

Enantioselective bis-alkoxycarbonylation of styrene catalyzed by novel chiral dipyridylphosphine cationic palladium(II) complexes

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Abstract

The preparation of new palladium complexes that are composed of a series of chiral dipyridylphosphines [(*R*)-P-Phos (**1**), (*R*)-tol-P-Phos (**2**) and (*R*)-Xyl-P-Phos (**3**)] have been described. The structure of the complex [$\{(R)\text{-1}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ was unambiguously determined by single-crystal X-ray diffractometry. These complexes were found to be effective in the asymmetric bis-methoxycarbonylation of styrene, reaching up to 84% e.e. and 79% chemoselectivity for dimethyl-2-phenylsuccinate (DMPS) under the optimal conditions. In addition, the complexes exhibited almost identical enantioselectivity on DMPS.

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1. Introduction

Transition metal-catalyzed asymmetric carbonylations of prochiral alkenes are potentially useful processes in providing pharmaceuticals or their intermediates, agrochemicals and other fine chemicals of high enantiopurity. Whilst recent development of catalytic asymmetric monocarbonylation (e.g. hydroformylation) has rendered the reaction to high efficiency [1], highly chemoselective and regioselective control of multiple carbonylation of olefins still remains a formidable challenge. Of particular relevance to the work to be delineated below is Pd(II)-catalyzed

bis-alkoxycarbonylation (Scheme 1)—a reaction first reported by Heck back in the early 1970s [2]. Surprisingly, an asymmetric version of this reaction appeared a long due 20 years after its discovery [3,4]. In a seminal report, Consiglio and co-workers disclosed that high enantioselectivity but modest chemoselectivity and poor conversion were achieved by employing atropisomeric diarylphosphines [3]. Later attempts by using chiral phosphine sulfides [5] and bisoxazolines [6] as ligands only led to poor e.e.s of the succinate. Despite this, asymmetric bis-alkoxycarbonylation offers an excellent opportunity for the synthesis of optically active butanedioic acid derivatives which are important intermediates for certain pharmaceuticals [7] and building blocks for renin inhibitors [8–12]. In addition, the reaction may serve as a starting ground for the preparation

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2.2. Spectroscopic measurements

^{31}P and ^1H NMR spectra were recorded on a Varian AS500 spectrometer. Low-resolution mass spectrometry was performed using a Finnigan MAT 95S model spectrometer. GC analyses were performed on an HP 5890 apparatus equipped with FID.

2.3. Synthesis of *P-Phos* palladium complexes

The catalyst precursors [$\{(R)\text{-1}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**7**), [$\{(R)\text{-2}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**8**) and [$\{(R)\text{-3}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**9**) were prepared by adopting a literature procedure [18,19]. The preparation of **7** is described in detail as follows.

2.3.1. Synthesis of [$\{(R)\text{-1}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$

A solution of $\text{PdCl}_2(\text{NPh})_2$ (0.49 g, 1.29 mmol) in toluene (50 ml) was heated to 70°C . To this reddish-brown solution was added (*R*)-2,2',6,6'-tetramethoxy-4,4'-bis(diphenylphosphine)-3,3'-bipyridine (*P-Phos*) (0.85 g, 1.32 mmol) in toluene (25 ml) dropwise. The solution became brighter, and a red precipitate was formed. The suspension was held for another 2.5 h at this temperature followed by cooling to room temperature. Addition of pentane (50 ml) induced more precipitation. The complex was filtered, washed with diethyl ether and dried under reduced pressure. Another crop of crystals was obtained from the mother solution by cooling at 4°C overnight. Without further purification, the combined crystals (0.50 g, 0.62 mmol) were dissolved in tetrahydrofuran (THF) (60 ml) and were treated with a solution of silver trifluoromethane sulfonate (0.32 g, 1.23 mmol) in THF (20 ml) in the exclusion of light. The reaction mixture was stirred for 2 h at room temperature. The precipitated AgCl was filtered off and was washed twice with THF (5 ml). The filtrate was concentrated to a total volume of 10 ml under reduced pressure. Pentane was added to initiate crystallization which was completed after 24 h at 4°C . The red precipitate was filtered and dried under reduced pressure. The crude product was recrystallized from CH_2Cl_2 /hexane to give **7** in 80% yield (0.54 g, 0.50 mmol).

