Systematic Study of the Asymmetric Methoxycarbonylation of Styrene Catalyzed by Palladium Systems Containing Chiral Ferrocenyl Diphosphine Ligands

by **Cyril Godard***, **Aurora Ruiz**, and **Carmen Claver***

Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, Marcelli Domingo w/n, 43007 Tarragona, Spain
(phone: +34-977-559575; fax: +34-977-559563, e-mail: cygodard@yahoo.fr or carmen.claver@urv.net)

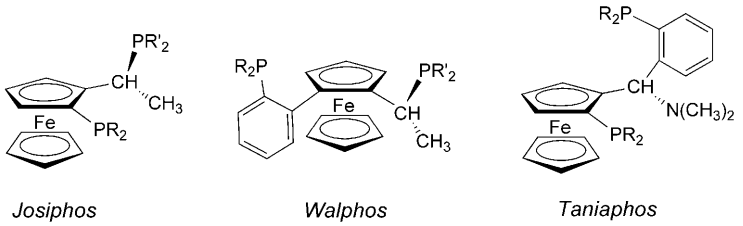
Dedicated to Professor *Giambattista Consiglio* in recognition of his contributions to enantioselective catalysis

We present the first systematic study of the Pd-catalyzed asymmetric methoxycarbonylation of styrene in the presence of chiral ferrocenyl phosphine ligands. The reaction conditions were optimized, and a screening of different catalyst precursors was performed. A number of 1,1′-bis(phosphino)ferrocenes of the *Mandyphos*, *Josiphos*, *Walphos*, and *Taniaphos* types were tested in combination with $[PdCl_2(NCPh)_2]$, in the presence of TsOH as the acid source. These systems afforded high enantioselectivities, although the regioselectivity of the reaction was found to be in favor of the (undesired) linear ester. The catalytic system made with the *Josiphos* ligand **1** gave rise to an enantiomeric excess (ee) of 86%.

Introduction. – Recently, chiral ferrocenyl phosphine ligands have been successfully used in many catalytic processes [1]. These compounds constitute a family of potentially chelating bi- or tridentate ligands, and their success is largely due to their unique structural features that allow multiple modifications by varying the properties of the substituents on the cyclopentadienyl (Cp) ligands as well as on the P-atoms. The use of ligands bearing analogous metallocenes has also been reported [2].

The prototypical ligand 1,1′-bis(diphenylphosphino)ferrocene (dppf) has been extensively used in Pd-catalyzed C–C and C–N bond-forming reactions such as cross-coupling [3], *Heck* reaction [4], carbonylation of chloro arenes [5], aryl halide amination [6], hydroamination of alkynes [7], and methoxycarbonylation of ethene [8]. High enantioselectivities were reported by *Xiao* and *Zhang* [9] for the asymmetric hydrogenation of acyclic imines with Ir ferrocene-binaphane complexes [9]. In recent years, 1,2-bis(phosphino)ferrocene has also been used in homogeneous catalysis and given rise to high enantioselectivities in various reactions. For instance, the *Solvias–Josiphos* ligands (*Fig. 1*), which combine planar chirality with the central chirality of a side group, constitute versatile ligands that can be used in a number of stereoselective processes by simply varying the substituents on the P-atoms [10]. Several related *Josiphos* ligands are being fruitfully employed in the Rh-catalyzed asymmetric hydrogenation of alkenes on industrial scale. Typically, the enantiomeric excess (ee) obtained in the hydrogenation of dimethyl itaconate (DMI) or methyl 2-acetamidoacrylate (MAA)

is in the range 90–99.9%. An industrial process based on Ru catalysts containing *Josiphos* ligands has also been developed for the large-scale production of methyl (+)-*cis*-dihydrojasmonate [11].



Josiphos *Walphos* *Taniaphos*

Fig. 1. *Selected ferrocenyl diphosphine ligands used in asymmetric processes*

Josiphos-type ligands are also the most-effective ligands for the Ir-catalyzed hydrogenation of imines, with high enantioselectivities, and turnover-frequency (TOF) values in the range of 10 to 300000 h^{-1} for aryl imines [12]. The hydrogenation of 2-methyl-6-ethylphenyl-1′-methyl-2′-methoxyethylimine to the corresponding optically enriched (80% ee) amine using a *Josiphos*-containing Ir catalyst is nowadays the largest-scale enantioselective catalytic process in industry [13], and the *Walphos* family is produced on a technical scale by *Solvias*. The nature of the active Ir species involved in this process was recently examined in detail by *Togni* and co-workers [14]. They showed by X-ray crystallography that the substrate coordinates in a κ^2 fashion to an Ir^I center.

Kagan and co-workers [15] have used *Josiphos* ligands, differing from the *Solvias–Josiphos* type by only displaying planar chirality, in the asymmetric hydrogenation of (*Z*)-α-methylacetamidocinnamate, with ee values up to 84%. These ligands were also screened in various Rh-catalyzed hydrogenation reactions affording enantioselectivities comparable to those obtained with *Solvias–Josiphos* ligands. The authors have, therefore, suggested that the planar chirality may be of major importance in chiral induction during the hydrogenation of prochiral alkenes [15]. Also, the experimental data obtained by *Hayashi* and *Kumada* [16] for *Grignard* cross-coupling reactions, when investigating the effect of the central chirality of the stereogenic C-atom of the *Josiphos* ligand, led them to the conclusion that, in these reactions, planar chirality plays the dominant role in terms of product configuration [16]. Furthermore, *Pastor* and *Togni* [17] investigated the effect of ligand chirality on the enantio- and diastereoselectivity of the reaction using (*R*,*S*)-, (*S*,*S*)-, and *(S*,*R*)-configured *Josiphos* ligands; they concluded that planar and central chirality might act either in a cooperative or in a non-cooperative way, and that, therefore, both stereogenic elements are important [17].

