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PALLADIUM-CATALYSED OXIDATION OF ALCOHOLS WITH CARBON TETRACHLORIDE, FORMATION OF 4,4,4-TRICHLORO KETONES FROM ALLYLIC ALCOHOLS AND CARBON TETRACHLORIDE OR BROMOTRICHLOROMETHANE, AND CONVERSION OF HALOHYDRINS TO KETONES

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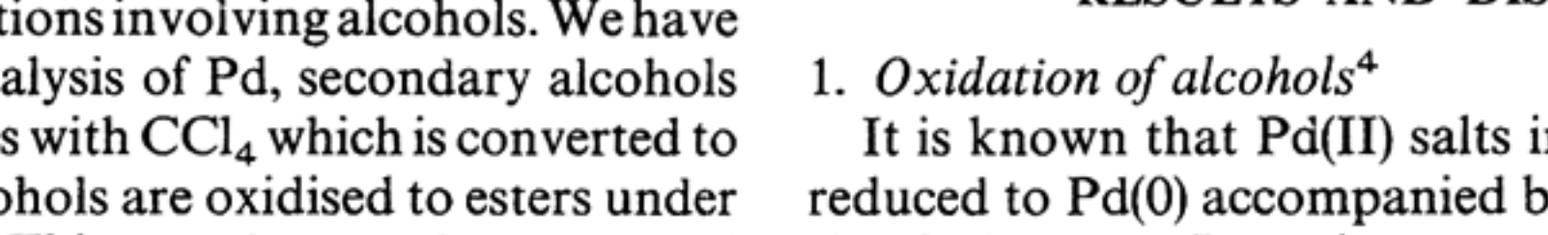
Abstract—Pd salts catalyse oxidation of alcohols with CCl_4 in the presence of K_2CO_3. Primary alcohols are oxidised to esters, and secondary alcohols to ketones. CCl_4 is converted to $CHCl_3$. The reaction of allylic alcohols bearing a terminal olefinic bond with CCl_4 or $BrCCl_3$ in the presence of palladium catalyst at 110° affords 4,4,4-trichloro ketones. At 40°, simple adducts of CCl_4 or $BrCCl_3$ having a halohydrin structure are obtained, which are converted to the corresponding trichloro ketones by the catalysis of palladium. Various halohydrins are converted to ketones by Pd catalysis.

In our continuing effort to study the Pd-catalysed reactions of polyhaloalkanes. our main interest has been to compare the reactivities of polyhaloalkanes with those of aryl and alkenyl halides in the presence of Pd catalysts. Their reactivities are clearly different in reactions involving olefins.[1–3] But we have found some similarities in the reactions involving alcohols. We have found that by the catalysis of Pd, secondary alcohols are oxidised to ketones with CCl_4 which is converted to $CHCl_3$.[4] Primary alcohols are oxidised to esters under the same conditions. This reaction can be compared with the Pd-catalysed oxidation reaction of alcohols with aryl halides reported by Tamaru *et al.*[5–7] Also we have found that the Pd-catalysed reaction of allylic alcohols with CCl_4 and $BrCCl_3$ is neither a simple addition of CCl_4 and $BrCCl_3$ to olefinic bonds, nor oxidation of the OH group. In this reaction introduction of a trichloromethyl group and oxidation of the OH group take place concomitantly to afford 4,4,4-trichloro ketones.[8] This reaction is closely related to the well-known reactions of aryl and alkenyl halides with allylic alcohols to form β-aryl and alkenyl ketones reported by Chalk and Magennis[9] and Melpolder and Heck.[10] In our reaction, polyhaloalkanes add to the olefinic bond of allylic alcohols to form halohydrins, which are converted to ketones by the catalysis of Pd. As an extension of this reaction, we have carried out the conversion of various halohydrins to ketones with Pd catalysts.[11] Preliminary reports on these reactions have been given,[4,8,11] and details of the reactions are presented in this paper.

