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Comparative investigation of the regioselectivity in styrene and α -methylstyrene hydroalkoxycarbonylation as a function of palladium catalyst structure

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Dedicated to: Professor László Markó on the occasion of his 70th birthday, in recognition of his outstanding service to organometallic chemistry.

Abstract

Catalytic pathways of the styrene and α -methylstyrene hydroalkoxycarbonylation in the presence of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{SnCl}_2$ catalyst precursors have been suggested. As a method, deuterium labelling with EtOD has been applied and it resulted in mixtures of mono- and polydeuterated reaction products, detected and determined by NMR methods. Comparative elucidation of the mechanisms governing these systems does support the assumption that the hydrido route is operative. The different behaviour of the metal–alkyl intermediates accounts for the observed strong influence of catalyst and substrate structure on regioselectivity. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Carbonylation; Palladium; Mechanism; Catalysis

1. Introduction

The palladium–monophosphine-catalysed hydroalkoxycarbonylation of vinyl aromatic olefins has attracted great interest due to its importance in obtaining non-steroidal anti-inflammatory drugs [1]. The reaction is known to be characterised by high α -selectivities [2], i.e. the formation of the branched ester. Adopting Knifton's [3] catalytic system, addition of SnCl_2 leads to a prevalence of the linear product. At the same time, vinylidene olefins such as α -methylstyrene, give the linear derivative [4] selectively under both reaction conditions. A satisfactory explanation of the regioselectivities is still to be given in the framework of the two accepted mechanisms [5] for hydroalkoxycarbonylation of olefins.

The first one, the 'hydrido' route [3,6,7], involves olefin insertion into the Pd-H bond followed by CO

insertion, yielding the final product upon nucleophilic attack of the alcohol. According to the 'carboalkoxy' mechanism [8,9], a Pd-acyl species is formed by the attack of the alcohol on Pd-CO . Insertion of the olefin into the Pd-COOR bond is followed by protonolysis of the metal–alkyl σ -bond to give the corresponding ester and regeneration of the active form. These two mechanisms are claimed to be operative depending on the reaction conditions and substrates [10]. We have shown previously [11] that in the $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{SnCl}_2$ catalysed styrene hydroalkoxycarbonylation the first one is acting.

In order to find out the pathways governing the systems studied and to determine the influence of substrate and catalyst structure on regioselectivities, deuterioalkoxycarbonylation of styrene and α -methylstyrene has been carried out. In the present paper we report a detailed investigation of the reaction performed at two temperatures and partial substrate conversions. The labelled species determined by NMR (^1H -, ^2H -, ^{13}C -) and MS techniques throw light on the catalytic routes of the reaction.

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2. Results and discussion

2.1. Deuterioalkoxycarbonylation experiments

Deuterioalkoxycarbonylation of styrene (**1**) and α -methylstyrene (**2**) (Scheme 1) has been carried out at 100 and 130°C and 40 atm of CO with Pd(PPh₃)₂Cl₂ (**A**) and Pd(PPh₃)₂Cl₂/SnCl₂ (**B**) as catalytic precursors in toluene. The reaction has been stopped in each case at about 75% substrate conversion determined unambiguously together with the ratio of the isomers by GLC analysis. Purified samples of the reaction products were obtained by column chromatography on silica gel.

The crude reaction mixtures and the purified samples of isomeric esters were analysed by MS and by ¹H-, ²H-, ¹³C-NMR spectroscopy in order to determine the extent and the position of deuterium incorporation in the molecules.

2.2. Deuterioalkoxycarbonylation of styrene (**1**)

The rapid and complete identification of the deuterated species present in solution has been accomplished by the inspection of the ²H-NMR spectra [12]. Fig. 1 shows one of these recorded from the reaction mixture formed at 100°C and 75% conversion in toluene (with residual EtOD removed) in the presence of Pd(PPh₃)₂Cl₂ (**A**) (Fig. 1(a)) and Pd(PPh₃)₂Cl₂/SnCl₂ (**B**) (Fig. 1(b)) as catalytic precursors. The main groups of signals are those arising from deuterio-styrenes, ethyl-deuterio-3-phenylpropanoate (**3**) and ethyl-deuterio-2-phenylpropanoate (**4**). In Fig. 1(a) the spectrum shows only the signals corresponding to the methyl group of the branched product (which is obtained in 97.4% regioselectivity) at 1.53 ppm and those corresponding to the two geometric isomers (*E*)- and (*Z*)-1-deuterio-vinylbenzene (at 5.28 and 5.75 ppm, respectively). Isotope incorporations can be observed neither in the positions situated α to the phenyl ring nor in the aromatic region.

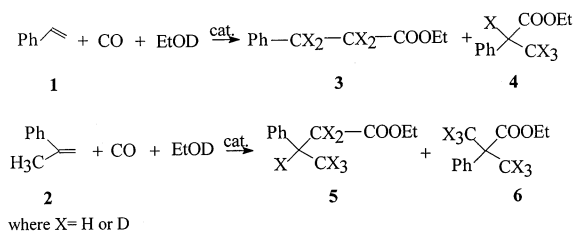
The spectrum of the reaction mixture obtained with system **B** is more complex. The signals at 2.50 ppm and 2.90 ppm can be ascribed to the methylene groups of the linear ester (formed in 74.5% selectivity) situated α and β to the ethoxycarbonyl moiety, respectively. The resonance at 3.66 ppm corresponds to the methine group of the branched product while that at 6.70 ppm corresponds to 2-deuteriovinylbenzene.

