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Highly regioselective palladium-catalyzed methoxycarbonylation of styrene using chiral ferrocene- and biphosphole-based ligands

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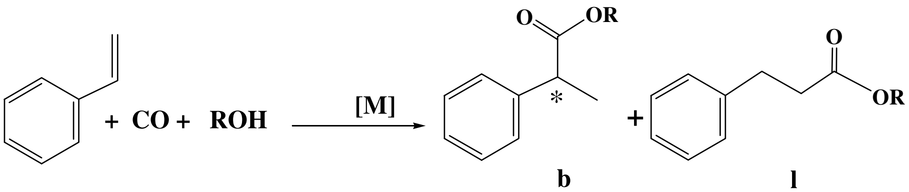
ABSTRACT

The methoxycarbonylation of styrene has been studied using $Pd(OAc)_2$/L/acid catalytic systems with L being chiral ferrocene- and biphosphole-based ligands. Good activities are obtained in mild conditions. Chemoselectivities and regioselectivities (up to 98% in favour of the branched isomer) are excellent but enantioselectivities remain moderate (ee up to 17%).

Functionalization of various substrates to produce oxygenated compounds with high selectivities is still a topic deserving interest and study in metal-catalyzed organic syntheses. Indeed, most of the products present interesting biological properties.[1]

Amongst them, carbonylation of olefins catalyzed by transition metals proved to be an efficient method to functionalize olefins in order to produce compounds and intermediates in fine chemistry.[2] For instance, the alkoxycarbonylation of vinylarenes (Scheme 1) attract much attention from both academic and industrial research groups since the products (2-arylpropionic acids[3] and derivatives) are non-steroidal anti-inflammatory agents.[4]

For this process, the regioselectivity is of critical importance, the branched chiral products being the most valuable isomers. The selective formation of the branched/linear product was shown to be closely related to the ligand properties and reaction conditions.[5] Palladium catalysts containing monodentate or bidentate phosphine ligands are generally employed for this reaction. Monodentate ligands usually favour the formation of the branched products whereas catalytic systems bearing bidentate ligands generally lead to a greater amount of linear products. Two exceptions were, however, reported by van Leeuwen et al.[6] and Tanaka et al.[7] which obtain regioselectivity up to 92% in favour of branched ester using bidentate diphosphine ligands. More recently, 97% regioselectivity in the branched isomer was reported in the Pd catalysed methoxycarbonylation of styrene using P,N donor ligand.[8]



Scheme 1. Alkoxycarbonylation of styrene.

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In this Letter, we report the results obtained in the methoxycarbonylation of styrene catalyzed by palladium(II) complexes bearing different types of chiral bidentate ligands; P,S ferrocene-based ligands and P,P biphosphole-based ligands. Moreover, this Letter deals with the study of the main reaction parameters to reach improved selectivities.

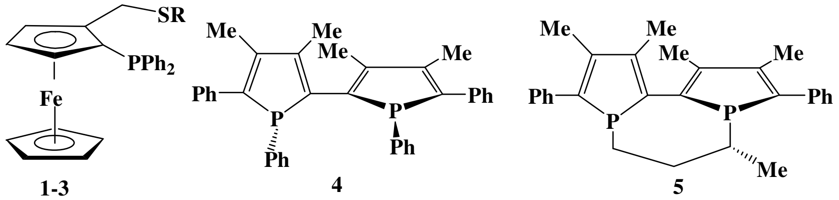
Previous studies carried out by our group have revealed the potential of ferrocene- and phosphole-based ligands such as those shown in Figure 1 with regard to coordination chemistry[9] and asymmetric catalysis.[10] In particular, numerous [$PdCl_2(L)$] complexes have been obtained and fully characterized by X-ray diffraction studies.[10a,11,12b,g] Moreover, these ligands proved to be active in Pd-catalyzed asymmetric allylic alkylation.[12]

In order to extend the use of these ligands to other catalytic systems, we have explored the methoxycarbonylation of styrene catalyzed by Pd(II) complexes (Scheme 1).

In the first set of experiments, the effect of the solvent and the promoting acid on the yield and selectivity of the reaction were investigated with the $Pd(OAc)_2/PPh_3$ system (Table 1, entries 1–3). Toniolo and co-workers have reported that such a precursor was successfully employed in the methoxycarbonylation of styrene.[13] In search of mild conditions, we first carried out the reaction at room temperature under 10 bar CO in the presence of 7.5 equiv (per palladium catalyst) of methanesulfonic acid.