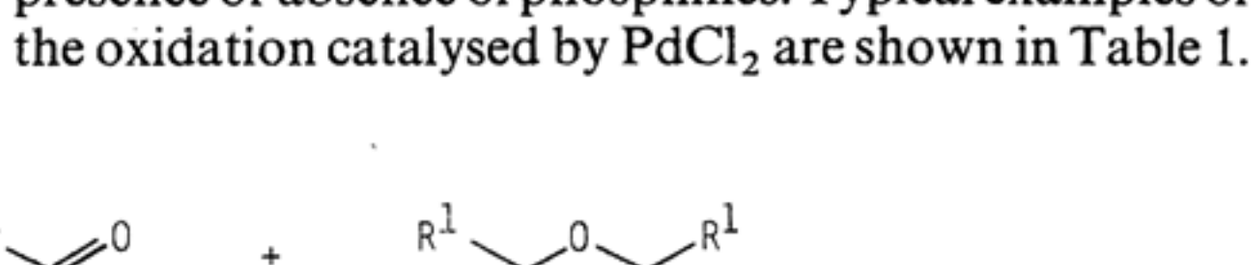
RESULTS AND DISCUSSION

1. *Oxidation of alcohols*[4]

It is known that Pd(II) salts in alcoholic media are reduced to Pd(0) accompanied by dehydrogenation of the OH group. In order to recycle the Pd, various oxidants of Pd(0) such as Cu salts[12] and aryl halides[5–7] are used. We have found that Pd salts catalyse the oxidation of alcohols with CCl_4 in the presence of excess K_2CO_3, in which CCl_4 is considered to be a novel oxidant of Pd(0). Several Pd salts such as $PdCl_2$ and $Pd(OAc)_2$ are active for the oxidation in the presence or absence of phosphines. Typical examples of the oxidation catalysed by $PdCl_2$ are shown in Table 1.



Scheme 1.



Scheme 2.

