Evidence of Formation of an *exo*-π-Allyl Complex Intermediate in the Pd^0-Catalyzed Alkylation of a Bicyclic Allylic Diacetate with Stabilized Carbon Nucleophiles

Jean Michel Brunel,[a] Michel Maffei,[b] Günter Muchow,[c] and Gérard Buono*[a]

Keywords: Palladium / exo-π-Allylpalladium complexes / Allylic alkylation / Spirobicyclic cyclopropanes

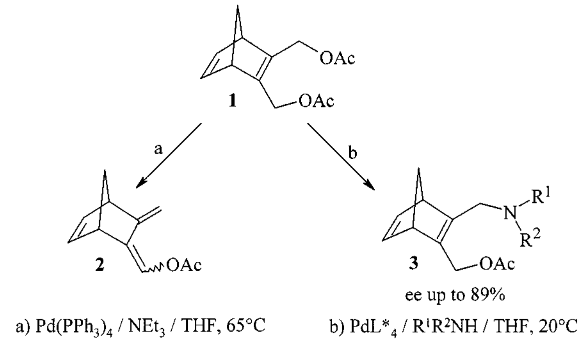
The palladium(0)-catalyzed alkylation of 2,3-bis(acetoxymethyl)bicyclo[2.2.1]hepta-2,5-diene **1** with malonate-type enolates as nucleophiles is investigated. A monoalkylated product is formed first, and undergoes (depending on the nucleophile used) a second intramolecular reaction leading to spirocyclopropane-annulated bicyclo[2.2.1]heptene derivatives **5**. The formation of *endo* spirobicyclic cyclopropanes adducts as major isomer is rationalized by assuming formation of an intermediate *exo*-(π-allyl)palladium complex.

Introduction

Palladium(0)-catalyzed alkylation of allylic acetates has gained increasing importance over the last 30 years because of its synthetic and mechanistic implications.[1] The existence of a (π-allyl)palladium complex as a reaction intermediate is now well established.[2] However, few studies on bicyclic allylic acetate substrates have been reported. Petit[3] and Godleski[4] were the first to provide evidence for an *exo*-(π-allyl)palladium dimeric complex, derived from norcamphene, by X-ray structure analysis that is in direct accordance with its reactivity towards the hydride nucleophile. Recently, we have described the synthesis of a new prochiral bicyclic diacetate, namely 2,3-bis(acetoxymethyl)bicyclo[2.2.1]hepta-2,5-diene **1**, and its use in palladium(0)-catalyzed elimination to produce compound **2**.[5] Moreover, its palladium(0)-catalyzed asymmetric amination has been achieved using various amines as nucleophiles, affording the monoaminated products **3** with enantiomeric excesses of up to 89% (Scheme 1).[6]

These results have been interpreted through the formation of an *exo*-(π-allyl)palladium complex. Nevertheless, all our attempts to obtain suitable crystals for X-ray structure analysis have failed. In the context of our studies, we report in this paper the evidence for the formation of an *exo*-(π-allyl)palladium intermediate based on the stereochemical considerations of the Pd^0-catalyzed alkylation reaction.

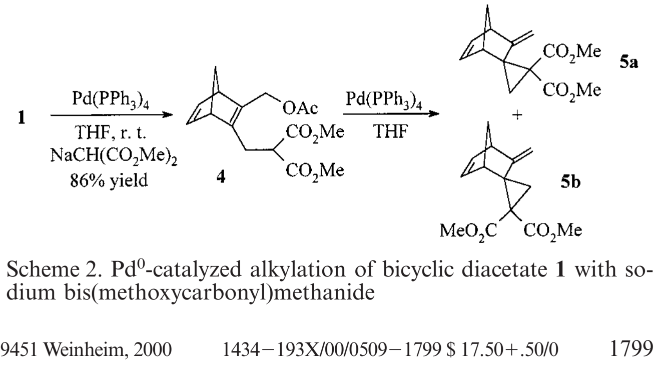
In order to get decisive information concerning this postulated structure, as well as new synthetic insights about the regioselectivity of the reaction, we decided to investigate the palladium(0)-catalyzed allylic alkylation of **1** using sodium bis(methoxycarbonyl)methanide as a nucleophile. In this case, and on the basis of numerous results already reported in literature for related linear or monocyclic substrates,[7] a double alkylation of substrate **1** could be expected to occur due to the "bisallylic diacetate" structure.[8]



