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Palladium-catalysed enantioselective bis-alkoxycarbonylation of 1-olefins. Synthesis of optically active 2-substituted-butanedioates

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Abstract

Cationic palladium(II) complexes of the type $[Pd(L \wedge L')(S_2)]X_2$ (where $L \wedge L'$ is a chelate ligand with C_2 symmetry, S is a solvent molecule, and X is an anion with low coordination properties) are able to catalyse the enantioselective bis-alkoxycarbonylation of 1-olefins to substituted succinates. Using atropisomeric fully aromatic ligands high enantio- and chemoselectivity have been obtained when styrene is the substrate. For aliphatic olefins, such as propene and 4-methyl-1-pentene, the chemoselectivity is lower than for styrene owing to multiple olefin insertion. In these cases enantioselectivity is usually modest, probably due to two competing regiochemical pathways for the insertion of the olefin into the palladium carbomethoxy-intermediate. In the case of 3-phenyl-1-propene, dicarbonylation products after isomerization processes are also formed. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Bis-alkoxycarbonylation; Olefin; Carbon monoxide; Palladium catalysts; Succinic acid derivatives

1. Introduction

At the beginning of the 1970s a convenient procedure was described for converting olefins into substituted butanedioates [1], namely through a Pd(II)-catalysed bis-alkoxycarbonylation reaction (Scheme 1).

In order to reoxidise the Pd(0) species formed and render this oxidative carbonylation catalytic, a stoichiometric amount of an oxidant is necessary [2,3]. Different catalytic systems were applied for this reaction [4–11], but it took 20 years before the first examples of an enantioselective bis-alkoxycarbonylation of olefins were reported [12,13]. To this purpose [$Pd(OTfa)_2$-((*R*,*R*)-DIOP)] was first used as the catalyst precursor for styrene as the substrate to form dimethyl (*R*)-2-phenyl-butanedioate with low enantioselectivity [12,13]. Better enantioselectivities were achieved using atropoisomeric diphosphines, at least when styrene was used as the substrate [12,13]. Independent of the catalyst precursor, the stereochemistry of the bis-alkoxycarbonylation was found to correspond to a syn-addition to the double bond [6,14].

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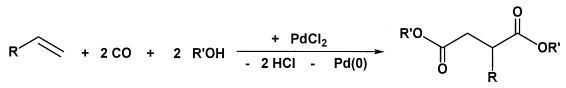


Scheme 1.

Optically active butanedioic acid derivatives are of current industrial interest. They possess potential application as building block for renin inhibitors [15–19]. Furthermore, they are important intermediates in the synthesis of pharmaceuticals [20]. Beside multistep syntheses the enantioselective bis-alkoxycarbonylation of olefins could be an elegant and much simpler method to prepare these chiral derivatives. Moreover, this conversion represents a model reaction for the first step of the synthesis of polyketones, which is of current interest [21]. Therefore, we have further investigated this reaction. Part of this work already appeared as a preliminary communication [13].

2. Experimental

2.1. Starting materials

The enantiomerically pure atropisomeric ligands **6**–**11** were a generous gift by Hoffmann-LaRoche AG, Switzerland. (*R*)(*Sp*)-PPF-PPh_2, (*R*)(*Sp*)-JOSIPHOS (**13** and **14**) [22] and (*S*)-Bu^i-PHOSOX [23] **15** were prepared according to published methods. (*S,S*)-BDPP **12** was a Strem product. Tetrakis(acetonitrile)-palladium (II)tetrafluoroborate $[Pd(CH_3CN)_4](BF_4)_2$ was purchased from Aldrich. The syntheses of the palladium complexes **6a**–**6d** [24], **6a′** [25], **7b** [26], **8a** [26], **12a** [26], **13a** [26], and **15a** [26] were already described.

2.2. Carbonylation of 1-olefin

A 250 ml stainless steel autoclave was charged under an atmosphere of N_2 with benzoquinone. After evacuation a solution of the catalyst precursor was transferred as well as 1-olefin. The autoclave was pressurized with CO and heated to the reaction temperature. After the reaction 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 (50 m column) using acetophenone as the internal standard. The enantiomeric excess was determined by gas chromatography using heptakis(6-*O*-TBDMS-2,3-*O*-methyl)-β-cyclodextrin as the stationary phase. After removal of the solvent from the reaction mixture under reduced pressure toluene was added causing most of the hydroquinone to precipitate. The filtrate was evaporated and the residue was purified by column chromatography.

2.3. Characterization of the carbonylation products

The characterization of the carbonylation products **1a** [14], **1b** [12], **2a** [14], **3a** [12], and **16** [27] was already reported in the literature.

2.3.1. Dimethyl 2-(methylphenyl)butanedioate ***1c***

^{1}H-NMR (500 MHz, $CDCl_3$, 25°C): 2.41 (dd, 1H, CH_2COOR; ^2J(H,H) = 16.8 Hz, ^3J(H,H) = 5.0 Hz), 2.67 (dd, 1H, CH_2COOR, ^2J(H,H) = 16.8 Hz, ^3J(H,H) = 9.2 Hz), 2.76 (dd, 1H, C$H_2C_6H_5$; ^2J(H,H) = 13.6 Hz, ^3J(H,H) = 8.4 Hz), 3.05 (dd, 1H, C$H_2C_6H_5$, ^2J(H,H) = 13.6 Hz, ^3J(H,H) = 6.4 Hz), 3.13 (m, 1H, CH), 3.63 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 7.14–7.33 (m, 5H, C_6H_5). ^{13}C-NMR (125.7 MHz, $CDCl_3$, 25°C): 34.9 (*C*H_2COOR), 37.7 (*C*$H_2C_6H_5$), 43.0 (CH), 51.7 (OCH_3), 51.9 (OCH_3), 126.7, 128.6, 129.0, 138.2 (C_6H_5), 172.3 (CH_2*C*OOR), 174.7 (CH*C*OOR).

2.3.2. Dimethyl 2-(methylpropyl)butanedioate ***1d***

^{1}H-NMR (500 MHz, $CDCl_3$, 25°C): 0.90 (d, 3H, CH_3; ^3J(H,H) = 6.3 Hz), 0.93 (d, 3H, CH_3; ^3J(H,H) = 6.3 Hz), 1.27 (m, 1H, CH), 1.58 (m, 2H, CH_2), 2.43 (dd, 1H, CH_2; ^2J(H,H) = 16.5

Hz, ^3J(H,H) = 5.0 Hz), 2.69 (dd, 1H, CH_2, ^2J(H,H) = 16.5 Hz, ^3J(H,H) = 9.5 Hz), 2.91 (m, 1H, CH), 3.67 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3). ^{13}C-NMR (125.7 MHz, $CDCl_3$, 25°C): 22.2 (CH_3), 22.5 (CH_3), 25.8 (CH), 36.3 (CH_2), 39.4 (CH), 41.2 (CH_2), 51.7 (OCH_3), 51.8 (OCH_3), 172.4 (COOR), 175.8 (COOR).