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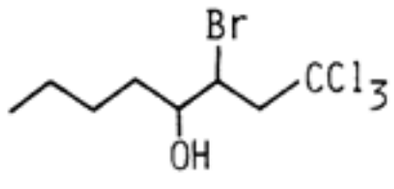
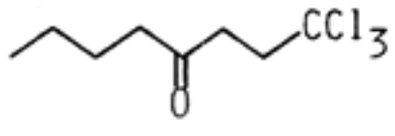
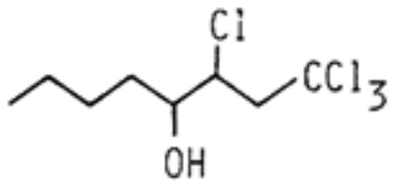
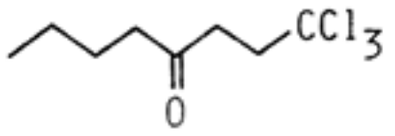
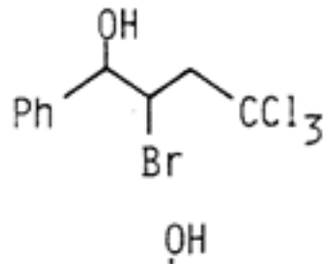
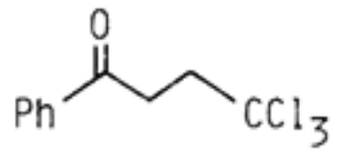
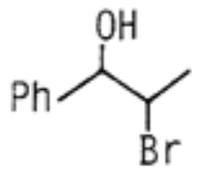
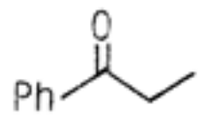
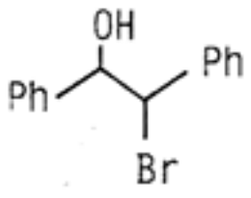
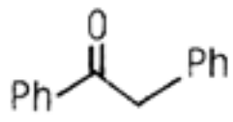
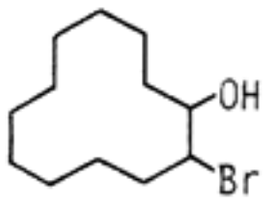
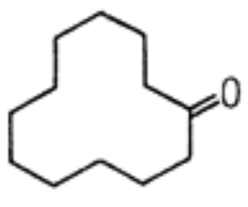
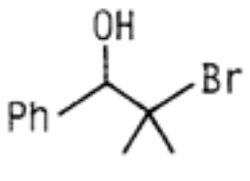
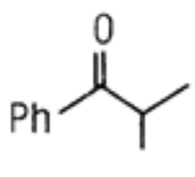
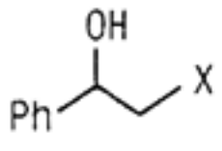
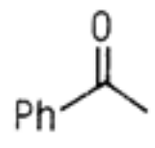
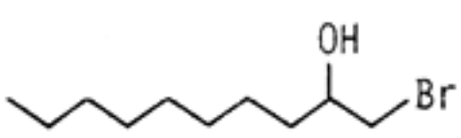
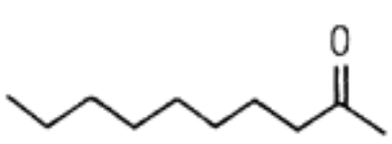
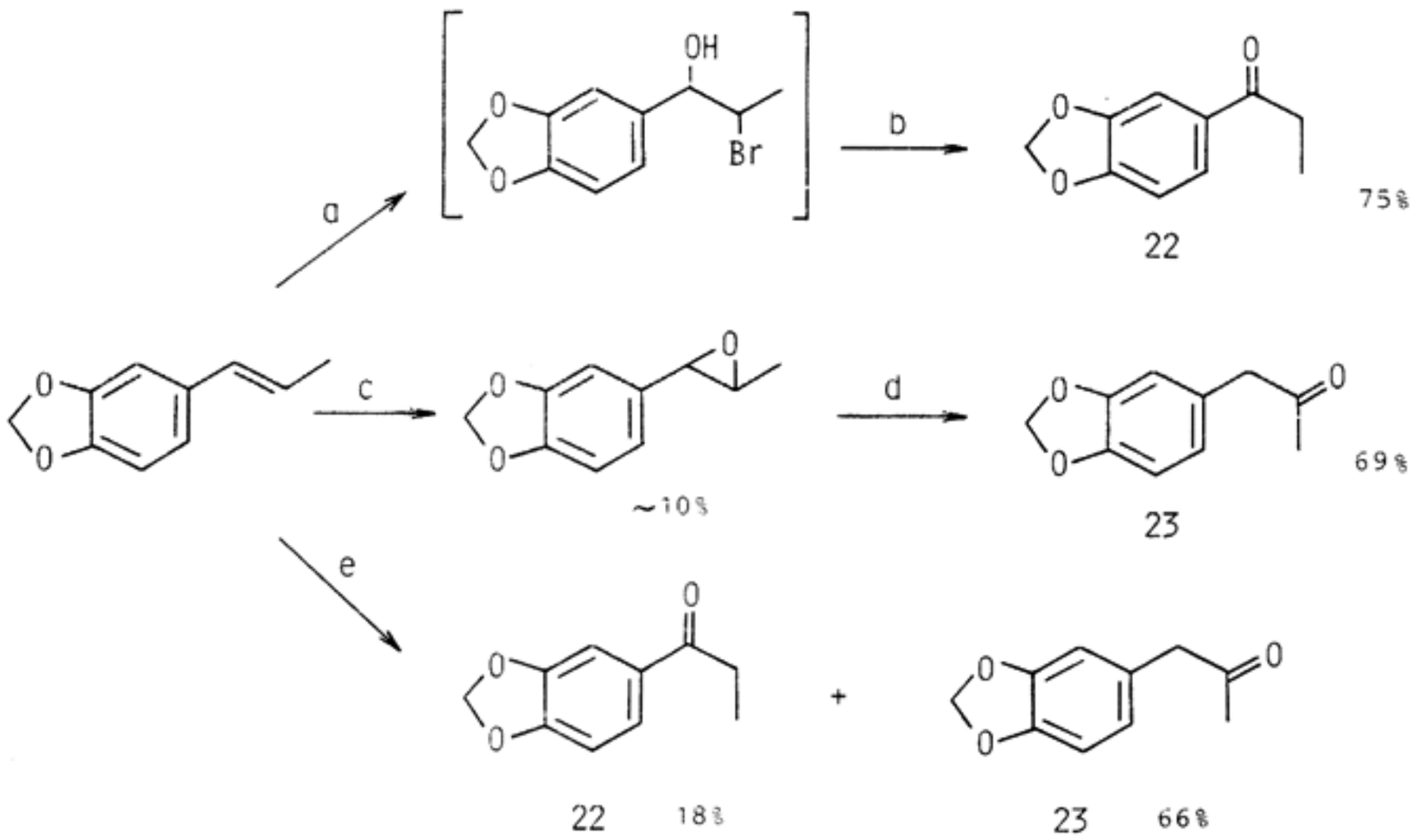
Table 4. Conversion of halohydrins to ketones

Entry	Adducts		Products		Yields (%)[a]
1		**11**		**2**	87
2		**12**		**2**	57
3		**13**		**7**	87
4		**14**			87
5		**15**			63
6		**16**			68
7		**17**			79
8		a X = Cl b X = Br c X = I	**18** **19** **20**		28 (34) 44 (22) 46 (20)
9		**21**			41 (28)

[a] Yields of the epoxides are shown in parentheses.