The MS analysis [13] of the crude mixtures proved the presence of mono-, di- and trideuterated styrenes as well as mono-, and polydeuterated esters, these latter ones also being detected by ¹³C-NMR [11]. The deuterium content at each of the labelled carbon atoms has been determined from the ²H-NMR spectra (after eliminating the residual d-ethanol and part of the toluene) on the basis of composition (GLC) and the incorpora-

tion calculated previously for the major carbonylated product by means of ¹H. The data (Table 1) brought us to the conclusion that the total amount of isotope incorporation increases by increasing the reaction temperature in both systems, the overall deuterium content being greater in the SnCl₂ modified system.

The results of our investigation show that variable deuterium incorporation occurs both in the substrate and in the reaction products when deuterioalkoxycarbonylation of styrene is carried out in the presence of catalyst precursors **A** or **B**. We have already reported [11] the accommodation of these species for the latter system in terms of the routes described in Scheme 2. Thus, the formation of the two Pd-alkyl intermediates *n*'₁ and *b*'₁ is reversible. Undergoing β -hydride elimination (controlled by the kinetic deuterium isotope effect [14]), they give the Pd-hydride π -complexes **I** and **II**. In complex **I**, the insertion of the olefin into the Pd-H bond could regenerate the starting linear palladium-alkyl *n*'₁ yielding the corresponding linear 3-deuterated ester (3-d₁-**3**) or produce the isomeric branched palladium-alkyl intermediate *b*'₂, from which the 2-deuterated branched ester (2-d₁-**4**) can be formed. Analogously, complex **II** gives rise to the linear palladium-alkyl intermediate *n*'₂ and so to the linear 2-deuterated ester 2-d₁-**3** or regenerates the branched intermediate *b*'₁ leading to the branched 3-deuterated ester 3-d₁-**4**. The overall process is, therefore, the isomerization of the starting branched metal-alkyl intermediate *b*'₁ to the linear isomeric intermediate *n*'₂ and, conversely, the isomerization of *n*'₁ to *b*'₂. On the other hand, π -complexes **I** and **II** can undergo an intermolecular exchange process with unlabelled styrene, producing monodeuteriostyrenes 2-d₁-**1** and 1-d₁-**1**, respectively and the unlabelled π -complex **III**. This last one can generate the corresponding linear and branched esters (**3** and **4**) through the linear (*n*) or branched (*b*) unlabelled metal-alkyls. Once labelled, styrene species may undergo further reactions resulting in di- and oligo-deuterated derivatives.

Surprisingly, when the reaction was carried out with catalyst **A**, no deuterium incorporation could be detected on the carbon atom bound to the phenyl ring both in the recovered substrate and the branched product even at temperatures as high as 130°C. This



Scheme 1. Deuterioalkoxycarbonylation reaction of styrene and α -methylstyrene.

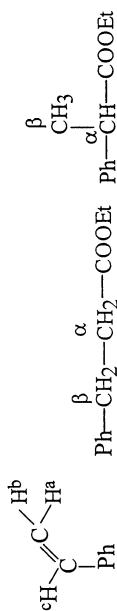
Table 1
Deuterium content of styrene, linear and branched derived esters ^a

Catalyst precursor	Reaction temperature (°C)	Regioselectivity ^b (%)	D content at the C atoms of styrene			D content at the C atoms of branched ester			D content at the C atoms of linear ester		
			a	b	c	NDM	D(C _α)	D(C _β)	NDM	D(C _α)	D(C _β)
A	100	2.6	0.36	0.37	0	0.73	0	1.25	1.25	n.d. ^c	n.d.
A	130	8.8	0.45	0.52	0	0.97	0	1.87	1.87	0.77	1.48
B	100	74.5	0.49	0.48	0.44	1.41	0.37	1.12	1.49	1.21	0.67
B	130	74.4	0.47	0.50	0.51	1.48	0.46	1.8	2.26	1.22	0.93

^a Reaction conditions: 10 ml of toluene solution containing 3.2 mmol of styrene, 28.9 mmol of d-ethanol, 75 mg of Pd(PPh₃)₂Cl₂ (A) or 75 mg of Pd(PPh₃)₂Cl₂, 55 mg of SnCl₂ and 50.1 mg of PPh₃ (B); CO, 40 atm; volume of reaction vessel 50 ml.

^b Refers to the linear ester.

^c Not determined.



fact indicates that, under the conditions given, the reactions leading to palladium–alkyl intermediates n₁' and n₂', do not take place.