2.3.3. Methyl 3,6-diphenyl-4-oxohex-5-enoate ***4a***

^{1}H-NMR ($CDCl_3$, 500 MHz): 2.64 (dd, 1H, CH_2COOR, ^2J(H,H) = 16.9 Hz, ^3J(H,H) = 5.3 Hz), 3.30 (dd, 1H, CH_2COOR; ^2J(H,H) = 16.9 Hz, ^3J(H,H) = 9.3 Hz), 3.67 (s, 3H, OCH_3), 4.47 (dd, 1H, CH; ^3J(H,H) = 5.3 Hz, ^3J(H,H) = 9.3 Hz), 6.71 (d, 1H, CHCO, ^3J(H,H) = 16.0 Hz), 7.63 (d, 1H, CHC_6H_5, ^3J(H,H) = 16.0 Hz), 7.27–7.47 (m, 10H, C_6H_5). ^{13}C-NMR ($CDCl_3$, 125.7 MHz): 37.2 (CH_2COOR), 51.8 (OCH_3), 53.3 (CH), 124.6, 127.7, 128.4, 128.5, 128.8, 129.2, 134.4, 137.6 (C_6H_5), 130.5 (CHCO), 143.3 (CHC_6H_5), 197.4 (CO).

2.3.4. Dimethyl 3,6-diphenyl-4-oxoheptanedioate ***5a***

^{1}H-NMR ($CDCl_3$, 400 MHz): 7.39–7.17 (m, 10H, (C_6H_5)), 3.62 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), first unit: $CH_3O(O)CCH(C_6H_5)CH_2CO$-: 4.08 (dd, 1H, ($C_6H_5$)CH, ^3J(H,H) = 4.2 Hz, ^3J(H,H) = 10.4 Hz), 3.32 (dd, 1H, CH_2, ^2J(H,H) = 18.4 Hz, ^3J(H,H) = 10.4 Hz), 2.81 (dd, 1H, CH_2, ^2J(H,H) = 18.4 Hz, ^3J(H,H) = 4.2 Hz), second unit:-$COCH(C_6H_5)CH_2C(O)OCH_3$: 4.14 (dd, 1H, ($C_6H_5$)CH, ^3J(H,H) = 4.8 Hz, ^3J(H,H) = 10.0 Hz), 3.21 (dd, 1H, CH_2, ^2J(H,H) = 17.0 Hz, ^3J(H,H) = 10.0 Hz), 2.53 (dd, 1H, CH_2, ^2J(H,H) = 17.0 Hz, ^3J(H,H) = 4.8 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 37.0 (CH_2), 45.2 (CH_2), 45.9 (CH), 51.8 (OCH_3), 52.2 (OCH_3), 53.9 (CH), 138.0, 137.1, 129.2-127.5 (C_6H_5), 172.4 ($COOCH_3$), 173.2 ($COOCH_3$), 206.7 (-CO-).

2.3.5. Dimethyl 3,6-bis(methylphenyl)-4-oxoheptanedioate ***5c***

^{1}*H*-NMR (500 MHz, $CDCl_3$, 25°C): first unit: $CH_3OOCCH(CH_2C_6H_5)CH_2CO$-: 2.64 (dd, 1H, C$H_2$CO; ^2J(H,H) = 18.3 Hz, ^3J(H,H) = 4.6 Hz), 2.76 (dd, 1H, $CH_2C_6H_5$; ^2J(H,H) = 13.6 Hz, ^3J(H,H) = 7.9 Hz), 2.88 (dd, 1H, CH_2CO, ^2J(H,H) = 18.3 Hz, ^3J(H,H) = 9.0 Hz), 2.97 (dd, 1H, C$H_2C_6H_5$, ^2J(H,H) = 13.6 Hz, ^3J(H,H) = 6.9 Hz), n.d. (m, 1H, CH); 3.61 (s, 3H, OCH_3); second unit: -$COCH(CH_2C_6H_5)CH_2COOH_3$: 2.26 (dd, 1H, C$H_2$COOR; ^2J(H,H) = 17.2 Hz, ^3J(H,H) = 4.2 Hz), 2.47 (dd, 1H, C$H_2C_6H_5$; ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 9.2 Hz), 2.70 (dd, 1H, CH_2COOR, ^2J(H,H) = 17.2 Hz, ^3J(H,H) = 10.2 Hz), 3.01 (dd, 1H, C$H_2C_6H_5$, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 5.9 Hz), n.d (m, 1H, CH), 3.53 (s, 3H, OCH_3). ^{13}C-NMR (125.7 MHz, $CDCl_3$, 25°C): first unit: $CH_3OOCCH(CH_2C_6H_5)CH_2CO$-: 37.7 ($CH_2C_6H_5$), 41.6 (CH), 43.5 ($CH_2CO$), 51.7 ($OCH_3$), 175.1 (COOR), 210.4 (CO); second unit: -$COCH(CH_2C_6H_5)CH_2COOH_3$: 34.7 ($CH_2$COOR), 37.3 ($CH_2C_6H_5$), 49.0 (CHCO), 51.7 ($OCH_3$), 172.6 (COOR).

2.3.6. Dimethyl 2-phenylpentanedioate ***17***

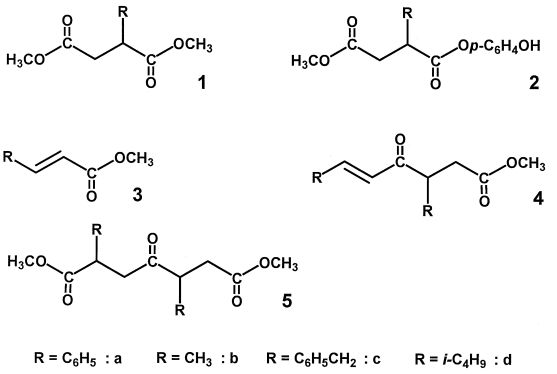
^{1}H-NMR (500 MHz, $CDCl_3$, 25°C): 2.13 (m, 1H, CH_2), 2.27 (t, 2H, CH_2COOR; ^3J(H,H) = 7.3 Hz), 2.35 (m, 1H, CH_2), n.d (1H, CH), 3.64 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 7.14-7.33 (m, 5H, C_6H_5). ^{13}C-NMR (125.7 MHz, $CDCl_3$, 25°C): 28.4 (CH_2), 31.7 (CH_2COOR), 50.5 (OCH_3), 51.6 (OCH_3), 52.1 (CH), 127.5, 128.0, 128.8, 138.3 (C_6H_5), 173.3 (CH_2COOR), 173.9 (CHCOOR).