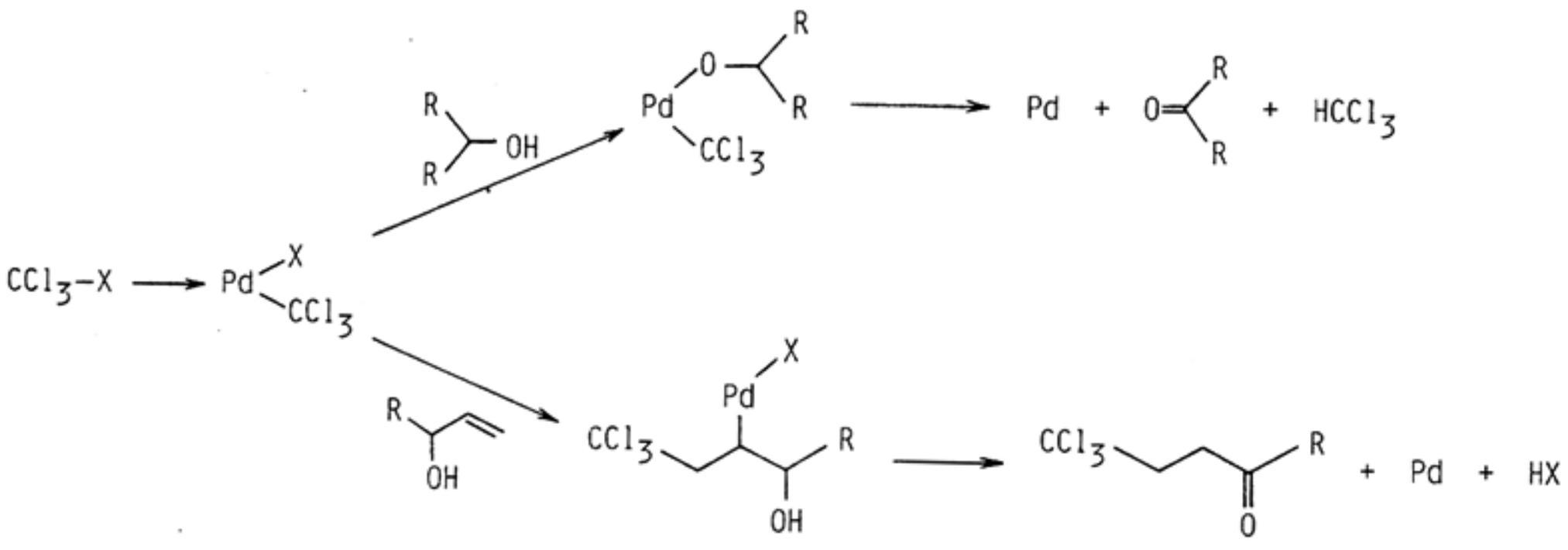
bromohydrin in a quantitative yield. Successive treatment of the bromohydrin with $Pd(OAc)_2$ (5 mol %) combined with P(*o*-Tol)$_3$ (10 mol %) in the presence of K_2CO_3, gave **22** in 75% yield. No regio-isomeric ketone was obtained. Epoxidation of iso-safrole with *m*-CPBA followed by treatment with BF_3–OEt_2 afforded **23** as the sole product. Furthermore, direct oxidation of iso-safrole with $PdCl_2$/CuCl catalyst under oxygen atmosphere afforded **22** and **23** in 18 and 66% yields, respectively. These results imply that the preparative



a. NBS/ DMSO aq.. b. $Pd(OAc)_2/P(o\text{-}Tol)_3/K_2CO_3$. c. m-CPBA.

d. $BF_3.OEt_2/Et_2O$. e. $PdCl_2/CuCl/O_2$.

Scheme 4.



Scheme 5.

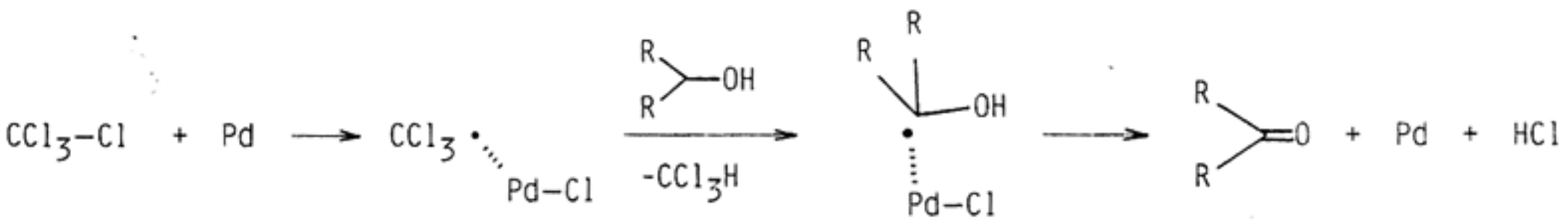
method of ketones from olefins via bromohydrins is useful, especially when the bromohydrins are formed from olefins with high selectivity.

