Catalytic triple carbonylation of olefins. Enantioselective synthesis of 2-oxoglutarates ☆

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Abstract

A new carbonylation reaction, namely "triple carbonylation" of olefins catalysed by cationic palladium complexes to substituted 2-oxoglutarates, has been developed. Even though the chemoselectivity is not high, this reaction allows a one-step synthesis of substituted 2-oxoglutarates with fair to excellent enantioselectivity (enantiomeric excess up to 92%). The reaction is completely regioselective for styrene whereas with aliphatic olefins two regioisomers are formed.

Keywords: Enantioselective catalysis; Triple carbonylation; Olefins; Palladium complexes; 2-Oxoglutarates

1. Introduction

Mechanistic studies have shown that consecutive insertions of carbon monoxide molecules into metal–carbon bonds are generally strongly disfavoured [1–3]. Nevertheless, the so-called double carbonylation of organic halides (Scheme 1) has been realized both with palladium [4–6] and with cobalt catalysts [7], probably because of the existence of a mechanistic pathway not implying the above consecutive insertions [1–3].

Catalytic double carbonylation reactions have considerable potential utility [2,8]. However, to the best of our knowledge a similar reaction has never been observed for olefinic substrates. We have recently reported on the first enantioselective double carbonylation of olefins to succinates using $[Pd(H_2O)_2\{(S)$-2,2′-dimethoxy-6,6′-bis(diphenylphosphino)biphenyl$\}](CF_3SO_3)_2$ as the catalyst precursor (Scheme 2) [9]. With this catalyst precursor, the reaction was found to be highly enantioselective (up to 93% enantiomeric excess (ee)) and fairly chemoselective (ca. 80% at 350 bar CO) for styrene.

$$Ar–X + 2\ CO + ROH \longrightarrow ArCOCOOR + \text{"HX"}$$
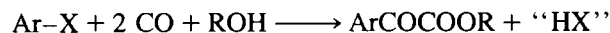
Scheme 1.

Aliphatic olefins such as propene or 4-methyl-1-pentene were dicarbonylated only with modest enantioselectivity.

Careful gas chromatographic analysis of the reaction mixture using a complete calibration has shown that chemoselectivity is, in fact, somewhat lower, particularly under high carbon monoxide pressure (e.g. ca. 70% at 350 bar CO). Formation of a secondary product, namely dimethyl 2-oxo-3-phenylglutarate (Scheme 3, 2, $R = C_6H_5$) takes place in increasing amounts on increasing the carbon monoxide pressure. We report here on the possibility of carrying out this triple carbonylation (Scheme 3) in a highly stereoselective way not only for styrene but also for aliphatic olefins. A high turnover
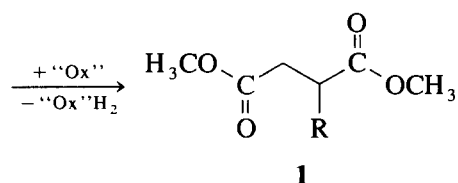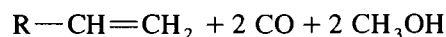
$$R–CH{=}CH_2 + 2\ CO + 2\ CH_3OH$$

1
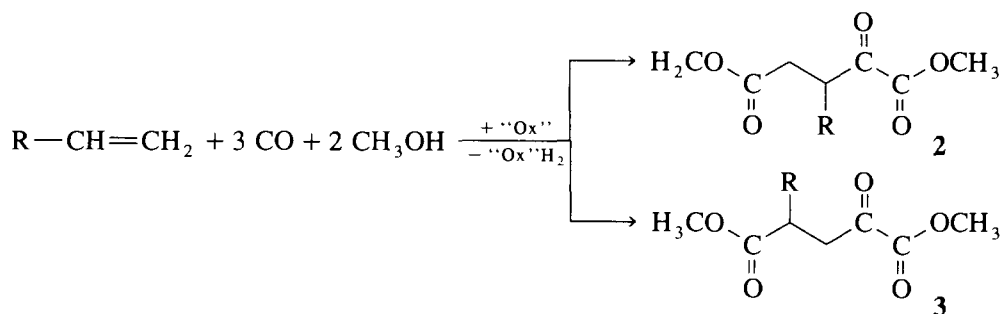
Scheme 2.

