Highly regioselective hydroformylation under mild conditions with new classes of π-acceptor ligands

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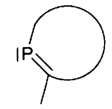
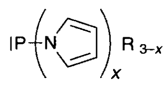
The first use of three new classes of π-acceptor ligands in homogeneous catalysis is reported; the corresponding rhodium catalysts combine high regioselectivity with high reactivity on hydroformylation of styrene.

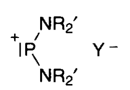
Almost 60 years since the discovery of homogeneous catalytic hydroformylation, the simultaneous control of reactivity and selectivity in the course of this industrially important process is still a major challenge.[1,2] Wilkinson's discovery of phosphine–rhodium complexes as extremely reactive and selective hydroformylation catalysts was a breakthrough.[3] Subsequent studies of this catalyst system led to an understanding of the factors that govern reactivity and selectivity:[4] σ-donor ligands may inhibit the reaction completely, switching to stronger π-acceptor ligands such as phosphites leads to more active and more selective hydroformylation catalysts.[5–7] To be a good π-acceptor ligand, the system should possess either a π* or a σ* orbital which is well suited in symmetry and energy to overlap efficiently with occupied transition-metal d orbitals. This holds for $\lambda^3\sigma^2$ phosphorus compounds, *e.g.* phosphabenzenes **1** and phosphaindolizines **2** (class **A**),[8] pyrrolyl-substituted phosphines **3** (class **B**)[9] as well as phosphenium cations **4** (class **C**).[10]

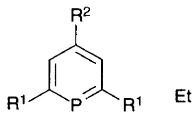
The π-acceptor ability of these systems increases from class **A** to **C** and covers electronically the range from phosphites to phosphorus trifluoride.† This could have beneficial effects in homogeneous catalysis. We therefore tested these ligands in the hydroformylation of styrene, a potentially useful reaction for the preparation of the anti-inflammatory 2-arylpropionic acids.[11] In this respect regioselectivity favouring the branched aldehyde combined with high reactivity is important.‡ We report here on the use of representative ligands of classes **A**, **B** and **C** in a highly regioselective hydroformylation of styrene under mild conditions. On the basis of these results we tailored new electronically differentiated bidentate ligands which give hydroformylation catalysts that combine high regioselectivity with high reactivity.

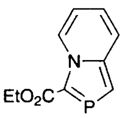
In a first series of experiments, rhodium catalysts with monodentate π-acceptor ligands were investigated. These were prepared *in situ* (Scheme 1) by reacting $Rh(CO)_2(acac)$ with the corresponding monodentate ligand in toluene followed by hydroformylation at ambient temperature (20 °C) employing the conditions indicated (Table 1).


class **A**


B


C


1a R^1 = H, R^2 = c-Hex
1b R^1 = Me, R^2 = Ph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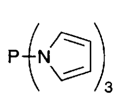
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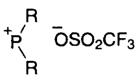
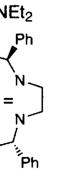
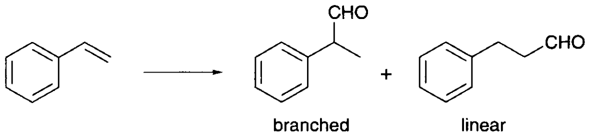

4a R = NEt_2


4b R, R =

Compared to the Rh–PPh_3 reference system[12] the phosphabenzene **1a** and the phosphaindolizine **2** ligands both unexpectedly inhibited hydroformylation completely. However, the introduction of two methyl substituents in *ortho*/*ortho'* positions of the phosphabenzene system (→ **1b**) resulted in a hydroformylation catalyst more than twice as active as the standard Rh–PPh_3 system. Similar activating effects have been observed with phosphite ligands, if their steric demand was increased.[5] When the trispyrrolylphosphine **3** was tested as a class **B** ligand, low conversion and poor regioselectivity resulted (Table 1, entry 6). To examine ligands with maximum π-acceptor ability, we chose the phosphenium cation systems **4a,b**. Although regioselectivity with these systems was excellent (entries 7, 8, 9), catalyst activity was low.

We then attempted to improve the performance of our π-acceptor catalysts. By looking at one of the most selective ligand systems known, Takaya's binaphos, a phosphine–phosphite ligand,[13] two structural features which seem to play an important role in the control of selectivities became apparent: first, a chelating bidentate binding mode, and secondly, an electronic differentiation of the binding sites. Taking this into account we modified the most active of our monodentate ligands, the 2,6-substituted phosphabenzene system. As a first



Scheme 1 *Reagents and conditions*: 0.357 mol l^{-1} $Rh(CO)_2(acac)$–L, CO–H_2 (1 : 1), 50 bar, 20 °C, 22 h

Table 1 Regioselective hydroformylation of styrene with novel monodentate π-acceptor ligands[a]

Entry	Ligand	χ^b	Rh : L	Conv. (%)[c]	b : l[c]
1	PPh_3	13	1 : 20	31	25.8 : 1
2	**1a**	23	1 : 20	—	—
3	**1b**	23	1 : 5	51	23.2 : 1
4	**1b**	23	1 : 2	80	26.6 : 1
5	**2**	29	1 : 20	—	—
6	**3**	36	1 : 20	8	6 : 1
7	**4a**	59	1 : 2	4	100 : —
8	**4a**	59	1 : 1	20	31.5 : 1
9[d]	**4b**	59	1 : 2	10	29.8 : 1