Scheme 1. Pd^0-catalyzed elimination and amination of allylic bicyclic diacetate **1**

Results and Discussion

Reaction of **1** with one equiv. of sodium bis(methoxycarbonyl)methanide in THF in the presence of 1.5 mol-% of Pd(PPh$_3$)$_4$ at room temperature, afforded after 5 min, com-



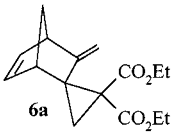
Scheme 2. Pd^0-catalyzed alkylation of bicyclic diacetate **1** with sodium bis(methoxycarbonyl)methanide

---

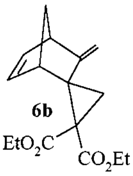
[a] E.N.S.S.P.I.C.A.M., UMR CNRS 6516, Faculté de Saint Jérôme,
Av. Escadrille Normandie Niemen, 13397 Marseille, Cedex 20, France
E-mail: buono@spi-chim.u-3mrs.fr
[b] Laboratoire des Organo-Phosphorés (E.S.A. 6009 du C.N.R.S.), B.P. 552, Faculté de Saint Jérôme,
Avenue Escadrille Normandie Niémen, 13397 Marseille Cedex 20, France
[c] Chambre de Commerce Industrie Marseille Provence,
2 rue Henri Barbusse, 13001 Marseille, France

1434–193X/00/0509–1799 $ 17.50+.50/0

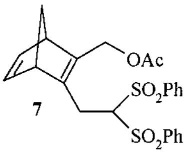
Table 1. Pd(0)-catalyzed alkylation of **1** with various nucleophiles



6a



6b



7

Entry	Nucleophile	Conditions	Product	Yield (%)
1	$NaCH(CO_2Me)_2$	1.5 mol% $Pd(PPh_3)_4$ room temp./5 min	**4**	86[a]
2	$NaCH(CO_2Me)_2$	0.5 mol% $Pd(PPh_3)_4$ room temp./30 min	**4**	96
3	$NaCH(CO_2Me)_2$	1.5 mol% $Pd(PPh_3)_4$ room temp./32 h	**5a/5b** (ratio 5 : 95)	93
4	$NaCH(CO_2Me)_2$	1.5 mol% $Pd(PPh_3)_4$ 65 °C/25 min	**5a/5b** (ratio 40 : 60)	75
5	$NaCH(CO_2Et)_2$	1.5 mol% $Pd(PPh_3)_4$ room temp./32 h	**6a/6b** (ratio 5 : 95)	87
6	$NaCH(SO_2Ph)_2$	1.5 mol% $Pd(PPh_3)_4$ 65 °C/32 h	**7**	79[b]

[a] Small amounts of **5a** and **5b** were also formed. – [b] No spirocyclopropane product detected.

pound **4** (86% isolated yield) together with two other minor unidentified products. Longer reaction times (room temperature, 32 h) or higher temperature (65 °C, 25 min) led to the complete conversion of **4** into two products, that were found to be the tricyclic compounds **5a** and **5b** (Scheme 2). In these cases, a mixture of the two isomers **5a** and **5b** was isolated in 80% yield, but in a ratio varying from 5/95 to 40/60 for **5a** and **5b**, respectively[9] (Table 1, entries 3 and 4).

Formation of **5a** and **5b** at first appeared to be the result of an intramolecular reaction of **4**, consisting in the allylic substitution of the remaining acetoxy group. On the other hand, a kinetic study clearly demonstrated the predominant formation of **4** at the early stage of the reaction and its further disappearance to afford the cyclopropane products **5a** and **5b**. Nevertheless, the outcome of the reaction depends on the temperature (Figure 1).