After 24 h, conversion was already high (92%) and excellent chemoselectivity have been observed: styrene is essentially transformed only into esters by the expected methoxycarbonylation reaction. The regioselectivity (97/3 in favour of the branched product) is even better than that observed in similar experiments carried out under 6 bar CO[7]. With p-$CH_3C_6H_4SO_3H$ (entry 2), the catalyst is more active affording a conversion of 99% but less selective since the regioselectivity is 95% for the branched ester. In a MeOH/THF mixture (entry 3), the catalyst shows the same activity (conversion: 92%) as in pure MeOH but it is slightly less selective (*b*/*l*: 95/5). In contrast with the results reported in the literature, the use of MeOH/THF does not help to improve the performance of the catalytic system, as it happens in the case of other catalyst precursors.[14]

For comparison purposes, ferrocene- and phosphole-based ligands (see Fig. 1) were tested in the conditions of run 1 (i.e., MeOH as solvent and CH_3SO_3H as acid). Racemic ferrocenyl ligands **1** and **2** provide palladium catalysts that are less active than those employing Ph_3P in the methoxycarbonylation of styrene affording lower conversion (15%) at room temperature under 20 bar CO after 24 h (entries 4 and 7). However, both activity and regioselectivity are enhanced if the temperature is raised to 50 °C (entry 4 vs entry 5 and entry 7 vs entry 8). Under 20 bar CO, ligand **1** gives the more active palladium catalytic system (entry 5). With ligand **1**, increasing the CO pressure to 40 bar results in a slight decrease in conversion (entry 5 vs entry 6). Interestingly, with ligand **2**, both activity and regioselectivity are enhanced when CO pressure is raised to 40 bar (entry 8 vs entry 9). This difference in the dependence of activity versus CO pressure using ligand **1** or **2** is difficult to rationalize but is may be related to the steric bulk of the ligands (*t*Bu substituent for **1**, Ph for **2**). In summary, all of the ferrocenyl ligands **1–3** give palladium-based catalysts that are highly regioselective with regard to the branched isomers (98% or 99%). These regioselectivities are even slightly higher to those usually obtained with the best bidentate ligands[6–8] or monodentate ligands.[5,14,16] Indeed, Pd/monophosphine catalytic systems generally afford the branched ester as the major isomer, whereas Pd/diphosphine systems yield mainly the linear one.[5] Such results have arisen the question about the coordination behaviour of the ferrocenyl ligands alongside the catalytic cycle in the methoxycarbonylation reaction. The P,S ligands **1–3** behave as bidentate ligands[9d,e,15] but could also act as hemilabile or monodentate ligands. Thus, we have extended our studies to the P,P ligand **4**, which is known to be an excellent bidentate ligand.[9a,b] Surprisingly, high regiose-



1-3

4

5

1: R= *t*-Bu
2: R= Ph
3 : R=Et

Figure 1. Chiral ligands used in this study.

Table 1
Palladium-catalyzed methoxycarbonylation of styrene using achiral or racemic ligands

Entry	Catalyst	Solvent	Acid	*T* (°C)	Time (h)	P(CO) (bar)	Conv. (%)	Yield (%)	*b*/*l*
1	$Pd(OAC)_2/PPh_3$	MeOH	CH_3SO_3H	25	24	10	92	92	97/3
2	$Pd(OAC)_2/PPh_3$	MeOH	*p*-TsOH	25	24	10	99	96	95/5
3	$Pd(OAC)_2/PPh_3$	MeOH/THF (1/1)	CH_3SO_3H	25	24	10	92	92	95/5
4	$Pd(OAc)_2$/**1**	MeOH	CH_3SO_3H	25	24	20	15.4	15.4	94/6
5	$Pd(OAc)_2$/**1**	MeOH	CH_3SO_3H	50	24	20	83	80	98/2
6	$Pd(OAc)_2$/**1**	MeOH	CH_3SO_3H	50	24	40	72	68	99/1
7	$Pd(OAc)_2$/**2**	MeOH	CH_3SO_3H	25	24	15	15	13.5	96/4
8	$Pd(OAc)_2$/**2**	MeOH	CH_3SO_3H	50	24	20	62	57	88/12
9	$Pd(OAc)_2$/**2**	MeOH	CH_3SO_3H	50	24	40	80	75	99/1
10	$Pd(OAc)_2$/**3**	MeOH	CH_3SO_3H	50	24	20	75	69	98/2
11	$Pd(OAc)_2$/**4**	MeOH	CH_3SO_3H	50	21	20	10	3	88/12
12	$Pd(OAc)_2$/dppe	MeOH	CH_3SO_3H	50	21	20	10	0	nd
13	$Pd(OAc)_2$/dppp	MeOH	CH_3SO_3H	50	21	20	60	50	40/60

Conditions: substrate = styrene; substrate/catalyst = 50; acid/catalyst = 7.5.

