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Tunable ferrocenyl diphosphine ligands for the Ir-catalyzed enantioselective hydrogenation of *N*-aryl imines

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On the occasion of the 65th birthday of Professor Henri Brunner under the motto 'No question: What's right is right!'

Abstract

Ferrocenyl diphosphines $R_2PF\text{-}P(R')_2$ are effective, tunable ligands for the iridium catalyzed enantioselective hydrogenation of *N*-aryl imines in the presence of iodide and acid promoters. Structure–activity/selectivity correlations were found for the hydrogenation of *N*-(2-ethyl-6-methylphenyl)-*N*-(1′-methoxymethyl)-ethylidene-amine (MEA-imine) and for 2,3,3-trimethylindolenine (TMI). Extremely high catalytic activity and moderate to good enantioselectivity were observed for the MEA imine using a catalyst generated in situ from $[Ir(cod)Cl]_2$ and (*R*)-(*S*)-PPF–$P(3,5\text{-}Xyl)_2$ (xyliphos). With the same type of catalysts, several other *N*-aryl imines can be hydrogenated with enantioselectivities between 31 and 96%, albeit with lower catalyst activities.

Keywords: Enantioselective hydrogenation; *N*-Aryl imines; Ferrocenyl diphosphines; Ir-diphosphine catalysts; Structure–activity correlation

1. Introduction

The technical application of catalytic enantioselective reactions is slowly gaining acceptance in the fine and specialty chemicals industry [1,2]. One major problem is the often very pronounced product specificity which means that the structure of the catalyst, usually a metal complex with chiral ligands, has to be tuned or tailored for each specific transformation [3]. Up to now the search for the optimal catalyst is a very empirical process where screening strategies and the intuition of the chemist are the dominant elements. A major hurdle in this endeavor is the difficult access to many chiral phosphines, because they are not available commercially and/or difficult to prepare. A particular advantage of a new class of ferrocenyl diphosphine ligands (see Fig. 1) developed by Togni and Spindler [4] is the fact that the two phosphine groups can be introduced sequentially. This means that a large number of different ligands can be prepared with a relatively small synthetic effort. In addition, their electronic and steric properties can be varied easily and thereby be tuned to the needs of a specific transformation. In this communication we describe the results of a structure–activity/selectivity study for the iridium-catalyzed hydrogenation of several *N*-aryl imines (see Fig. 2).

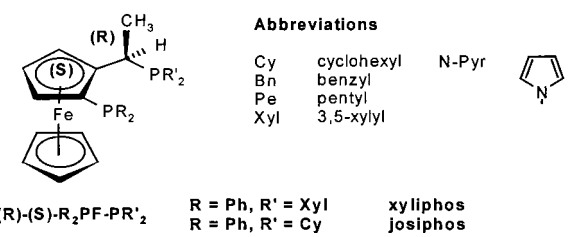

Fig. 1. Structure of the ferrocenyl diphosphine ligands and abbreviations used in this study.

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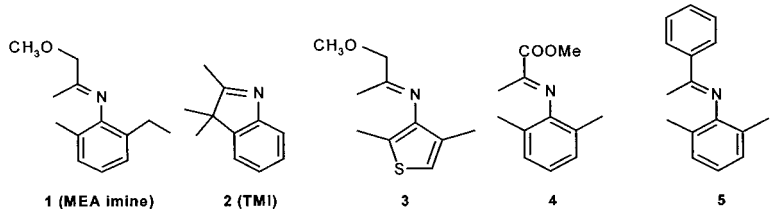

Fig. 2. Structure of imine substrates used in this study.