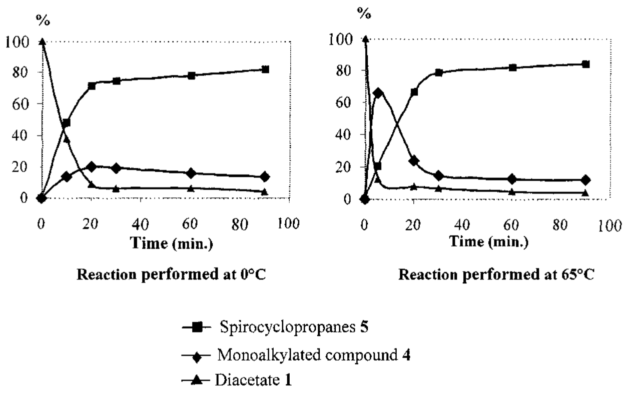


Figure 1. Kinetics of Pd^0-catalyzed alkylation of diacetate **1** with sodium bis(methoxycarbonyl)methanide

Thus, only the monoalkylated product **4** was obtained in 86% yield when the reaction was performed at 0 °C, while cyclopropanes **5a** and **5b** were preferentially observed at 65 °C.

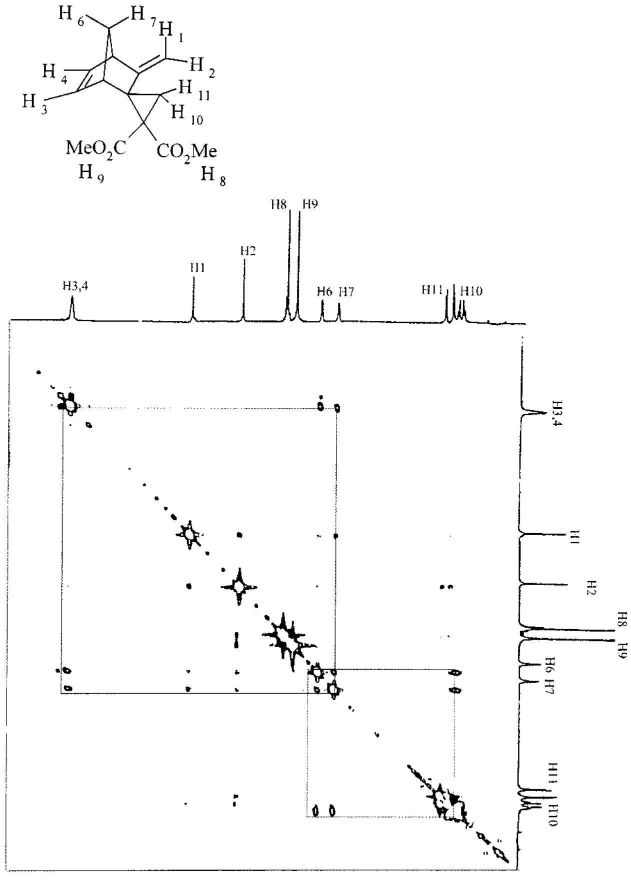
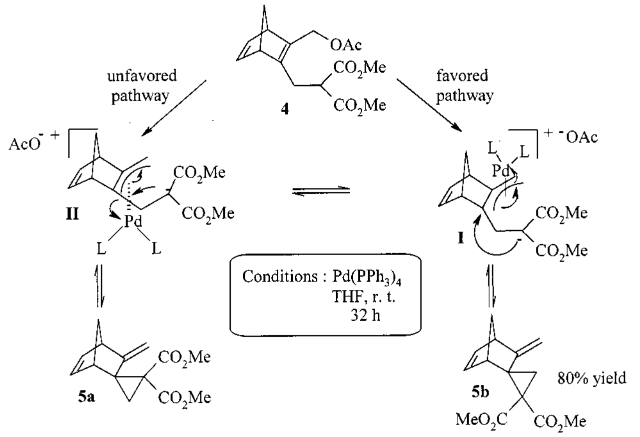


Figure 2. NOESY NMR sequence of a 5/95 mixture of **5a/5b**

The structures of compounds **5a** and **5b** were confirmed by COSY and NOESY NMR experiments (Figure 2).