Suitable single crystals for X-ray diffraction study were obtained by vapor diffusion of *n*-hexane into a THF solution of [$\{(R)\text{-1}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**7**) at room temperature. Crystals were coated in an inert

oil prior to transfer to a cold nitrogen gas stream on a Bruker CCD area-detector diffractometer system equipped with $\text{Mo K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). Data were collected with narrow ($R_{\text{int}} = 0.0534$) frame exposures. Intensities were corrected empirically for absorption, based on SADABS (Sheldrick, 1996) program, $T_{\text{min}} = 0.8982$, $T_{\text{max}} = 0.9174$, and 18,879 measured reflections. The structure were refined on F^2 values for all unique data. All H atoms were obtained by geometrical analysis with 1740 Friedel pairs, and Flack parameter = 0.01 (10). Programs used were SHELXS97 (Sheldrick, 1997) and SHELXTL-NT for structure solution, refinement, and molecular graphics.

Other spectral data for [$\{(R)\text{-1}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**7**): MS ($5.68 \times 10^4 \text{ eV}$) *m/e* (int (%)): 785 (12); 787 (10) [$M-(2x\text{OTf})]^+$; 861 (29); 862 (68); 863 (100); 865 (65); 867 (33); 868 (13). ^1H NMR (CDCl_3 , 500 MHz): δ 3.57 (s, 6H, OCH_3), 3.73 (d, 6H, OCH_3), 6.19 (d, 2H, PyH), 7.41–7.92 (m, 20H, PhH). ^{31}P NMR (CDCl_3 , 202 MHz): δ 30.62.

2.3.2. [$\{(R)\text{-2}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**8**)

Complex **8** was prepared using a procedure similar to 2.3.1: MS ($4.95 \times 10^4 \text{ eV}$) *m/e* (int (%)): 841 (15); 826 (40); 825 (77); 824 (100) [$M-(2x\text{OTf}-\text{H}_2\text{O})]^+$; 807 (43); 806 (37); 205 (81); 203 (67). ^1H NMR (CDCl_3 , 500 MHz): δ 2.40 (d, 12H, $J_{\text{H,P}} = 15 \text{ Hz}$, PhCH_3), 3.57 (s, 6H, OCH_3), 3.71 (s, 6H, OCH_3), 6.15 (d, 2H, PyH), 7.25–7.64 (m, 12H, PhH). ^{31}P NMR (CDCl_3 , 202 MHz): δ 30.57.

2.3.3. [$\{(R)\text{-3}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**9**)

Complex **9** was prepared using a procedure similar to 2.3.1: MS ($2.52 \times 10^4 \text{ eV}$) *m/e* (int (%)): 899 (23) [$M-(2x\text{OTf})]^+$; 897 (26); 896 (16); 205 (57); 203 (62); 183 (99); 181 (100); 137 (51) ^1H NMR (CDCl_3 , 500 MHz): δ 2.34 (d, 12H, $J_{\text{H,P}} = 10 \text{ Hz}$, PhCH_3), 3.61 (s, 6H, OCH_3), 3.76 (s, 6H, OCH_3), 6.23 (d, 2H, PyH), 7.18–7.25 (m, 12H, PhH). ^{31}P NMR (CDCl_3 , 202 MHz): δ 32.22.

2.4. General procedures for the asymmetric bis-alkoxycarbonylation of styrene

A 50 ml stainless steel autoclave was charged with benzoquinone, the catalyst precursor, styrene, and methanol under an atmosphere of N_2 . The autoclave

was pressurised with CO and heated to the reaction temperature. The reaction mixture was stirred well with a magnetic stirrer. After a prescribed period of time of reaction, the autoclave was cooled to room temperature and the residue gas was released. The solvent was removed in vacuo, followed by the addition of toluene causing the precipitation of solid hydroquinone. The mixture was filtered and the filtrate was purified by column chromatography. The characterisation of the carbonylation products 10–13 was carried out using methods reported in the literature [20]. The data on conversion and chemoselectivities were determined immediately by GC on an AT-1 column (25 m × 0.25 mm i.d.) using acetophenone as the internal standard. The enantiomeric excess of the asymmetric bis-alkoxycarbonylation of styrene were analysed by GC using a Chrompack Chirasil-Dex CB column (50 m × 0.25 mm i.d.). The absolute configuration of dimethyl-2-phenylsuccinate (DMPS) **10** was determined by optical rotation in comparison with literature value [3].

