Mild alkane functionalisation leading to ethers: oxidative alkoxylation of cyclohexane with the dibromobis(phosphine)palladium(II)–sodium alkoxide system

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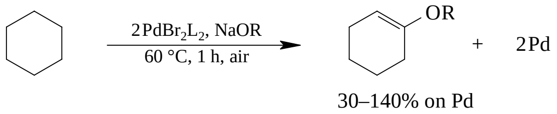
Dibromobis(phosphine)palladium(II) complexes, $PdBr_2(L)_2$ [L = PPh_3, P(*p*-Tol)$_3$], react with cyclohexane and an alcoholic solution of sodium alkoxide, NaOR (R = Me, Et, Pr^i), at 30–60 °C affording the corresponding alkyl cyclohex-1-enyl ethers, ROC_6H_9, in 30–140% yield on palladium both under argon and under air; benzene is inert under the reaction conditions, sodium *tert*-butoxide does not enter the hydrocarbon alkoxylation.

Palladium(II) complexes play an important role in solving problems of activation of inert C–H bonds and enable the elaboration of new alkane functionalisation reactions.[1–6] A series of such catalytic reactions is known that includes the oxidative carboxylation of n-hexane, cyclohexane,[1] methane, ethane and propane,[2] oxidative trifluoroacetoxylation of methane,[3] adamantane,[4] oxidative methane aminomethylation,[5] and alkane C–H bond and tetrachloromethane C–Cl bond metathesis.[6] Most of these reactions proceed in a highly acidic media such as trifluoroacetic acid.[1–5] An electrophilic mechanism of alkane C–H bond activation with palladium(II) species is usually assumed.[1–5]

We report here the first example of mild oxidative alkoxylation of a saturated hydrocarbon, cyclohexane, with dibromopalladium(II) complexes in highly nucleophilic hydrocarbon–alcohol solutions of sodium alkoxides, Scheme 1.



L = PPh_3, P(*p*-Tol)$_3$
R = Me, Et, Pr^i

Scheme 1

The reaction (Scheme 1) can be carried out at 30–60 °C as follows. A benzene–cyclohexane (1:1 v/v) solution of dihalogenobis(phosphine)palladium(II) complex (5 mmol dm^{-3}) was mixed with an alcoholic solution (2 volume parts) of sodium alkoxide (50 mmol dm^{-3}) under an argon atmosphere and then thermostatted. The yellow-orange starting dihalogenopalladium(II) complex solution turned immediately brown. After several minutes cyclohexene and the corresponding alkyl cyclohex-1-enyl ether appeared, according to GLC-MS analyses and chemical tests.[†,‡] One hour after the reaction had started palladium black began to precipitate. After 2 h the solution discoloured and the reaction stopped.

The highest results were obtained when the reaction was conducted in the air (Table 1). No alkoxylation products for all of the alcohols studied were obtained in the absence of the dibromopalladium(II) complexes both under argon and under air. More than 1 mol of isopropyl cyclohex-1-enyl ether per 2 mol of palladium was obtained under aerobic conditions whereas only a 30% yield of the ether was obtained under an argon atmosphere. A moderate or high yield of alkyl cyclohex-1-enyl ethers was obtained under aerobic conditions also when alkyl was methyl or ethyl, but not *tert*-butyl. In the case of sodium *tert*-butoxide, the colour of the reaction mixture changed in a similar way but no metal precipitate formed after several hours of heating at 60 °C. Benzene and toluene turned out to be inert for the alkoxylation with sodium methoxide, ethoxide or isopropoxide. In these cases no ether was formed in the absence of cyclohexane though palladium precipitation was observed. The latter is consistent with the known ability of palladium(II) compounds to oxidise secondary and primary alcohols in the presence of potassium carbonate.[7] The inertness of both benzene and toluene and the ability of cyclohexane to enter the alkoxylation reaction may indicate that it is not an electrophilic process. Another interesting observation was made on competitive alkoxylation of cyclohexane in reaction mixtures containing two alcohols. When either methanol or ethanol were present in the mixture with propan-2-ol (1:1 v/v), the main reaction product was cyclohex-1-enyl isopropyl ether (see Table 1). Since the primary alcohols are only slightly more acidic than isopropyl alcohol the observed product distribution may be attributed to the higher nucleophilicity of isopropoxide as compared with the nucleophilicity of methoxide or ethoxide anions. When the more soluble tris(*p*-tolyl)-phosphine complex of dibromopalladium(II) was used the same reaction products and no tolyl ethers were detected indicating that a ligand P–C bond is not involved in the ether formation.

In order to learn more about the reaction we studied the effect of concentration of all the reagents involved on the yield of the ether. It turned out that the yield rises as the hydrocarbon or sodium alkoxide concentration increases. The effect of alcohol concentration on the yields is extremal and passes through a maximum. An increasing concurrence of alcohol oxidation with palladium(II) and the reaction allow us to explain the diminution of ether yield at higher alcohol concentrations. We have also found that the reaction can be stopped if phosphine is introduced into the reaction mixtures in a 2:1 free phosphine:palladium ratio. This effect may be due to trapping of active coordinatively unsaturated palladium complex with free phosphine.

