Electronic Effect of Diphosphines on the Regioselectivity of the Palladium-Catalyzed Hydroesterification of Styrene

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Summary: The electronic character of the diphosphine ligands controls the regioselectivity of the Pd-catalyzed carbonylation of styrene. In the presence of electron-poor phosphines branched esters are produced and high activities of the catalytic systems are observed.

The metal-catalyzed carbonylation of olefins is an attractive process for the production of valuable compounds with several pharmaceutical and agrochemical applications.[1] Vinyl aromatics are of special interest as starting materials, as they lead to important products such as ibuprofen. In this reaction both branched and linear carboxylic acid esters are formed. Regioselectivities depend on the catalytic system employed as well as on the reaction conditions used.[2] It is well-known that the alkoxycarbonylation reaction might proceed by two different mechanisms, which differ in the involvement of Pd−H or Pd−COOR intermediates.[3] It has been reported that insertion of styrene into a metal−acyl bond leads to branched products, while insertion into hydrides leads to linear products.[4] Furthermore, regiocontrol depends on whether monophosphines or diphosphines are used as the ligands, even though both systems involve Pd−H species. It was found that monophosphines favor trans intermediate species, and it was speculated that these trans complexes lead to the formation of branched esters after replacement of one coordinated monophosphine by the olefin.[5] On the other hand, high linearity is achieved by using chelating systems, in which diphosphines promote the most favored cis-coordinated complexes. Also, a correlation between the selectivity and the P−Pd−P bite angles was found. Thus, diphosphines with wide bite angles provide high conversions and almost exclusively linear product.[6] For instance, the palladium systems based on DPEphos (natural bite angle 102.7°) (**1**) and Xantphos (110°) (**2**) showed high regioselectivity toward the linear product[7] (Scheme 1). In contrast with this last statement, Tanaka and co-workers[8] recently reported an unexpected selectivity for the formation of branched products using a palladium catalyst bearing a bulky electron-donor diphosphine but no evidence of the presumed coordination as a cis bidentate ligand was given to correlate the geometry with the observed regioselectivity.

In addition to the bite angle effect, other parameters such as electronic and steric effects may be taken into consideration, since they could play an important role in the regioselectivity-determining step.[9] Unfortunately, bidentate ligands lead preferentially to linear products and, thus, as yet the plethora of chiral bidentates cannot be used to produce esters enantioselectively. Our aim is to obtain branched esters utilizing bidentate systems and to show how the electronic and steric parameters of the ligand influence the catalytic activity and product selectivity of this reaction. Highly selective palladium-catalyzed formation of branched esters from styrene and carbon monoxide using DPEphos-based diphosphines and a Brønsted acid will be presented. These findings may have a great impact on the design of chiral bidentate systems that perform the reaction in an enantioselective way.

The DPEphos-type ligands **3** and **4** were synthesized having markedly different electronic properties, while the ligand **5**[10] causes considerable steric hindrance (Scheme 1). The complexes $PdCl_2$(**1**) (**8**), $PdCl_2$(**3**) (**9**), $PdCl_2$(**4**) (**10**), and $PdCl_2$(**5**) (**11**) were prepared by direct reaction of $Pd(COD)Cl_2$ with the corresponding phosphines. The preferential coordination mode of the ligands toward the Pd center is cis, as determined by $^{13}C\{^1H\}$ NMR spectroscopy at room temperature. The geometry assignment is straightforward because of the well-known recognizable AX spin system observed in $^{13}C\{^1H\}$ NMR attributed to the ipso aromatic carbon of the cis isomer.[11] Reaction of **3** with $Pd(COD)CH_3Cl$ led to the quantitative formation of the corresponding Pd complex $Pd(CH_3)Cl$(**3**) (**14**). The ^{31}P NMR spectrum of **14** revealed that the ligand is coordinated in a cis