Table 1
Hydrogenation of MEA imine **1** catalyzed by Ir–R_2PF–PR'_2 catalysts: aryl versus alkyl substituents and effect of configuration (for R and R′ see Fig. 1) [a]

Entry	Ligand		Time (h)	Conv. (%)	Tof (h^{-1})	ee [b] (%)	Comments
	R	R′					
1.1	Ph	′Bu	18	6	3	n.d.	
1.2	Ph	Cy	18	low	n.d.	47	[c]
1.3	Ph	Cy	18	65	29	61	Me_5-cp derivative
1.4	4-CF_3–Ph	Cy	18	80	18	21	
1.5	4-CF_3–Ph	Ph	18	100	44	81	
1.6	Ph	3,5-Xyl	2	99	396	79	Xyliphos
1.7	Ph	3,5-Xyl	18	92	41	39 [d]	(*R*)-(*R*)-configuration

[a] Reaction conditions: 50 ml autoclave, 24 mmol MEA-imine, 10% v/v acetic acid, 150 mg TBAI, s/c 800. 25 bar, 25°C, catalyst: $[Ir(cod)Cl]_2$/ligand.
[b] Excess (*S*)-amine.
[c] Solvent: MeOH/toluene, no acetic acid.
[d] Excess (*R*)-amine.

Table 2
Hydrogenation of MEA imine **1** catalyzed by Ir-(*R*)-(*S*)-R_2PF–PR'_2 catalysts: effect of the nature of R and R′ on ee (%, bold) and maximum rate (mmol min^{-1}) (definition of R and R′, see Fig. 1) [a]

R′/R	3,5-Xyl	3-tol	Ph	4-MeO–Ph	3-MeO–Ph	3,5-$(CF_3)_2$–Ph	4-CF_3–Ph
4-CF_3–Ph	**82**/0.4		**81**/0.1				**69**/0.01
Ph	**80**/0.8	**79**/0.6	**78**/0.7	**76**/0.6	**74**/0.5	**38**/0.01	**71**/n.d. [d]
3,5-$(CF_3)_2$–Ph	**79**/0.02		**81**/0.01		**n.d.**/<0.01		
2-Naphth	**80**/0.7	**80**/0.6	**77**/0.6				
3,5-Xyl	**76**/0.8		**72**/0.7	**76**/ [b]		**49**/0.02	

Additional results: R = Ph, R′ = 4-′Bu–Ph: **82** [c]/0.7; R = Ph, R′ = 3,5-$(SiMe_3)_2$–Ph: **64**/0.6

[a] Reaction conditions: 50 ml autoclave, 24 mmol MEA-imine, 10% v/v acetic acid, 150 mg TBAI, s/c 800. 25 bar, 25°C, catalyst: $[Ir(cod)Cl]_2$/ligand.
[b] Conditions as in Table 3.
[c] 87% ee at −15°C.
[d] Solvent MeOH/toluene instead of acetic acid.

2. Hydrogenation of MEA imine 1

The effect of the structure of the diphosphine ligand on the hydrogenation of MEA imine **1** was investigated in great detail using catalysts generated in situ from $[Ir(cod)Cl]_2$, the respective ligand and in presence of acid and iodide [5]. The first test series were carried out in a 50 ml autoclave stirred with a stirring bar at an s/c ratio of 800 at 25°C and 25 bar hydrogen pressure (Tables 1 and 2). Later, we found that the faster reactions were probably diffusion limited, making the activity data only partially meaningful. Therefore, experiments for the final ligand optimization were carried out in a well mixed 300 ml autoclave (Table 3).

The results of a preliminary study as shown in Table 1 can be summarized as follows: (i) Only ferrocenyl diphosphine ligands gave catalysts with medium to good ee values and satisfactory catalyst stability (results with other phosphine classes not shown). (ii) The two elements of chirality must be matched for a good catalyst performance and the absolute configuration of the planar chirality element determines the sense of

Table 3
Hydrogenation of MEA imine **1** catalyzed by Ir-ferrocenyldiphosphine catalysts: Effect of the nature of the 4-substituent in 3,5 dialkyl-phenyl groups (for R and R′ see Fig. 2) [a]