3. Results

In Scheme 2 the different products are shown, which form during the bis-methoxycarbonylation of an 1-olefin leading to substituted dimethyl butanedioates **1** with selectivities higher than 0.5% [12,14].

3.1. Styrene as the substrate

Since the best preliminary results were obtained with (*S*)-MeO-BIPHEP **6** as the modify-



Scheme 2.

ing ligand (Scheme 3) and styrene as the substrate we have pursued our screening experiments with Pd(II)-complexes of this diphosphine [24]. The reaction were carried out using 1,4-benzoquinone (BQ) as the oxidant. All carbonylation products formed with a chemoselectivity $> 0.5\%$ are mentioned in the following tables. The difference to 100% chemoselectivity is due to the formation of dimethyl 2-oxo-3-phenylglutarate (formally a product of a triple carbonylation of styrene) [28], the synthesis of which will be separately discussed. It is noteworthy that **5a** obtained in the course of these screening experiments was identified as the opposite diastereomer (most probably the *l*-one) referred to the one previously characterized [14].

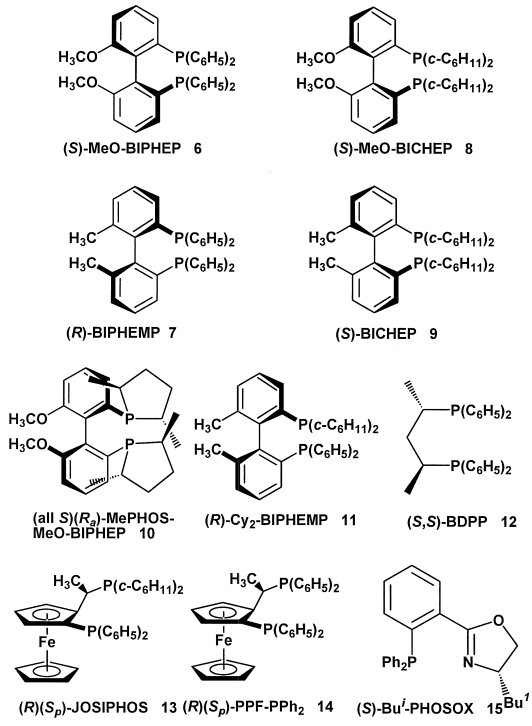
3.1.1. Influence of the nature of the counter-anion

Complexes of the type [PdX_2((*S*)-(MeO-BIPHEP)] with triflate (OTf^-) **6a**, tetra-fluoroborate (BF_4^-) **6b**, tosylate (OTs^-) **6c** and trifluoracetate ($OTfa^-$) **6d** as the weakly coordinating anion X^- were used as catalyst precursors (Table 1) [24].

Two series of experiments were effected, namely using molar ratios styrene to BQ of 1 and 2. Comparing the data obtained with the same catalyst precursor no significant change in the chemoselectivity of the formed products is observed when this ratio is varied. With the exception of a slight higher conversion for **6b**–**6d** in the second and a somewhat lower conversion for **6c** in the first series of data no significant influence on the catalytic activity was observed when the counter-anion was changed. The selectivity in the formation of **1a** is larger for **6a** than for **6b**–**6d**. Furthermore, **6a** provides the highest enantioselectivity (93% *ee*) and almost no products of further olefin insertion (**4a** and **5a**) are obtained. The formation of **2a** slightly increases when stoichiometric amounts of BQ are used for all catalyst precursors but **6c**.

3.1.2. Influence of the reaction time

The results of the bis-methoxycarbonylation of styrene at different reaction times but otherwise identical conditions are shown in Table 2. The conversion almost doubled while leaving the reaction 20 h instead of 10 h and then remains constant due to the consumption of the oxidant. In no case was the precipitation of metallic palladium observed after the catalysis.



Scheme 3.

Table 1
Enantioselective bis-methoxycarbonylation of styrene using [styrene]/[BQ] ratios of 1 (upper line) and 2 (lower line): influence of the anion X^-

Anion X^- (complex)	[styrene]/[BQ]	Conversion (%)	**3a** (%)	**1a** (%)	*ee* **1a** (%) (absolute configuration)	**2a** (%)	**4a** (%)	**5a** (%)
OTf^- (**6a**)	1/1	80	2	62	92 (*S*)	8	1	2
	2/1	40	2	68	93 (*S*)	4	1	3
BF_4^- (**6b**)	1/1	83	4	45	92 (*S*)	14	3	6
	2/1	53	3	46	92 (*S*)	11	2	4
OTs^- (**6c**)	1/1	64	5	46	89 (*S*)	6	4	7
	2/1	54	5	49	89 (*S*)	6	4	7
$OTfa^-$ (**6d**)	1/1	76	3	49	91 (*S*)	13	2	5
	2/1	54	4	50	91 (*S*)	11	2	6

Reaction conditions: 35 mmol styrene in 20 ml CH_3OH; $T = 50°C$, [styrene]/[**6a–d**] = 1000; $t = 20$ h; 350 bar CO (initial pressure at room temperature).

Both the chemoselectivities and the enantioselectivity in the formation of **1a** were not significantly affected by varying the reaction time.

3.1.3. Influence of the concentration of the oxidant

The influence of the concentration of BQ on the bis-methoxycarbonylation was investigated using **6a** as the catalyst precursor (Table 3).

The conversion decreases when less oxidant is present. A remarkable decrease in the formation of **1a** is detected going from a ratio [styrene]/[BQ] of 2 to 8, while just a slight decrease for **1a** occurs decreasing the molar ratio from 2 to 1. The selectivity to **2a** decreases when the concentration of BQ is diminished. The decrease of **1a** and **2a** by decreasing the concentration of BQ occurred partly at the expense of an increased formation of **3a**, **5a** and **4a**. The enantioselectivity in the formation of **1a** is not influenced by the concentration of BQ.

3.1.4. Influence of the concentration of the catalyst precursor

Table 4 shows the results of the bis-methoxycarbonylation of styrene varying the concentration of **6a**, which was used as the catalyst precursor. Except for a slight decrease in the formation of **1a** and **2a**, no change in chemoselectivity was observed decreasing the concentration of **6a** up to a ratio [styrene]/[**6a**] of 3000. On the other hand, the conversion of the carbonylation reaction decreased substantially at lower catalyst concentration.