The *Walphos* ligands (*Fig. 1*) were also used successfully in various homogeneous asymmetric hydrogenation reactions [18]. In particular, the formation of (*R*)-2-alkyl-3-phenylpropanoic acid from the corresponding prochiral alkene was achieved in 95% ee and 100% yield with a Rh catalyst formed *in situ* in the presence of a *Walphos* diphosphine ($R = C_6H_5$, $R' = 3,5\text{-}(CF_3)_2\text{–}C_6H_3$) [19]. These ligands differ from the *Josiphos* compounds by a C_6H_4 spacer between a Cp ring and a P-atom. Thus, the coordination of both P-atoms would lead to the formation of eight-membered metalla rings.

Eight-membered chelates are also formed with the *Taniaphos* ligands (*Fig. 1*), which display a stereogenic center between a Cp ring and a C_6H_4 spacer, in addition to the planar chirality. These diphosphines have been shown to be particularly efficient in Rh-catalyzed hydrogenation reactions of functionalized C=C bonds in alkenes, β-keto esters, 1,3-diketones, and hydrazones [11b].

Such ligands were also used in carbonylation processes. Rh-catalyzed hydroformylation of styrenes was reported using *Solvias–Josiphos* diphosphines, with ee values of up to 76% [20]. In these systems, both activity and selectivity were shown to be affected by the phosphorus substituents. The highest ee values were, in this case, obtained with diphenyl-alkyldiaryl diphosphines. *Van Leeuwen* and co-workers [20] also reported the use of Rh systems with chiral ferrocenyl diphosphines for this process (*Fig. 2*). However, relatively low yields and regioselectivities were obtained, although both TOF and ee values could be improved with electron-withdrawing groups on the P-atoms [21].

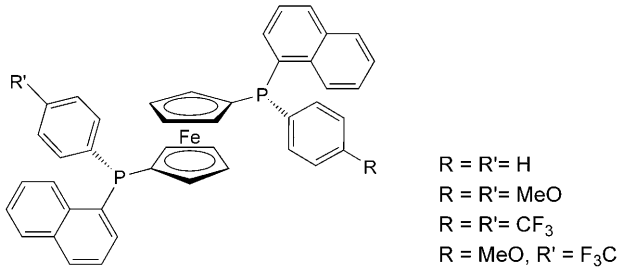
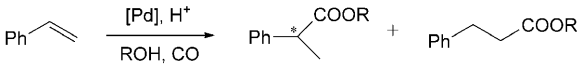


Fig. 2. *Chiral ferrocenyl diphosphine ligands used in the asymmetric hydroformylation of styrene*

The asymmetric Pd-catalyzed methoxycarbonylation of vinyl arenes has been extensively studied as a route to 2-arylpropanoic acids (*Scheme*), the most-important class of non-steroidal anti-inflammatory drugs [22]. Catalysts containing bidentate diphosphine ligands have been frequently used for this transformation, but generally give rise to relatively low regioselectivities of the branched product, despite good enantioselectivities [23]. With systems containing bidentate diphosphines, the regioselectivity of the reaction was shown to vary dramatically with the length of the carbon chain separating the two P-atoms [24]. Nevertheless, the highest ratio of branched to linear ester are usually obtained with monophosphine-based systems, although these generally afford low enantioselectivities [25].

Scheme. *Palladium-Catalyzed Methoxycarbonylation of Styrene*



Recently, a few successful chiral systems have been reported for the asymmetric methoxycarbonylation of styrene with 1,1′-bis(phosphino)ferrocene ligands (*Fig. 3*) [26]. Using an oxazoline-substituted diphosphine (*Fig. 3*, *a*), *Wang et al.* [26b] obtained

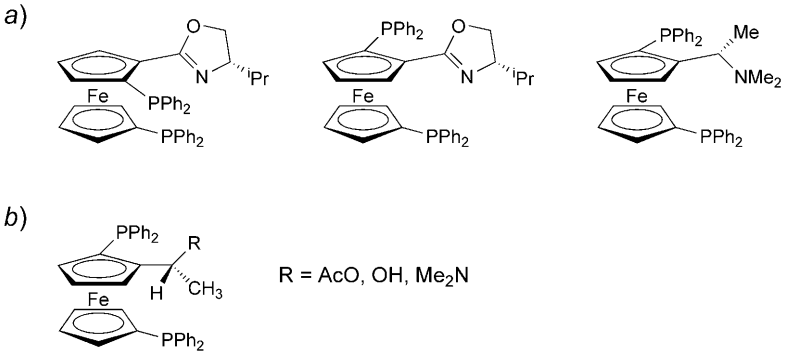


Fig. 3. *Ferrocenyl diphosphine ligands used by* a) Wang *and co-workers* [26b] *and* b) Inoue *and co-workers* [26a]

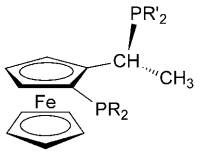
40% of the branched ester and 64% ee, while *Inoue* and co-workers [26a] reported 44% regioselectivity for the branched product with 86% ee for $R = (Me)_2N$ (*Fig. 3*, *b*).