The predominant formation of **5b** with respect to **5a** can be explained by the preferential formation of complex **I** in



Scheme 3. Mechanistic rationale for the Pd^0-catalyzed alkylation of diacetate **1** with sodium bis(methoxycarbonyl)methanide

which the palladium atom sits in the *exo* position (Scheme 3).

Thus, the cyclopropane formation proceeds *via* an oxidative addition of compound **4** onto the catalytically active species, leading to the elimination of HOAc and subsequent ring closure. Since the incoming nucleophilic attack towards (π-allyl)palladium complexes is known to proceed in an *anti* fashion with respect to the metal,[2c,10] the structure of the predominant final product **5b** allows us to predict an *exo* configuration for the (π-allyl)palladium intermediate. Nevertheless, the formation of a large amount of **5a** at high temperature may only result from an interconversion between the two (π-allyl)palladium complexes **I** and **II** (See below).

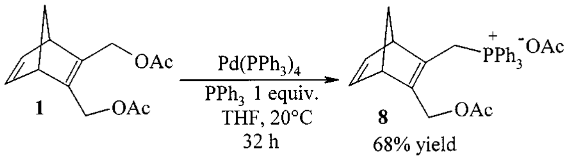
As an extension of this work, we have investigated the influence of the nucleophiles used on the stereochemical outcome of the reaction.

It appears that similar results in terms of selectivity have been obtained using sodium bis(ethoxycarbonyl)methanide instead of sodium bis(methoxycarbonyl)methanide (ratio **6a/6b**: 5/95). Nevertheless, it is noteworthy that whatever the experimental conditions, no trace of the expected cyclopropane adducts was detected using the sodium salt of bis(phenylsulfonyl)methane. Moreover, isolation of compound **7** in 79% yield and its subsequent treatment with NaH or BSA/KOAc in presence of a catalytic amount of $Pd(PPh_3)_4$ did not afford any other product.

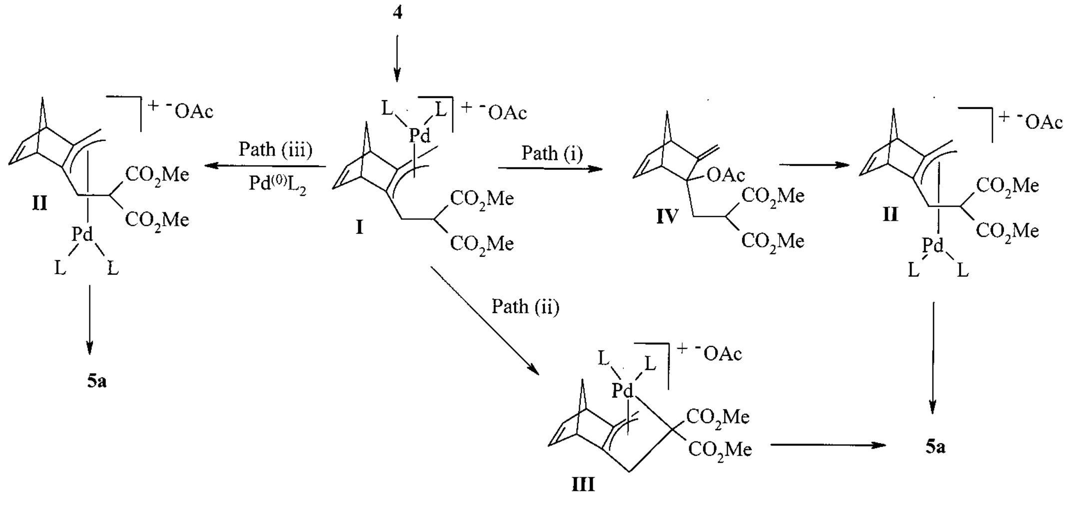
The fact that the amount of **5a** increases with the temperature may indicate a possible interconversion between the two (π-allyl)palladium complexes **I** and **II**.[11] This phenomenon can be related to the isomerization of (π-allyl)palladium complexes, which has been put forward to explain the loss of stereospecificity of some palladium-catalyzed reactions of allylic substrates with nucleophiles.[12] This isomerization has been accounted for by three different processes: (i) isomerization of the starting material **4**, (ii) *syn* addition of nucleophile, and (iii) Pd^0-catalyzed isomerization of the intermediate π-allyl complex (Scheme 4).