3. Results and discussion

3.1. Synthesis and characterisation of $[\{(R)\text{-1}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$

According to the literature method [18,19], the diphosphines were first converted to $[\{(R)\text{-1}\}\text{PdCl}_2]$ (**4**), $[\{(R)\text{-2}\}\text{PdCl}_2]$ (**5**), and $[\{(R)\text{-3}\}\text{PdCl}_2]$ (**6**) by reacting ligands **1–3** with $\text{PdCl}_2(\text{NPh})_2$, which were then treated without further purification with AgOTf in tetrahydrofuran leading to the formation of the complexes $[\{(R)\text{-1}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**7**), $[\{(R)\text{-2}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**8**) and $[\{(R)\text{-3}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**9**) as red microcrystalline solids (Scheme 2).

Suitable single crystals of the catalyst precursor $[\{(R)\text{-1}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**7**) were obtained by vapor diffusion of *n*-hexane into a 10^{-5} M CH_2Cl_2 solution of **7** at room temperature. An ORTEP diagram of $[\{(R)\text{-1}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**7**) is shown in Fig. 2.

$[\{(R)\text{-1}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**7**) was crystallized in the monoclinic space group $P2_1$ as red platelets. The

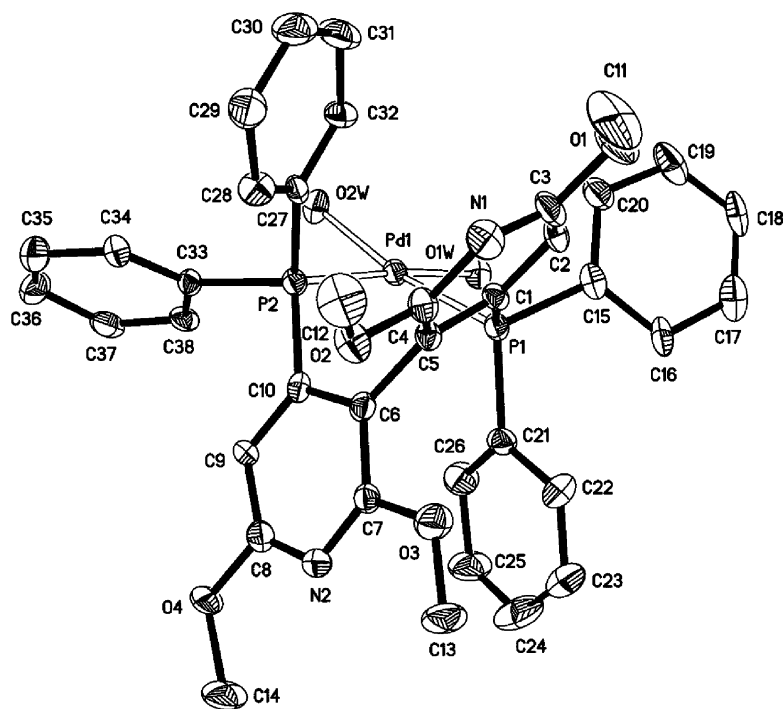


Fig. 2. ORTEP diagram of $[\{(R)\text{-1}\}\text{Pd}(\text{H}_2\text{O})_2](\text{OTf})_2$. Selected bond distances (Å): $\text{Pd}(1)\text{-O}(1w) = 2.118(2)$, $\text{Pd}\text{-O}(2w) = 2.155(2)$, $\text{Pd}(1)\text{-P}(2) = 2.247(9)$, $\text{Pd}(1)\text{-P}(1) = 2.256(9)$. Selected bond angles ($^\circ$): $\text{O}(1w)\text{-Pd}(1)\text{-O}(2w) = 87.14(9)$, $\text{O}(1w)\text{-Pd}(1)\text{-P}(2) = 173.89(7)$, $\text{O}(2w)\text{-Pd}(1)\text{-P}(2) = 92.74(7)$, $\text{O}(1w)\text{-Pd}(1)\text{-P}(1) = 89.29(7)$, $\text{O}(2w)\text{-Pd}(1)\text{-P}(1) = 170.96(7)$, $\text{P}(2)\text{-Pd}(1)\text{-P}(1) = 91.69(3)$.