Entry	Ligand		Time (h)	Conv. (%)	Tof (h^{-1})	ee (%)
	R	R′				
3.1	Ph	4-$^{n}Pr_2N$-3,5-Xyl	3.5	100	28 000	83 [b]
3.2	Ph	4-$^{n}Pe_2N$-3,5-Xyl	26	85	3300	83
3.3	Ph	4-Me_2N-3,5-Xyl	1	100	100 000	80
3.4	Ph	3,5-Xyl	0.6	100	167 000	76
3.5	Ph	4-Bn_2N-3,5-Xyl	21	92	4400	76
3.6	Ph	4-Me_2N–Ph	79	23	3400	74
3.7	Ph	4-(*N*-Pyr)-3,5-Xyl	3	100	33 000	69
3.8	Ph	4-Bn_2N-3,5-$^{i}Pr_2$–Ph	22	99	4500	64
3.9	Ph	4-Me_2N-3,5-$^{i}Pr_2$–Ph	22	98	4500	61

[a] Reaction conditions: 300 ml autoclave, 0.51 mol MEA-imine, 10% v/v acetic acid, 70 mg TBAI, s/c 100,000, 80 bar, 50°C, catalyst: $[Ir(cod)Cl]_2$/ligand.
[b] 87% at −15 °C.

induction. With (*R*)-(*S*)-xyliphos, the (*S*)-enantiomer was obtained with high activity and with 79% ee. (entry 1.6). The diastereomeric ligand (*R*)-(*R*)-xyliphos produced 39% ee of the (*R*)-enantiomer with a much lower activity (entry 1.7). This effect might be due to different conformations of the two diastereomeric Ir-xyliphos complexes. (iii) Aryl groups at the two phosphorus were essential, when the R′ group was alkyl both ee and tof dropped very strongly (entries 1.1–1.4, compared with entries 1.5 and 1.6). With these results in hand, we concentrated our efforts on the variation the P-aryl groups in the (*R*)-(*S*)-R_2PF–PR'_2 series.

The results of a systematic variation of the R and R′ groups are summarized in Table 2. Except for electron deficient R′ groups, the enantioselectivities of the different combinations varied within narrow limits between 74 and 82% ee. A comparison of the various combinations indicated some relatively weak trends. For phenyl substituents in the R position at the cyclopentadienyl ring, the presence of CF_3 groups slightly increased the enantioselectivity, methyl groups had a negative effect on ee, a 2-naphthyl group gave the same ee as the phenyl group. Stronger effects were observed for the R′ position at the stereogenic center where CF_3 groups significantly decreased the enantioselectivity while methyl groups in meta position slightly increased the ee values. The highest ee values in this screening series were observed with R = 4-^{t}Bu–Ph (87% at −15°C). The variations in initial rate were much stronger and especially the presence of trifluoromethyl groups both in the R and R′ position led to a significant rate decrease. Unfortunately, the diffusion problems mentioned above precluded the assessment of the effect of strongly activating substituents (limit for initial rate ca. 0.8 mmol min^{-1}).

For the final ligand optimization we decided to keep the unsubstituted phenyl group in the *R* position. For R′ we chose a number of 4-amino substituted 3,5-xylyl derivatives. This choice was based on further indications from process development work that the 3,5-xylyl group had a significant accelerating effect and we interpreted the results with R = 4-^{t}Bu–Ph on an electronic basis. These tests were carried out with an s/c ratio of 100 000 at 50°C and 80 bar under conditions were rates were not diffusion controlled and the results are compared in Table 3. Indeed, we found combinations that led to increased enantioselectivities compared to xyliphos (entries 3.1–3.3, compared to 3.4 and 3.6), thereby confirming the positive effect of the 3,5-methyl groups and of an electron donating 4-substituent. The nature of the amine substituents had a significant but unsystematic effect, with *N*-propyl and *N*-pentyl as optimum. The effect was negative for a 4-(*N*-Pyr) (entry 3.7) and for bulkier groups in the 3,5 position (entries 3.8, 3.9). Unfortunately, the catalyst activities of all catalysts were significantly lower than for Ir/xyliphos. For this as well as for preparative reasons, xyliphos was chosen as ligand for the commercial process [5].