3.1.5. Influence of the solvent

The bis-methoxycarbonylation of styrene leading to **1a** is generally carried out in methanol as the solvent, since the latter is needed both for the formation of the catalytic active species (supposed to be a $[Pd\text{-}COOCH_3(L \wedge L')]^+$ species) [29] and for the termination reaction affording the second ester function. The influ-

Table 2
Enantioselective bis-methoxycarbonylation of styrene using **6a** as the catalyst precursor: influence of the reaction time

Reaction time (h)	Conversion (%)	**3a** (%)	**1a** (%)	*ee* **1a** (%) (absolute configuration)	**2a** (%)	**4a** (%)	**5a** (%)
10	23	1	74	92 (*S*)	3	–	1
20	40	2	68	93 (*S*)	4	1	3
40	44	1	67	91 (*S*)	6	1	2

Reaction conditions: 35 mmol styrene in 20 ml CH_3OH; [styrene]/[**6a**] = 1000; $T = 50°C$, [styrene]/[BQ] = 2; 350 bar CO (initial pressure at room temperature).

Table 3
Enantioselective bis-methoxycarbonylation of styrene using **6a** as catalyst precursor: influence of the concentration of 1,4-benzoquinone

BQ (mmol)	[styrene]/[BQ]	[BQ]/[**6a**]	Conversion (%)	**3a** (%)	**1a** (%)	*ee* **1a** (%) (absolute configuration)	**2a** (%)	**4a** (%)	**5a** (%)
35	1	1000	80	2	62	92 (*S*)	8	1	2
17.5	2	500	40	2	68	93 (*S*)	4	1	3
4.4	8	125	12	6	48	92 (*S*)	1	3	5

Reaction conditions: 35 mmol styrene in 20 ml CH_3OH; [styrene]/[**6a**] = 1000; $T = 50°C$, $t = 20$ h; 350 bar CO (initial pressure at room temperature).

ence of a co-solvent of different polarity was investigated using **6a** as catalyst precursor. Table 5 shows the results when a 1:1 mixture (v/v) of methanol and the co-solvent was used. Note that even in the presence of a co-solvent the ratio [methanol]/[styrene] is larger than 7.

When a co-solvent is present the conversion decreases remarkably, especially with co-solvents of low polarity. With the exception of toluene a decrease in the selectivity to **1a** is observed. Moreover, in the presence of a co-solvent the chemoselectivity of the reaction is shifted both towards the formation of products of further insertion **4a** and **5a** (e.g., from 4% up to 35%) and towards **3a** and **4a** (e.g., from 3% up to 42%), which derive from β-hydrogen elimination reactions. The former shift is even more pronounced for co-solvents having a higher polarity. The ratio [**1a**]/[**3a**] is much higher than [**5a**]/[**4a**] when methanol is the unique solvent, whereby, diester formation is always favoured ([**1a**]/[**2a**], [**5a**]/[**4a**] > 1). When a co-solvent is present the ratio [**5a**]/[**4a**] is always smaller than 1.

An experiment was carried out in which the amount of methanol was doubled. In this case the catalytic activity decreased more than twice. On the other hand, the chemoselectivity towards **1a** increased at the expense of both products of further insertion **4a** and **5a** and of **2a**. The enantioselectivity of **1a** was not affected when changing either the composition or the amount of the solvent used.

3.1.6. Influence of the carbon monoxide pressure

The influence of the CO pressure in the bis-methoxycarbonlyation of styrene using **6a** as catalyst precursor is shown in Table 6. No significant influence on the conversion was observed when the CO pressure was varied from 50 to 350 bar. Increasing the carbon monoxide pressure caused a decrease in the formation of **3a**. The yield of **1a** diminished in the same direction mainly at the profit of the product of triple carbonylation [30]. On the other hand, the selectivity towards **4a** and **5a** remains almost constant for all runs of Table 6. The variation of

Table 4
Enantioselective bis-methoxycarbonylation of styrene using **6a** as catalyst precursor: influence of the concentration of the catalyst precursor

6a ($\times 10^{-5}$ mol)	[styrene]/[**6a**]	Conversion (%)	**3a** (%)	**1a** (%)	*ee* **1a** (%) (absolute configuration)	**2a** (%)	**4a** (%)	**5a** (%)
3.5	1000	80	2	62	91 (*S*)	8	1	2
1.75	2000	45	3	55	91 (*S*)	7	1	3
1.17	3000	19	2	55	93 (*S*)	5	–	3

Reaction conditions: 35 mmol styrene in 20 ml CH_3OH; [styrene]/[BQ] = 1; $T = 50°C$, 350 bar CO (initial pressure at room temperature); $t = 20$ h.

Table 5
Enantioselective bis-methoxycarbonylation of styrene using **6a** as catalyst precursor: influence of the solvent

Solvent	Conversion (%)	**3a** (%)	**1a** (%)	*ee* **1a** (%) (absolute configuration)	**2a** (%)	**4a** (%)	**5a** (%)
Methanol	80	2	62	92 (*S*)	8	1	2
Methanol[a]	29	2	71	91 (*S*)	3	–	0.3
tert-Butanol	38	18	43	90 (*S*)	2	21	14
Acetone	26	16	46	91 (*S*)	2	22	12
Terahydrofuran	21	19	54	90 (*S*)	2	16	9
Dichloromethane	19	21	46	92 (*S*)	3	21	9
Toluene	20	20	65	91 (*S*)	2	8	5

Reaction conditions: 35 mmol styrene in 10 ml CH_3OH and 10 ml of solvent; [styrene]/[BQ] = 1; [styrene]/[**6a**] = 1000; $T = 50°C$, $t =$ 20 h; 350 bar CO (initial pressure at room temperature).
[a]Total amount of 40 ml of methanol was used.

the carbon monoxide pressure had no influence on the enantioselectivity of the formed **1a**.

3.1.7. Influence of the temperature

The bis-methoxycarbonylation of styrene was effected at three different reaction temperatures using **6a** as the catalyst precursor (Table 7). An increase of the temperature brought about an increase in catalytic activity. At 25°C, almost no conversion of styrene has taken place. Increasing the reaction temperature from 50 to 75°C **1a** was formed with decreased selectivity. On the other hand, a remarkable increase of **3a** was observed.

3.1.8. Influence of the number of counter-anion

Besides the nature of the weakly coordinating anion, the number of counter-anions present in the catalyst precursor was also varied. For this purpose, in addition to [Pd((*S*)-MeO-BIPHEP)$(H_2O)_2$](OTf)$_2$ **6a** the monocationic complex [Pd(η^3-C_3H_5)((*S*)-MeO-BIPHEP)](OTf) **6′a** was used. The results obtained in the bis-methoxycarbonylation of styrene using these two catalyst precursors are reported in Table 8.