Pd atom is located on the two-fold rotation axes and there are two independent half molecules in the crystal. The square planar Pd complex is ligated by the (*R*)-P-Phos ligand in a bidentate fashion and the other two vacancies are occupied by two water molecules in a *cis* manner. The triflates act as counteranions and are arranged disorderly in the complex. The dihedral angle of the pyridine rings of the bipyridine system in the ligand is 111.7° (6). The seven-membered heterometallacyclic ring involving the (*R*)-P-Phos ligand adopts a skew(v) boat conformation with λ absolute configuration [21,22]. It is noteworthy that two of the four phosphorus–phenyl rings oriented quasi-axially and the other two phenyl groups oriented quasi-equatorially with respect to the P(1)–Pd–P(2) plane. Since the quasi-equatorial phenyl groups are pushed toward the palladium center, it is believed that this steric requirement around the coordination sphere of the metal is responsible for the very high enantioface discrimination observed in the formation of optically active DMPS [3] (*infra vide*). The rigidity of the axially dissymmetric bipyridyl system could also be taken into account during the insertions of the styrene into a [Pd]–COOCH₃ bond [23,24].

3.2. Enantioselective bis-alkoxycarbonylation

In the preliminary study, complex **7** was used as the catalyst precursor to investigate the effects of various parameters on the conversion, chemoselectivity and enantioselectivity of **10**. Typically the reaction was carried out in 1 ml methanol at 50 °C under 152 bar CO pressure for 20 h, using 1.8 mmol styrene, 1.8×10^{-3} mmol catalyst precursor and 1.8 mmol 1,4-benzoquinone as oxidant. The reaction usually produced a mixture of dimethyl-2-phenylsuccinate (**10**), methyl cinnamate (MC) (**11**), methyl 2-phenylpropionate (**12**) and methyl 3-phenylpropionate (**13**) (MP), and other unidentified oligomeric products (Fig. 3).

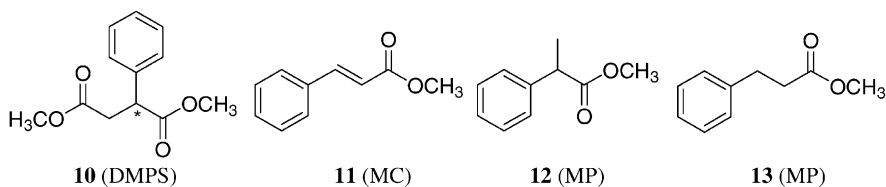


Fig. 3. Products of the bis-alkoxycarbonylation of styrene.

3.2.1. Effect of concentration of the catalyst precursor and 1,4-benzoquinone

As the loading of catalyst increased, a small improvement of the conversion of styrene to DMPS was observed. For instance, at a substrate-to-catalyst precursor ratio (S/C) of 2000, the conversion was only 24% in which only 16% were detected as the desired DMPS (Table 1, entry 1). However, the reaction occurred more readily when the catalyst loading was increased to S/C = 250 which gave 51% conversion to DMPS (Table 1, entry 5). Further increase of catalyst loading to S/C = 62.5 and concomitantly doubling the amount of BQ added saw an increase in both the styrene conversion and the yield of DMPS (entry 9). This result represents the best chemoselectivity so far reported for this reaction.

The precipitation of metallic palladium was not observed after the catalysis. No change in the conversion was noted while allowing the reaction to proceed for 44 h (Table 1, entries 3 and 5 versus entries 4 and 6), probably due to the consumption of the oxidant to re-oxidise palladium(0) formed in possible competitive reactions [25]. The general rise in the level of MC formation was resulted from the use of higher catalyst level. The enantioselectivity of DMPS was not significantly affected by varying the concentrations of the catalyst precursor and/or BQ.