Some hypotheses have been advanced to explain the marked difference in regioselectivity determined by the presence of SnCl₂. According to Knifton [3], the moderately basic PPh₃ raises the hydridic character of the active species, thus promoting both anti-Markownikov addition to the olefin and formation of a linear palladium–alkyl. On the other hand, competing electronic factors [15–17] would result in the preferential formation of the secondary metal–alkyl intermediate stabilised by the π-benzylic interaction of the phenyl group with Pd. It seems likely that the SnCl₃[−] ligand provides a particularly sterically hindered catalyst [3] in which steric constraints are powerful enough to overcome the unfavourable electronic effects.

It would be interesting to consider the 'kinetic effect' of SnCl₃[−] described for the closely related Pt-containing intermediates [18] where fast β-hydride elimination of olefin from a secondary σ-complex, possessing a Pt–Sn bond, takes place. In our systems the lifetime of the analogous branched Pd–Sn species may be too short to allow CO insertion to compete with hydride elimination.

2.3. Deuterioalkoxycarbonylation of α-methylstyrene

The reaction mixtures of α-methylstyrene were also investigated by ²H-NMR spectroscopy; the identification of the deuterated species made possible by the similarity of the chemical shifts of the ¹H and ²H nuclei. In Fig. 2(a) the ²H-NMR spectrum of a reaction mixture synthesised with the catalyst **A** is reported. The signals of the linear ester (formed in 82.7% regioselectivity) are centred at 1.30 ppm (corresponding to the methyl group), at 2.55 ppm (corresponding to the methylene group) and at 3.27 ppm (corresponding to the methine group). The signal at 1.55 ppm denotes D incorporation at the methyl groups of the branched ester. The two resonances of the olefinic region (5.18 and 5.55 ppm) are attributed to the *E*- and *Z*-1-deuterio-2-methyl vinylbenzene, while the D incorporation in the methyl group of the unconverted substrate is detectable at 2.15 ppm.

The same signals are also present in the spectrum of the reaction mixture formed with catalyst **B** (Fig. 2(b)). However, the extent of isotope incorporation is rather different.

MS analyses of the reaction mixtures proved again the presence of mono-, di- and trideuterated olefins together with mono-, and polydeuterated esters (detected also by ¹³C-NMR, see Section 4). The deuterium content has been determined similarly as described for styrene. The data acquired (Table 2)