In this paper, we report a study on the catalyzed methoxycarbonylation of styrene (*Scheme*) with the aid of Pd^{II} and Pd^0 precursors and *Solvias*-type ferrocenyl-1,2- and ferrocenyl-1,1′-diphosphine ligands. These ligands can be classified in four distinct families: *Josiphos* (**1**–**5**), *Mandyphos* (**6**), *Walphos* (**7** and **8**), and *Taniaphos* (**9** and **10**). Optimization of the reaction conditions and comparison of the performance of various Pd precursors were performed with ligand **1**. The results of the Pd-catalyzed methoxycarbonylation of styrene are discussed, and a comparison of the rate of conversion and selectivity as a function of the different types of ligands is made.

Experimental. – 1. *General.* All reactions were carried out in dried and distilled solvents under N_2 atmosphere using standard *Schlenk* techniques. The catalyst precursor $[PdCl_2(NCPh)_2]$ was prepared according to [27]. Compounds $[PdCl_2]$, $[Pd_2(dba)_3]$, $[Pd(acac)_2]$, and $[Pd(OAc)_2]$ were purchased from *Johnson Mattey*, and used without further purification. The diphosphine ligands were offered by *Solvias*. Carbonylation reactions were performed in a 100-ml stainless-steel *Bergof* autoclave magnetically stirred and electrically heated. Other chemicals and solvents were purchased from commercial sources and used without further purification, unless otherwise stated. Carbon monoxide (CO; 99.99%) was supplied by *Air Liquide*. All NMR measurements were performed on *Varian Mercury VX-400* or *Varian Gemini-300* spectrometers in 5-mm triple or 10-mm high-pressure tubes. High-pressure experiments were carried out in a 10-mm sapphire tube; chemical shifts δ (in ppm) for ^1H- and ^{13}C-NMR rel. to residual solvent signals, coupling constants J in Hz. ^{31}P-NMR Chemical shifts were referenced to H_3PO_4 as external standard. Elemental analyses were carried out on a *Carlo Erba Microanalyser EA-1108*. The chemical and regioselectivity of reactions were determined by gas-chromatographic (GC) analyses on a *Hewlett–Packard 5890A* instrument (split/splitless injector, *J&W Scientific*; *Ultra-2* 25-m column, i.d. 0.2 mm, film thickness 0.33 mm; 150 kPa He as carrier gas; FID detector) equipped with a *Hewlett-Packard 3396* series-II integrator. The enantiomeric excess (ee) was determined by HPLC analysis (*Daicel CHIRACEL OJ*; hexane/i-PrOH 95 : 5, 1.5 ml min^{-1}).

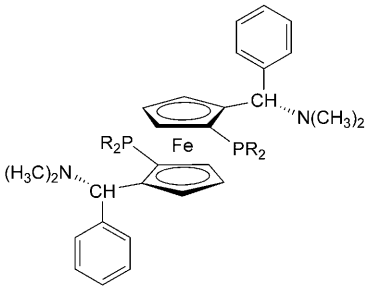
2. *Typical Procedure for Methoxycarbonylation Reactions.* A mixture of THF/MeOH 1 : 1 (5 ml) containing the Pd precursor, the appropriate diphosphine, and the acid was prepared under N_2 atmosphere using *Schlenk* techniques. Immediately after addition of the substrate, the soln. was introduced into the evacuated autoclave by aspiration, and then heated and pressurized with CO. After 24 h, the autoclave was cooled and slowly depressurized. After separation by column chromatography (CC), the obtained soln. was analyzed by GC, and the ee was determined by HPLC.

Josiphos



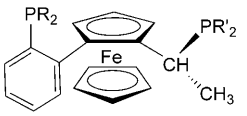
1 R = C_6H_5, R'= 3,5-Me_2-C_6H_3
2 R = R' = C_6H_{11} (Cy)
3 R = C_6H_5, R' = *t*-Bu
4 R = C_6H_5, R' = C_6H_{11}
5 R = Et, R' = *t*-Bu

Mandyphos



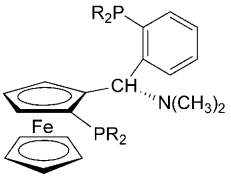
6 R = Ph

Walphos



7 R = C_6H_5, R' = 3,5-$(CF_3)_2$-C_6H_3
8 R = R' = C_6H_5

Taniaphos



9 R = C_6H_5
10 R = C_6H_{11}

3. *Synthesis of Pd Complexes*[1]). 3.1. *Synthesis of Neutral Complexes of the type [$PdCl_2$(P–P′)]* ([P–P′ = **1**, **9**, **10**). The appropriate ligand (1.1 equiv.) in toluene (10 ml) was added to a soln. of [$PdCl_2$(NCPh)$_2$] at r.t., and the mixture was stirred for 1 h. During this time, the color of the soln. changed from dark-yellow to bright-orange. The volume of the soln. was then reduced to *ca.* 5 ml, and the product was precipitated by addition of hexane. The resulting solid was filtered, washed with several fractions of hexane, and dried under vacuum.