Scheme 3.

number can be obtained even though the chemoselectivity is not very high at the moment.

2. Results and discussion

Some results obtained with a few monosubstituted ethylenes in isochronous experiments are shown in Table 1. In fact, this allows a comparison of the relative reactivities of the various substrates. The most important features can be summarized as follows.

(i) Complete regioselectivity to dimethyl 2-oxo-3-phenylpentanedioate (2, $R = C_6H_5$) and high enantioselectivity (92% ee) were obtained with styrene as the substrate.

(ii) Regioselectivity of 64% towards dimethyl 2-oxo-4-methylglutarate (3, $R = CH_3$) with respect to 36% towards dimethyl 2-oxo-3-methylglutarate (2, $R = CH_3$) was obtained in the case of propene. The enantiomeric excess for both compounds is similar (61 and 59%, respectively) and is more than twice as large as the value obtained for dimethyl 2-methylsuccinate (1, $R = CH_3$) (29% ee, the S-enantiomer prevailing) which is contemporaneously formed. The conversion is comparable to that of styrene but the chemoselectivity is lower.

(iii) Substantially no regioselectivity is observed in the triple carbonylation of 4-methyl-1-pentene yielding in dimethyl 2-oxo-4-(2-methylpropyl)glutarate (3, $R = $ i-C$_4$H$_9$) (62% ee) and 2-oxo-3-(2-methylpropyl)glutarate (2, $R = $ i-C$_4$H$_9$) (81% ee), which are formed in equal amounts.

(iv) For allylbenzene the regioselectivity is also low but the enantioselectivity is fairly high, at least for one of the two isomers; dimethyl 2-oxo-4-[methylphenyl]-glutarate (3, $R = C_6H_5CH_2$) (30% ee) and 2-oxo-3-(methylphenyl)glutarate (2, $R = C_6H_5CH_2$) (78% ee) are formed in a 46:54 molar ratio. For this substrate, however, we could identify by GC–MS products formally deriving from isomerization steps after olefin insertion.

(v) In all cases except propene, the major product is represented by the succinate 1. For propene dimeric co-oligomers are also formed.

A mechanistic description of this new carbonylation reaction can be proposed on the basis of previous studies on the double carbonylation of organic halides [3] and on model platinum chemistry [10] (Scheme 4).

This scheme implies insertion of the olefin followed by carbon monoxide insertion in a [Pd]–COOCH$_3$[11] species and formation of a carbomethoxy group at the same metal centre. Reductive elimination of the formed acyl moiety and the carbomethoxy group leads to the oxoglutarates. Complete regioselectivity in the case of styrene is in keeping with the normally observed secondary insertion of this substrate into palladium–acyl intermediates [12,13]. Aliphatic olefins do not normally show such a level of regioselectivity control [14–17] and, in fact, we observe the formation of both products corresponding to the two possible insertions. This implies, if the mechanism is correct, prevailing primary insertion for propene and this again is in keeping with the prevailing primary insertion observed for propene in

Table 1
Triple carbonylation of olefins to dimethyl 2-oxoglutarates using [Pd(H$_2$O)$_2${(S)-2,2'-dimethoxy-6,6'-bis(diphenylphosphino)biphenyl}](CF$_3$SO$_3$)$_2$ as the catalyst precursor

Substrate	Total conversion (%)	Selectivity [a] (%)	Regioselectivity [b] 2/3 (%)	Enantiomeric excess (%)
Styrene	80	25	100/0	92
Propene	60	5	36/64	59/61
4-Methyl-1-pentene [c]	13	17	50/50	81/62
3-Phenyl-1-propene [c]	5	8	54/46	78/30

