}ClNO_5$: C, 63.73; H, 3.56; N, 3.54. Found: C, 63.77; H, 3.77; N, 3.46.
A mixture of 3-(1-(4-chlorophenyl)-3-(4-nitrophenyl)-2-propen-1-yl)-4-hydroxy-6-methyl-2-pyrone, **25b**, and its isomer 3-(3-(4-chlorophenyl)-1-(4-nitrophenyl)-2-propen-1-yl)-4-hydroxy-6-methyl-2-pyrone, **24b**, in a ratio 85:15 (See below). Mp 191-4ºC; Ir(KBr): 3600-2400 (broad), 1672, 1635, 1592, 1577, 1514, 1406, 1342 cm^{-1}; 1H-NMR($CDCl_3$): δ for **25b**: 2.10 (s, 3H), 2.33 (broad s, 1H), 5.11 (d, J = 8.9 Hz, 1H), 5.94 (s, 1H), 6.55 (d, J = 15.7 Hz, 1H), 7.08 (dd, J = 8.9 and 15.7 Hz, 1H), AA'BB' system centered at 7.19 and 7.26 (4H), AA'BB' system centered at 7.47 and 8.10 (4H), for **24b** (only well defined and integrated peaks): 5.16 (d, J = 8.9 Hz, 1H), 6.85 (dd, J = 8.9 and 15.7 Hz, 1H); Ms: m/e 397(M^+, 28), 261(100), 43(59).
Calcd. for $C_{21}H_{16}ClNO_5$: C, 63.40; H, 4.05; N, 3.52. Found: C, 63.56; H, 4.11; N, 3.42.
Ozonolysis of a mixture **25a:24a** (89:11). General Method. A stream of O_2/O_3 (4 mmole of O_3 per hour) was bubbled during one hour through a solution of a mixture of the indicated composition (1H-NMR at 400 MHz) (393 mg, 1 mmole) in dichloromethane at -78ºC. Then, argon was bubbled for 5 minutes and dimethyl sulfide (0.3 mL) was added. The mixture was kept 10 minutes at -78ºC and allowed to warm up. After one hour at room temperature the mixture was chromatographed trough silica gel. A mixture (84%) of 4-nitrobenzaldehyde and 4-methoxybenzaldehyde (89:11) was eluted first with hexane:ethyl acetate (70:30). Further elution with more polar solvents did not give defined products.
Reaction of Na(acac), **28**, with **20a**. THF (20 mL) was added to a 60% sodium hydride suspension (160 mg, 4 mmole) washed with dry hexane. Pentane-2,4-dione (500 mg, 5 mmole) was added to the above mixture. When gaseous evolution ceased, triphenylphosphine (79 mg, 0.7 mmole) and $Pd(dba)_2$ (57 mg, 0.1 mmole) were also added. Finally, **20a** (654 mg, 2 mmole) in THF (10 mL) was introduced with a syringe. All the operations were performed under argon atmosphere. The mixture was magnetically stirred for 4h (tlc monitoring). Acetic acid (1 mL) and saturated solution of sodium chloride (150 mL) were added and the mixture was partitioned with ether (3 x 30 mL). The organic layer was washed with aqueous sodium chloride, dried and evaporated. The residue was chromatographed through silica gel. The following compounds were eluted in the indicated order:
3-Acetyl-4-(4-methoxyphenyl)-6-(4-nitrophenyl)hexa-2Z,4-dien-2-ol, **29**, 52 mg (7%). Mp 149-50ºC; Ir(KBr): 1600, 1510, 1345, 950 cm^{-1}; 1H-NMR($CDCl_3$): δ 1.95 (s, 6H), 3.55 (d, J = 7.2 Hz, 2H), 3.83 (s, 3H), 6.33 (t, J = 7.2 Hz, 1H), AA'BB' system at 6.79, 6.90, 7.25, 7.36 (4H), AA'BB' system at 7.27, 7.39, 8.10, 8.22 (4H), 16.7 (s, 1H); 13C-NMR($CDCl_3$): δ 23.17, 35.71, 55.14, 110.09, 114.09, 123.73, 126.76, 126.93, 128.93, 132.34, 137.17, 146.52, 147.74, 159.50, 191.10; Ms: m/e 367(M^+, 10), 307(20), 306(22), 231(93), 213(23), 43(100).
Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.71; H, 5.56; N, 3.95.
(E)- And (Z)-3-acetyl-4-(4-methoxyphenyl)-6-(4-nitrophenyl)-5-hexen-2-one, **30**, 404 mg (55%) in a ratio Z:E = 7:48, as a foam; Ir(KBr): 1695, 1600, 1515, 1350, 985 cm^{-1}; 1H-NMR($CDCl_3$) (E isomer): δ 1.97 (s, 3H), 2.24 (s, 3H), 3.78 (s, 3H), 4,32 (broad s, 2H), 6.39 (broad s, 2H), 6.75, 6.85, 7.10, 7.20 (AA'BB' system, 4H), 7.32, 7.43, 8.05, 8.16 (AA'BB' system, 4H); 13C-NMR($CDCl_3$) (E isomer): δ 29.72, 48.02, 55.13, 74.07, 114.52, 123.76, 126.75, 128.96, 129.33, 131.02, 134.75, 143.10, 146.91, 158.88, 201.98, 202.22; Ms: m/e 367(M^+, 2), 349(73), 324(79), 307(27), 306(28), 268(58), 251(27), 222(36), 207(22), 188(52), 178(41), 43(100).
3,5-Dimethyl-4-(1-(4-methoxyphenyl)-3-(4-nitrophenyl)-2-propen-1-yl)pyrazole, **31**. A mixture of **Z** and **E-30** (20:80) (734 mg, 2 mmole), hydrazine hydrate (0.11 mL, 2.2 mmole) and methanol (20 mL) was left at 0ºC for 27h (tlc monitoring). The solution was evaporated to afford 730 mg of a solid residue from which by recrystallization in methanol pure **E-31** was obtained (500 mg). Mp 146-8ºC; Ir(KBr): 3500-2500 (broad), 1600,