Table 2
Palladium-catalyzed methoxycarbonylation of styrene using enantiomerically pure chiral ligands

Entry	Catalyst	*T* (°C)	Time (h)	Conversion (%)	Yield (%)	*b*/*l*	ee (%)
14	$Pd(OAc)_2/(S)$-**1**	50	24	83	80	98/2	10
15[a]	$Pd(OAc)_2/(R)$-**1**	50	24	60	58	99/1	13
16	$Pd(OAc)_2/(S)$-**1**	25	48	20	19	99/1	17
17	$Pd(OAc)_2/(S)$-**2**	50	24	50	42	99/1	7.5
18	$Pd(OAc)_2/(S)$-**2**	30	50	89	87	98/2	13
19	$Pd(OAc)_2/(S)$-**3**	55	24	95	88	97/3	2
20	$Pd(OAc)_2$/**5**	50	48	14	8	84/16	13

Conditions: substrate = styrene; substrate/catalyst = 50; L/Pd = 1; acid (CH_3SO_3H)/catalyst = 7.5; acid/substrate = 0.015; 20 bar CO in MeOH.

[a] Substrate/catalyst = 50; L/Pd = 2.

lectivity was recorded giving predominantly the branched ester (88%) although with lower activity and chemoselectivity (entry 11). These results are another example of unusual regioselectivity in favour of branched ester using a bidentate ligand as already reported only to the best of our knowledge by van Leeuwen et al.[6] and Tanaka et al.[7] Using ligand **4** or dppe, which have the same length of the bridge between the two phosphorus atoms, different chemoselectivities are observed (entries 11 and 12, respectively). Therefore, such results cannot be attributed only to the size of the chelate ring on the complex,[5a] but probably to the electronic effect on phosphorus atoms.[6,7]

Coming back to the results observed with the P,S ferrocenyl ligands **1–3**, we could envisage that these ligands, if they are bidentate ligands in this catalytic reaction, primarily affect the catalytic outcome through the electronic effect of the sulfur atom, since the use of dppp which has the same length of the carbon chain between the coordinating atoms than ligands **1–3** leads to completely different regioselectivities (entries 11 and 12 vs entry 13).

Stereoelectronic effects of the ligands on the methoxycarbonylation reaction are still to be understood and further investigations ought to be conducted.

Because of these excellent results in terms of regioselectivity, we decided to explore the asymmetrical version of this reaction by using ligands **1**–**3** and **5** which can be easily obtained in enantiomerically pure forms. Due to the importance of enantiomerically pure esters or derivatives, the development of enantioselective alkoxycarbonylation reactions are of great interest. However, if good regioselectivities or enantioselectivities[6,7,14,16] have already been reported, to the best of our knowledge, no catalytic systems possess both types of selectivities. The results are listed in Table 2.[17]

Enantiomerically pure ferrocenyl ligands **1** have been tried in the same conditions as described above (50 °C, 20 bar CO, 24 h) (Table 2, entry 14): the catalytic systems produced esters in good yields (80%) with excellent chemoselectivity (96%), regioselectivity (98%) but low enantiomeric excess (10%) as usually observed for highly regioselective systems.[6,7,14,16] The enantiomeric excess can be improved up to 13% using an excess of ligand (L/Pd = 2, Table 2, entry 15) or 17% decreasing the temperature down to 25 °C (Table 2, entry 16). With other ferrocenyl ligands **2** and **3**, good yields, excellent chemoselectivities and regioselectivities can also be obtained (Table 2, entries 17 and 18). However, enantioselectivities are lower than using **1**.

With phosphole-based ligand **5**,[18] good regioselectivity (84%) and significant enantioselectivity (ee = 13%) are observed but the catalytic activities and the chemoselectivities remain at a low level (Table 2, entry 20).

In this study, we have shown that palladium complexes of ferrocene- and biphosphole-based ligands can catalyze the methoxycarbonylation of styrene in rather mild conditions ($T = 50$ °C, $P_{CO} = 20$ bar, 15 mol % of promoting acid per substrate molecule). Indeed, esters can be obtained in good yields (up to 92%). In addition, high regioselectivities (up to 99%) in favour of the branched isomer are observed even in presence of the bidentate biphospholes **4** and **5**. However, enantiomeric excesses are moderate (up to 17%).

Taking advantage of the high modularity of ferrocenyl P,S ligands and of biphospholes, we will try to improve enantioselectivities in this reaction by modulating the stereoelectronic properties of the ligands in both families.

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17. *Typical procedure for methoxycarbonylation reactions:* A solution of MeOH (1 ml) containing the Pd precursor (4 mg, 0.017 mmol), the appropriate ligand (0.017 mmol) and the acid (14 mg, 0.13 mmol) was prepared under N_2 atmosphere using Schlenk techniques. Immediately after addition of the substrate (0.1 ml, 0.86 mmol), the solution was introduced into the autoclave, and then heated and pressurized with CO. After 24 h, the autoclave was cooled and slowly depressurized. After separation by column chromatography (CC), the solution was analyzed by GC, using tetradecane as internal standard, and the ee was determined by chiral GC.
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