4. *Mechanistic consideration*

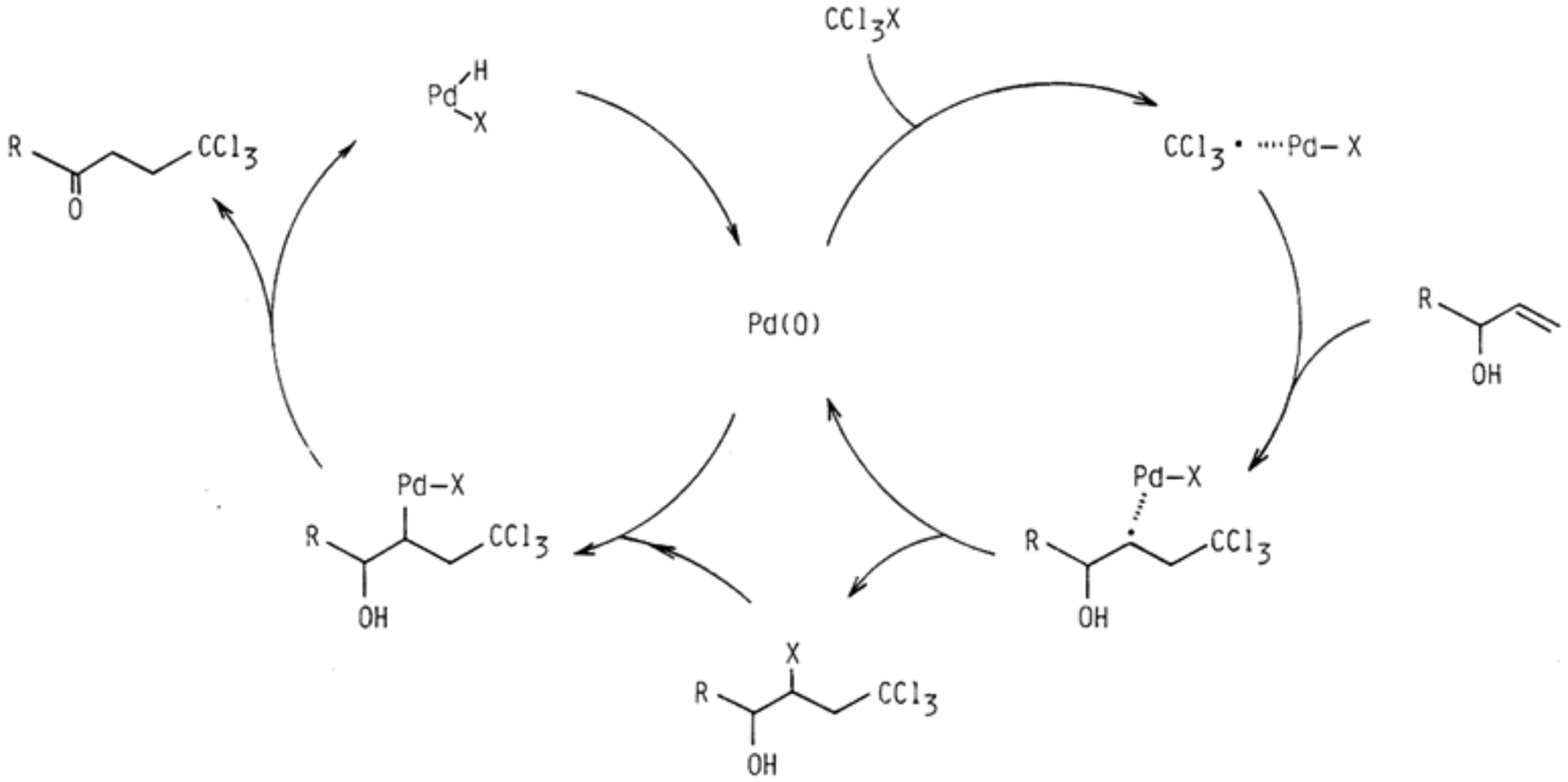
The oxidation of alcohols with CCl_4, and formation of trichloroketones reported in this paper correspond to the oxidation of alcohols with aryl halides,[5–7] and formation of β-aryl ketones from allylic alcohols and aryl halides.[9,10] Thus, one may expect that the reactions proceed via a mechanism similar to the reactions of aryl halides, namely oxidative addition of polyhaloalkanes to Pd(0), followed by nucleophilic substitution of halide on Pd by alkoxide and successive β-hydride elimination, or followed by insertion of olefinic bond of allylic alcohols and successive β-hydride elimination (Scheme 5). However, results described below do not necessarily support this mechanism.