3. Hydrogenation of other imines

A rather broad ligand screening was also carried out with trimethylindolenine (TMI) **2** used as model for cyclic *N*-aryl imines with fixed C=N geometry. In Table 4 results are sorted according to ee values. Compared to MEA imine **1**, enantioselectivities for **2** were significantly higher, whereas tofs were much lower (no diffusion problems here). Both values varied less for different substitution patterns. As for MEA imine **1**, ligands with basic substituents showed almost no activity, so that the ee was not determined. In contrast to the results for MEA imine **1**, both 3,5-CF_3 groups as

Table 4
Enantioselective hydrogenation of TMI **2** catalyzed by Ir-ferrocenyldiphosphine catalysts: effect of ligand structure (for R and R′ see Fig. 1) [a]

Ligand		*p* (bar)	*T* (°C)	Time (h)	Conv. (%)	Tof (h^{-1})	ee (%)	Comments
R	R′							
3,5-Xyl	3,5-Xyl	40	30	47	100	5	93	94% ee at 5 and 15°C
3,5-$(CF_3)_2$–Ph	3,5-Xyl	80	15	18	99	14	89	
4-MeO–Ph	3,5-Xyl	40	30	17	100	15	88	
Ph	4-Me_2N-3,5-Xyl	80	50	17	96	56	88	91% ee at 15°C
Ph	3,5-Xyl	40	30	23	100	11	87	
Ph	4-^{t}Bu–Ph	80	50	18	99	14	86	
Ph	4-Pr_2N-3,5-$^i Pr_2$–Ph	80	50	17	100	15	85	
Ph	4-Pr_2N-3,5-Xyl	80	50	20	100	13	80	
3,5-$(CF_3)_2$–Ph	Ph	80	50	17	98	14	76	
Ph	2-MeO–Ph	40	30	68	29	1	n.d.	
Ph	Cy	40	30	18	6	<1	n.d.	
Ph	^{t}Bu	40	30	24	5	<1	n.d.	
Cy	Cy	40	30	33	2	<1	n.d.	

[a] Reaction conditions: 50 ml autoclave, 3.1 mmol TMI, 10 ml toluene, 0.05 ml CF_3COOH, 12 mg TBAI, s/c 250, catalyst: $[Ir(cod)Cl]_2$/ligand.

Table 5
Enantioselective hydrogenation of various *N*-aryl imines catalyzed by Ir-(*R*)-(*S*)-R_2PF–PR'_2 catalysts: effect of ligand structure on ee (best results bold, for R and R′ see Fig. 2) [a]

R/R′ imine	Ph/3,5-Xyl (xyliphos)	Ph/4-CF_3–Ph	Ph/Ph	3,5-Xyl/3,5-Xyl	3,5-$(CF_3)_2$–Ph/Ph
MEA imine **1**	80	71	78	76	**81**
TMI **2**	87			**93**	76
Imine **3**	76		**78**	74	
Imine **4**	**31** (*R*)				24 (*S*)
Imine **5**	67	**96**			

[a] Reaction conditions: MEA imine **1**: see Tables 1–3. TMI **2**: see Table 4. Imine **3**: 5 mmol imine; 5 ml toluene, 2 ml CH_3COOH, 30 mg TBAI, s/c: 200, *T*: 25°C, $p(H_2)$: 30 bar. Imine **4**: 2.47 mmol imine; 8 ml toluene, 2 ml CH_3COOH, 30 mg TBAI, s/c: 100, *T*: 25°C, $p(H_2)$: 40 bar. Imine **5**: 2.23 mmol imine; 8 ml toluene; 0.03 ml CF_3COOH, 12 mg TBAI, s/c 200, *T*: 25°C, $p(H_2)$: 80 bar.

well as electron donating substituents in the 4-position led to lower ee values for **2**. However, the positive 3,5-xylyl effect was more pronounced here as reported for several other catalytic reactions with aryl phosphine ligands [6].