*Data of [$PdCl_2$(**1**)]*. Yield: 91%. ^{1}H-NMR ($CDCl_3$): 3.61 (*s*, η^5-C_5H_5); 4.00 (br., 1 H of η^5-C_5H_3); 4.35 (br., 1 H of η^5-C_5H_3); 4.42 (br., 1 H of η^5-C_5H_3); 3.66 (*m*, MeC*H*); 0.99 (*dd*, *J*(H,H) = 7, *J*(P,H) = 13, *Me*CH); 2.18 (*s*, 2 Me of Tol); 2.41 (*s*, 2 Me of Tol); 7.0–8.1 (16 arom. H). ^{31}P{^{1}H}-NMR ($CDCl_3$): 16.4 (*d*, *J*(P,P) = 18, PPh_2); 47.85 (*d*, *J*(P,P) = 18, P(Tol)$_2$). ^{13}C{^{1}H}-NMR ($CDCl_3$): 125–140 (arom. signals); 20.8 (*d*, *J*(P,C) = 2, *Me*CH); 33.5 (*dd*, *J*(PC) = 28, 7, Me*C*H); 71.5 (*s*, η^5-C_5H_5); 68.8 (*d*, *J*(P,C) = 11, η^5-C_5H_3); 70.2 (*d*, *J*(P,C) = 7, η^5-C_5H_3); 71.8 (*dd*, *J*(P,C) = 6, 7, η^5-C_5H_3); 74.7 (*d*, *J*(P,C) = 4, η^5-C_5H_3); 93.5 (*dd*, *J*(P,C) = 18, 4, η^5-C_5H_3); 22.2 (*s*, Me of Tol); 22.4 (*s*, Me of Tol). Anal. calc. for $C_{40}H_{40}Cl_2FeP_2Pd$: C 58.89, H 4.94; found: C 58.68, H 5.58.

*Data of [$PdCl_2$(**9**)]*. Yield: 87%. ^{1}H-NMR ($CDCl_3$): 2.35 (*s*, Me_2N); 3.40 (br., 1 H of η^5-C_5H_3); 4.47 (br., 1 H of η^5-C_5H_3); 4.64 (*s*, η^5-C_5H_5); 5.01 (br., 1 H of η^5-C_5H_3); 5.54 (*s*, Me_2NC*H*); 6–8 (arom. H). ^{31}P{^{1}H}-NMR ($CDCl_3$): 17.0 (*s*, Ph_2P–Fc); 23.9 (*s*, Ph_2P–C_6H_4). ^{13}C{^{1}H}-NMR ($CDCl_3$): 21.7 (*s*, Me_2*C*H); 44.0 (*s*, *Me*$_2$NCH); 62.75 (*d*, *J*(P,C) = 12, η^5-C_5H_3); 69.75 (*d*, *J*(P,C) = 6, η^5-C_5H_3); 71.3 (*d*, *J*(P,C) = 8, η^5-C_5H_3); 72.6 (*s*, η^5-C_5H_5); 76.2 (*d*, *J*(P,C) = 2, η^5-C_5H_3); 96.95 (*d*, *J*(P,C) = 14, η^5-C_5H_3), 120–145 (30 arom. C). Anal. calc. for $C_{43}H_{38}Cl_2FeP_2Pd$: C 59.71, H 4.55, N 1.62; found: C 59.64, H 4.90, N 1.72.

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[1]) Abbreviations: Cy, cyclohexyl; Fc, ferrocenyl; P–P′, diphosphine ligands (see chemical formulae); Tol, tolyl; Ts, tosyl (= (4-methylphenyl)sulfonyl).

*Data of [$PdCl_2$(**10**)]*. Yield: 76%. ^{1}H-NMR ($CDCl_3$): 0–3.5 (P–Cy); 2.74 (*s*, Me_2N); 4.34 (*s*, 1 H of η^5-C_5H_3); 4.42 (*s*, 1 H of η^5-C_5H_3); 4.57 (*s*, η^5-C_5H_5); 4.61 (*s*, NH); 5.0 (*s*, 1 H of η^5-C_5H_3); 7–8 (P–C_6H_4). ^{31}P{^{1}H}-NMR ($CDCl_3$): 24.8 (*s*); 41.1 (*s*). ^{13}C{^{1}H}-NMR ($CDCl_3$): 0–50 (P–Cy); 63.8 (*d*, *J*(P,C) = 7.55, η^5-C_5H_3); 67.9 (*d*, *J*(P,C) = 7.8, η^5-C_5H_3); 68.45 (*d*, *J*(C,P) = 39.6, η^5-C_5H_3); 72.2 (*s*, η^5-C_5H_5); 73.1 (*s*, η^5-C_5H_3); 73.65 (*s*, η^5-C_5H_3); 120–145 (C_6H_4). Anal. calc. for $C_{43}H_{63}Cl_2FeNP_2Pd$: C 58.09, H 7.14, N 1.58; found: C 57.7, H 9.13, N 1.76.

3.2. *Synthesis of [Pd(**1**)(TsO)(H_2O)]$^+$TsO$^-$*. Prepared according to [2]. To a soln. of [$PdCl_2$(**1**)] (100 mg, 0.12 mmol) in CH_2Cl_2 (15 ml) was added TsOAg (72 mg, 0.25 mmol) at r.t. The mixture was stirred overnight, filtered through a short column of *Celite*, and concentrated under vacuum. Addition of Et_2O led to the precipitation of the crude title complex as an orange solid, which was washed with Et_2O and dried. Yield: 35%. ^{1}H-NMR ($CDCl_3$): 1.47 (*dd*, *J*(P,H) = 15, *J*(H,H) = 7, *Me*CH); 2.03 (*s*, 6 H, $Me_2C_6H_3$); 2.23 (*s*, 6 H, $Me_2C_6H_3$); 2.31 (*s*, Me of Ts); δ 3.97 (*s*, η^5-C_5H_5); 4.12 (*s*, 1 H of η^5-C_5H_3); 4.47 (*s*, 1 H of η^5-C_5H_3); 4.85 (*s*, 1 H of η^5-C_5H_3); 5.03 (very br., MeC*H*); 6.5–8.5 (16 arom. H). ^{31}P{^{1}H}-NMR ($CDCl_3$): 15.1 (*d*, *J*(P,P) = 12); 50.3 (*d*, *J*(P,P) = 12). ^{13}C{^{1}H}-NMR ($CDCl_3$): 120–150 (24 arom. C); 91.6 (*dd*, *J*(P,C) = 17, 4, η^5-C_5H_3); 73.1 (*s*, η^5-C_5H_3); 72.25 (*m*, η^5-C_5H_3); 72.1 (*s*, η^5-C_5H_5); 70.8 (*dd*, *J*(P,C) = 8, 3, η^5-C_5H_3); 70.35 (*d*, *J*(P,C) = 9, η^5-C_5H_3); 30.9 (*d*, *J*(P,C) = 28, Me*C*H); 21.55 (*s*, Me of Ts); 21.4 (*s*, 2 Me_2Ph); 21.43 (*s*, 2 Me_2Ph).