It is known that CCl_4 or 1,1,1-trichloroalkanes are reduced in alcoholic media to $CHCl_3$ or 1,1-dichloroalkanes, respectively, by the catalysis of $RuCl_2(PPh_3)_3$.[17] Alcohols act as hydrogen donors and a trapper of HCl is formed. Thus, from isopropanol, a mixture of acetone and 2-chloropropane is formed. In the Ru-catalysed reaction, we found that presence of K_2CO_3 leads to successful oxidation of alcohols with CCl_4 at an elevated temperature without forming the corresponding chloride. Similarly, other transition metal catalysts active for the addition of CCl_4 to olefins are also active, more or less, for the oxidation of alcohols under similar conditions. These reactions can be explained by H-abstraction from alcohol by the trichloromethyl radical generated by transition metal catalysts. As described in the preceding papers, the trichloromethyl radical is considered to be formed by the action of Pd(0), and hence, a mechanism illustrated in Scheme 6 is proposed.

In contrast, the formation of trichloro ketones cannot be accomplished by other transition metal catalysts or under free radical conditions. Asscher and Vofsi reported simple addition of CCl_4 to 2-propen-1-ol with Fe catalysts,[18] and similar simple addition of CCl_4 or $BrCCl_3$ to 1-hepten-3-ol was confirmed by us by the catalysis of $RuCl_2(PPh_3)_3$ or $(PhCO_2)_2$. However, the Pd-catalysed formation of trichloro ketones seems to involve the simple addition, followed by the conversion of halohydrins formed to ketones. In both steps, catalysis by Pd is essential. The mechanism of the Pd-catalysed conversion of halohydrins to ketones is not clear, but may involve oxidative addition of the carbon–halogen bond onto Pd(0) and successive β-hydride elimination. The overall process is illustrated in Scheme 7.



Scheme 6.



Scheme 7.

EXPERIMENTAL

General

NMR spectra were taken on a Hitachi R-24A (60 MHz) or R-40 (90 MHz) spectrometer. The chemical shifts are recorded by δ units in ppm relative to TMS. IR spectra were taken with a JASCO IRA-2 spectrometer and recorded in wave number. The known products were identified by comparison of spectral data with those of authentic samples. Physical data of new compounds are shown below.

General procedure for the oxidation of alcohols with CCl_4

To a mixture of $PdCl_2$ (2 mg, 0.01 mmol) and K_2CO_3 (138 mg, 1 mmol) was added alcohol (1 mmol) dissolved in excess CCl_4. The suspension was refluxed under argon. After the reaction was complete, K-salt was filtered off, and the filtrate was concentrated. Purification of the residue by column chromatography (silica gel, hexane–ether) afforded the desired ketone or ester. In some cases, the reaction was carried out in a pressure bottle at 110°.

General procedure for the 4,4,4-*trichloro ketone formation from allylic alcohols and* $BrCCl_3$ *or* CCl_4

In a pyrex tube fitted with a screw cap, were placed $Pd(OAc)_2$ (2 mg, 0.01 mmol), P(*o*-Tol)$_3$ (6 mg, 0.02 mmol) and K_2CO_3 (276 mg, 2 mmol). A benzene soln of allylic alcohol (1 mmol) and $BrCCl_3$ (198.3 mg, 1 mmol) was added, and the mixture was heated at 110° for several hr. After removal of the solvent, the mixture was purified by column chromatography (silica gel, hexane–ether) to give the corresponding ketone. Application of 5 equiv. of CCl_4 also afforded the desired ketone.