Path (ii) appears to be very unlikely due to the steric constraints existing in intermediate **III**. Since GC monitoring of the substitution reaction never gave any evidence for compound **IV** [path (i)], path (iii) ought to be the most favorable one between the two remaining possibilities. Furthermore, this mechanism *via* a σ-allylpalladium intermediate has been shown to operate in several related examples.[12] However, none of these paths can be definitively ruled out.

An additional interesting feature in these reactions of **1** is the fact that a phosphonium salt **8** was isolated in varying amounts during work up of the reaction mixtures. Its structure was unequivocally assigned by careful examination of its NMR data and mass spectrum. The formation of allylic phosphonium salts *via* attack of (π-allyl)palladium complexes by triphenylphosphane has been reported by several groups.[13] We further found that **8** can also be obtained in 68% yield by simple reaction of **1** with 1 equivalent of



Scheme 5. Pd^0-catalyzed alkylation of bicyclic diacetate **1** with triphenylphosphane



Scheme 4. Possible isomerization pathways for the interconversion of complexes **I** and **II**

triphenylphosphane in the presence of 1.5 mol-% of $Pd(PPh_3)_4$ at room temperature for 32 h (Scheme 5).

In summary, our results show that the alkylation of **1** with stabilized carbon nucleophiles proceeds in two steps: the initial regioselective formation of the expected monoalkylated compound leads to the tricyclic derivatives *via* a second intramolecular alkylation with loss of acetic acid and subsequent ring closure. Kinetic control allows the reaction to stop at either one of the products. The almost exclusive formation of the *endo*-disubstituted spirocyclopropane compound under the appropriate conditions underlines that the reaction proceeds through an *exo*-(π-allyl)palladium complex. The formation of these spirotricyclic cyclopropane derivatives is of interest since numerous vinylcyclopropanes are naturally occurring compounds,[14] or constitute important synthetic intermediates.[15] Further work dealing with asymmetric induction is currently under investigation.

Experimental Section

All solvents were purified according to reported procedures, and reagents were used as commercially available. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Ethyl acetate and petroleum ether (35–60 °C) were purchased from SDS and used without any further purification. Column chromatography was performed on SDS silica gel (70–230 mesh). ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC 200 spectrometer working at 200.00 MHz and 50.16 MHz, respectively (the usual abbreviations are used: s: singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet). Tetramethylsilane was used as internal standard. All chemical shifts are given in ppm (δ values).

General Procedure for the Palladium-Catalyzed Alkylation of 1 with Sodium Bis(methoxycarbonyl)methanide: To a solution of $Pd(PPh_3)_4$ (0.350 g; 0.3 mmol) in THF (5 mL) was added a solution of **1**[5] (2.36 g, 10 mmol) in THF (5 mL) under a nitrogen atmosphere. After stirring for 5 min. at room temperature, a solution of sodium bis(methoxycarbonyl)methanide (10 mmol) in 25 mL of THF (prepared by reaction of 1.32 g of dimethyl malonate and 0.24 g of NaH) was added by syringe. The reaction mixture was stirred at room temperature for 5 min., and quenched with a saturated NH_4Cl solution. Most of the THF was removed in vacuo, and the aqueous layer was extracted with ether (3 × 20 mL). After drying over Na_2SO_4, the solvents were removed in vacuo. The residue was purified by flash chromatography on a silica gel column (eluent: diethyl ether) affording 2.86 g of compound **2** (93% yield).