Results. – *Synthesis.* The Pd^{II} precursors [$PdCl_2$(**1**)], [$PdCl_2$(**9**)], and [$PdCl_2$(**10**)] were obtained by reaction between the bis(benzonitrile) complex [$PdCl_2(NCPh)_2$] and the corresponding diphosphine ligand in toluene at room temperature. Similarly, reaction of [$PdCl_2$(**1**)] with TsOAg yielded the cationic complex [Pd(**1**)(H_2O)(OTs)]$^+$TsO$^-$ after precipitation with Et_2O. These new complexes were characterized by multinuclear NMR spectroscopy and elemental analysis (see *Experimental*). The '*in situ*' catalytic systems for the methoxycarbonylation reaction were prepared under N_2 atmosphere in THF/MeOH 1:1 containing the catalyst precursor, the appropriate diphosphine ligand, and the acid.

Optimization of Reaction Conditions for the System [$PdCl_2(NCPh)_2$] and Ligand **1**. The catalytic conditions were first optimized for 0.15 μmol of [$PdCl_2(NCPh)_2$] and TsOH as the source of acid. The reactions were carried out in THF/MeOH 1:1 over 24 h. In *Table 1*, the conversion, the regioselectivity (percentage of branched *vs.* linear esters), the chemoselectivity (formation of acids instead of esters), and the enantiomeric excess (ee) and configuration of the desired branched esters are collected.

When the reaction was performed with a 10-fold excess of acid to Pd precursor at a CO pressure of 30 bar and at 50° (*Entry 1* in *Table 1*), no reaction products could be detected. Increasing the temperature to 90° (*Entry 2*) resulted in a conversion of 11%, with the expected linear and branched esters as the only reaction products. The regioselectivity of the reaction was in favor of the linear ester (78%), and a moderate ee value of 57% was obtained under these conditions. When a 100-fold excess of TsOH was used at 100° (*Entry 3*), the conversion increased to 59%, but the presence of 13% of byproducts (acids) was detected, the regioselectivity being slightly lowered (16% of branched product). When the temperature was increased to 150°, a 78% conversion was achieved, with a chemoselectivity of 75%. The regioselectivity remained basically constant (15% branched), and 86% ee was observed under these conditions. An increase in CO pressure to 50 bar (*Entry 5*) resulted in a conversion of 94%, with the regio- and chemoselectivities remaining unchanged (15 and 76%, resp). However, in this case, the ee decreased to 70%. When CF_3CO_2H was used as the acid (*Entry 6*), the conversion and enantioselectivity of the reaction decreased to 48 and 55%, respec-

Table 1. *Methoxycarbonylation of Styrene with [$PdCl_2(NCPh)_2$] and Ligand* **1** (see *Scheme*). Conditions: 0.15 μmol [$PdCl_2(NCPh)_2$] and 1.1 equiv. of **1** in THF/MeOH 1:1 (5 ml), 1 mol-% of Pd rel. to styrene, 24 h.

Entry	T [°]	P_{CO} [bar]	TsOH/Pd	Conversion	Regiosel. [%][a])		Chemosel. [%][b])	ee [%] (Config.)
					B	L		
1	50	30	10	0	–	–	–	–
2	90	30	10	11	22	78	100	57 (*S*)
3	100	30	100	59	16	84	87	–
4	150	30	100	78	15	85	75	86 (*S*)
5	150	50	100	94	15	85	76	70 (*S*)
6	150	30	100[c])	48	21	79	100	55 (*S*)

[a]) Regioselectivity: branched (B) *vs.* linear (L) ester. [b]) Chemoselectivity: percentage of main ester products rel. to acid side products. [c]) CF_3CO_2H was used instead of TsOH.

tively. However, the regioselectivity was slightly higher (21% branched) than when TsOH was used, and the chemoselectivity of the reaction was 100% (no side products).

In view of these results, the reaction conditions used in *Entry 4*, providing high ee values, were considered to be convenient for this study, and were used for the experiments described in the following sections. In order to compare the activities of different Pd precursors, the reaction was repeated under the conditions described in *Entry 4* using Pd^{II} and Pd^0 precursors in the presence of the diphosphine **1**.

Effect of Palladium Precursor. In *Table 2*, the conversion, and the regio-, chemo-, and enantioselectivities for the methoxycarbonlyation of styrene in the presence of the precursor catalysts [$PdCl_2(NCPh)_2$], [$Pd(OAc)_2$], [$Pd(acac)_2$], and [$Pd_2(dba)_3$] are compared. In the case of [$Pd_2(dba)_3$], the reaction was also run in the absence of TsOH to find out whether MeOH could also act as a source of H^+ under these conditions. In general, the conversions were between 72 and 83% after 24 h. The highest conversions and regioselectivities were obtained with the Pd^0 precursor [$Pd_2(dba)_3$] (*Entry 5* in *Table 2*), while the lowest was observed for [$Pd(acac)_2$] (*Entry 4*). However, when [$Pd_2(dba)_3$] was used in the *absence* of TsOH (*Entry 6*), no reaction products could be detected.