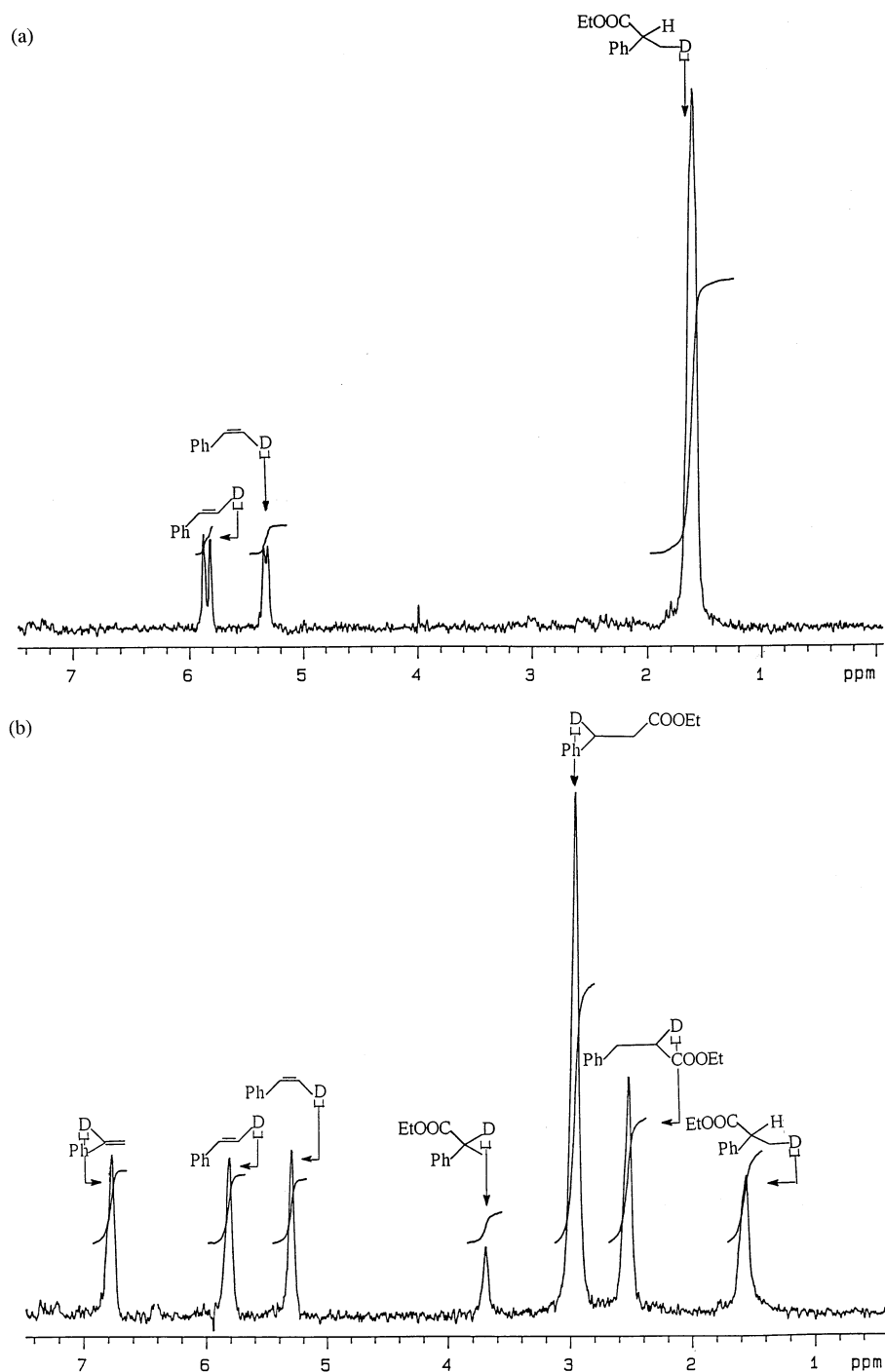


Fig. 1. (a) ^2H -NMR spectrum (46 MHz, 20°C, toluene) of the reaction products obtained by deuterioalkoxycarbonylation of styrene at 100°C, 75% conversion with catalyst A. (b) ^2H -NMR spectrum (46 MHz, 20°C, toluene) of the reaction products obtained by deuterioalkoxycarbonylation of styrene at 100°C, 75% conversion with catalyst B.

show the same temperature dependence of isotope incorporation, while the total deuterium content is greater in the absence of SnCl_2 . The pathways leading to these species are presented in Scheme 3.

According to this, when α -methylstyrene (**2**) gives the

π -complex **IV'** with a $\text{Pd}-\text{D}$ species, a primary (p'_1) and a tertiary (t'_1) palladium alkyl may be formed. Intermediate p'_1 can lead only to the corresponding labelled linear ester **3-d₁-5** because no β -hydride elimination is possible. On the other hand, according to our data, CO

insertion practically does not occur at the tertiary metal–alkyl as this would produce the branched ester which is formed in very low amounts. However, it undergoes β -hydride elimination resulting in the two π -complexes **V** and **VI**. In a subsequent addition **V** leads to p'_2 , and so the linear product 2-d₁-5, while **VI** gives rise to p'_3 and the derived ester 4-d₁-5. After intermolecular exchange processes with the starting olefin, in addition to complex **IV** which gives unlabelled **5**, 1-d₁-2 and 3-d₁-2 are formed.

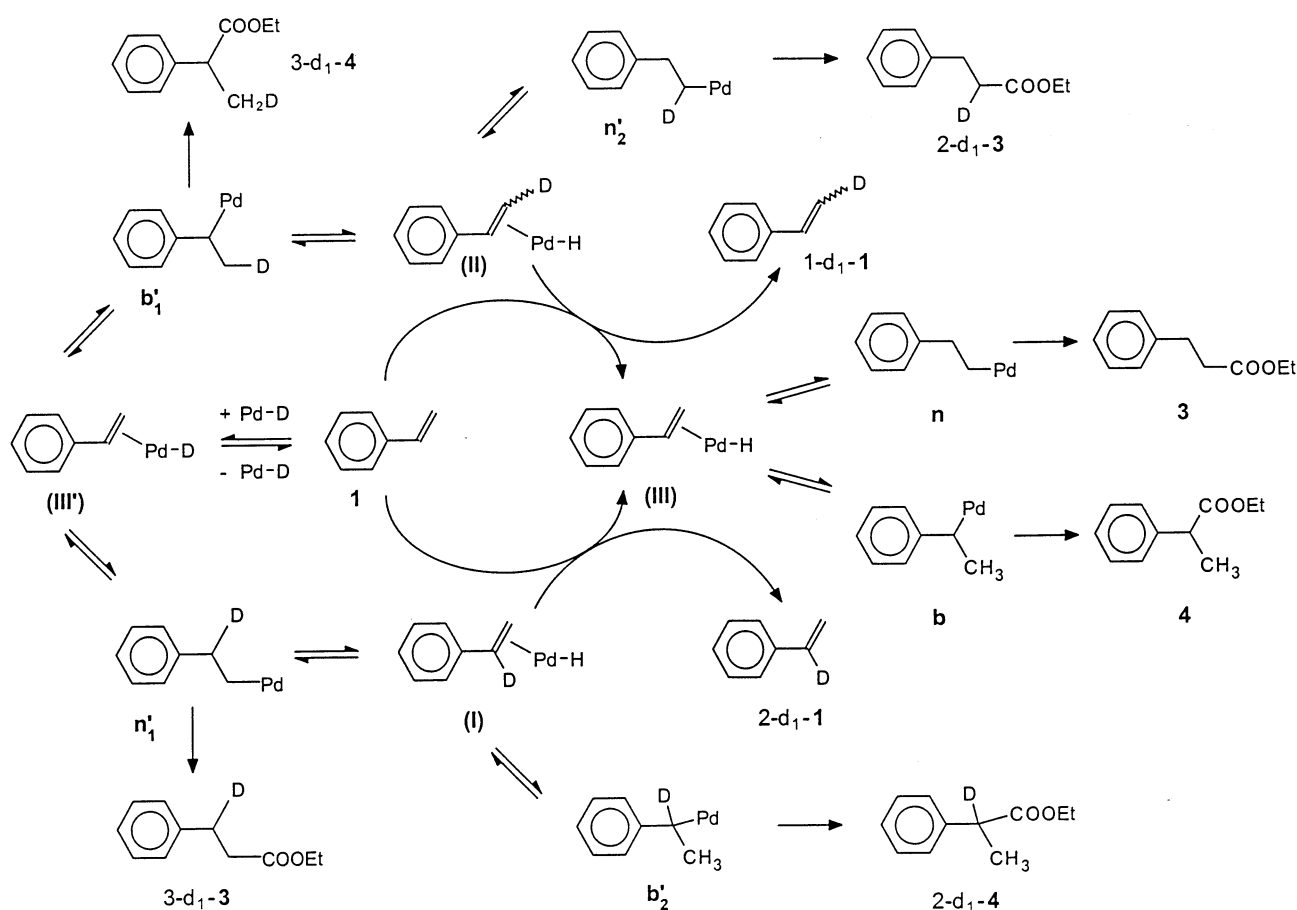
The large numbers of mono- and polydeuterated species supports, analogous to the reaction of styrene, the dominance of the hydrido route. Moreover, the presence of 1- and 3-labelled α -methylstyrene, together with the 2- and 4-deuterated linear esters (detected already at 20% conversion) clearly evidences the formation of the tertiary alkyl–palladium intermediate (t'_1). The ratio $D(C_\beta)/[D(C_\alpha) + D(C_\gamma)]$ (see Table 2) is less than one in each of the reactions which indicates that the tertiary species is favoured over the primary one, but the first undergoes mainly β -hydride elimination followed by intermolecular exchange with unlabelled olefin or consecutive isomerization. The