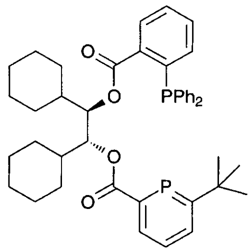
[a] Reactions were carried out in toluene (0.65 mol l^{-1}) in a 200 ml stainless-steel autoclave under an atmosphere of H_2 and CO (1 : 1), 50 bar initial total pressure for 22 h at 20 °C. [b] See footnote †. [c] Conversions and b : l (branched : linear) ratios were determined by GC on a 0.25 mm × 30 m Supelcowax column with pentadecane as internal standard. In all cases aldehyde selectivity was 100%. [d] No significant ee (> 5%) could be detected by oxidizing the crude product with $KMnO_4$ to the corresponding carboxylic acids followed by separation of the enantiomers by GC on a β-cyclodextrin column.

test system we investigated a phosphine–phosphabenzene combination (→ **5**).§

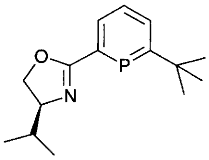
Using exactly the same reaction conditions as for the monodentate ligands (Table 2), system **5** gave 42% conversion (somewhat higher than for the Rh–PPh_3 system) and a good regioselectivity of 21.4 : 1 (b : l). In order to increase the electronic differentiation of the two coordinating elements, we therefore introduced an oxazoline functionality at the *ortho* position of the phosphabenzene. Two ligands with this combination of strong σ-donor, the oxazoline nitrogen, and the π-acceptor phosphabenzene moiety, were investigated: system **6** capable of forming a five-membered chelate ring and system **7a** leading formally to an eight-membered chelate system.§ While ligand **6** (Table 2, entry 2) did not improve the catalyst properties, the results with ligand **7a** were the best. Standard hydroformylation reaction at ambient temperature (20 °C) led to a quantitative conversion of styrene to 2-phenylpropionaldehyde with a regioselectivity of 24.8 : 1, *i.e.* reactivity more than three times higher than that for the Rh–PPh_3 system, while regioselectivity maintained the same high level.

To clarify the role of the phosphabenzene system in **7a** during catalysis, ligand **7b**, which lacks the coordinating ability of the phosphabenzene unit, was prepared. Standard experiments with **7b** clearly showed a much reduced catalytic activity (only 29% conversion) in comparison to the quantitative conversion with **7a**. This indicates the involvement of the phosphabenzene moiety in ligand **7a** during rhodium-catalysed hydroformylation of styrene.

In conclusion, we have introduced three novel classes of strong π-acceptor ligands to homogeneous catalysis. Notably, two of these ligands (**1b**, **7a**) containing a phosphabenzene-nucleus showed reactivity more than 3 times higher than that of the standard Rh–PPh_3 system in combination with high regioselectivity on hydroformylation of styrene. Although these improvements might not justify the commercial application of these ligands yet, the results open up a novel direction for the development of more reactive and regioselective hydroformylation catalysts. Further studies to clarify the activity as well as investigations on the limit and scope of these novel classes of π-acceptor ligands in homogeneous catalysis are under way.



5



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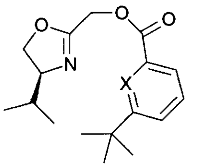

7a X = P
7b X = CH

Table 2 Regioselective hydroformylation of styrene with bidentate phosphabenzene ligands[a]

Entry	Ligand	Rh : L	Conv. (%)[b]	b : l[b]
1[c]	**5**	1 : 2	42	21.4 : 1
2[c]	**6**	1 : 2	5	100 : —
3[c]	**7a**	1 : 2	98	24.8 : 1
4[c]	**7b**	1 : 2	29	46.7 : 1

[a–c] See footnotes to Table 1.

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Footnotes

† All three classes of compounds are known to form σ-transition-metal complexes,[8,10] in particular σ-rhodium complexes are known for class **A** and **B** systems.[9,14] A quantitative description of a ligands π-acceptor ability can be made by the electronic parameter χ introduced by Tolman.[15] This would require the IR spectral data for the $LNi(CO)_3$ complexes of the ligands **1**, **2** and **3**. While these complexes are unknown, their CO stretching frequencies may be estimated from the IR spectra of the known $LCr(CO)_5$ complexes for **1**[16] and **2**[17] and a $LFe(CO)_4$ complex of **4**[10] according to ref. 18. For representatives of class **A** ligands, the phosphabenzenes **1** and phosphaindolizines **2**, χ is determined as 23 and 29, respectively. The π-acceptor ability of these systems therefore should be comparable to that of phosphites. The pyrrolylphosphine-based systems (class **B**) show enhanced π-acceptor ability with χ = 36 for **3**,[9] which is comparable to that of the $P(C_6F_5)_3$. The strongest π-acceptor systems are the phosphenium cations (class **C**) with χ = 59 for **4**, *i.e.* their π-acceptor ability is therefore similar to that of PCl_3 (χ = 55).

‡ The most active catalyst known for hydroformylation of styrene is a phosphanorbornadiene–Rh-system reported by Neibecker and Réau.[12] The high reactivity however compromises the regioselectivity, which decreased in the above-mentioned reaction to 11 : 1 (b : l) in comparison to the second most active Rh–PPh_3 system (25.8 : 1).

§ As a key step in the preparation of the new phosphabenzene ligands **5**, **6** and **7a**, thermal reaction of the corresponding α-pyrone with *tert*-butylphosphaalkyne, a method developed by Rösch and Regitz,[19] was used. Comprehensive ligand synthesis will be reported elsewhere.

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