1,1,1-*Trichloro*-4-*octanone* (**2**). NMR (90 MHz, $CDCl_3$) 0.7–1.1 (m, 3H, C$\underline{H}_3$), 1.1–1.9 (m, 4H, alkyl), 2.33–2.70 (m, 2H, C$\underline{H}_2$CO), 2.70–3.20 (m, 4H, COC$\underline{H}_2$C$\underline{H}_2$CCl$_3$); IR (neat) 1720, 780, 690; *m/e* 230 (M), 232 (M+2), 234 (M+4); high resolution mass: calc for $C_8H_{13}OCl_3$ (M): 230.0026; found: 230.0001.

1-*Phenyl*-4,4,4-*trichloro*-1-*butanone* (**7**). NMR (90 MHz, $CDCl_3$) 3.0–3.7 (m, 4H, COC$\underline{H}_2$C$\underline{H}_2$CCl$_3$), 7.3–8.25 (m, 5H, phenyl); IR (neat) 1690, 1600, 1580, 750, 690; *m/e* 250 (M), 252 (M+2), (M+4); high resolution mass: calc for $C_{10}H_9OCl_3$: 249.9718; found: 249.9723.

3-*Methyl*-1,1,1-*trichloro*-4-*octanone* (**8**). NMR (90 MHz, $CDCl_3$) 0.8–1.1 (m, 3H, C$\underline{H}_3$), 1.1–1.8 (m, 4H, alkyl), 1.23 (d, 3H, J = 7.5 Hz, C$\underline{H}_3$CHCO), 2.4–2.76 (m, 3H, CCl$_3$C$\underline{H}$, COC$\underline{H}_2$), 3.1 (m, 1H, C$\underline{H}$CO), 3.6 (dd, 1H, J = 7.5, 15 Hz, CCl$_3$C$\underline{H}$); IR (neat) 1720, 770, 700; *m/e* 244 (M), 246 (M+2), 248 (M+4); high resolution mass: calc for $C_9H_{15}OCl_3$: 244.0187; found: 244.0156.

2-*Methyl*-1-*phenyl*-4,4,4-*trichloro*-1-*butanone* (**9**). NMR (90 MHz, $CDCl_3$) 1.31 (d, 3H, J = 7.5 Hz, C$\underline{H}_3$), 2.75 (d, 1H, broad, CCl$_3$C$\underline{H}$), 3.63–4.20 (m, 2H, CCl$_3$C$\underline{H}$C$\underline{H}$CO), 7.35–8.25 (m, 5H, phenyl); IR (neat) 1680, 1600, 1580, 780, 743, 705; *m/e* 264 (M), 266 (M+2), 268 (M+4); high resolution mass: calc for $C_{11}H_{11}OCl_3$: 263.9872; found: 263.9847.

2-*Methyl*-4,4,4-*trichlorobutanal* (**10**). NMR (90 MHz, $CDCl_3$) 1.33 (d, 3H, J = 7.5 Hz, CH_3), 2.60 (dd, 1H, J = 4, 15 Hz, C$\underline{H}$CCl$_3$), 2.82–3.16 (m, 1H, C$\underline{H}$CH$_3$), 3.53 (dd, 1H, J = 6, 15 Hz, C$\underline{H}$CCl$_3$), 9.8 (s, 1H, CHO); IR (neat) 1735, 910, 775, 700. (Calc for $C_5H_7OCl_3$: C, 31.70; H, 3.72; Cl, 56.14. Found: C, 31.60; H, 3.69; Cl, 57.89%.) B.p. 78°/12 mmHg.

Preparation of allylic alcohols. Allylic alcohols **1** and **3–5** were prepared from acrolein or methacrolein with n-BuLi or PhMgBr.

2-*Methyl*-1-*phenyl*-2-*propen*-1-*ol* (**5**). NMR (60 MHz, CCl_4) 1.55 (s, 3H, allylic), 2.6 (s, 1H, OH), 4.7–5.3 (m, 3H, C$\underline{H}$OH, olefinic), 7.3 (s, 5H, phenyl); IR (neat) 3400, 1650, 905. (Calc for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.67; H, 8.45%.)

Preparation of halohydrins. The halohydrins **11–13** were prepared following the procedure described in the preceding paper,[8] and **14–16** were prepared by reaction of olefins with N-bromosuccinimide in aqueous DMSO.[16] The compounds **17–21** were prepared by the reduction of the corresponding halo ketones with $NaBH_4$ in ethanol.