Entry 3 in *Table 2* shows the product distribution of the reaction after 45 instead of 24 h, using [$Pd(OAc)_2$] as precursor. When compared with the results of *Entry 2*, very small variations were observed. Indeed, the conversion was found to only increase by 5% (from 82 to 87%). Neither the regio- nor the enantioselectivity of the reaction was significantly affected over the extra 21 h, but the chemoselectivity decreased from 46 to 40%.

The regioselectivity of the reaction was found to be in the range 13–20% with the above Pd precursors. The highest regioselectivity (highest yield of branched ester) was obtained with [$Pd_2(dba)_3$] (*Entry 5*). However, the chemoselectivity was found to vary between 46 and 75%, depending on the precursor used. The dichloride complex (*Entry 1*) afforded the highest ratio of ester, while, in the case of [$Pd_2(dba)_3$] and $Pd(acac)_2$ (*Entries 4* and *5*, resp.), less than 60% of the products were esters. In the case of [$Pd(OAc)_2$], the major product was the carboxylic acid rather than the ester.

Table 2. *Variation of Catalyst Precursor in the Methoxycarbonylation of Styrene in the Presence of* **1** *and TsOH*. Conditions: 0.15 μmol $[PdCl_2(NCPh)_2]$ and 1.1 equiv. of **1** in THF/MeOH 1:1 (5 ml), 1 mol-% of Pd rel. to styrene, $T = 150°$, $P_{CO} = 30$ bar, TsOH/Pd 100:1, 24 h.

Entry	Precursor	Conversion [%]	Regiosel. [%][a])		Chemosel. [%][b])	ee [%] (Config.)
			B	L		
1	$[PdCl_2(NCPh)_2]$	78	15	85	75	86 (*S*)
2	$[Pd(OAc)_2]$	82	14	86	46	52 (*S*)
3[c])	$[Pd(OAc)_2]$	87	16	84	40	55 (*S*)
4	$[Pd(acac)_2]$	72	13	87	58	55 (*S*)
5	$[Pd_2(dba)_3]$	83	20	80	56	59 (*S*)
6[d])	$[Pd_2(dba)_3]$	0	–	–	–	–

[a]) Regioselectivity: branched (B) *vs.* linear (L) ester. [b]) Chemoselectivity: percentage of main ester products rel. to acid side products. [c]) Reaction time 45 h. [d]) Without TsOH.

In terms of enantioselectivity, the highest ee value (86%) was obtained with $[PdCl_2(NCPh)_2]$ (*Entry 1*). When the other precursors were used, the ee reached 50–60%. In view of these results, $[PdCl_2(NCPh)_2]$ seems to be the catalyst precursor of choice for the methoxycarbonylation of styrene under these conditions.

Effect of Phosphine Ligand. Next, we compared the effect of the different ligands **1**–**10** on the methoxycarbonylation of styrene with the catalytic system $[PdCl_2(NCPh)_2]$ and ligands **1**–**10** (*Table 3*). The conversion was 58–79%, depending on the ligand. The highest value was achieved with **4** (79% conversion), although very similar values were obtained for the diphosphines **1**, **8**, and **9**. The percentage of branched ester formed during the reaction was found to vary between 15 and 31%, the most-selective system favoring the ester comprising ligand **6**. The formation of 2-phenylpropanoic acid as a side product varied between 17 and 41%, the lowest amount being produced with **1** and **9** (75%), when 1.1 equiv. of the ligand was used relative to Pd. With ligands **5** and **6**, less than 60% of the products were esters. However, when the ratio **6**/Pd was changed from 1:1.1 to 1:2.2, a better chemoselectivity was achieved (83 instead of 59%; *Entries 6* and *7*). The ee values obtained ranged from 44% (for **6**) to 86% (for **1**).

Within the series of the *Josiphos* ligands **1**–**5**, significant variations in the catalytic results were observed (*Entries 1* to *5* in *Table 3*). The system containing the diphosphine **1** (*Entry 1*) gave the highest conversion (78%), chemoselectivity (75%), and ee (86%). The generally modest regioselectivity (15%) obtained during the reaction was very similar to that obtained with the other ligands of this type (15–19% of branched product).

The *Mandyphos*-type ligand **6** yielded a relatively low conversion (58%; *Entry 6*), but the use of a higher ligand-to-metal ratio increased the conversion to 73% (*Entry 7*). In terms of regioselectivity, the reactions carried out in the presence of 1.1 equiv. of **6** (*Entry 6*) yielded 31% of branched product. The use of 2.2 equiv. of **6** lowered the regioselectivity of the reaction (23% branched). The ee values obtained with this ligand were moderate (44 and 47%).

When the ligands of the *Walphos* type were used (**7** and **8**), conversions of 78 and 75% were obtained, with 62 and 75% chemoselectivity, respectively, and with 16% of branched product. A high ee value (73%) was also obtained with ligand **8**. In con-

Table 3. *Variation of Ligand in the Methoxycarbonylation of Styrene in the Presence of [$PdCl_2(NCPh)_2$] and TsOH.* Conditions: 0.15 μmol [$PdCl_2(NCPh)_2$] and 1.1 equiv. of ligand in THF/MeOH 1:1 (5 ml), 1 mol-% of Pd rel. to styrene, $T = 150°$, $P_{CO} = 30$ bar, TsOH/Pd 100:1, 24 h.

