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STEREOSPECIFIC PALLADIUM-CATALYZED 1,4-ACETOXYCHLORINATION OF 1,3-DIENES

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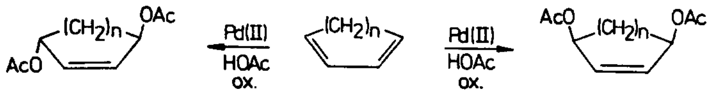
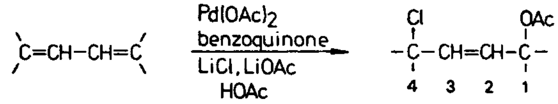
Summary: Palladium-catalyzed oxidation of 1,3-dienes in acetic acid in the presence of LiCl and LiOAc produces 1-acetoxy-4-chloro-2-alkenes in high selectivity. The 1,4-adducts were stereo- and regioselectively functionalized.

We recently reported a method for stereoselective palladium-catalyzed 1,4-diacetoxylation of cyclic 1,3-dienes (Scheme 1).[1] A remarkable control of the stereochemistry of the reaction could be obtained by varying the concentrations of acetate and chloride ligands. Thus, it was possible to prepare either cis- or trans-1,4-diacetoxy-2-cycloalkenes depending on the ligand concentrations. During this work we observed that the use of a moderately increased chloride ion concentration drastically changed the product pattern to give 1-acetoxy-4-chloro-2-alkenes as the sole product. We now report on this palladium-catalyzed 1,4-acetoxychlorination of 1,3-dienes (eq. 1).

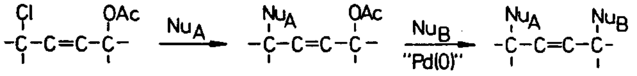
Scheme 1





$$\text{>C=CH-CH=C<} \xrightarrow[\text{LiCl, LiOAc} \atop \text{HOAc}]{\text{Pd(OAc)}_2 \atop \text{benzoquinone}} -\underset{4}{\overset{\text{Cl}}{\text{C}}}-\underset{3}{\text{CH}}=\underset{2}{\text{CH}}-\underset{1}{\overset{\text{OAc}}{\text{C}}}- \qquad \text{(eq. 1)}$$

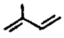
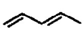
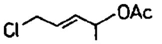
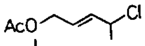
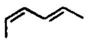
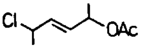
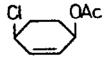
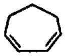
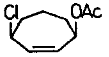
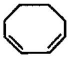
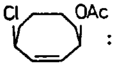
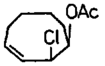
The reaction produces selectively 1-acetoxy-4-chloro-2-alkenes, which are useful synthons for organic synthesis. They can be selectively functionalized in the allylic positions using for example a classical nucleophilic substitution of the chloro group followed by a metal-catalyzed (Pd, Cu, Fe)[2] nucleophilic substitution of the acetoxy group (eq. 2).



$$-\overset{\text{Cl}}{\text{C}}-\text{C}=\text{C}-\overset{\text{OAc}}{\text{C}}- \xrightarrow{\text{Nu}_A} -\overset{\text{Nu}_A}{\text{C}}-\text{C}=\text{C}-\overset{\text{OAc}}{\text{C}}- \xrightarrow[\text{"Pd(0)"}]{\text{Nu}_B} -\overset{\text{Nu}_A}{\text{C}}-\text{C}=\text{C}-\overset{\text{Nu}_B}{\text{C}}- \qquad \text{(eq. 2)}$$

The acetoxychlorinations of the dienes were performed in acetic acid at room temperature using 5 - 10 mol % of $Pd(OAc)_2$ as catalyst. Benzoquinone was used as the oxidant. To avoid Diels-Alder addition of the diene to benzoquinone it was necessary, in most of the cases, to slowly add the diene to the reaction mixture. In a typical procedure 1,3-cyclohexadiene (0.62 g, 7.7 mmol) was added during 3 h to a well stirred solution of $Pd(OAc)_2$ (87 mg, 0.39 mmol), LiCl (0.65 g, 15 mmol), LiOAc (1.58 g of the dihydrate, 15 mmol) and benzoquinone (1.76 g, 16 mmol) in acetic acid (28 ml) at room temperature. After the addition was complete the reaction mixture was allowed to stir for another 2 h at room temperature. Saturated NaCl (30 ml) was added and the mixture was extracted with pentane (5 x 50 ml), (filtration of precipitates). The pentane phase was washed (water, sat. Na_2CO_3), dried ($MgSO_4$) and evaporated to give 1.25 g of crude product. Kugelrohr distillation gave