Attempts to reoxidise palladium(0) in order to make the reaction catalytic on the metal and to achieve higher results than those obtained under aerobic conditions have been undertaken. Small amounts of halogenohydrocarbons such as iodobenzene or 1,2-dichloroethane were used. The addition of iodobenzene into reaction mixture after 1 h was not effective. The addition of dichloroethane increased the yield of ether only slightly (see Table 1).

The described cyclohexane functionalisation with the dibromobis(phosphine)palladium(II) – sodium alkoxide system can be considered as follows. We believe that alkyl cyclohex-1-enyl ethers are formed *via* cyclohexene complexes of palladium(II). Indeed, on the one hand, cyclohex-1-enyl ethers were always observed along with cyclohexene. On the other hand, the ability of alkene complexes of palladium(II) to react with strong nucleophiles to produce vinylic derivatives is well known.[8] In a separate experiment we showed that cyclohexene readily reacts on dibromopalladium(II) complexes and sodium

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[†] All of the ethers react readily in solution with iodine or bromine and slowly undergo hydrolysis when the reaction mixture is acidified with aqueous sulfuric acid. Mass spectra of alkyl cyclohex-1-enyl ethers, *m/z*: 98 ($C_6H_{10}O$), 97 (C_6H_9O). ^{1}H NMR spectra of a sample of $Pr^iOC_6H_9$ obtained from reaction mixture by preparative GLC (C_6D_6) δ: 4.33–4.21 (m, 1H, CH=C–O), 3.57 (heptet, 1H, $^3J_{H-H}$ 6.5 Hz, $CHMe_2$), 2.5–1.6 (m, 8H, C_4H_8), 1.40 [d, 6H, $^3J_{H-H}$ 6.5 Hz, $(CH_3)_2C$–O].

[‡] Cyclohexane was carefully checked for the presence of cyclohexene before the experiments. No detectable amounts of the alkene were found.

Table 1 Results for oxidative alkoxylation of cyclohexane with $PdBr_2(PPh_3)_2$–NaOR under air, Scheme 1.[a]

ROH	t/h	T/°C	Yield of ROC_6H_9 according to Scheme 1, % on Pd[b]
MeOH	1	60	50
MeOH	2	60	58[c]
EtOH	1	60	62
Pr^{i}OH	1	60	144
Pr^{i}OH	1	60	30[d]
MeOH, Pr^{i}OH	1	30	7.4 (CyOMe), 46 (CyOPr^i)
EtOH, Pr^{i}OH	1	60	5.4 (CyOEt), 78 (CyOPr^i)

[a] Cyclohexane : benzene : alcohol = 1:1:2 v/v. Palladium(II) complex concentration 5 mmol dm^{-3}, palladium : sodium alkoxide = 1:10. [b] According to GLC determination, moles of ether per two moles of palladium. [c] After first hour of the reaction 50 μl of 1,2-dichloroethane per 1 ml of reaction mixture (640 mmol dm^{-3}) was added. [d] Under anaerobic conditions, yield of cyclohexene is 60% on palladium. [e] Cyclohexane : benzene : ROH : R′OH = = 1:1:2:2 v/v.

isopropoxide benzene–isopropyl alcohol solution to produce the same product as in the corresponding cyclohexane containing reaction mixtures. The species responsible for the formation of cyclohexene is postulated by us to be coordinatively unsaturated palladium(0) complex which is formed by the reduction of palladium(II) with sodium methoxide, ethoxide or isopropoxide. *tert*-Butoxide anion is not able to reduce the palladium(II) complex under the considered conditions in accordance with its inertness in the reaction. Finally, the effect of air oxygen on the reaction may be due to the decreasing amount of the metal complex needed for cyclohexane oxidative dehydrogenation.

Further investigations are now in progress on the mechanism of the reaction.

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References

1 Y. Fujiwara, K. Takaki, J. Watanabe, Y. Uchida and H. Taniguchi, *Chem. Lett.*, 1989, 1687.

2 (*a*) K. Nakata, Y. Yamaoka, T. Miyata, Y. Taniguchi, K. Takaki and Y. Fujiwara, *J. Organomet. Chem.*, 1994, **473**, 329; (*b*) K. Takaki, K. Nakata, Y. Taniguchi and Y. Fujiwara, *J. Synth. Org. Chem. Jpn.*, 1994, **52**, 809.

3 A. Sen, *Plat. Met. Rev.*, 1991, **35**, 126.

4 (*a*) J. K. Beattie, A. F. Masters and M. L. Sparkes, *Appl. Organomet. Chem.*, 1991, **5**, 521; (*b*) J. Muzart and F. Henin, *Comptes Rendu de l’Academie di Science*, 1988, **307**, 479.

5 Y. Fujiwara, K. Takaki and Y. Taniguchi, *Synlett.*, 1996, 591.

6 (*a*) A. N. Vedernikov, A. I. Kuramshin and B. N. Solomonov, *J. Chem. Soc., Chem. Commun.*, 1994, 121; (*b*) A. N. Vedernikov, A. I. Kuramshin and B. N. Solomonov, *Zh. Org. Khim.*, 1993, **29**, 2129 (*Russ. J. Org. Chem.*, 1993, **29**, 1767).

7 S. Aitmohand, F. Henin and J. Muzart, *Tetrahedron Lett.*, 1995, **36**, 2473.

8 J. P. Collman, L. S. Hegedus, J. R. Norton and R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, California, 1987, ch. 17.

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