Entry	Ligand	Conversion [%]	Regiosel. [%][a])		Chemosel. [%][b])	ee [%] (Config.)
			B	L		
1	**1**	78	15	85	75	86 (*S*)
2	**2**	61	17	83	74	62 (*S*)
3	**3**	70	15	85	67	51 (*S*)
4	**4**	79	17	83	72	77 (*S*)
5	**5**	72	19	81	57	45 (*S*)
6	**6**	58	31	69	59	47 (*S*)
7[c])	**6**	73	23	77	83	44 (*S*)
8	**7**	78	16	84	62	52 (*S*)
9	**8**	75	16.5	83.5	75	73 (*S*)
10	**9**	65	28	72	72	63 (*S*)
11	**10**	64	25	75	70	62 (*S*)

[a]) Regioselectivity: branched (B) *vs.* linear (L) ester. [b]) Chemoselectivity: percentage of main ester products rel. to acid side products. [c]) With 2.2 (instead of 1.1) mol-equiv. of **6** rel. to Pd.

trast, conversions obtained in the presence of the *Taniaphos* compounds **9** and **10** were moderate (65 and 62%, resp.).

Comparison with Isolated Complexes. In *Table 4*, a comparison is made for the methoxycarbonylation of styrene in the presence of isolated neutral and cationic Pd precursors. Here, the conversions were 70–93%. The highest value (93% conversion) was obtained with [$PdCl_2$(**9**)]. The highest regioselectivity was achieved with the *Taniaphos*-type ligand **10** (23% branched, *Entry 3* in *Table 4*). The chemoselectivity of the reaction was found to vary between 53 (*Entry 1*) and 91% (*Entry 2*). In terms of enantioselectivity, the highest ee value (70%) was obtained with [$PdCl_2$(**1**)] (*Entry 1*). The lowest ee (52%) was found for the system containing ligand **8**.

Table 4. *Methoxycarbonylation of Styrene Using Isolated* (neutral and cationic) *Complexes.* Conditions: 0.15 μmol [$PdCl_2(NCPh)_2$] and 1.1 equiv. of ligand (**1**, **9**, or **10**) in THF/MeOH 1:1 (5 ml), 1 mol-% of Pd rel. to styrene, $T = 150°$, $P_{CO} = 30$ bar, TsOH/Pd 100:1, 24 h.

Entry	Complex	Conversion [%]	Regiosel. [%][a])		Chemosel. [%][b])	ee (%) (Config.)
			B	L		
1	[$PdCl_2$(**1**)]	72	15	85	53	70 (*S*)
2	[$PdCl_2$(**9**)]	93	20	80	91	64 (*S*)
3	[$PdCl_2$(**10**)]	86	23	77	71	59 (*S*)
4	[Pd(**1**)(TsO)(H_2O)]$^+$(TsO)$^-$	86	13	87	67	62 (*S*)

[a]) Regioselectivity: branched (B) *vs.* linear (L) ester. [b]) Chemoselectivity: percentage of main ester products rel. to acid side products.

Discussion. – *Reaction Conditions.* Some 15 μmol of $[PdCl_2(NCPh)_2]$ and 1.1 equiv. of ligand **1** were reacted in THF/MeOH 1:1 (for solubility reasons) over 24 h to optimize the reaction conditions (*Table 1*). With TsOH as the acid source, a 100-fold excess of acid was necessary to achieve conversions >50%, together with a temperature of 100° and a CO pressure of 30 atm. Increasing the temperature to 150° led to an increase in conversion to 78%, with an ee of 86%. The necessity of elevated temperature and a large excess of acid could be attributed to the high stability of the $[PdCl_2(P-P')]$ complexes formed *in situ*, which are thought to lead to the production of an active species in the presence of acid [28]. However, other reasons cannot be discarded.

The regioselectivity of the reaction was constant (*ca.* 15% of branched ester) when the temperature was above 90°. At lower temperatures, a higher proportion of desired branched product was obtained, but the conversion was poor. Hence, the formation of the branched ester is favored at lower temperature, reaching a constant value above 90°. Under otherwise identical conditions, the use of CF_3COOH as the acid source gave rise to a conversion of 48%, with an ee of 55%, and the regioselectivity increased to 21% in favor of the branched product. The lower conversion observed could be rationalized by the weaker acidity of the medium. However, the variations in regio- and enantioselectivity indicate that the counter-ion may also influence the selectivity of the reaction. Such an effect had previously been observed [20].

Finally, when the CO pressure was increased to 50 atm, the conversion was found to be >90%; however, the ee was only 70%. This decrease in chiral induction at higher CO pressure (*Entry 4 vs. 5* in *Table 1*) had been reported before in an alkoxycarbonylation [29].

Effect of Catalyst Precursor. The results obtained with $[Pd(OAc)_2]$, $[Pd(acac)_2]$, and $[Pd_2(dba)_3]$ as catalyst precursors were similar to those previously obtained with $[PdCl_2(NCPh)_2]$ in terms of conversion (*ca.* 80%) and regioselectivity (*ca.* 15%; *Table 2*). However, only $[PdCl_2(NCPh)_2]$ afforded a high enantioselectivity (86%); other precursors yielded ee values <60%. The production of side products (acids) was also minimized with the Pd^{II} bis(benzonitrile) complex.

To probe the potential formation of active species from a Pd^0 precursor and MeOH, the reaction was also run with $[Pd_2(dba)_3]$ in the absence of TsOH (*Entry 6* in *Table 2*). However, no products were detected after 24 h. Hence, we conclude that a stronger acid is required for the formation of active species from $[Pd_2(dba)_3]$ under these conditions.