Dimethyl 2-{[2-(3-Acetoxymethyl)norbornadien-2-yl]methyl}malonate (4): ^1H NMR: $\delta = 1.85$ (s, 3 H), 1.97 (m, 2 H), 2.93 (m, 2 H), 3.36 (m, 2 H), 3.45 (s, 3 H), 3.49 (s, 3 H), 4.76 (m, 3 H), 6.74 (m, 2 H). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 20.8$, 28.2, 50.2, 52.0, 52.1, 52.7, 53.9, 60.3, 71.8, 142.3, 145.8, 150.0, 168.9, 169.2, 170.1. – IR: 833, 909, 1024, 1169, 1234, 1439, 1742, 2868, 2961. – $C_{16}H_{20}O_6$ (308.3): calcd. C 62.3, H 6.5; found C 62.5, H 6.3.

Dimethyl *endo*-3′-Methylenspiro(cyclopropane-1,2′-norborn-4-ene)-2,2-dicarboxylate (5b): major compound; ^1H NMR: $\delta = 1.54$ (m, 2 H), 1.84 (dd, 2 H, $J = 34.7$, $J = 5.1$ Hz), 3.10 (s, 1 H), 3.30 (s, 1 H), 3.58 (s, 3 H), 3.71 (s, 3 H), 4.22 (s, 1 H), 4.78 (s, 1 H), 6.22 (m, 2 H). – ^{13}C NMR: $\delta = 26.2$, 40.5, 43.6, 47.2, 50.1, 52.5, 52.7, 53.1, 100.8, 135.2, 136.7, 152.4, 167.4, 169.7. – IR: 886, 1108, 1162, 1224, 1266, 1364, 1434, 1606, 1728, 2858, 2930, 2950, 3060. – $C_{14}H_{16}O_4$ (248.2): calcd. C 67.7, H 6.5; found C 67.4, H 6.5.

Dimethyl *exo*-3′-Methylenspiro(cyclopropane-1,2′-norborn-4-ene)-2,2-dicarboxylate (5a): minor compound; ^1H NMR: $\delta = 1.54$ (m, 2 H), 1.76 (dd, 2 H, $J = 28.6$, $J = 5.1$ Hz), 3.10 (s, 1 H), 3.30 (s, 1 H), 3.62 (s, 3 H), 3.74 (s, 3 H), 4.22 (s, 1 H), 4.74 (s, 1 H), 6.27 (m, 2 H). – ^{13}C NMR: $\delta = 26.2$, 41.5, 44.2, 45.6, 50.2, 51.7, 52.5, 52.8, 101.0, 134.9, 138.7, 152.2, 167.5, 169.8. – IR: 886, 1108, 1162, 1224, 1266, 1364, 1434, 1606, 1728, 2858, 2930, 2950, 3060. – $C_{14}H_{16}O_4$ (248.2): calcd. C 67.7, H 6.5; found C 67.4, H 6.5.

Diethyl *endo*-3′-Methylenspiro(cyclopropane-1,2′-norborn-4-ene)-2,2-dicarboxylate (6b): major compound; ^1H NMR: $\delta = 1.15$–1.33 (m, 6 H), 1.65–1.90 (m, 4 H), 3.19 (s, 1 H), 3.38 (s, 1 H), 4.09–4.16 (m, 4 H), 4.28–4.42 (m, 2 H), 6.18 (m, 2 H). – ^{13}C NMR: $\delta = 25.3$, 40.4, 42.9, 47.1, 50.2, 51.6, 52.7, 52.8, 61.0, 71.6, 100.8, 135.1, 136.7, 152.1, 166.8, 169.3. – IR: 879, 1108, 1162, 1222, 1266, 1362, 1434, 1606, 1730, 2858, 2930, 2950, 3058. – $C_{16}H_{20}O_4$ (276.2): calcd. C 69.5, H 7.2; found C 69.3, H 7.2.