[a] Mol of oxoglutarates/mol of converted substrate.
[b] Molar ratio, cf. Scheme 3.
[c] 17.5 mmol of the oxidant were used.
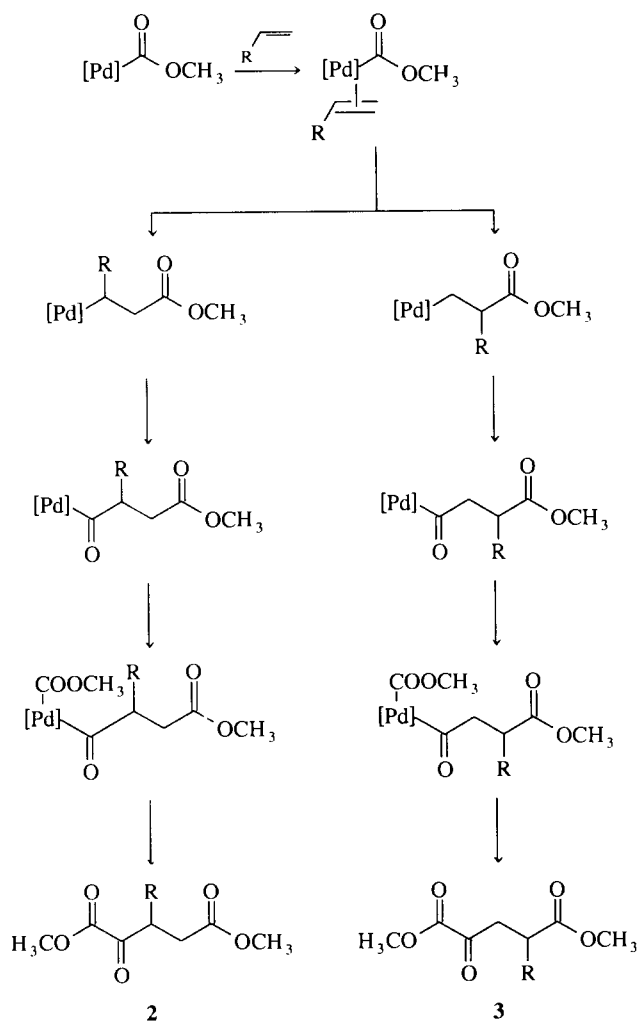
Scheme 4.

the copolymerization with carbon monoxide [15]. An unexpected shift of the regioselectivity of the olefin insertion towards secondary insertion was observed for 4-methyl-1-pentene and 3-phenyl-1-propene.

At present we are studying the generality of this synthetic method. The results reported show a possible facile approach to products of considerable synthetic interest [18] and of biological importance [19], although the chemoselectivity of these new triple carbonylation reactions is relatively low. Furthermore, these results are significant since they show the existence of an unexpected termination reaction during the formation of olefin–carbon monoxide copolymers [20].

3. Experimental procedure

The carbonylation of styrene is reported as an example. A 250 ml stainless-steel autoclave equipped with a glass insert was charged under an atmosphere of N_2 with 0.035 mmol of catalyst precursor, 35 mmol of

benzoquinone and 35 mmol of styrene in 20 ml of methanol, pressurized with 350 bar of CO and heated to 50°C. After 20 h the autoclave was cooled to room temperature and the residual gas released. Immediate quantitative gas chromatographic analysis was carried out on a Hewlett-Packard HP1 column (50 m) using acetophenone as the internal standard. Response factors were obtained from a three-point calibration with the pure isolated compounds. Correlation factors of 0.998–1.0 were generally obtained for the calibration graphs. After removal of the methanol from the reaction mixture under reduced pressure, about 50 ml of toluene were added, causing most of the hydroquinone to precipitate. The filtrate was evaporated and the residue fractionally distilled by the Kugelrohr method. Each fraction was purified by column chromatography over silica (70–230 mesh) using hexane–diethylether (3:1) as the eluent. The products were characterized by NMR and GC–MS. The enantiomeric excess was determined by gas chromatography using heptakis(6-O-TBDMS-2,3-O-methyl)-β-cyclodextrin as the stationary phase. The NMR spectra were measured on Bruker AMX 400 and AMX 500 spectrometers, respectively, with tetramethylsilane as the internal standard. Two-dimensional spectra (COSY, INADEQUATE and HC and HCC correlation) were effected to allow correct assignments. ^1H and ^{13}C NMR parameters of the compounds in $CDCl_3$ are given below.