1510, 1345, 980 cm^{-1}; 1H-NMR($CDCl_3$): δ 2.16 (s, 6H), 3.83 (s, 3H), 4.81 (broad s, 1H), 4.87 (d, J = 6.0 Hz, 1H), 6.31 (d, J = 16.0 Hz, 1H), 6.84 (dd, J = 16.0 and 6.0 Hz, 1H), 6.80, 6.93, 7.05, 7.18 (AA'BB' system, 4H), 7.44, 7.55, 8.11, 8.22 (AA'BB' system, 4H); 13C-NMR($CDCl_3$): δ 11.59, 42.98, 55.13, 113.79, 115.65, 123.84, 126.54, 128.58, 128.94, 133.80, 136.99, 142.24, 143.75, 146.64, 158.20; Ms: m/e 363(M^+, 100), 348(34), 346(22), 332(37), 267(31), 242(37), 213(52), 189(20), 178(25), 121(46), 109(79).

Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 68.77; H, 5.72; N, 11.21.

A sample of Z-31 was obtained by the general method of ozonization of a Z:E mixture (55:45) (264 mg, 0.75 mmole) but limiting the time to 15 minutes. Isomer Z (21%) was isolated after column chromatography on silica-gel. Solid foam; Ir(KBr): 3500-2500, 1598, 1513, 1343 cm^{-1}; 1H-NMR($CDCl_3$): 2.06 (s, 6H), 3.83 (s, 3H), 4.99 (d, J = 10.0 Hz, 1H), 6.18 (dd, J = 11.0 and 10 Hz, 1H), 6.40 (broad s), 6.72 (d, J = 11 Hz, 1H), 6.78, 6.90, 7.04, 7.15 (AA'BB' system, 4H), 7.31, 7.42, 8.12, 8.23 (AA'BB' system, 4H); Ms: m/e 363(M^+, 100), 348(28), 332(37), 242(22), 231(23), 213(29), 121(37), 109(50).

3,5-Dimethyl-4-(3-(4-aminophenyl)-1-(4-methoxyphenyl)propyl)pyrazole, 32. A mixture of E-31 (363 mg, 1 mmole), 5% Pd-C (72 mg) and absolute ethanol (30 mL) was shaken under hydrogen for 40 minutes (end of hydrogen absorption). The mixture was filtered over celite eluting with more ethanol (50 mL). The solvent was evaporated to afford 325 mg (97%) of 32 as a foam which could not be recrystallized. Ir(KBr): 3500-2500, 1613 cm^{-1}; 1H-NMR($CDCl_3$): δ 2.15 (s, 3H), 2.18-2.63 (m, 4H), 3.78 (s, 3H), 3.82-4.00 (m, 1H), 4.67 (broad s, 3H), 6.56, 6.67, 6.87, 6.97 (AA'BB' system, 4H), 6.74, 6.85, 7.04, 7.14 (AA'BB' system, 4H); 13C-NMR($CDCl_3$): δ 11.72, 33.28, 36.06, 38.88, 55.13, 113.55, 115.26, 117.52, 128.39, 129.05, 132.02, 136.88, 141.87, 144.19, 157.55; Ms: m/e 335(M^+, 11), 239(34), 215(100), 106(26).