Diethyl *exo*-3′-Methylenspiro(cyclopropane-1,2′-norborn-4-ene)-2,2-dicarboxylate (6b): minor compound; ^1H NMR: $\delta = 1.20$–1.32 (m, 6 H), 1.63–1.77 (m, 4 H), 3.19 (s, 1 H), 3.41 (s, 1 H), 4.13–4.15(s, 4 H), 4.25–4.42 (s, 2 H), 6.19 (m, 2 H). – ^{13}C NMR: $\delta = 27.8$, 41.6, 43.0, 45.6, 51.0, 52.2, 52.7, 53.5, 60.2, 70.9, 108.5, 141.9, 142.4, 153.4, 168.5, 170.8. – IR: 886, 1108, 1162, 1224, 1266, 1364, 1434, 1606, 1728, 2858, 2930, 2950, 3060. – $C_{16}H_{20}O_4$ (248.2): calcd. C 69.5, H 7.2; found C 69.1, H 7.1.

2-(Acetoxymethyl)-3-[(2′,2′-bis(phenylsulfonyl)ethyl]bicyclo[2.2.1]hepta-2,5-diene (7): ^1H NMR: $\delta = 1.85$ (s, 3 H), 1.90 (m, 2 H), 2.91 (m, 2 H), 3.36 (m, 2 H), 4.76 (m, 3 H), 6.74 (m, 2 H), 7.1–7.6 (m, 10 H). – ^{13}C NMR: $\delta = 28.2$, 50.2, 52.0, 52.1, 52.7, 53.9, 65.3, 71.8, 120.3, 128.1, 129.3,131.2, 130.1,142.3, 150.0, 169.2. – IR: 833, 909, 1024, 1169, 1234, 1439, 1742, 2868, 2961. – $C_{24}H_{24}S_2O_6$ (472.0): calcd. C 61.0, H 5.0, S 13.5, found: C 61.6, H 5.2, S 13.0.

[(2-Acetoxymethyl)bicyclo[2.2.1]hepta-2,5-dienyl)methyl]triphenylphosphonium Acetate (8): This compound was obtained from **1** following the general procedure above. The residue was purified by flash chromatography on a silica gel column (eluent: diethyl ether). – ^1H NMR: $\delta = 1.57$ (s, H), 1.93 (d, H, $J = 10.1$ Hz), 2.27 (m, H), 2.63 (d, H, $J = 10.1$ Hz), 2.81 (m, H), 3.10 (dd, H, $J = 19.0$, $J = 3.1$ Hz), 3.3 (s, 1 H), 3.56 (s, H), 3.72(s, H), 3.88 (dd, H, $J = 5.1$ Hz, $J = 7.0$ Hz), 6.37 (m, 1 H), 6.86 (m, 1 H), 7.61 (m, 9 H), 7.71 (m, 6 H). – ^{13}C NMR: $\delta = 19.8$, 22.3, 27.8, 32.3, 43.4, 52.7, 53.0, 65.3, 72.2, 110.1 (d, $J = 160.3$ Hz), 128.1, 130.2, 133.2, 134.2, 135.1. –^{31}P NMR (40.5 MHz, $CDCl_3$): $\delta = 23.2$. – IR: 833, 909, 1024, 1169, 1234, 1439, 1742, 2868, 2961. – HRMS: calcd. for $C_{31}H_{31}O_4P$: 498.5573, found [MH^+] 498.5576.

---

[1] [1a] J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer Verlag, Heidelberg, **1980**. – [1b] J. Tsuji, I. Minami, *Acc. Chem. Res.* **1987**, *20*, 140–145. – [1c] B. M. Trost, T. R. Verhoeven, in *Comprehensive Organometallic Chemistry*, Pergamon Press, Oxford, **1982**, vol.8, p.799 -.[1d] R. F. Heck, *Palladium Reagents in Organic Syntheses*, Academic Press, New York, **1985**. – [1e] C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089–1122. – [1f] J. Tsuji, *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, John Wiley Sons, **1995**, pp. 290–422. – [1g] J. L. Malleron, J. C. Fiaud, J. Y. Legros, *Handbook of Palladium-Catalyzed Organic Reactions*, Academic Press, **1997**, pp. 147–170.

[2] [2a] B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, T. J. Dietsche, *J. Am. Chem. Soc.* **1978**, *100*, 3416–3426. – [2b] T.