Dimethyl 2-oxo-3-phenylglutarate (2, R = C_6H_5). ^1H NMR: 2.72 (dd, 1H, CH_2COOR; $^2J_{H,H}$ = 17.3, $^3J_{H,H}$ = 4.9), 3.29 (dd, 1H, CH_2COOR; $^2J_{H,H}$ = 17.3, $^3J_{H,H}$ = 10.3), 3.67 (s, 3H, OCH$_3$), 3.78 (s, 3H, OCH$_3$), 4.97 (m, 1H, CH; $^3J_{H,H}$ = 4.9, $^3J_{H,H}$ = 10.3); 7.23–7.37 (m, 5H, C_6H_5). ^{13}C NMR: 36.3 (CH$_2$COOR), 49.0 (CH), 51.6 (OCH$_3$), 52.6 (OCH$_3$), 127.8, 128.4, 128.9, 134.3 (C_6H_5), 160.3 (COCOOR), 171.5 (CH$_2$COOR), 191.2 (CO). MS (m/z, relative intensity (%)): 250 (M$^+$, 1), 219 (4), 191 (3), 163 (19), 131 (5), 122 (8), 121 (100), 104 (14), 103 (14), 91 (10), 78 (10), 77 (13), 59 (18), 51 (7), 15 (17).

Dimethyl 2-oxo-3-methylglutarate (2, R = CH$_3$). ^1H NMR: 1.21 (d, 3H, CH$_3$; $^3J_{H,H}$ = 7.2), 2.51 (dd, 1H, CH$_2$; $^2J_{H,H}$ = 17.0, $^3J_{H,H}$ = 5.4), 2.84 (dd, 1H, CH$_2$; $^2J_{H,H}$ = 17.0, $^3J_{H,H}$ = 8.9), 3.66 (s, 3H, OCH$_3$), 3.68 (m, 1H, CH); 3.90 (s, 3H, OCH$_3$). ^{13}C NMR: 15.9 (CH$_3$), 36.8 (CH$_2$), 38.3 (CH), 52.0 (OCH$_3$), 53.0 (OCH$_3$), 161.3 (COCOOR), 172.15 (COOR), 195.9 (CO). MS (m/z, relative intensity (%)): 157 (M – 31, 1), 129 (40), 101 (10), 59 (100), 42 (8), 41 (14), 39 (7), 29 (8), 15 (17).

Dimethyl 2-oxo-4-methylglutarate (3, R = CH$_3$). ^1H NMR: 1.25 (d, 3H, CH$_3$; $^3J_{H,H}$ = 7.2), 2.89 (dd, 1H, CH$_2$; $^2J_{H,H}$ = 18.6, $^3J_{H,H}$ = 5.3), 3.01 (m, 1H, CH); 3.32 (dd, 1H, CH$_2$; $^2J_{H,H}$ = 18.6, $^3J_{H,H}$ = 8.4), 3.69 (s, 3H, OCH$_3$), 3.88 (s, 3H, OCH$_3$). ^{13}C NMR: 17.0 (CH$_3$), 34.7 (CH), 42.4 (CH$_2$), 52.0 (OCH$_3$), 53.0

(OCH$_3$), 161.1 (COCOOR), 175.4 (COOR), 192.1 (CO). MS (m/z, relative intensity (%)): 157 (M − 31, 2), 129 (34), 101 (9), 69 (8), 59 (100), 42 (10), 41 (17), 39 (8), 29 (9), 15 (25).

Dimethyl 2-oxo-3-(2-methylpropyl)glutarate (**2**, R = i-C$_4$H$_9$). ^{1}H NMR: 0.92 (d, 3H, CH$_3$; $^3J_{H,H}$ = 6.2), 0.95 (d, 3H, CH$_3$; $^3J_{H,H}$ = 6.4), 1.25 (m, 1H, CH), 1.57 (m, 2H, CH$_2$), 2.56 (dd, 1H, CH$_2$; $^1J_{H,H}$ = 17.1, $^3J_{H,H}$ = 4.4), 2.81 (dd, 1H, CH$_2$, $^1J_{H,H}$ = 17.1, $^3J_{H,H}$ = 10.4), 3.65 (s, 3H, C(O)OCH$_3$), 3.75 (m, 1H, CH); 3.90 (s, 3H, C(O)C(O)OCH$_3$). ^{13}C NMR: 22.1 (CH$_3$), 22.8 (CH$_3$), 26.0 (CH), 36.0 (CH$_2$), 40.1 (CH$_2$), 41.1 (CH), 52.0 (OCH$_3$), 53.0 (OCH$_3$), 161.4 (COCOOR), 172.4 (COOR), 196.3 (CO). MS (m/z, relative intensity (%)): 199 (M − 31, 2), 171 (100), 155 (2), 139 (2), 111 (52), 93 (3), 83 (60), 69 (54), 59 (38).