The conversion remarkably decreased when only one counter-anion per atom of palladium is present. With respect to the chemoselectivities only slight changes were observed. However, using complex **6′a**, there is a higher tendency to form the unsaturated compound **3a** and **2a** at the expense of **1a**. The enantiomeric excess of **1a** was not affected.

3.1.9. Other chiral ligands

In Table 9 the results of the bis-methoxycarbonylation of styrene using catalyst precur-

Table 6
Enantioselective bis-methoxycarbonylation of styrene using **6a** as catalyst precursor: Influence of the CO pressure

Pressure (bar)	Conversion (%)	**3a** (%)	**1a** (%)	*ee* **1a** (%) (absolute configuration)	**2a** (%)	**4a** (%)	**5a** (%)
50	85	8	77	91 (*S*)	9	1	1
90	78	6	77	91 (*S*)	7	1	1
150	81	4	70	91 (*S*)	8	1	2
250	75	3	62	91 (*S*)	9	1	2
350	80	2	62	92 (*S*)	8	1	2

Reaction conditions: 35 mmol styrene in 20 ml CH_3OH; [styrene]/[BQ] = 1; $T = 50°C$, [styrene]/[**6a**] = 1000; $t = 20$ h; initial CO pressure at room temperature.

Table 7
Enantioselective bis-methoxycarbonylation of styrene using **6a** as catalyst precursor: influence of the temperature

Temperature (°C)	Conversion (%)	**3a** (%)	**1a** (%)	*ee* **1a** (%) (absolute configuration)	**2a** (%)	**4a** (%)	**5a** (%)
25	3	3	54	91 (*S*)	–	–	–
50	45	3	55	91 (*S*)	7	1	3
75	64	30	43	90 (*S*)	7	5	2

Reaction conditions: 35 mmol styrene in 20 ml CH_3OH; [styrene]/[BQ] = 1; t = 20 h; [styrene]/[**6a**] = 2000; 350 bar CO (initial pressure at room temperature).

sors modified by different chiral chelate ligands (Scheme 3) are reported.

The two palladium complexes ([Pd((*R*)-BIPHEMP)$(H_2O)_2$]$(BF_4)_2$ **7b** and ([Pd((*S*)-MeO-BIPHEP)$(H_2O)_2$]$(BF_4)_2$ **6b**, showed good conversion as well as chemoselectivities to the carbonylation products. The enantioselectivity in the formation of **1a** is, however, lower for **7b** (*ee* of 81%) than for **6b** (92%). All the other ligands tested gave almost no conversion. Nevertheless, trace amounts of **1a** could be detected by GC and the enantioselectivity for its formation could be determined. Except for (*S*)-MeO-BICHEP **8**, which lead still to a fair enantioselectivity for **1a**, all the other ligands **13**–**15** resulted in much lower *ee*-values compared to the fully aromatic atropisomeric biphenyl-ligands.

3.2. Enantioselective bis-methoxycarbonylation of aliphatic 1-olefins

3-Phenyl-1-propene, 4-methyl-1-pentene and propene were used as substrates in order to investigate the scope of the enantioselective bis-methoxycarbonylation. The enantioselectivity of the formed 2-substituted dimethyl butanedioates were hereby of main interest. To this purpose the reaction conditions optimised for styrene were applied and no further screening was effected.

The bis-methoxycarbonylation of 3-phenyl-1-propene has once been described in the literature [7]. Dimethyl 2-(phenylmethyl)-butanedioate **1c** has been obtained in 70% yield with a conversion of 70% after 48 h. We observed, in addition to **1c** two further carbonylation products, namely methyl (*E*)-1-phenyl-1-butenoate **16** [27] and dimethyl 2-phenylpentanedioate **17** [31–33]. Using **6a** as the chiral catalyst precursor, a low conversion of 7% was observed under the reaction conditions used (similar to those reported in Table 1 for styrene). **1c** was formed with a high chemoselectivity of 80% but with low enantioselectivity (8% *ee*). The catalytic systems ([Pd((*S*)-MeO-BICHEP)(H_2O)-(THF)]$(OTf)_2$ **8a** showed almost no activity under the same reaction conditions. However, the enantioselectivity in the formation of **1c** was evaluated to amount to an enantiomeric excess of 53%. The absolute configuration of the prevailing enantiomer is unknown. Remarkably,

Table 8
Enantioselective bis-methoxycarbonylation of styrene using a di- and a mono-cationic catalyst precursor (**6a** and **6′a**)

Catalyst precursor	Conversion (%)	**3a** (%)	**1a** (%)	*ee* **1a** (%) (absolute configuration)	**2a** (%)	**4a** (%)	**5a** (%)
[Pd(L-L)$(H_2O)_2$]$(OTf)_2$	40	2	68	93 (*S*)	4	1	3
[Pd(η^3-C_3H_5)(L-L)](OTf)	6	11	61	92 (*S*)	9	–	–

Reaction conditions: 35 mmol styrene in 20 ml CH_3OH; [styrene]/[BQ] = 2; T = 50°C, [styrene]/[catalyst precursor] = 1000; t = 20 h; 350 bar (initial pressure at room temperature).

Table 9
Enantioselective bis-methoxycarbonylation of styrene using different chiral ligands

Ligand (L–L′)	Conversion (%)	**3a** (%)	**1a** (%)	*ee* **1a** (%) (absolute configuration)	**2a** (%)	**4a** (%)	**5a** (%)
(*S*)-MeO-BIPHEP[b]	83	4	45	92 (*S*)	14	3	6
(*R*)-BIPHEMP[b]	95	2	49	81 (*R*)	21	2	4
(*S*)-MeO-BICHEP[c]	[a]	–	–	74 (*S*)	–	–	–
(*R*)(*S*$_p$)-JOSIPHOS[d]	[a]	–	–	24 (*S*)	–	–	–
(*R*)(*S*$_p$)-PPF-PPh$_2$[d]	[a]	–	–	2 (*R*)	–	–	–
(*S*)-Bu^i-PHOSOX[c]	[a]	–	–	44 (*R*)	–	–	–

Reaction conditions: 35 mmol styrene in 20 ml CH_3OH; [styrene]/[BQ] = 1; T = 50°C, [styrene]/[catalyst precursor] = 1000; t = 20 h; 350 bar CO (initial pressure at room temperature).
[a] Conversion < 1%.
[b] $[Pd(L–L')(H_2O)_2](BF_4)_2$ as the catalysts precursor.
[c] $[Pd(L–L')(H_2O)_2](OTf)_2$ as the catalysts precursor.
[d] Catalyst formed in situ from $[Pd(CH_3CN)_4](BF_4)_2$ and ligand (1/1 mixture).

the two homochiral catalyst precursors **6a** and **8a** gave the heterochiral compound **1c**. Attempts to determine the enantioselectivity of the formed **17** were unsuccessful. Furthermore, dimethyl 2,5-di(phenylmethyl)-4-oxo-heptanedioate **5c** (probably obtained as a single diastereomer) was isolated from the reaction mixture and characterised by 2D-NMR spectroscopy. Note that **5c** is formed by two insertions of 3-phenyl-1-propene with the same regioselectivity.

