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Asymmetric catalytic hydroformylation of styrene: stereoselective ferrocenylethyldiphosphine rhodium catalysts

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Abstract

The use of a variety of chiral ferrocenylethyl diphosphines and a rhodium(I) precursor for the asymmetric hydroformylation of styrene is described. Some of these catalysts yield the chiral 2-phenylpropionic aldehyde with high enantioselectivity. The selectivity and activity of the catalysts are influenced by the substitution pattern of the phosphines. High enantioselectivity was achieved even at high reaction temperatures with a dialkylaryl–alkyldiaryl diphosphine ligand. *o*-Anisyl substituents at the side-chain phosphorus yield optical inductions of up to 76% ee, but at low conversion rates.

Keywords: Rhodium; Hydroformylation; Asymmetric catalysis; Diphosphines; Ferrocenylphosphines

1. Introduction

Hydroformylation is the largest-volume technical process of organometallic catalysis [1,2]. Beyond that, asymmetric hydroformylation of styrene derivatives promises a shortcut access to anti-inflammatory drugs, yielding chiral 2-arylpropionic aldehydes, which can easily be oxidized to pharmaceutically active 2-arylpropionic acids like Naproxen or Ibuprofen [3]. However, efficient catalysts for this reaction are still rare, and asymmetric hydroformylation is still a challenging topic in enantioselective catalysis [4]. Remarkable results with rhodium-based catalyst systems were obtained by Takaya and co-workers using the phosphine–phosphite ligand BINAPHOS [5] and by DuPont researchers employing a diphosphite ligand [6]. However, simple phosphines yield only little enantioselectivity [4].

Diastereomerically pure ferrocenylethyl diphosphines are conveniently synthesized from enantiopure 1-ferrocenylethylamine after diastereoselective *ortho*-lithiation of the ferrocenyl backbone, reaction with chlorophosphines and subsequent nucleophilic displacement of the amino function with a secondary phosphine [7]. These ligands possess two elements of chirality: the chiral center in the side chain and the planar chirality of the disubstituted ferrocene. They have been used for catalytic asymmetric reactions and proved to be efficient in asymmetric hydrogenation, but also in hydroboration, Kumada coupling and allylic alkylation reactions [8].

Despite their widespread application in asymmetric catalysis, their use for enantioselective hydroformylation has not yet been reported. We now describe asymmetric hydroformylation using chiral ferrocenylethyl diphosphines with rhodium as catalyst metal.

2. Results and discussion

Several in situ rhodium catalysts formed from $Rh(CO)_2(acac)$ and two equivalents of various ferrocenylethyl diphosphines were tested for the enantioselective hydroformylation of styrene. Styrene was chosen as model olefin, because vinylic aromatics are the most interesting substrates for an application of this reaction in the synthesis of fine chemicals (Scheme 1). The reaction yields the branched main product 2-phenylpropionic aldehyde **1** and a small amount of the linear 3-phenylpropionaldehyde **2**.

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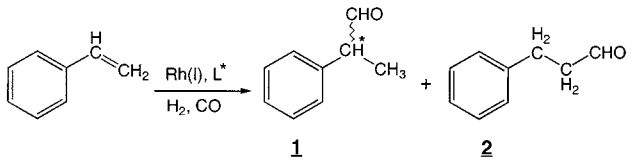

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Scheme 1. Hydroformylation of styrene yields chiral 2-phenylpropionic aldehyde and 3-phenylpropionic aldehyde as a side product.

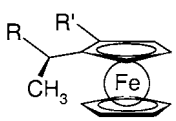
Initially, all catalysts were tested at 60°C. However, catalysts formed from ligands with alkyl-substituted phosphorus showed very little conversion at that temperature and were subsequently tested at a temperature of 80°C (Table 1, entries 1–4).

The first four entries of Table 1 show a strong influence of the substitution pattern of the phosphorus atoms on the activity and selectivity of the rhodium catalysts. When the basic phosphorus moiety bearing two cyclohexyl groups is located in the side chain of the ferrocenyl backbone (entry 1), the ligand has one trialkyl and one triaryl function coordinating to the rhodium metal. In this case a conversion of 32% and an excess of 34% of the (*R*)-enantiomer is observed. *t*-Butyl substituents at the side-chain phosphorus cause a comparable selectivity but a reduced activity of the catalyst (entry 2). The exchange of the phosphorus substituents (entry 3) results in a ligand with one dialkylaryl and one alkyldiaryl phosphino group. When this ligand is used, the reaction rate is smaller, whereas the enantioselectivity of the catalyst is higher, yielding 61% ee, notably of the opposite (*S*)-enantiomer. Increasing the electronic difference between the two phosphine atoms of the ligand by the introduction of *o*-trifluoromethyl substituents in the aryl substituents does not influence the reaction rate but reduces the selectivity severely (entry 4). However, the additional steric bulk of this group could also be a reason for the observed effect.