CO insertion leading to the corresponding branched ester is probably sterically hindered. To the best of our knowledge, the existence of this intermediate has not been evidenced yet in hydroesterification of olefinic substrates, although it has been shown to be present in the related rhodium-catalysed hydroformylation reaction [19].

3. Conclusions

The composition of the rather complex reaction mixtures was successfully elucidated by MS analysis and combined NMR methods. The labelled derivatives detected can be deduced in terms of the reaction pathways described and support the ‘hydrido’ mechanism operating in the systems studied.

At the same time, the results obtained in our experiments throw light on the different behaviour of alkyl–palladium intermediates determined by catalyst and substrate structure. Transforming styrene with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{SnCl}_2$ as precursor ethyl-3-phenylpropanoate is the major product. The formation of



Scheme 2. Proposed pathways for deuteration of styrene and the derived deuterated isomeric esters.

Table 2
Deuterium content of α -methylstyrene, linear and branched derived esters^a

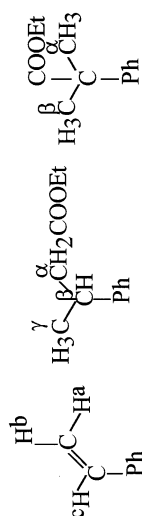
Catalyst precursor	Reaction temperature (°C)	Regioselectivity ^b (%)	D content at the C atoms of α -methyl styrene			D content at the C atoms of the branched ester			D content at the C atoms of the linear ester		
			a	b	c	NDM ^d	D(C _{α})	D(C _{β})	NDM	D(C _{α})	D(C _{β})
A	100	82.7	0.53	0.56	1.77	2.86	average:	1.75	3.50	1.23	0.50
A	130	93.2	0.57	0.59	1.85	3.01	n.d. ^c	n.d.	n.d.	1.33	1.25
B	100	97.8	0.40	0.35	1.38	2.13	n.d.	n.d.	n.d.	0.44	0.91
B	130	98.0	0.48	0.49	1.50	2.47	n.d.	n.d.	n.d.	0.48	1.18

^a Reaction conditions: 10 ml toluene solution containing 3.2 mmol of α -methylstyrene, 28.9 mmol of d-ethanol, 75 mg of Pd(PPh₃)₂Cl₂ (A) or 75 mg of Pd(PPh₃)Cl₂, 55 mg of SnCl₂ and 50.1 mg of PPh₃ (B); CO, 40 atm; volume of reaction vessel 50 ml.

^b Refers to the linear ester.

^c Not determined.

^d Number of deuterium atoms per molecule.



both linear and branched Pd-alkyls is reversible and, as a consequence, D-labelling occurs at all carbon atoms of the side-chains of substrate and esters.

In the absence of SnCl₂, when ethyl-2-phenylpropanoate is formed regioselectively, no isotope was found in the positions adjacent to the phenyl ring. So, the routes leading to the linear metal-alkyls must be blocked.

