The Highly Enantioselective Hydrogenation of *N*-Diphenylphosphinylketimines with Cationic Rh Ferrocenyldiphosphine Catalysts**

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The enantioselective hydrogenation of a suitable C=N–X precursor would be an attractive method to synthesize 1-phenylethylamines which are versatile chiral auxiliaries. However, few catalysts with high enantioselectivity and good catalyst activity are known.[1–7] We thought that phosphinylimines might be attractive starting materials for the following reasons: i) they are easily accessible from the corresponding oximes, ii) the N–P=O group might serve as a second anchoring group, iii) in contrast to imines, one stereoisomer (*syn/anti*) of the phosphinylimine is expected to dominate, iv) acid-catalyzed removal of the phosphinyl group is known be easy. Indeed, phosphinylimines have already served as substrate for Co-catalyzed hydride reductions with reasonable success.[6] The following note describes the development of Rh-ferrocenyldiphosphine catalysts for the highly effective hydrogenation of several *N*-diphenylphosphinylacetophenone imines with ee's up to 99%.

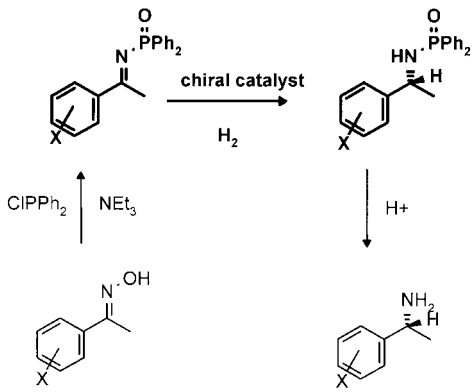

Figure 1. Synthesis of enantiomerically enriched primary phenylethyl amines via asymmetric hydrogenation of *N*-diphenylphosphinylacetophenone imines

A relatively broad catalyst screening program was carried out with the unsubstituted *N*-diphenylphosphinylacetophenone imine. According to the NMR spectrum the substrate was present exclusively as the *anti*-isomer. Somewhat surprisingly, Ir catalysts with different diphosphine ligands which were very successful with *N*-arylimines[5] as well as Ru-binap which work well with *N*-sulfonylimines[7] were practically inactive and gave less than 10% conversion in 20–70 h (s/c 100, 25–60 °C, 70–80 bar; results not shown)! We realized noticeable activity and, even more important, significant enantioselectivities only when we turned to cationic Rh diphosphine catalysts prepared *in situ* in methanolic solvent (for selected results see Table 1).

While the enantioselectivities with ligands like chiraphos, mod-diop and also duphos were low to moderate, ferrocenyl-based ligands (*R*)-(*S*)-R_2PF-PR'_2 (see Figure 2) of the josiphos type[8] proved to be very selective. The modular character of this ligand class which allows easy tuning of its electronic properties proved to be particularly advantageous. As can be seen from the second part of Table 1, this was the dominant parameter controlling enantioselectivity of the Rh catalysts. With one exception, (R′ = 4-NMe_2-3,5-xyl) the major product enantiomer had always the (*R*)-configuration. There was no unequivocal correlation between the enantioselectivity and the basicity of the substituents. Ligands with R = Ph generally gave low to moderate ee's whereas those with more basic R groups, especially in combination with R′ = ^{t}Bu or *c*-C_6H_{13} (cy) led to very high enantioselectivities. These findings are in contrast to the effects observed for the hydrogenation of various C=N groups where best results were generally found with bis(diaryl)diphosphines.[3] Of particular interest are the results with the all-cyclohexyl derivative which under our conditions gave an ee of 99%, a not optimized TON of 500 and an average TOF of up to

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Table 1. Enantioselective hydrogenation of *N*-diphenylphosphinylacetophenone imine[a]: Ligand screening (for ligand structures see Figure 2)