3.2.1. Propene

Under reaction conditions similar to those applied to styrene the bis-methoxycarbonylation of propene leads to significant amounts of carbonylation products deriving from further propene insertions into palladium–acyl bonds [26]. The results of a screening under variation of the catalytic systems are listed in Table 10.

The catalysis was effected either using preformed triflate (**6a**, **8a**, **12a**, **13a**, and **15a**) or tetrafluoroborate (**7b**) complexes or in situ sys-

Table 10
Enantioselective bis-methoxycarbonylation of propene

Ligand	Catalyst precursor	Conversion (%)	**1b** (%)	*ee* **1b** (%)	Dimers[a] (%)	Other[b] (%)
(*R*)-MeO-BIPHEP	**6a**	66	30	29 (*R*)	35	35
(*S*)-MeO-BICHEP	**8a**	23[c]	13	60 (*S*)	31	56
(*R*)-BIPHEMP	**7b**	91	30	25 (*R*)	30	40
(*S*)-BICHEP[d]	**9b**[g]	5	33	48 (*S*)	27	40
(*all S*)-MePHOS-(*R*$_a$)-MeOBIPHEP[e]	**10b**[g]	71	25	8 (*S*)	29	46
(*R*)-Cy$_2$-BIPHEMP	**11b**[g]	37[c]	41	36 (*S*)	14	44
(*R*)(*S*$_p$)-JOSIPHOS[f]	**13a**	55	24	52 (*R*)	31	45
(*R*)(*S*$_p$)- PPF-PPh$_2$	**14a**[g]	32	59	8 (*S*)	18	23
(*S*)-Bu^i-PHOSOX	**15a**	2	54	12 (*R*)	24	22
(*S,S*)-BDPP	**12a**	80	38	6 (*S*)	25	37

Reaction conditions: 165 mmol propene in 100 ml CH_3OH; [propene]/[BQ] = 2; T = 50°C, t = 20 h (unless otherwise specified); [propene]/[catalyst precursor] = 1000; 250 bar CO (initial pressure at room temperature).
[a] Σ(**5b** and isomers thereof).
[b] Mostly co-trimers.
[c] 110 h.
[d] 260 h.
[e] 70 h.
[f] 150 bar CO.
[g] in situ system: 1:1 mixture of $[Pd(CH_3CN)_4](BF_4)_2$ and ligand.

tems using $[Pd(CH_3CN)_4](BF_4)_2$ as the source of palladium. Therefore, in addition to the ligand, the weakly coordinating anion present in the catalytic system can be different.

The catalytic systems modified by atropisomeric diphosphines containing two diphenylphosphino groups **6a** and **7b** led to a moderate or high conversion after 20 h, whereas the complexes (**8a** and **9b**) containing the chiral diphosphines (*S*)-MeO-BICHEP **8** and (*S*)-BICHEP **9**, which bear two dicyclohexylphosphino groups, provided low conversion even at prolonged reaction times. On the other hand, the enantioselectivity in the formation of **1b**, is higher for the latter systems. Independent of the substitution pattern at the phosphorus atoms, the diphosphines with methoxy substitution in the biphenyl system led to slightly higher enantioselectivities for **1b** as compared to their methyl substituted analogoues. The ligand (*R*)-Cy_2-BIPHEMP **11**, possessing a diphenylphosphino as well as a dicyclohexylphosphino group, holds an intermediate position with regard to conversion and enantioselectivity. No significant influence on the chemoselectivities towards the carbonylation products varying the atropisomeric diphosphine was observed. The major part of the carbonylation products listed in the column 'other' are according to mass determination cotrimers with carbomethoxy terminations.

The catalyst precursor ($[Pd((S)\text{-}Bu^i\text{-}PHOSOX)(H_2O)_2](OTf)_2$ **15a** bearing the chiral phosphino-oxazoline led to low conversion. On the other hand, high catalytic activity was observed using $[Pd((S,S)\text{-}BDPP)(H_2O)_2](OTf)_2$ **12a**. For both precursors the enantiomeric excess of the formed **1b** was low.

Comparing the two catalyst precursors containing the ferrocenyl diphosphine ligands, $[Pd((R)(Sp)\text{-}PPF\text{-}PPh_2)(H_2O)_2](OTf)_2$ **14a** and $[Pd((R)(Sp)\text{-}JOSIPHOS)(H_2O)_2](OTf)_2$ **13a**, the former showed a chemoselectivity towards **1b**, which was more than twice as high as the latter. However, **13a** gave a higher conversion. With regard to the enantioselectivity in the formation of **1b**, **14a** led only to an enantiomeric excess of 8% compared to 52% of **13a**. Homochiral ligands gave heterochiral **1b**.

3.2.2. 4-methyl-1-pentene

The bis-methoxycarbonylation of 4-methyl-1-pentene to a single diester product, namely dimethyl 2-(2-methylpropyl)-butanedioate **1d** was already described [5]. Table 11 shows the results of the enantioselective bis-methoxycarbonylation of 4-methyl-1-pentene using $[Pd((S)\text{-}MeO\text{-}BIPHEP)(H_2O)_2](BF_4)_2$ **6b** and $[Pd((R)\text{-}BIPHEMP)(H_2O)_2](BF_4)_2$ **7b** as the catalyst precursor. In addition to **1d** further carbonylation products with higher molecular weight were isolated. Furthermore, small amounts of an unidentified constitutional isomer of **1d** (1–4% with respect to **1d**) were formed. The conversion of the bis-methoxycarbonylation reaction was about three times higher at lower carbon monoxide pressures. The chemoselectivity to **1d** slightly decreased under higher CO pressure. On the other hand, formation of the unidentified constitutional isomer was more pronounced at lower CO pressure. These effects were observed

Table 11
Enantioselective bis-methoxycarbonylation of 4-methyl-1-pentene

Catalyst precursor	Pressure (bar CO)	Conversion (%)	**1d** (%)	*ee* **1d**[a] (%)	Other[a] (%)
(*S*)-**6b**	120	33	78	14 (*S**)	22
(*S*)-**6b**	350	13	67	14 (*S**)	33
(*R*)-**7b**	105	33	79	7 (*R**)	21
(*R*)-**7b**	350	11	69	7 (*R**)	31

Reaction conditions: 52.5 mmol 4-methyl-1-pentene in 30 ml CH_3OH; $T = 50°C$, $t = 20$ h; [4-methyl-1-pentene]/[BQ] = 2; [4-methyl-1-pentene]/[catalyst precursor] = 1000; initial CO pressure at room temperature.
[a]Carbonylation products with higher molecular weight.

independently whether **6b** or **7b** was used as catalyst precursor. The enantioselectivity in the formation of **1d** was low in all experiments, but somewhat higher for **6b** than for **7b**. Heterochiral precursors gave heterochiral **1d**.