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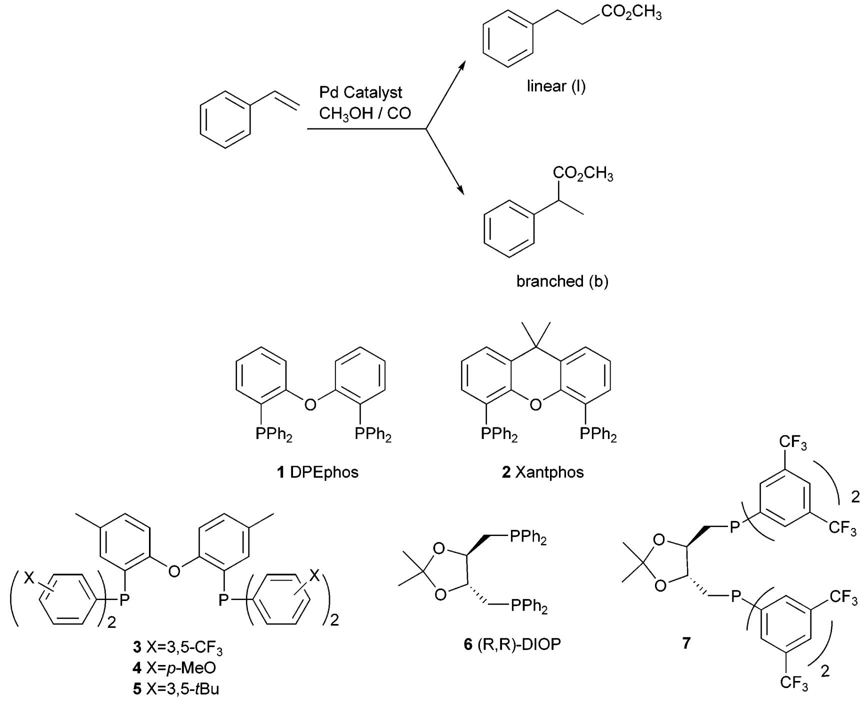
Scheme 1. Pd-Catalyzed Hydroesterification of Styrene and Applied Bidentate Ligand Systems



fashion to the metal center, as indicated by the two doublets at δ 31.4 and 11.1 ppm ($^2J_{P-P} = 30.3$ Hz). Single crystals of **14** suitable for X-ray diffraction could be obtained by slow crystallization from hexane. The molecular structure is depicted in Figure 1, confirming the presence of a cis complex exhibiting a P−Pd−P angle of 100.28(2)°.

We investigated the regioselectivity of these catalytic systems toward the formation of linear (l) and branched (b) carboxylic esters. Thus, in a typical experiment, the corresponding palladium(II) precursor, styrene, and hydrogen chloride in toluene−MeOH were investigated at 70 bar of CO. Table 1 summarizes the results obtained.

Under the reaction conditions applied, the neutral palladium complexes prepared from the DPEphos family effectively catalyzed the alkoxycarbonylation of styrene with high selectivities and moderate regioselectivies (Table 1, entries 2 and 3 and entries 8 and 9). At 100 °C and 70 bar of CO pressure the selectivity toward esters was >90% and neither oligomers nor polymers were observed, and palladium metal was not formed. The latter suggests that we are dealing with a stable catalytic system. Only (1-methoxyethyl)benzene was detected by GC-MS analysis as a byproduct of the reaction. The activity

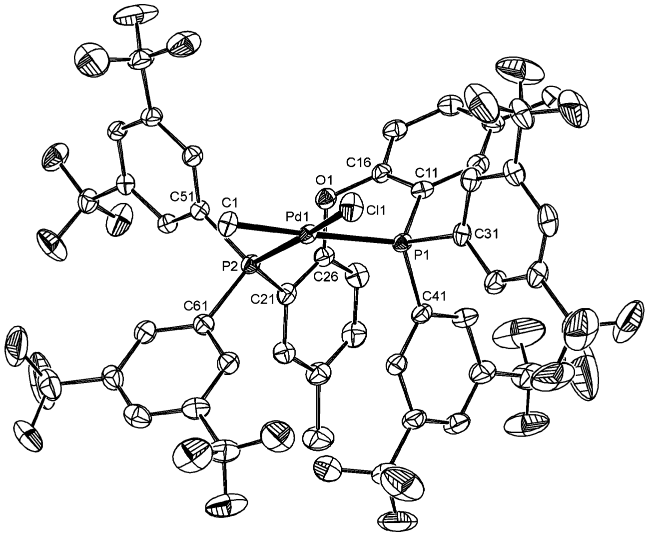


Figure 1. Molecular structure of the complex Pd(CH$_3$)Cl(**3**) (**14**) in the crystal. Displacement ellipsoids are shown at the 50% probability level. Hydrogen atoms and disordered solvent molecules are omitted for clarity. Only the major conformation of the rotationally disordered CF$_3$ groups is shown. Selected bond lengths (Å) and angles (deg): Pd(1)−P(1) = 2.3961(6), Pd(1)−P(2) = 2.2215(6), Pd(1)−C(1) = 2.114(2), Pd(1)−Cl(1) = 2.3368(6); P(1)−Pd(1)−P(2) = 100.28(2), Cl(1)−Pd(1)−C(1) = 84.73(7), C(16)−O(1)−C(26) = 115.40(18).

increased with an increasing amount of acid used (entries 3 and 6).