The catalytic conditions used by the groups of *Inoue* and *Wang*, using ferrocenyl 1,1′-diphosphine ligands, were fairly different from those found to be best in our system. *Wang* and co-workers [26b] used $[PdCl_2]$/TsOH at 50° and 170 atm of CO. *Inoue* and co-workers [26a] achieved 86% ee under formation of 44% of branched product using the system $[Pd(OAc)_2]$/TsOH at room temperature and 20 atm CO. This latter result was, however, obtained with a lower substrate/Pd ratio, and the conversion to the esters was only 17% after 20 h.

Effect of Ligand. The highest conversions after 24 h were obtained for the systems containing the *Josiphos* ligands **1** and **4**, as well as the *Walphos* diphosphines **7** and **8** (*Table 3*), with values >75%. Ligands **1** and **4** both contain a Ph_2P unit reducing their electron-donating properties. When compared to other ligands from the *Josiphos* family, compounds **3** and **5** gave rise to a conversion of *ca.* 70%, while the more-basic

ligand **2**, containing two $(Cy)_2P$ units, was the least active (61%). The *Walphos* ligands, containing either two unsubstituted Ph_2P fragments (**8**), or one Ph_2P and one [3,5-$(CF_3)_2$–$C_6H_3]_2P$ unit (**7**), both effected high conversions, suggesting a small influence of the electron-withdrawing CF_3 groups. Like the *Walphos* ligands, the diphosphines from the *Taniaphos* family (**9** and **10**) also contain an aromatic spacer between a Cp ring and one P-atom, further separated by an alkyl group substituted with a Me_2N unit. These two ligands both gave rise to conversions of *ca.* 65%, without a significant effect of the R_2P substituents (R = Ph or Cy). When 1.1 equiv. of **6** was used, only 58% of styrene was consumed after 24 h.

Under the conditions used in this study, the 1,2-bis(phosphino)ferrocene ligands **1**–**5** and **7**–**10** gave rise to higher conversions than the 1,1′-bis(phosphino)ferrocene **6**. However, as only one ligand of the latter type was probed in this study, no clear conclusion can be drawn.

The use of ligand **6** yielded the highest regioselectivity in terms of branched ester (31%). Interestingly, 2.2 equiv. of this ligand resulted in an increase of the conversion and chemoselectivity, but also to a decrease in regioselectivity (23%). The formation of complexes containing more than one diphosphine ligand being sterically more hindered and, thus, favoring the formation of the *linear* ester, might rationalize the observed variations in the final product distribution. The systems containing ligands from the *Taniaphos* family (*Entries 10* and *11* in *Table 3*) also afforded regioselectivities of >25% (branched ester), independently of the nature of the substituents R of the R_2P units. The systems containing the *Josiphos* and *Walphos* ligands, **1**–**5** and **7**–**8**, respectively, afforded the lowest regioselectivities, although some of them yielded the highest ee values (*Entries 1*, *4*, and *9*). In an opposite manner, the most-regioselective system, generated with **6**, afforded the lowest ee value (47%) across the series.

Within each family of ligands, the variation in the nature of the R_2P units yielded substantial variations in the final ee values. In the *Josiphos* family, the ee changed from 45 to 86%. The system containing ligand **1**, which contains two $(Ar)_2P$ units, yielded the highest ee value. However, the replacement of these groups by more-electron-donating substituents such as Cy, *t*-Bu, or Et led to a decrease in ee. The effect of the steric hindrance induced by these substituents on the chiral input involved in the catalytic process was not clearly indicated here. The *Walphos* ligands **7** and **8**, which differ by the presence or absence of two *meta*-positioned CF_3 substituents on the two phenyl rings attached to one of the two P-atoms, respectively, gave rise to ee values of 52 and 73%, respectively. The presence of these electron-withdrawing groups, thus, resulted in a decrease of enantioselectivity by *ca.* 20%.

When the *isolated* neutral complexes [$PdCl_2$(**1**)], [$PdCl_2$(**9**)], and [$PdCl_2$(**10**)] were used as catalyst precursors in the asymmetric methoxycarbonylation of styrene, the results differed considerably from those obtained by the *in situ* method (*Table 4*). Especially, higher conversions were obtained with the isolated compounds. The regioselectivities, however, were hardly affected. The ee values obtained were found to be equal or slightly inferior to those obtained with the *in situ* method. This could be due to the presence of a small excess of ligand in case of the *in situ* method.

Finally, the use of the cationic complex [Pd(**1**)(H_2O)(TsO)]$^+$TsO$^-$, when compared with the neutral complex [$PdCl_2$(**1**)], yielded a higher conversion and chemoselectivity,

but a slightly reduced ee value, the regioselectivity of the reaction remaining almost unchanged (*ca*. 15% of branched product).

Conclusions. – We have reported a systematic study on the Pd-catalyzed asymmetric methoxycarbonylation of styrene using chiral 1,2-bis(phosphino)ferrocene ligands. The precursors used for the catalytic reactions, either isolated $[Pd^{II}Cl_2]/(P-P')$ complexes or '*in situ*' $[PdCl_2(NCPh)_2]/P-P'$ systems, were found to be efficient catalysts. Although the regioselectivity of the reaction was largely in favor of the (undesired) linear ester, high conversion and high enantiomeric excess (up to 86% with the *Josiphos* ligand **1**) were achieved. Investigations into the mechanism involved in this reaction by means of high-pressure NMR techniques are currently in progress and will be reported in due course.

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