Using α -methylstyrene as starting material, in both catalytic systems ethyl-3-phenylbutanoate was obtained predominantly and no significant difference in the deuterium distribution could be detected. For the first time, evidence has been given for the existence of the tertiary alkyl-palladium species. This intermediate, although favoured over the primary one, in its formation undergoes overwhelmingly β -hydride elimination, since releasing of the derived branched ester is probably sterically hindered. These findings reveal the different behaviour of primary, secondary and tertiary alkyl-palladium intermediates under hydroalkoxycarbonylation conditions.

4. Experimental

Toluene was distilled from sodium under an argon atmosphere. d-Ethanol was purchased from Fluka. The compound Pd(PPh₃)₂Cl₂ was prepared as reported in the literature [20]. Anhydrous SnCl₂ was obtained by allowing SnCl₂·2H₂O to react with acetic anhydride and washing with ether. GLC analyses were performed on a HP 5830 gas chromatograph equipped with SPB-1 columns (30 m $\times$ 1 μ m film depth) and a flame ionization detector, helium was used as the carrier gas. Column chromatography was carried out on a silica gel column using hexane, benzene, chloroform, dichloromethane and acetone as eluents.

Mass spectra were measured with a VG ZAB-SEQ instrument at 10–12 eV ionization connected to a HP-5890A gas chromatograph with CP-Sil-8 CB columns (25 m $\times$ 0.25 μ m film depth) using helium as carrier gas.

The ¹H-, ²H- and ¹³C-NMR spectra were recorded on a Varian Unity 300 spectrometer, operating at 300, 46 and 75.4 MHz, respectively. Chemical shifts of the ²H-NMR measurements were determined by reference to CDCl₃ as external standard.

4.1. Deuterioalkoxycarbonylation of styrene and α -methylstyrene: general procedure

The catalyst (75 mg, 0.11 mmol Pd(PPh₃)₂Cl₂ (A) or 75 mg, 0.11 mmol Pd(PPh₃)Cl₂; 55 mg, 0.29