Ligand/R and R′ in Figure 2[b]		time (h)	conv. (%)	ee (%)[c]	comments
cy-biphemp		4	17	n. d.	
chiraphos		66	23	15	
Me-duphos		70	40	31	
mod-diop		68	71	38	
Ph	cy	20	76	5	
Ph	4-NMe_2-3,5-xyl	19	34	21	(*S*)-product
Ph	xyl	68	71	38	
Ph	^{t}Bu	20	>98	68	
4-tol	^{t}Bu	70	100	ca. 85	
4-CH_3O-Ph	^{t}Bu	17.3	93.5	93	
cy	^{t}Bu	18.5	83	95	
cy	cy	<1	100	99	
cy	cy	1	100	99	s/c = 500
cy	cy	16.5	98	91	80 °C
cy	cy	66	60	41	30 °C
cy	cy	18	58	7	$[Rh(nbd)Cl]_2$, toluene

[a] Reaction conditions: methanol, 60 °C, 70 bar, s/c 100, catalyst prepared *in situ* from $[Rh(nbd)_2]BF_4$ and diphosphine (for exceptions see comments).
[b] Cyclohexyl.
[c] Product has (*R*) configuration.

Table 2. Best results for the hydrogenation of *para*-substituted acetophenone derivatives with the Rh/(*R*)-(*S*)-cy_2PF-Pcy_2 catalyst[a]

para-subst.	time (h)	conv. (%)	ee (%)	comments
OCH_3	19	100	62	
CH_3	21	100	97	
CF_3	18	98	93	
Cl	19	53	30	
Cl	17	85	28	80 °C
Cl	18	93	67	(*R*)-(*S*)-cy_2PF-P^tBu_2

[a] Reaction conditions: methanol, 60 °C, 70 bar, s/c 100, catalyst prepared *in situ* from $[Rh(nbd)_2]BF_4$ and (*R*)-(*S*)-cy_2PF-Pcy_2 (for exceptions see comments).

500 h^{-1}. Whereas higher s/c ratios did not affect the enantioselectivity, changes in temperature had an unexpectedly large influence and $[Rh(nbd)Cl]_2$ as precursor complex led to a drop of the ee to 7%. These effects were not investigated further.

para-Substituted *N*-diphenylphosphinylacetophenone imines were hydrogenated with significantly lower enantioselectivities (see Table 2). Especially OCH_3 and Cl decreased the ee's below 70%, whereas the presence of CF_3 group lowered the enantioselectivity only slightly to 93% ee. Interestingly, the optimal ligand for the *p*-chloro-substituted derivative was (*R*)-(*S*)-cy_2PF-P^tBu_2 and not the all cyclohexyl derivative. There is no correlation between the enantioselectivity for a given substituent and its Hammett constant and we do not have a ready explanation for these substituent effects.

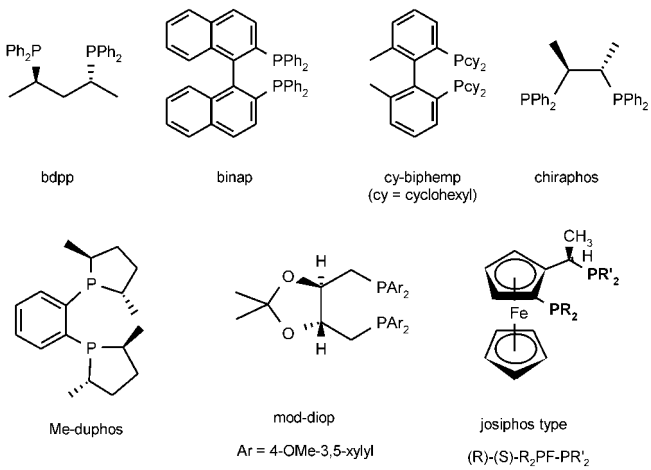

Figure 2. Ligand structures

Table 3 shows a comparison of the Rh/cy_2PF-Pcy_2 catalyst with other catalytic systems suitable for the enantioselective synthesis of primary arylalkylamines. For this class of substrates, the new catalyst is clearly the most selective and effective and in addition, the removal of the protecting/activating group X to obtain the primary amine is easy and can be scaled up without difficulty, which is not the case for some of the other compounds.