Dimethyl 2-oxo-4-(2-methylpropyl)glutarate (**3**, R = i-C$_4$H$_9$). ^{1}H NMR: 0.90 (d, 3H, CH$_3$; $^3J_{H,H}$ = 6.3), 0.94 (d, 3H, CH$_3$; $^3J_{H,H}$ = 6.2), 1.31 (m, 1H, CH), 1.58 (m, 2H, CH$_2$), 2.92 (dd, 1H, CH$_2$; $^2J_{H,H}$ = 18.2, $^3J_{H,H}$ = 4.4), 2.97 (m, 1H, CH); 3.25 (dd, 1H, CH$_2$, $^2J_{H,H}$ = 18.2, $^3J_{H,H}$ = 9.1), 3.68 (s, 3H, C(O)OCH$_3$), 3.87 (s, 3H, C(O)C(O)OCH$_3$) ^{13}C NMR: 22.3 (CH$_3$), 22.4 (CH$_3$), 25.8 (CH), 38.2 (CH), 41.0 (CH$_2$), 41.2 (CH$_2$), 52.0 (OCH$_3$), 53.0 (OCH$_3$), 161.0 (COCOOR), 175.5 (COOR), 192.3 (CO).

Dimethyl 2-oxo-3-(phenylmethyl)glutarate (**2**, R = C$_6$H$_5$CH$_2$). ^{1}H NMR: 2.50 (dd, 1H, CH_2COOR; $^2J_{H,H}$ = 17.3, $^3J_{H,H}$ = 4.4), 2.62 (dd, 1H, CH_2C$_6$H$_5$, $^2J_{H,H}$ = 13.6, $^3J_{H,H}$ = 8.8), 2.81 (dd, 1H, CH_2COOR; $^2J_{H,H}$ = 17.3, $^3J_{H,H}$ = 10.2), 3.07 (dd, 1H, CH_2C$_6$H$_5$, $^2J_{H,H}$ = 13.6, $^3J_{H,H}$ = 5.9), 3.61 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 3.98 (m, 1H, CH); 7.14–7.31 (m, 5H, C$_6$H$_5$). ^{13}C NMR: 34.9 (CH$_2$), 36.9 (CH$_2$C$_6$H$_5$), 44.9 (CH), 52.0 (OCH$_3$), 53.0 (OCH$_3$), 127.0, 128.7, 129.1, 137.3 (C$_6$H$_5$), 161.0 (COCOOR), 172.2 (CH$_2$$C$OOR), 195.4 (CO). MS ($m/z$, relative intensity (%)): 264 (M$^+$, 7), 205 (40), 173 (84), 145 (82), 135 (21), 131 (21), 117 (100), 115 (29), 91 (80), 77 (10), 65 (23), 59 (27), 51 (10).

Dimethyl 2-oxo-4-(phenylmethyl)glutarate (**3**, R = C$_6$H$_5$CH$_2$). ^{1}H NMR: 2.77 (dd, 1H, CH_2C$_6$H$_5$; $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 8.6), 2.83 (dd, 1H, CH_2COOR, $^2J_{H,H}$ = n.d., $^3J_{H,H}$ =), 3.12 (dd, 1H, CH_2C$_6$H$_5$; $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 5.3), 3.24 (m, 1H, CH); 3.26 (dd, 1H, CH_2COOR, $^2J_{H,H}$ = 16.9, $^3J_{H,H}$ = 9.4), 3.67 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 7.15–7.31 (m, 5H, C$_6$H$_5$). ^{13}C NMR: 37.5 (CH$_2$C$_6$H$_5$), 39.8 (CH$_2$), 41.9 (CH), 52.1 (OCH$_3$), 53.0 (OCH$_3$), 126.9, 129.0, 129.1, 137.9 (C$_6$H$_5$), 160.9 (COCOOR), 174.3 (CH$_2$$C$OOR), 192.1 (CO). MS ($m/z$, relative intensity (%)): 264 (M$^+$, 1), 205 (18), 173 (88), 163 (24), 162 (61), 150 (20), 145 (88), 135 (16), 131 (23), 118 (14), 117 (100), 115 (26), 91 (98), 65 (24), 59 (21).

Acknowledgements

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