Takaya and co-workers have observed that in catalytically active $RhH(CO)_2(P \cap P')$ complexes ($P \cap P'$: chelating ligand) the C_1-symmetric ligand BINAPHOS shows a preferred coordination of its phosphite arm in an apical position opposite to the hydride ligand [9]. A similar behavior of the ferrocenylethyl diphosphines, which are also C_1-symmetric, is made plausible by the change of selectivity observed when the positions of the different phosphines are switched. If one phosphine unit favors coordination in the apical position, the ligand must turn round upon exchange of the different phosphine substituents. This could lead to the observed change of the preferred product enantiomer.

Entries 5–9 show the influence of the substitution pattern of aromatic substituents at the phosphine in the chiral side chain. Entries 5 and 6 demonstrate that the steric bulk of *ortho*-substituents influences the selectiv-

Table 1
Catalytic hydroformylation of styrene with different ferrocenylethyl diphosphines [a]



Entry	R	R′	Conversion (%)	ee (%)
1	Pcy_2	PPh_2 (80°C)	32	34 (*S*)
2	$P(^tBu)_2$	PPh_2 (80°C)	4	30 (*R*)
3	PPh_2	PCy_2 (80°C)	13	60 (*S*)
4	Pcy_2	$P[2\text{-}(CF_3)\text{–}C_6H_4]_2$ (80°C)	29	4 (*S*)
5	$P(o\text{-Tol})_2$	PPh_2	54	5 (*R*)
6	$P(m\text{-Tol})_2$	PPh_2	66	36 (*S*)
7	$P(o\text{-Anis})_2$	PPh_2	26	51 (*S*)
8	$P(m\text{-Anis})_2$	PPh_2	16	30 (*S*)
9	$P(p\text{-Anis})_2$	PPh_2	11	3 (*S*)
10	$P[2\text{-}(CF_3)\text{–}C_6H_4]_2$	PPh_2	100	–
11	$P[3,5\text{-}(CF_3)_2\text{–}C_6H_3]_2$	PPh_2	82	2 (*R*)
12	$P[4\text{-}(^tBu)\text{–}C_6H_4]_2$	PPh_2	51	3 (*S*)
13	$P[3,5\text{-}(CH_3)_2\text{–}C_6H_3]_2$	PPh_2	46	3 (*S*)
14	$P[3,5\text{-}(CH_3)_2\text{-}4\text{-}NBu_2\text{–}C_6H_3]_2$	PPh_2	72	4 (*S*)

[a] Reaction conditions: $Rh(CO)_2(acac)$–ligand–styrene ratio: 1:2:300; 10 MPa H_2–CO (1:1 mixture). Temperature: 60°C unless otherwise stated. Reaction time: 16 h. Branched/linear-ratios were between 9 and 15 in all cases. ($Cy = C_6H_{11}$, $^tBu = t\text{-}C_4H_9$, $Ph = C_6H_5$, $Tol = CH_3\text{–}C_6H_4$, $Anis = CH_3O\text{–}C_6H_4$).

ity and activity of the catalyst negatively: The reaction with the *ortho*-tolyl-substituted ligand yields only an enantiomeric excess of 5% (*R*), which is considerably lower than the 36% ee (*S*) for the *meta* substituents. In entries 7–9, the ring position of a methoxy substituent at the side-chain phosphorus illustrates that the presence of a donor substituent in the close vicinity of the phosphorus atom can increase the excess of the preferred enantiomer. Whereas the *para*-anisyl-substituted ligand only yields 3% ee, the ligand with *meta*-anisyl substituents generates an enantiomeric excess of 30%, and the *ortho*-substituted ligand shows 51% ee for the same enantiomer. As the steric influence of the *ortho*-methoxy substituent on the rhodium atom is the strongest among the three isomeric ligands, its negative effects on the selectivity of the catalyst must be compensated by another effect. A plausible explanation of this behavior is that the oxygen of the *ortho*-methoxy substituents helps to stabilize one of several possible complex configurations in the catalytic cycle and therefore influences the product distribution of the overall reaction.

Other chiral ferrocenylethyl diphosphines with electronically different phosphorus moieties listed in entries 10–14 did not show enantioselectivities comparable to those of the ligands discussed before.