In conclusion, Rh complexes with ferrocenyl based ligands of the josiphos type are highly effective catalysts for the enantioselective hydrogenation of various *N*-diphenylphosphinylacetophenone imines with ee's up to 99% and turnover frequencies of up to 500 h^{-1}. The best catalyst is a cationic Rh complex prepared *in situ* from $[Rh(nbd)_2]BF_4$ and the ferrocenyldiphosphine (*R*)-(*S*)-cy_2PF-Pcy_2. The catalytic system is highly specific and even relatively small changes in ligand structure, metal precursor and substrate structure significantly decrease the catalyst ef-

Table 3. Comparison of best results for the hydrogenation of aryl alkyl C=N–X systems.

C=N–X group	catalyst	pH_2[a] (bar)	T (°C)	ee (%)	s/c	TOF (h^{-1})	removal of X group	Ref.
$P(O)Ph_2$	Rh/cy_2PF-Pcy_2	70	60	99	500	500	H^+/H_2O; easy	
Bzl	Rh/$bdpp_{sulf}$	70	20	94–96	100	16–85	Pd/C, H_2; medium	[4]
NHCOPh	Rh/duphos	4	0	88–96	500	14–42	SmI_2; difficult	[5]
Ts	Ru/binap	70	40	84	20	<1	H^+/H_2O; medium	[7]
$P(O)Ph_2$	Co/salen	"H"	0	90	100	34	H^+/H_2O; easy	[6]

[a] Or reducing agent, "H" = modified borohydride.

ficiency. The new enantioselective transformation opens up a preparative access to enantiomerically pure 2-phenylethylamines.

Experimental Section

Materials

The diphosphine ligands bdpp, mod-diop, binap, chiraphos, and Me-duphos were obtained from commercial sources; cy-biphemp was a gift of Dr. R. Schmid (F. Hoffmann-La Roche, Basel), the josiphos type ligands were synthesized according to published methods[8, 11] and can be obtained in multigram amounts from Solvias AG. All other reagents were from Fluka and used without further purification, solvents for the hydrogenation reactions were degassed before use.

Syntheses and Hydrolysis of *N*-Alkylidenediphenylphosphinamides

The preparation of the *N*-alkylidenediphenylphosphinamides starting from the corresponding ketoximes and chlorodiphenylphosphine as well as their cleavage to yield the primary amines were carried out according to procedures described by Krzyzanowska and Stec.[9,10]

Enantioselective Hydrogenation of *N*-Alkylidenediphenylphosphinamides

In a typical experiment, 0.5 g (1.55 mmol) *N*-(1-phenylethylidene)diphenylphosphinamide were dissolved in 7 mL methanol under argon. A catalyst solution was prepared by dissolving 5.8 mg (0.0155 mmol) $Rh(nbd)_2]BF_4$ and 10.6 mg (0.0173 mmol) (*R*)-(1)-{[((*S*)-2-dicyclohexylphosphino)ferrocenyl]ethyl}dicyclohexylphosphine [(*R*)-(*S*)-cy_2PF-Pcy_2] in 8 mL methanol under argon. This solution was stirred for 15 min at rt. The substrate and the catalyst solutions were transferred via a steel capillary into a 50-mL stainless steel autoclave. The inert gas was then replaced by hydrogen (three cycles) to an initial pressure of 70 bar, and the reaction temperature set to 60 °C. After 21 h, the reaction was stopped, and the conversion was measured by GLC [DB-17, 30 m, temperature program 60 °C (1 min), 10 °C/min, 220 °C (15 min)]. The enantiomeric purity of the *N*-(1-phenylethyl)diphenylphosphinamide was 99% (*R*) as determined by GLC after derivatization with perfluorobutyric acid anhydride [Lipodex-D, 50 m; T: 160 °C, isotherm; carrier He (170 kPa)].

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