Di-μ-chlorobis(3-(4-chlorophenyl)-1-(4-nitrophenyl)-η^3-allyl)dipalladium, 34. Thionyl chloride (0.13 mL, 1.7 mmole) was slowly added over alcohol 21b (0.503 g, 1.7 mmole) kept at 0ºC. The mixture was allowed to reach room temperature and left for 24 h. The mixture was evaporated to eliminate the remaining HCl. The oily residue (0.342 g, 100%) was characterized as a mixture of allyl chlorides 33. Ir(film): 1598, 1519, 1345, 967 cm^{-1}; 1H-NMR($CDCl_3$): δ 5.63 (68%) (d, J = 6.7 Hz) and 5.69 (32%) (d, J = 7.8 Hz) (1H), 6.42 (32%) (dd, J = 7.9 and 15.8 Hz, 1H of the minor isomer), 6.65 (m, 2H + 68% of 1H of the major isomer), 7.31-7.42 (m, 4H), AA'BB' systems centered at 7.52 and 8.19 (68%) and 7.65 and 8.25 (32%) (4H). A mixture of the isomeric chlorides 33 (0.898 g, 2.92 mmole) in benzene was added over a suspension of the complex $Pd_2(dba)_3 \cdot HCCl_3$ (1.19 g, 1.1 mmole) in benzene (22 mL). The solvent was degasified and the operation was performed under argon atmosphere. The mixture was magnetically stirred for 168h. The very insoluble complex 34 (0.919 g, 100%) was filtered off and washed with benzene. Mp 298-300ºC (dec.); Ir(KBr): 1596, 1512, 1487, 1342, 1092, 845, 819 cm^{-1}.

Calcd. for $C_{30}H_{22}Cl_4N_2O_4Pd_2$: C, 43.46; H, 2.67; N, 3.38; Cl, 17.10. Found: C, 44.45; H, 2.81; N, 3.19; Cl, 16.54.

(3-(4-Chlorophenyl)-1-(4-nitrophenyl)-η^3-allyl)(bis(1,2-diphenylphosphino)ethane)palladium tetrafluoroborate, 35. Complex 34 (214 mg, 0.25 mmole) was added over a solution of silver tetrafluoroborate (102 mg, 0.5 mmole) in acetone (5 mL) kept in the dark. The mixture was magnetically stirred at room temperature for 1h. The formed silver chloride was filtered off and bis(diphenylphosphino)ethane (203 mg, 0.50 mmole) was added to the filtrate. The mixture was magnetically stirred at room temperature for 24h, filtered and the filtrate evaporated to afford 327 mg (76%) of 35 as a brown solid. A pure sample was obtained by preparative tlc on silica gel (eluent EtOAc) of 75 mg of the brown solid, 33 mg of pure 35 being isolated. Mp about 140ºC. Many attempts were made to obtain better quality crystals. From EtOAc yellow crystals of mp 180ºC were isolated; Ir(KBr): 1594, 1514, 1486, 1436, 1339, 1100, 1055, 820, 748, 692 cm^{-1}; 1H-NMR($CDCl_3$): δ 2.0-2.4 (m, 4H), two apparent triplets corresponding to the protons at both allylic termini at 5.37 (dd, J(H-nearest P) = 12 Hz, J(H-H at C2) = 10 Hz, 1H), 5.48 (dd J(H-nearest P) = 12 Hz, J(H-H at C2) = 10 Hz, 1H), 6.6-7.8 (complex absorption including H at C2, 29H); 31P-NMR($CDCl_3$, reference: H_3PO_4): δ 48.23 and 48.54 (d, J = 50.2 Hz, 1P), 49.42 and 49.73 (d, J = 50.2 Hz, 1P). See ref. 21 for interpretation of NMR data of cationic π-allylpalladium complexes.

Calcd. for $C_{41}H_{35}BClF_4NO_2P_2Pd$: C, 56.97; H, 4.08; N, 1.62. Found: C, 55.97; H, 4.36; N, 1.55.

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