Particularly interesting is the result obtained using the catalytic system [PdCl$_2$(**3**)] (**9**), based on the phosphine ligand **3**. This catalyst proved to be highly active and selective, providing a b/l ratio of the carboxylic esters of ca. 74/26 (Table 1, entry 3) and a TOF of 834 h^{-1} when the styrene to palladium ratio was 800 (entry 5). An extra 1 equiv of **3** was added to this catalytic solution to ensure the coordination of the ligand during the catalytic process, which did not change the results (entry 3). Lower selectivity toward esters as well as an almost equimolar

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(12) Selected data for **9** are as follows. ^{1}H NMR (400 MHz, in CDCl$_3$): δ 8.00 (m, 11H, arom), 7.26 (m, 3H, arom), 6.94 (m, 2H, arom), 6.47 (m, 2H, arom), 2.11 (s, 6H, CH$_3$). ^{13}C{^{1}H} NMR (100.6 MHz, in CDCl$_3$): δ 157.0 (d, J = 6.84 Hz, C arom), 136.7 (CH arom), 136.4 (CH arom), 134.8 (br, CH arom), 132.0 (br, C arom), 126.7 (C arom), 125.8 (br, CH arom), 122.6 (d, J = 273,1 Hz, CF$_3$), 122.3 (br, C arom), 119.3 (C, arom), 116.8 (CH arom), 20.7 (CH$_3$). ^{31}P{^{1}H} NMR (161.9 MHz, in CDCl$_3$): δ 20.96 ppm. IR (cm^{-1}): 1616, 1464, 1351, 1271, 1119, 683. MS (MALDI-ToF): *m/z* 1250 (M$^+$ − Cl).

(13) Selected data for **13** are as follows. ^{1}H NMR (400 MHz, in CDCl$_3$): δ (m, 12H, arom.), (m, 2H, CH), (m, 4H, CH$_2$), (s, 6H, CH$_3$).^{31}P-{^{1}H} NMR (161.9 MHz, in CDCl$_3$): δ 20.78 ppm.

(14) Catalysis: in a stainless steel autoclave were placed a degassed mixture of the corresponding palladium complex (0.015 mmol), styrene (3 mmol), anhydrous MeOH (30 mmol), and anhydrous HCl in an ethereal solution (2 M, 3 mmol), along with 5 mL of toluene under argon. The autoclave was then flushed three times with 5 bar of CO and then pressurized with 70 bar of CO. The reaction was allowed to proceed with stirring at 100 °C for 16 h. The reaction mixture was analyzed by GC using acetophenone (5 mmol) as the internal standard.

Table 1. Alkoxycarbonylation of Styrene Using the Complexes [PdCl$_2$(1)] (8), [PdCl$_2$(3)] (9), [PdCl$_2$(4)] (10), [PdCl$_2$(5)] (11), [PdCl$_2$(6)] (12) and [PdCl$_2$(7)] (13)[a]

entry	catalyst precursor	[acid]/[Pd]	P_{CO} (bar)	*t* (h)	conversn (%)	selectivity in esters (%)	b/l ratio	ee (%)
1	[PdCl$_2$(PhCN)$_2$]	500	70	16	0			
2	**8**	200	70	16	100	93.7	0.29 (23:77)	
3[b]	**9**	200	70	1	99.4	98.3	2.86 (74:26)	
4[c]	**9**	200	70	0.5	79	93.1	2.43 (71:29)	
5[d]	**9**	200	70	0.5	44.5	88.4	2.25 (70:30)	
6	**9**	100	70	16	66	95.4	3.46 (77:23)	
7[e]	**9**	200	70	16	100	40.2	1.16 (53:46)	
8	**10**	200	70	16	100	91.9	0.38 (27:73)	
9	**11**	200	70	16	99.9	94	0.40 (29:71)	
10[b,f]	**12**	100	30	24	25	77	1.04 (51:49)	30 (*S*)
11[b,f]	**13**	100	30	24	65	92	11.5 (92:8)	3 (*S*)
12[b,f]	**13**	100	40	24	82	94	1.85 (65:35)	12 (*S*)
13[b,f]	**13**	10	30	24	73	95	2.03 (67:33)	14 (*S*)
14[b,e,f]	**13**	10	30	24	76	94	0.92 (48:52)	23 (*S*)