Table 1. Palladium-catalyzed acetoxychlorination of 1,3-dienes.[a]

entry	diene	addition time of diene (hrs)	total reaction time (hrs)	product	Yield(%)[b]
1		16	20		78
2		16	20	 c,d	70
3	 e	16	20	 :  (1.5:1)	51
4		16	20		54
5		3	5	 (>98% cis)	89
6		f	6	 (>98% cis)	74
7	 g	f	36	 :  (3:1)[h]	61

a. Pd(OAc)$_2$ was used as catalyst (5 mol % in entries 5 and 6 and 10 mol % in entries 1 - 4 and 7. Entries 1 - 6: room temperature, entry 7: 40°C; b. Isolated yield of pure products after distillation; c. E : Z = 3.3 : 1 as determined by ^{1}H NMR. The assignement of the E isomer was done using NOE measurements; d. Contains also a small fraction (1/9) of the other 1,4-regioisomer; e. cis-1,3-pentadiene gave the same result; f. The diene was added in one portion; g. A higher concentration of LiOAc was used (7 eq.); h. Only the cis-isomers were observed.

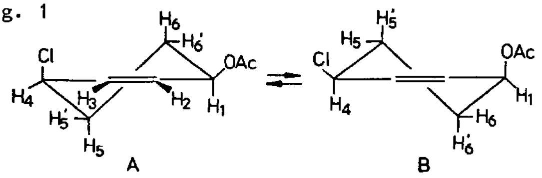
1.19 g (89 %) of cis-1-acetoxy-4-chloro-2-cyclohexene (>98% cis). Results from the oxidation of some other 1,3-dienes are given in Table 1.

It is interesting to note the high regioselectivity for the addition to isoprene, making the chloroacetate from this diene useful as a building block for terpenoids. 1,4-Acetoxychlorination of 1,3-pentadiene, however, was less regioselective giving rise to two regioisomers in a ratio of 1.5: 1. This is consistent with the observation that reaction of 1,3-pentadiene with Pd(II) in methanol produces two isomeric π-allyl complexes.[3] All the acetoxychlorination reactions of the dienes studied, except for 1,3-cyclooctadiene, show an unusual selectivity for 1,4-addition (>95-100%).

One side reaction in the 1,4-acetoxychlorination reaction is Diels-Alder addition of the diene to benzoquinone. Although this side reaction could be avoided by slow addition of the diene, we tried to replace benzoquinone by other oxidants. For example, chloranil and 2,6-dimethylbenzoquinone as oxidants gave no reaction at all, cupric chloride was less selective, and surprisingly isoamylnitrite gave only 1,4-dichloro-2-alkenes with high selectivity.[4] Thus, among the oxidants tried, benzoquinone was the one most selective for 1,4-acetoxychlorination.

The stereochemistry of the acetoxychlorination reaction was established on the product from 1,3-cyclohexadiene. The coupling constants determined from ^{1}H NMR spectroscopy (200 MHz, CDCl$_3$) given in Fig. 1, are consistent only with an equilibrium of the conformations A and B, the former being slightly favoured.[5,6] The fact that both J_{45} and $J_{45'}$ are < 5 Hz is compatible only with the chloro and acetoxy groups being cis to one another.[5]

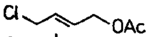
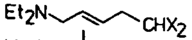
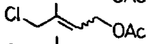
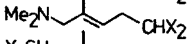
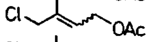
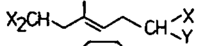
Fig. 1



δ_1 = 5.28 ppm
$J_{16} \sim J_{16'}$ = 6.5 Hz
J_{12} = 2.8 Hz
J_{13} = 1.5 Hz
J_{14} = 1.4 Hz

δ_4 = 4.56 ppm
$J_{45} \sim J_{45'}$ = 4.8 Hz
J_{34} = 3.6 Hz
J_{24} = 1.0 Hz
J_{23} = 10.3 Hz