4. Discussion

A mechanistic description [29] for the formation of the various products is reported in Fig. 1, in which only the secondary regioselectivity for the insertion of the olefin substrate is represented.

In general, slight differences with respect to the selectivity of the carbonylation products are observed by varying the weakly coordinating anion. In the carbonylation of styrene, the triflate complex **6a** shows the best chemoselectivity toward **1a** (Table 1). However, the enantiomeric excess of **1a** seems not to be influenced by the counter-anion within the limits of the experimental error. Also the reaction time causes no significant variation of the selectivity (Table 2). Under the conditions used, the maximum turnover number requires about 20 h and is around 400.

Based on the stoichiometry and the commonly accepted mechanistic scheme [9,21,29] (Fig. 1), the formation of **3a** and **1a** should not be influenced by the concentration of the oxidant. Therefore, a constant ratio [**3a**]/[**1a**] is expected when the amount of BQ is varied. However, when decreasing the concentration of BQ up to a ratio [styrene]/[BQ] of 8 (Table 3) a remarkable drop in selectivity to **1a** accompanied by an increased formation of **3a** is observed. Moreover, the selectivity toward **4a** and **5a** that derive from further styrene insertions also increased. Thus, instead of methanolysis of the palladium-acyl intermediate, decarbonylation followed by β-hydrogen elimination leading to **2a** or a second styrene insertion takes

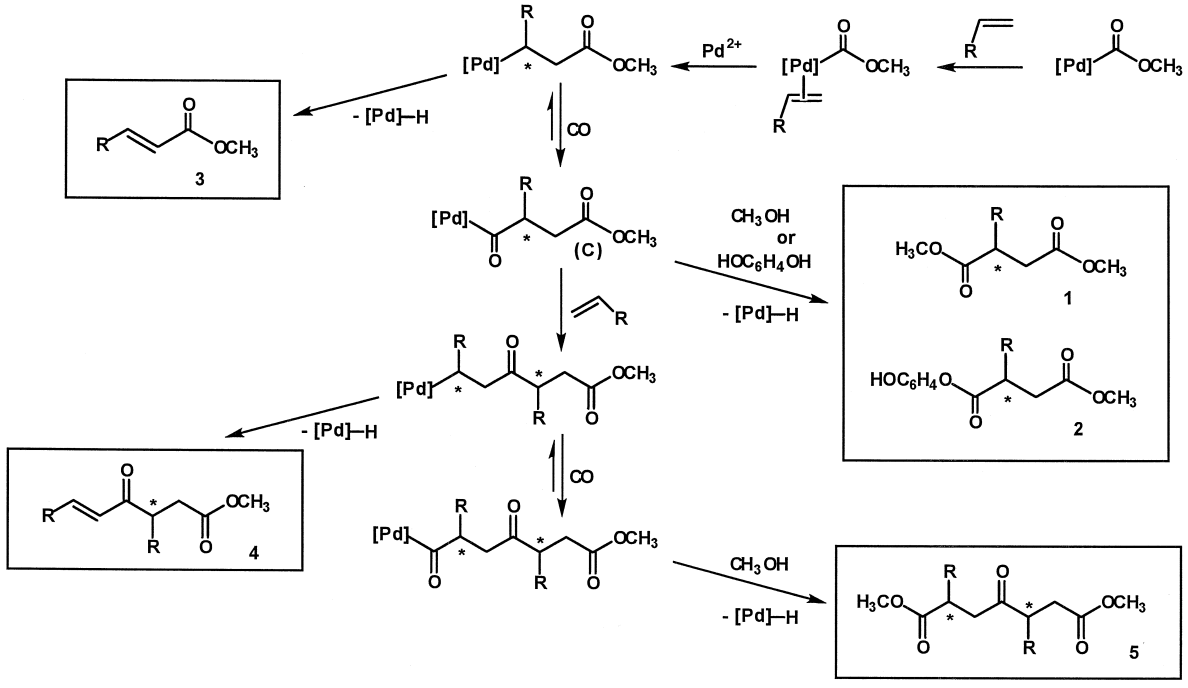


Fig. 1. Reaction scheme for the bis-methoxycarbonylation of olefins and for competing reactions (only the regioselectivity corresponding to secondary insertion is considered; [Pd] = [(L ^ L′)Pd^{2+}]).

place. These competitive pathways require a free coordination site at the palladium center. This implies that the vacant site at the metal can be occupied by BQ or by the formed hydroquinone. Coordinative interactions of BQ with palladium are indeed known [34–36].

For the bis-methoxycarbonylation of styrene catalysed by cationic palladium complexes bearing bidentate nitrogen ligands, the alcoholysis by hydroquinone has been proposed to proceed more rapidly than the analogous methanolysis [14]. Similarly, the comparison of the ratios [methanol]/[BQ] with [**1a**]/[**2a**] for all entries of Table 3 supports the aforementioned suggestion. Calculation of the analogous ratios from the literature data [14] suggests that this effect seems to be more pronounced for dinitrogen ligands. The ratio between the ratios [methanol]/[BQ] and [**1a**]/[**2a**] remains almost constant for all runs of Table 3. The decrease of **2a** when decreasing the concentration of BQ is, however, in agreement with the expected lower concentration of formed hydroquinone.

Hydroquinone has very recently been reported to form stable PN-ligated methylpalladium(II) aryloxides [37]. Therefore, the formation of **2a** could also take place by starting with such a carboaryloxy group, although this seems not very likely with respect to the observed regioselectivity of the incorporated styrene unit in **2a**. Moreover, insertion of CO seems to occur more readily into palladium-alkoxide bonds than into palladium–aryloxide bonds [37,38].