3.2.2. Effect of temperature

An increase of reaction temperature brought about an increase in the catalytic activity as shown in Table 2. At 30 °C, the conversion of styrene was slow (Table 2, entry 1). A better conversion of styrene was achieved by elevating the reaction temperature from 30 °C to higher temperatures. The conversion plateaued at 70 °C and the chemoselectivity for DMPS decreased while the production of MC increased markedly proceeding from 50 to 70 °C (Table 2, entry 2 versus

Table 1
Enantioselective bis-alkoxycarbonylation of styrene using (*R*)-P-Phos as a ligand^a

Entry	[Styrene]/catalyst precursor (M/M)	[Styrene]/[BQ] (M/M)	Conv. (%) ^b	MP (%) ^{b,c,d}	MC (%) ^{b,c}	DMPS (%) ^{b,c}	e.e. DMPS (%; abs. config.) ^e
1	2000	1	24	1.9	2.2	16	88 (<i>R</i>)
2	1000	1	37	1.4	7.7	34	83 (<i>R</i>)
3	500	1	48	1.1	13	46	83 (<i>R</i>)
4 ^f	500	1	48	1.6	9.1	30	85 (<i>R</i>)
5	250	1	49	1.0	15	51	83 (<i>R</i>)
6 ^f	250	1	50	1.1	14	46	84 (<i>R</i>)
7 ^g	250	0.5	57	4.3	19	45	82 (<i>R</i>)
8 ^g	125	0.5	67	2.7	20	71	83 (<i>R</i>)
9 ^h	62.5	0.5	71	1.5	18	79	84 (<i>R</i>)

Influence of the concentration of the catalyst precursor and 1,4-benzoquinone.

^a Reaction conditions: 200 μ l styrene (1.80 mmol) in 1.0 ml CH₃OH; 195 mg [BQ] (1.80 mmol); *T* = 50 °C; *t* = 20 h; CO, 152 bar (initial pressure at room temperature).

^b The data on conversion and chemoselectivities of DMPS, MP and MC were determined by GC with an AT-1 column (25 m \times 0.25 mm i.d.) using acetophenone as the internal standard.

^c Yields based on converted styrene; the rest of the materials were unidentified oligomeric by-products.

^d Combined yields of **12** and **13**.

^e The enantiomeric excess was determined by GC with a Chrompack Chirasil-Dex CB column (50 m \times 0.25 mm i.d.).

^f *t* = 44 h.

^g 100 μ l styrene (0.9 mmol); 195 mg [BQ] (1.80 mmol).

^h 50 μ l styrene (0.45 mmol); 97 mg [BQ] (0.9 mmol).

entry 3). The DMPS enantioselectivity decreased only slightly with rising reaction temperature.

3.2.3. Effect of CO pressure

The carbon monoxide pressure did not affect the conversion to any great extent. An initial increase of the CO pressure led to a general increase of chemoselectivity for both DMPS and MC (Table 3, entries 1–5). These chemoselectivities reached a maximum at 110 bar CO pressure (Table 3, entry 5) before expe-

riencing a drop at a higher pressure (Table 3, entry 6). Notably, the enantioselectivity of DMPS also improved with increasing CO pressure.

3.2.4. Effect of different chiral catalyst precursor

The effect of various palladium(II) complexes modified by the series of the P-Phos ligands on the asymmetric bis-alkoxycarbonylation was summarized in Table 4. The introduction of more sterically encumbered groups on the diphosphine ligand gave lower

Table 2
Palladium-catalyzed enantioselective bis-alkoxycarbonylation of styrene using **7** as a ligand^a

Entry	Temperature (°C)	[Styrene]/[7] (M/M)	Conv. (%) ^b	MP (%) ^{b,c,d}	MC (%) ^{b,c}	DMPS (%) ^{b,c}	e.e. DMPS (%; abs. config.) ^e
1	30	500	27	0.32	1.0	11	86 (<i>R</i>)
2	50	500	45	1.1	11	45	83 (<i>R</i>)
3	70	500	43	2.3	20	25	78 (<i>R</i>)

Influence of reaction temperature.

^a Reaction conditions: 200 μ l styrene (1.80 mmol) in 1.0 ml CH₃OH; 195 mg [BQ] (1.80 mmol); *t* = 20 h; CO, 152 bar (initial pressure at room temperature).