[a] Reaction conditions: [styrene]/[Pd] = 200, [MeOH]/[styrene] = 10, [Pd] = 1.45−2.4 mM, acid HCl, toluene/MeOH = 4, 100 °C. [b] Pd precursor plus 1 equiv of free ligand. [c] [styrene]/[Pd] = 400, toluene/MeOH = 1.65. [d] [styrene]/[Pd] = 800, toluene/MeOH = 0.8, TOF = 834 h^{-1}. [e] Acid TsOH. [f] [styrene]/[Pd] = 100, THF/MeOH = 1, 90 °C.

mixture of branched and linear products was obtained in the presence of noncoordinating anions, such as TsO$^-$, derived from the addition of TsOH (entry 7). On the other hand, and in agreement with previous literature data, a b/l ratio of ca. 23/77 was found when [PdCl$_2$**1**] (**8**) was used as the catalyst with 100% selectivity toward the formation of esters (entry 2).[7a,b] For [PdCl$_2$(**4**)] (**10**) the observed b/l ratio was 27/73 (entry 8). Since ligands **1**, **3**, and **4** have similar steric properties and only differ in the basicity of the phosphorus atom, the regiocontrol should be governed by an electronic effect. The steric influence on the regioselectivity was evaluated using the precatalyst [PdCl$_2$(**5**)] (**11**). Under the reaction conditions used, the achieved regioselectivity was b/l = 29/71 (entry 9). Explanation of these results remains somewhat speculative. In the presence of ligand **3**, the corresponding electron-poor catalyst might lead to the formation of (alkoxycarbonyl)palladium species which direct the insertion of the olefin to branched compounds. An alternative explanation for the branched regiocontrol observed using [PdCl$_2$(**3**)] might be found in the capability of the electron-poor ligand **3** to enhance isomerization to a trans-coordinated species during the catalytic cycle or even to act as a monodentate ligand.

Encouraged by these results, with the aim of finding an enantioselective catalyst able to perform this reaction with both high regio- and enantiocontrol, we envisioned the synthesis of ligand **7** based on the DIOP scaffold but containing fewer basic substituents than DIOP. Under the reaction conditions tested, the catalyst precursor [PdCl$_2$(**6**)] (**12**) based on (*R*,*R*)-DIOP (**6**) catalyzed the reaction without regiocontrol, giving a b/l ratio of ca. 1 (Table 1, entry 10). [PdCl$_2$(**7**)] (**13**) performed with higher activity and selectivity and superior regiocontrol, providing ca. 92% of the branched isomer (b/l = 11.5, entry 11). Presumably, higher CO pressures favor linear carboxylic esters, due to a faster insertion of CO in the σ-alkyl intermediates (entries 11 and 12). These results are in agreement with the aforementioned hypothesis of an electronic control of regioselectivity by means of electron-poor bidentate ligands.

Unfortunately, [PdCl$_2$(**7**)] (**13**) was hardly enantioselective (3−23%) and was even less stereoselective than [PdCl$_2$(**6**)] (**12**) (Table 1, entries 10 and 11). When the CO pressure was increased, [PdCl$_2$(**7**)] (**13**) showed higher enantiocontrol (entries 11 and 12), while lower concentrations of the Brønsted acid promoted a decrease of the b/l ratio but enhanced the enantioselectivity (entries 11, 13, and 14). The use of noncoordinating anions (such as TsO$^-$) was preferred over that of coordinating anions (such as Cl$^-$) in order to achieve higher enantioselectivities (entries 13 and 14). Some structural studies are required to verify the bidentate coordination of the ligand during the catalytic reaction and unravel the reason for this low enantiocontrol.

In summary, we have found highly effective and stable catalytic systems for producing predominantly branched esters from vinyl aromatics using a diphosphine/palladium(II) system. The mechanism of the observed electronic control on the regioselectivity of the reaction and the lack of enantioselectivity are currently under investigation.

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Supporting Information Available: Text giving details of the syntheses of the compounds in this paper, figures giving NMR spectra for **4**, and a CIF file giving details of the single-crystal X-ray structure determination of **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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