Rather small variations in selectivity are observed by varying the concentration of the catalyst precursor (Table 4). By contrast, large effects of the solvent are observed (Table 5). The decrease of the conversion in the presence of a co-solvent is probably the consequence of both concentration and polarity effects. The shift of selectivity toward **4a** and **5a** implies that the rate of insertion of a second styrene molecule becomes more favoured than the rate of methanolysis. Recent studies on the insertion of alkenes into palladium–acyl bonds revealed that the nature of the solvent is important since it will compete with the alkene for the coordination site on the metal center [39]. Accordingly, the increase of **3a** and **4a** compared to **1a** and **5a** in the presence of a co-solvent can be accounted for by considering the coordination ability of methanol preventing decarbonylation or β-hydrogen elimination or both to take place. Interestingly, the selectivity towards **4a** and **5a** can be shifted up to a value of 35%; however, compounds having three styrene units incorporated were not observed. The effect of a double amount of methanol is in keeping with this interpretation. On the other hand, the remarkable drop in catalytic activity is rather due to the dilution of the reaction mixture than to an increased efficiency in blocking the coordination sites.

The carbon monoxide pressure does not influence significantly the conversion (Table 6). On the other hand, increasing the carbon monoxide pressure leads to a decrease of the formation of **3a**, which results from β-hydrogen elimination. This indicates that CO competes for and blocks the free coordination sites more successful at higher pressure probably due to the formation of palladium–carbonyl species. These species have indeed been observed in model studies on the insertion of CO into related cationic palladium–alkyl bonds [40–43].

Increasing the temperature up to 75°C brings about an increase in conversion but also an increased tendency to β-hydrogen elimination, as already observed in similar carbonylation reactions of olefins [44]. Essentially no influence on the enantioselectivity of the formation of **1a** was observed in the temperature range investigated.

The monocationic complex [Pd(η^3-C_3H_5)-((*S*)-MeO-BIPHEP)](OTf) **6′a** used as catalyst precursor shows a decreased catalytic activity as compared to the dicationic complex [Pd-((*S*)-MeO-BIPHEP)(H_2O)$_2$](OTf)$_2$ **6a** (turnover number of 60 vs. 400 with respect to styrene in 20 h). Even if carbonylation of palladium allyl compounds requires forcing conditions and the appropriate choice of the counter-anion [45–47],

the generation of the catalytic active species by an initial olefin insertion should be possible [44,48]. Once generated, the catalytic active species should be the same independent on the precursor [21,29]. Therefore, the shift to the formation of **2a** and **3a** at the expense of **1a** when using **6′a** as catalyst precursor seems to be connected with the number of counter-anions present in the reaction mixture.

The use of chiral atropisomeric diphosphine ligands, among which (*S*)-MeO-BIPHEP is the most effective, lead to high enantioselectivity for **1a**. Not only showed the ferrocenyldiphosphines and the phosphino-oxazoline ligand almost no conversion, the values of *ee* were also low to moderate.

In the enantioselective bis-methoxycarbonylation of propene a higher conversion was observed for the all-phenyl substituted atropisomeric diphosphines as compared to the dicyclohexyl substituted counterparts (Table 10). Even if this is in agreement with the higher productivity of the former observed in the related copolymerisation reaction of propene with CO [49], the remarkable drop in catalytic activity in the bis-methoxycarbonylation seems unlikely to be solely caused by the more basic ligand systems. The catalyst precursor **8a** (containing the (*S*)-MeO-BICHEP diphosphine **8**) showed almost no conversion also in the bis-methoxycarbonylation of styrene (Table 9) and of allylbenzene. Therefore, interactions between these ligands systems and the oxidant used, i.e., 1,4-benzoquinone, inactivating the catalytic precursor could also account for the decrease in conversion. On the other hand, substitution of the phenyl groups at the phosphorus atoms by cyclohexyl groups has a beneficial effect with respect to the enantiomeric excess of the formed **1b** and of **1c**. Based on the mechanistic description [29], this can be due to a better control of the regiochemistry (primary vs. secondary) during the insertion of the olefin. Accordingly, in the copolymerisation of propene with carbon monoxide (*S*)-MeO-BIPHEP causes formation of regioirregular copolymers whereas (*R*)-MeO-BICHEP leads to a regioregular enchainment [49]. Analogously, the methoxy-substitution in the biphenyl system leads to higher *ee*'s in the bis-methoxycarbonylation reaction (Table 10) as well as to more regioregular propene-copolymers [49].

The catalyst precursors [Pd((*S*)-Bu^{i}-PHOSOX)$(H_2O)_2$](OTf)$_2$ **15a** and [Pd((*S,S*)-BDPP)$(H_2O)_2$](OTf)$_2$ **12a** cause formation of **1b** with only low enantiomeric excess, even if with the latter some regioregularity in the copolymerisation reaction has been achieved [50]. The ferrocenyldiphosphines are highly active catalytic systems for the regioregular copolymerisation of propene with CO [51]. As in the bis-methoxycarbonylation reaction, the system containing (*R*)(*Sp*)-JOSIPHOS **13** as the modifying ligand causes a higher catalytic activity when compared to (*R*)(*Sp*)-PPF-PPh$_2$ **14**. The enantioselectivity for **1b** was moderate with the former but low with the latter ligand system.

The formation of the rearranged carbonylation products **16** and **17** from 3-phenyl-1-propene can be rationalised assuming secondary insertion of the substrate into the palladium-carbomethoxy bond followed by β-hydrogen elimination. Dissociation would lead to **16**; alternatively readdition of the hydride and subsequent methoxycarbonylation would give **17**. Rearrangements of this type are not uncommon for unsaturated palladium–alkyl complexes [5,48] The fact that only rearranged carbonylation products deriving from an initial secondary 3-phenyl-1-propene insertion are observed is in agreement with earlier suggestions that these pathways are favoured by steric hindrance [5].

The lower conversion at higher CO pressures observed in the bis-methoxycarbonylation of 4-methyl-1-pentene may be due to a more efficient coordination of carbon monoxide to the vacant ligand site on palladium, therefore retarding olefin coordination. Accordingly, the rate of rearrangement toward the formation of the isomer of **1d** decreases at higher carbon monoxide pressures. A similar dependency of conversion and competitive pathways on the CO pres-

sure has already been reported for the bis-methoxycarbonylation of cyclopentene [5].

5. Conclusion

Reaction conditions were developed for which a high conversion as well as a high chemoselectivity and enantioselectivity to **1a** was obtained. On the other hand, the present results show that the chemoselectivity of the bis-methoxycarbonylation is strongly affected by the reaction conditions. In particular, the proper choice of the solvent and the applied pressure of carbon monoxide was important for a selective catalysis. The observed sensitivity on the selectivity may be related to the active species involved in the catalytic scheme (cf. Fig. 1). These cationic palladium species contain a vacant fourth coordination site for which competition seems to occur thus affecting the selectivity of the catalysis. Similar results were observed in the copolymerisation reaction of olefins and CO for which analogous palladium catalyst precursors were known to be highly efficient [21].

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