3-*Bromo*-1,1,1-*trichloro*-4-*octanol* (**11**). NMR (60 MHz, CCl_4) 0.7–1.15 (m, 3H, CH_3), 1.15–1.9 (m, 6H, alkyl), 1.9–2.2 (m, 1H, OH), 3.2–3.35 (m, 2H, CCl$_3$C$\underline{H}_2$), 3.35–3.75 (m, 1H, C$\underline{H}$OH), 4.15–4.45 (m, 1H, C$\underline{H}$Br); IR (neat) 3400, 2950, 800, 705. (Calc for $C_8H_{14}OBrCl_3$: C, 30.75; H, 4.52; Br + Cl, 59.61. Found: C, 30.53; H, 4.63; Br + Cl, 59.95%.)

1,1,1,3-*Tetrachloro*-4-*octanol* (**12**). NMR (60 MHz, CCl_4) 0.7–1.1 (m, 3H, CH_3), 1.1–1.9 (m, 6H, alkyl), 2.0–2.4 (m, 1H, OH), 3.0–3.5 (m, 2H, C$\underline{H}_2$CCl$_3$), 3.5–4.0 (m, 1H, C$\underline{H}$OH), 4.05–4.4 (m, 1H, C$\underline{H}$Cl); IR (neat) 3400, 2920, 785, 700. (Calc for $C_8H_{14}OCl_4$: C, 35.85; H, 5.27; Cl, 52.91. Found: C, 35.62; H, 5.16; Cl, 53.33%.)

2-*Bromo*-1-*phenyl*-4,4,4-*trichloro*-1-*butanol* (**13**). NMR (60 MHz, CCl_4) 2.7–2.8 (m, 1H, OH), 3.05–3.25 (m, 2H, CCl$_3$C$\underline{H}_2$), 4.12–4.50 (m, 1H, BrC$\underline{H}$), 4.8–5.1 (m, 1H, C$\underline{H}$OH), 7.2 (s, 5H, phenyl); IR (neat) 3300, 2900, 790, 700. (Calc for $C_{10}H_{10}OBrCl_3$: C, 36.13; H, 3.03. Found: C, 36.30; H, 2.94%.)

General procedure for the conversion of halohydrins to ketones

In a flask fitted with a reflux condenser were placed $Pd(OAc)_2$ (2 mg, 0.01 mmol), P(*o*-Tol)$_3$ (6 mg, 0.02 mmol), and K_2CO_3 (138 mg, 1 mmol), and the atmosphere was replaced by argon. Halohydrin (1 mmol) dissolved in benzene (2 ml) was added, and the suspension was refluxed for several hr under argon. The K-salts were filtered off, and the filtrate was purified by column chromatography (silica gel, ether–hexane) to give the ketone.

Oxidation of iso-safrole

Method A (*via bromohydrin*). Bromohydrin was prepared from iso-safrol according to the procedure of Dalton *et al.*[16] In a pyrex tube fitted with a screw cap were placed $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), P(*o*-Tol)$_3$ (30.4 mg, 0.1 mmol) and K_2CO_3 (138 mg, 1 mmol) under argon. The bromohydrin (259 mg, 1 mmol) dissolved in benzene (1 ml) was added, and then the mixture was heated at 100° for 5 hr. After the work-up as above, purification of the residue by column chromatography (silica gel, hexane–ether) afforded the desired **22**.

Method B (*via epoxide*). To a soln of iso-safrole (1.62 g, 10 mmol) in CH_2Cl_2 (10 ml) was added mCPBA (3.24 g, 15 mmol) dissolved in CH_2Cl_2 (10 ml). The mixture was stirred at 0° for 30 min. Usual work-up and chromatographic purification (silica gel, hexane–ether) afforded the epoxide (190 mg) in 11% yield. The epoxide (190 mg, 1.07 mmol) was treated with BF_3–OEt_2 (1 ml) in ether at room temp for 20 min. The soln was quenched with $NaHCO_3$ aq, and the ethereal layer was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (silica gel, hexane–ether) to give **23** in 69% yield (132 mg).

Method C (*the Wacker oxidation*). In a flask fitted with a balloon filled with O_2 were placed $PdCl_2$ (35.5 mg, 0.2 mmol) and CuCl (79.2 mg, 0.8 mmol) in aqueous DMF (DMF–H_2O 7 : 1, 2 ml). The suspension was stirred under O_2 at room temp for 2 hr. Then, iso-safrole (324.4 mg, 2 mmol) dissolved in the aqueous DMF (2 ml) was introduced, and the mixture was heated at 50° for 10 hr. Usual work-up and purification by column chromatography (silica gel, hexane–ether) afforded **22** (236 mg, 66%) and **23** (65 mg, 18%).

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