The temperature dependence of the selectivity and activity of the catalyst employing the dialkylaryl and alkyldiaryl phosphine (Table 1, entry 3) was studied because the conversion of styrene at 80°C was still very low. Therefore, temperatures of 90, 100 and 120°C were applied (Table 2).

In these experiments an increased activity of the catalyst at higher temperatures was observed, accompanied by an increasing loss of enantioselectivity. However, the enantiomeric excess of the *iso*-aldehyde product remained nearly constant at about 60% ee up to a temperature of 100°C.

The catalyst system used in Table 1, entry 7, showed a comparable temperature dependence of the enantioselectivity (Table 3).

In this case the selectivity of the catalyst could even be improved on running the reaction at lower temperatures. At 40°C, the 2-phenylpropionic aldehyde was formed with 76% ee, the highest enantiomeric excess obtained with a rhodium diphosphine catalyst system. At 75°C, however, the catalyst was considerably less selective and yielded only 31% ee. This supports the concept of a weak additional coordination of the oxygen atom in the *ortho*-anisyl group to the rhodium atom. As this interaction competes with the strongly binding phosphine and carbonyl ligands, it will not be observable in the resting state of the catalyst. However, dissociation of one carbonyl ligand or one arm of the diphosphine opens a free coordination site. This coordinatively unsaturated complex might then be stabilized in one preferred configuration by the oxygen, before it is attacked by the substrate styrene. Higher temperatures would make an interaction of this kind more difficult.

Table 2
Temperature dependence of the selectivity observed for R = Ph and R′ = Cy [a]

Entry	Temperature (°C)	Conversion (%)	ee (%)
15	60	3	63 (*S*)
16	80	13	60 (*S*)
17	90	31	57 (*S*)
18	100	47	57 (*S*)
19	120	84	45 (*S*)

[a] Reaction conditions: $Rh(CO)_2(acac)$–ligand–styrene ratio: 1:2:300; 10 MPa H_2–CO (1:1 mixture). Reaction time: 16 h.

Table 3
Temperature dependence of the selectivity observed for R = *o*-Anis and R′ = Ph [a]

Entry	Temperature (°C)	Conversion (%)	ee (%)
20	40	3	76 (*S*)
21	50	8	75 (*S*)
22	60	26	50 (*S*)
23	75	78	31 (*S*)

[a] Reaction conditions: $Rh(CO)_2(acac)$–ligand–styrene ratio: 1:2:300; 10 MPa H_2–CO (1:1 mixture). Reaction time: 16 h.

3. Conclusions

The stepwise introduction of the phosphine moieties in the synthesis of ferrocenylethyl phosphines permits the design of bidentate ligands with two sterically and electronically different phosphine atoms. This opens the opportunity to study the influence of different electronic and steric properties of both phosphorus atoms independent from one another.

The use of these ligands for the asymmetric hydroformylation of styrene with a rhodium(I) precursor has been described for the first time. Some of them show remarkably high stereoselectivities. The substitution pattern of the phosphine atoms strongly influences the selectivity and activity of the catalyst. With one dialkylaryl–alkyldiaryl diphosphine, high enantioselectivity was achieved even at high reaction temperatures and therefore increased conversion of the substrate. *o*-Anisyl substituents at the side-chain phosphorus allow up

to 76% ee; however, the conversion rates are still too low for technical applications.

4. Experimental

All reactions were carried out using standard Schlenk techniques in an oxygen-free nitrogen atmosphere. Solvents were dried with standard methods and distilled under nitrogen. Chiral ferrocenylethyl diphosphines were prepared following published methods [10]. Their diastereomeric excess was 96% or higher. Hydroformylation experiments were performed in a Parr 300 ml stainless-steel autoclave, using dried and degassed styrene and a 1:1 mixture of hydrogen and carbon monoxide. The catalysts were formed in situ from $Rh(CO)_2(acac)$ and two equivalents of ligand in toluene, before the calculated amount of styrene was added and the mixture transferred to the autoclave under nitrogen. Modification of the commercially available autoclave allowed several catalytic reactions to be run at the same time without cross-contamination of the different samples. Through this modification the volume of the reaction mixtures could be reduced to 1.5 ml and the amount of rhodium catalyst to 1 μmol. Conversions were determined on an HP 5890 gas chromatograph with a 12 m HP-1 capillary column and flame ionization detection using the method of internal standardization. Enantiomeric excesses of the aldehydes were measured on a Chrompack CP 9000 gas chromatograph (50 m Lipodex A column, carrier gas helium, split injector, flame ionization detector) after reduction to the corresponding alcohols with sodium borohydride. Their absolute configuration was determined by comparison with an authentic sample of (*R*)-(+)-2-phenylpropanol.

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