Hayashi, T. Hagihara, M. Konoshi, M. Kumada, *J. Am. Chem. Soc*. **1983**, *105*, 7767–7768. – [2c] J. C. Fiaud, J. Y. Legros, *J. Org. Chem.* **1987**, *52*, 1907–1911.

[3] [3a] F. Petit, Y. Castanet, *Tetrahedron Lett*. **1979**, *20*, 3221–3222. – [3b] F. Petit, Y. Castanet, *J. Mol. Catal*. **1986**, *35*, 143–160.

[4] S. A. Godleski, K. B. Gundlach, H. Y. Ho, E. Keinan, F. Frolow, *Organometallics* **1984**, *3*, 21–25.

[5] G. Muchow, J. M. Brunel, M. Maffei, G. Buono, *J. Org. Chem.* **1995**, *60*, 852–855.

[6] G. Muchow, J. M. Brunel, M. Maffei, O. Pardigon, G. Buono, *Tetrahedron* **1998**, *54*, 10435–10448.

[7] [7a] J. P. Genêt, F. Piau, J. Ficini, *Tetrahedron Lett*. **1980**, *21*, 3183–3186. – [7b] B. M. Trost, G. B. Tometzki, M. H. Hung, *J. Am. Chem. Soc*. **1987**, *109*, 2176–2177. – [7c] J. E. Bäckvall, J. O. Vågberg, C. Zercher, J. P. Genêt, A. Denis, *J. Org. Chem.* **1987**, *52*, 5430–5435 and references cited therein. – [7d] T. Hayashi, A. Yamamoto, Y. Ito, *Tetrahedron Lett*. **1988**, *29*, 669–672. – [7e] B. M. Trost, S. Tanimori, P. T. Dunn, *J. Am. Chem. Soc*. **1997**, *119*, 2735–2736.

[8] It is only very recently that the reaction of (*Z*)-1,4-diacetoxy-2-butene with dimethyl malonate under Pd(0) catalysis has been shown to lead to polymeric structures, see: N. Nomura, K. Tsurugi, M. Okada, *J. Am. Chem. Soc*. **1999**, *121*, 7268–7269.

[9] The almost exclusive formation of monoalkylated product **4** could be achieved when kinetic control was applied. At 0 °C and in the presence of 1.5 mol-% of $Pd(PPh_3)_4$ the isolated yield was 80% after 40 min. (Figure 1). The high reaction rate was confirmed by a similar run with only 0.5 mol-% of catalyst which occurred with a turnover of 960 h^{-1}.

[10] E. Keinan, Z. Roth *J. Org. Chem.* **1983**, *48*, 1769–1772.

[11] Surprisingly, we have not observed any isomerization between the products **5a** and **5b** and studies are in progress to explain this phenomenon.

[12] [12a] J. E. Bäckvall, K. L. Granberg, A. Heumann, *Isr. J. Chem.*, **1991**, *31*, 17–24. – [12b] K. L. Granberg, J. E. Bäckvall, *J .Am. Chem. Soc*., **1992**, *114*, 6858–6863 and references cited therein.

[13] [13a] J. Powell, B. L. Shaw, *J. Chem. Soc., Chem. Commun. A*, **1968**, 774–777. – [13b] Y. Tsukahara, H. Kinoshita, K. Inomata, *Bull. Chem. Soc. Jpn.*, **1984**, *57*, 3013–3014. See also ref. 11b.

[14] [14a] B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1167–1192. – [14b] V. Michelet, I. Besnier, J. P. Genêt, *Synlett*, **1996**, 215–217. – [14c] J. Cossy, N. Blanchard, C. Meyer, *Synthesis* **1999**, 1063.

[15] [15a] F. Colobert, J. P. Genêt, *Tetrahedron Lett.* **1985**, *26*, 2779–2782. – [15b] S. K. Kang, D. C. Park, J. H. Jeon, H. S. Rho, C. M. Yu, *Tetrahedron Lett.* **1994**, *35*, 2357–2360.

Received October 12, 1999
[O99576]