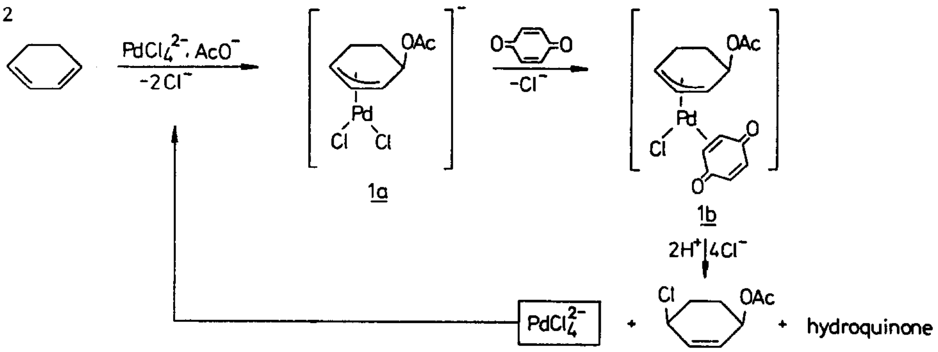
Table 2. Functionalizations of chloroacetates according to equation 2.

entry	chloroacetate	$Nu_A^{a,b}$	$Nu_B^{a,c}$	product^{d}	Yield(%)^{e}	
					A	B
1		Et_2NH	$NaCHX_2$		83	79
2		Me_2NH	$NaCHX_2$		76	74
3		$NaCHX_2$	Me_2NH	 ^{f}	76	89
4		$NaCHX_2$	NaCHXY		79	74
5		Me_2NH	$NaCHX_2$		93	80

a. X = COOMe, Y = COMe; b. Acetonitrile was used as solvent; c. THF was used as solvent; d. All products were characterized by spectral data; e. Isolated yield of pure products. The yield in each step is given under A and B respectively; f. E : Z = 4 : 1

A likely mechanism for the catalytic cycle is shown in Scheme 2. Formation of an intermediate π-allyl complex 1a via a trans-acetoxypalladation[1] of one of the double bonds followed by an external trans-attack by a chloride ion would give the observed cis-product. The regiochemistry observed for isoprene supports that acetate is the first nucleophile introduced, since isoprene is known[3] to react with Pd(II) in acetic acid to give 2-methyl-4-acetoxy-1,2,3-η^3-butenylpalladium complexes.[7] It is likely that benzoquinone coordinates to palladium (1b), thus increasing the rate of nucleophilic attack on the π-allyl group. Protonation of the coordinated benzoquinone[8] in 1b would facilitate an electron transfer from palladium to coordinated benzoquinone. Such an inner-sphere electron transfer[9] would keep palladium from being reduced and concerted formation of Pd(II) would take place during the attack by chloride.

Scheme 2

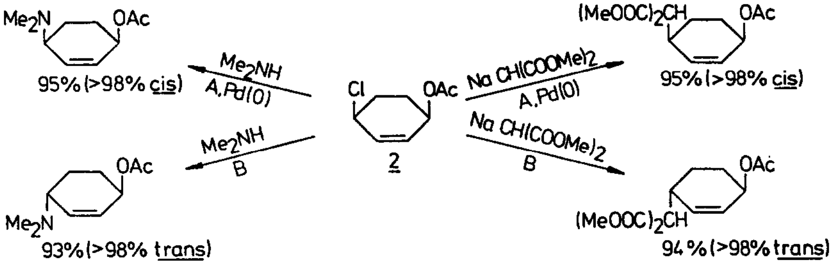


The high stereoselectivity of the acetoxychlorination together with the fact that the chloro and acetoxy groups can be selectively substituted one after the other opens a new way of using 1,3-dienes as building blocks in organic synthesis. In Table 2 and Scheme 3 we have given some examples

Scheme 3

A: 2 mol % of $Pd(acac)_2$ or $Pd(OAc)_2$, PPh_3, THF, 25°C

B: acetonitrile, reflux



of functionalizations of products from 1,4-acetoxychlorination. As can be seen from Table 2 (entries 2 and 3) one can select the regiochemistry for the isoprene unit one way or the other. Entry 4 shows an example of regioselective carbon-carbon bond formation. As shown in Scheme 3 the cyclic products offer a dual choice of stereochemistry. Thus, by utilizing a mild palladium-catalyzed substitution or a classical nucleophilic substitution, the chloro group in 2 was replaced with either retention or inversion respectively. An important aspect on the products thus obtained is that the allylic acetoxy group can readily be stereospecifically (retention) substituted by a second nucleophile using palladium catalysis (cf. entry 5, Table 2).[2b,2c] In this way one can selectively prepare a great number of either *cis*- or *trans*-1,4-disubstituted 2-cycloalkenes.[10]

Similar functionalizations of 1,3-diene systems may be obtained by other methods.[11,12] These methods, however, require prior epoxidation of one of the double bonds in the diene. Furthermore none of the previous methods allow the selective preparation of both stereoisomers in the cyclic systems shown in Scheme 3.

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