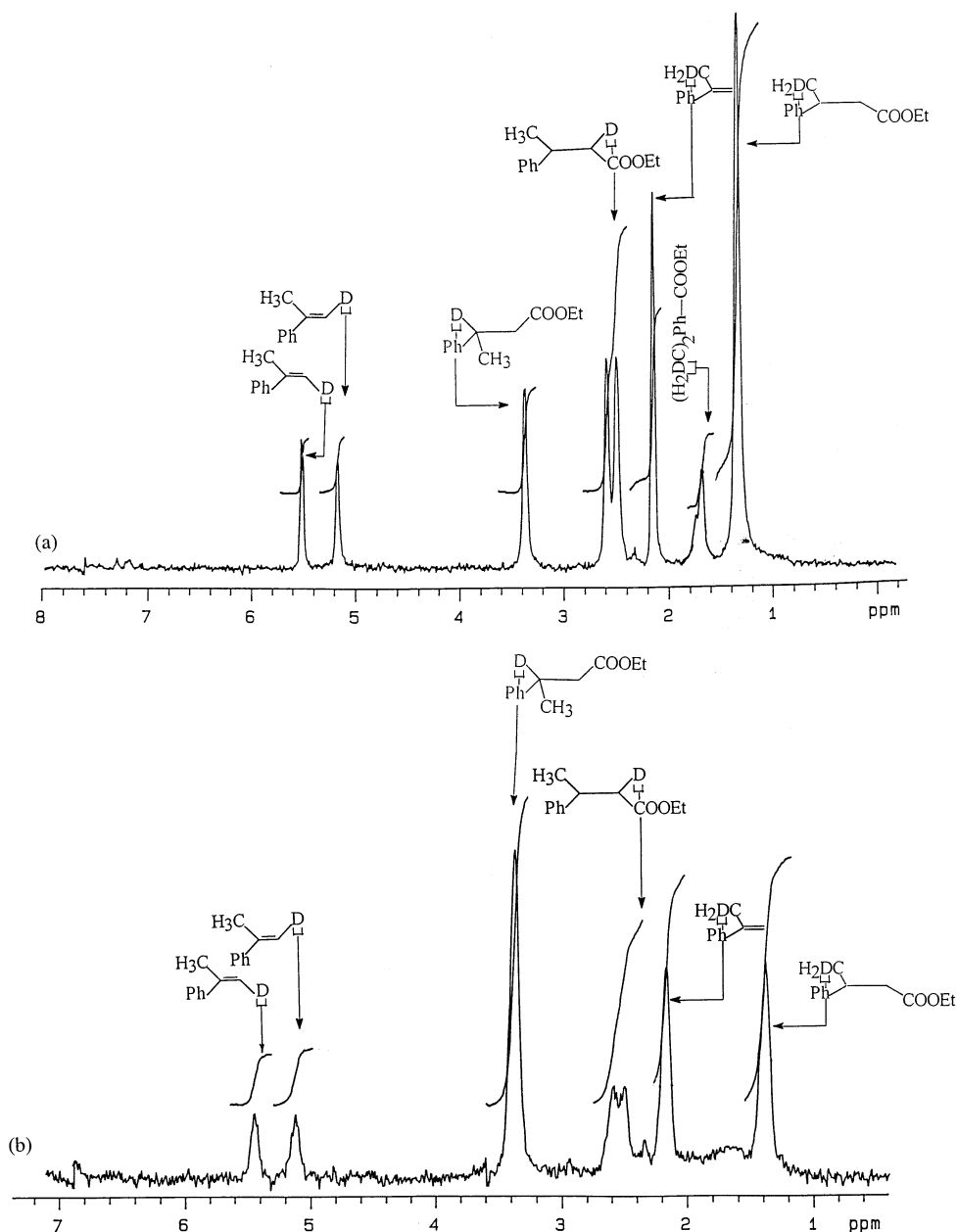


Fig. 2. (a) ^2H -NMR spectrum (46 MHz, 20°C , toluene) of the reaction products obtained by deuterioalkoxycarbonylation of α -methylstyrene at 100°C , 75% conversion with catalyst A. (b) ^2H -NMR spectrum (46 MHz, 20°C , toluene) of the reaction products obtained by deuterioalkoxycarbonylation of α -methylstyrene at 100°C , 75% conversion with catalyst B.

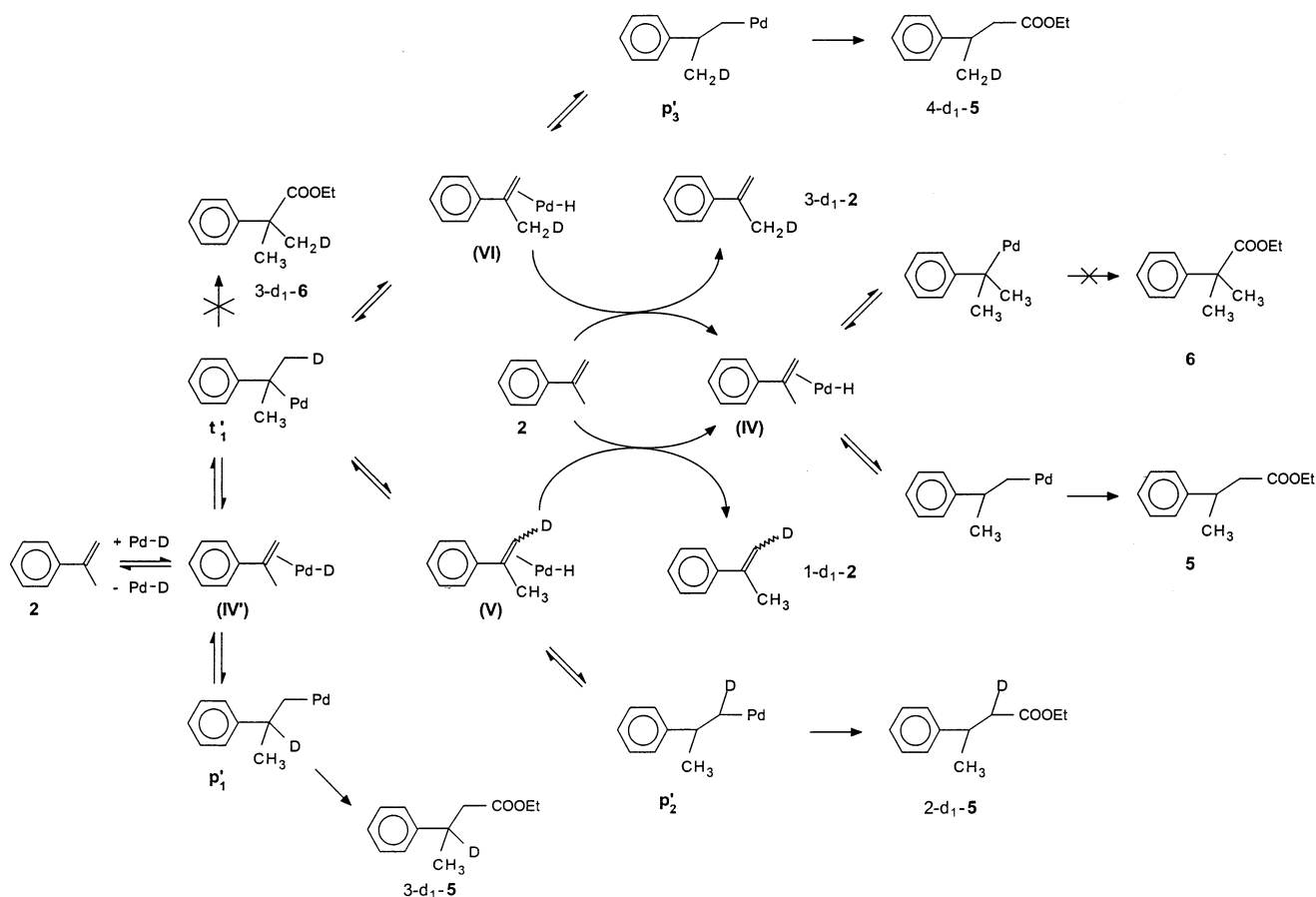
mmol anhydrous SnCl_2 ; 50.1 mg, 0.19 mmol PPh_3 (**B**) was introduced to a 50 ml stainless steel autoclave. After sealing, a solution of olefin (0.37 ml, 3.2 mmol styrene or 0.42 ml, 3.2 mmol α -methylstyrene), d-ethanol (1.7 ml, 28.9 mmol) in toluene (10 ml) was introduced by suction. Then, carbon monoxide was charged (40 atm at room temperature) and the mixture was magnetically stirred at the reaction temperature until the conversion desired. After cooling, the reaction mixture was siphoned out, and GLC was used to determine the composition with toluene as internal

standard. d-Ethanol and the solvent were removed under vacuum before ^2H -, ^1H -NMR and MS analyses. Isomeric esters were separated by column chromatography and studied further.