^b The data on conversion and chemoselectivities of DMPS, MP and MC were determined by GC with an AT-1 column (25 m \times 0.25 mm i.d.) using acetophenone as the internal standard.

^c Eight yields based on converted styrene; the rest of the materials were unidentified oligomeric by-products.

^d Combined yields of **12** and **13**.

^e The enantiomeric excess was determined by GC with a Chrompack Chirasil-Dex CB column (50 m \times 0.25 mm i.d.).

Table 3

Palladium-catalyzed enantioselective bis-alkoxycarbonylation of styrene using **7** as a ligand^a

Entry	CO pressure (bar)	Conv. (%) ^b	MP (%) ^{b,c,d}	MC (%) ^{b,c}	DMPS (%) ^{b,c}	e.e. DMPS (%; abs. config.) ^e
1	41	31	3.9	9.5	9.8	74 (<i>R</i>)
2	55	34	2.5	17	17	78 (<i>R</i>)
3	69	36	2.5	29	25	77 (<i>R</i>)
4	83	31	2.8	18	36	81 (<i>R</i>)
5	110	28	1.3	22	54	82 (<i>R</i>)
6	152	37	1.4	7.7	34	83 (<i>R</i>)

Influence of the CO pressure.

^a Reaction conditions: 200 μ l styrene (1.80 mmol) in 1.0 ml CH₃OH; 195 mg [BQ] (1.80 mmol); *T* = 50 °C; *t* = 20 h; S/C = 1000; initial CO pressure at room temperature.^b The data on conversion and chemoselectivities of DMPS, MP and MC were determined by GC with an AT-1 column (25 m \times 0.25 mm i.d.) using acetophenone as the internal standard.^c Yields based on converted styrene; the rest of the materials were unidentified oligomeric by-products.^d The characterization of the MP products was determined by GC–MS with a SGE Bexs column (30 m \times 0.25 mm i.d.).^e The enantiomeric excess was determined by GC with a Chrompack Chirasil-Dex CB column (50 m \times 0.25 mm i.d.).

Table 4

Palladium-catalyzed enantioselective bis-alkoxycarbonylation of styrene using different chiral ligands: (*R*)-P-Phos (**1**), (*R*)-tol-P-Phos (**2**), and (*R*)-Xyl-P-Phos (**3**)^a

Entry	Catalyst precursor	Conv. (%) ^b	MP (%) ^{b,c,d}	MC (%) ^{b,c}	DMPS (%) ^{b,c}	e.e. DMPS (%; abs. config.) ^e
1	7	67	2.7	20	71	83 (<i>R</i>)
2	8	58	4.4	24	52	82 (<i>R</i>)
3	9	56	1.7	28	42	82 (<i>R</i>)

^a Reaction conditions: 100 μ l styrene (0.90 mmol) in 1.0 ml CH₃OH; 195 mg [BQ] (1.8 mmol); *T* = 50 °C; *t* = 20 h; S/C = 125; CO, 152 bar (initial pressure at room temperature).^b The data on conversion and chemoselectivities of DMPS, MP and MC were determined by GC with an AT-1 column (25 m \times 0.25 mm i.d.) using acetophenone as the internal standard.^c Yields based on converted styrene; the rest of the materials were unidentified oligomeric by-products.^d The characterization of the MP products was determined by GC–MS with a SGE Bexs column (30 m \times 0.25 mm i.d.).^e The enantiomeric excess was determined by GC with a Chrompack Chirasil-Dex CB column (50 m \times 0.25 mm i.d.).

conversions than that of the unsubstituted P-Phos (Table 4, entries 2 and 3 versus entry 1). Also reduced was the chemoselectivity for DMPS going from the original P-Phos **7** to the more hindered analogs **8** & **9**. On the other hand, gradual increase of MC formation was noticed. The steric bulk on the P-Phos derived palladium complexes had almost no influence on the enantioselectivity.

4. Conclusion

The cationic palladium complexes prepared from the P-Phos family effectively catalyzed the bis-methoxycarbonylation of styrene with moderate to good conversions and high chemoselectivities

and enantioselectivities with respect to dimethyl 2-phenylbutanedioate.

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