4.2. $^{13}\text{C}\{^1\text{H}\}$ -NMR data for labelled α -methylstyrene derivatives **5** and **6**

4.2.1. Ethyl-3-phenyl-[2- ^2H , 3- ^2H , 4- ^2H]-butanoate (**5**)

NMR δ 13.98 ($\text{CH}_2\text{--}\text{CH}_3$), 36.37 (s, CH--CH_3), 36.32 (s, $\text{CH--CH}_2\text{D}$, $\Delta^2 = 4.7$ Hz), 36.24 (s, CH--



Scheme 3. Proposed pathways for deuteration of α -methylstyrene and the derived deuterated isomeric esters.

CHD₂), 36.17 (s, CH–CD₃); 42.90 (s, CH₂–CH), 42.80 (s, CH₂–CD, $\Delta^2 = 7.8$ Hz), 42.56 (t, CHD–CH, $\Delta^1 = 19.7$, $J_{\text{CD}}^1 = 19.7$ Hz), 42.46 (t, CHD–CD, $\Delta^2 = 7.1$, $J_{\text{CD}}^1 = 19.7$ Hz), 60.20 (CH₂–CH₃), 125.45, 126.27, 126.54, 128.30, 128.40 (phenyl ring).

4.2.2. Ethyl-2-([²H]-methyl)-2-phenyl-[3-²H]-propanoate (**6**)

NMR δ 14.10 (CH₂–CH₃), 26.45 (s, C–CH₃), 26.42 (s, C–CH₃), 26.17 and 26.20 (t, CH₂D, $\Delta^1 = 22.0$, $J_{\text{CD}}^1 = 19.8$ Hz), 25.78 and 25.80 (q, $\Delta^1 = 25.7$, $J_{\text{CD}}^1 = 18.6$ Hz), 60.70 (CH₂–CH₃), 125.45, 126.52, 126.54, 128.30, 128.40 (phenyl ring).

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References

- [1] H.S. Yun, K.H. Lee, J.S. Lee, J. Mol. Cat. A.: Chem. 95 (1995) 11.
- [2] K. Bittler, N. Kutepow, D. Neubauer, Angew. Chem. Int. Ed. Engl. 80 (1968) 352.
- [3] J.F. Knifton, J. Org. Chem. 41 (1976) 2885.
- [4] G. Consiglio, M. Marchetti, Chimia 30 (1976) 26.
- [5] J. Tsuji, Palladium Reagents and Catalysts, Wiley, New York, 1995, pp. 510–511.
- [6] G. Cavinato, L. Toniolo, J. Organomet. Chem. 398 (1990) 187.
- [7] R. Bardi, A. Del Pra, A.M. Piazzesi, L. Toniolo, Inorg. Chim. Acta 35 (1979) L345.
- [8] D.M. Fenton, J. Org. Chem. 38 (1973) 3192.
- [9] R.F. Heck, J. Am. Chem. Soc. 94 (1972) 2712.
- [10] K.H. Shaughnessy, R.M. Waymouth, Organometallics 16 (1996) 1001.
- [11] Cs. Benedek, G. Szalontai, Á. Gömöry, Sz. Törös, B. Heil, J. Organomet. Chem. 579 (1999) 147.
- [12] G. Uccello-Barretta, R. Lazzaroni, R. Settambolo, P. Salvadori, J. Organomet. Chem. 417 (1991) 111.
- [13] A. Raffaelli, S. Pucci, R. Settambolo, G. Uccello-Barretta, R. Lazzaroni, Organometallics 10 (1991) 3892.
- [14] J. Evans, J. Schwartz, P.W. Urquhart, J. Organomet. Chem. 81 (1974) C37.
- [15] S. Toda, M. Miyamoto, H. Kinoshita, K. Inomata, Bull. Chem. Soc. Jpn. 64 (1991) 3600.

- [16] D.L. Reger, P.J. McElligott, J. Organomet. Chem. 216 (1981) C12.
- [17] R. Lazzaroni, A. Raffaelli, R. Settambolo, S. Bertozzi, G. Vitulli, J. Mol. Catal. 50 (1989) 1.
- [18] T. Kégl, L. Kollár, L. Radics, Inorg. Chim. Acta 265 (1997) 249.
- [19] R. Lazzaroni, G. Uccello-Barretta, S. Scamuzzi, R. Settambolo, A. Caiazzo, Organometallics. 15 (1996) 4657.
- [20] H. Itatani, J.C. Bailar, J. Am. Oil Chem. Soc. 44 (1967) 147.