Only very few experiments were carried with imines **3–5**. Imine **3**, a potential intermediate for a herbicide originally developed by Sandoz [7] is closely related to MEA imine **1**. Imine **4** is an intermediate for the fungicide (*S*)-metalaxyl [8], while imine **5** is a model substrate. Whereas **3** could be hydrogenated with ee values up to 78% (best ligand R, R′ = Ph), imine **4** is clearly not a good substrate for the Ir–ferrocenyl diphosphine catalyst with best ee values of 31% for xyliphos (with a different absolute configuration for the two best ligands!). Somewhat unexpectedly, the highest enantioselectivities were reached for imine **5** where the PPF–P(4-CF_3–Ph)$_2$ gave 96% ee. In all cases, significantly lower activities were observed (results not shown).

4. Comparison and conclusions

The enantioselectivities with selected Ir–ligand complexes for the various imines are compared in Table 5. With the exception of imine **3**, the Ir–ferrocenyldiphosphine catalysts with aryl-P substituents gave reasonable to very high enantioselectivities for all *N*-aryl imines tested. However, the catalyst activities varied drastically and the optimal combination of R and R′ groups on the ferrocenyl backbone was different for each substrate. At the moment, we are unable to give an explication for these findings. However, it is obvious that especially the optimal electronic needs seem to be quite different for each *N*-aryl imine.

In conclusion, this new class of ferrocenyl diphosphine ligands is very well suited for the Ir catalyzed hydrogenation of *N*-aryl imines with moderate to very high enantioselectivities and low to very high activities and turnover numbers. Clearly, the modular character of the ligands was a prime success factor for finding the optimal catalyst with a reasonable synthetic effort.

5. Experimental

5.1. Materials

$[Ir(COD)Cl]_2$ was purchased from Johnson-Matthey, 2,3,3-trimethylindoleneine from Aldrich. The imines **1**, **3**, **4** and **5** were prepared by reacting the 2,6-dialkylaniline with the corresponding ketone according to standard procedures.

The ferrocenyl diphosphine ligands were synthesized according to [4]: 1-ferrocenylethyl-*N*,*N*-dimethylamine was reacted with the appropriate P-chlorophosphine $ClPR_2$ to yield the corresponding 1-(2-phosphinoferrocenyl)ethyl-*N*,*N*-dimethylamine which after treatment with one equivalent of the sec.-phosphine HPR'_2 in acetic acid was converted to the 1-(2-phosphinoferrocenyl)-ethylphosphine ($R_2PF-PR'_2$). $ClPR_2$ and HPR'_2 were obtained either from commercial suppliers or prepared in analogy to reported procedures [9].[4]

5.2. Typical hydrogenation procedure

Hydrogenation reactions were performed in a well stirred stainless steel autoclave (50 or 300 ml capacity). Imine, the catalyst and the other reaction components were placed in the autoclave (details see below); the autoclave was sealed, flushed three times with hydrogen pressurizing typically to 20 bars at ambient temperature and venting the gas back, and finally charged with hydrogen to the specified reaction pressure. After the specified time at the indicated temperature, the autoclave was opened and after removal of the solvent the conversion and ee were determined as described below.

Table 6
Details for determination of enantiomeric purity of hydrogenation products by HPLC

Imine	Column	Conditions/retention times
1	Chiralcel OD	*T*: 25°C, hexane/2-propanol: 99.7:0.3/9.9 min (*R*), 10.9 min (*S*)
2	Chiralcel OD-H	*T*: 25°C, hexane/^{i}PrOH: 97:3/11.4 min (−), 12.6 min (+)
3	Chiralcel OD	*T*: 25°C, hexane/^{i}PrOH: 99.9:0.1/82.2 min (*R*), 97.0 min (*S*)
4	Chiralcel OD-H	*T*: 25°C, hexane/^{i}PrOH: 99.8:0.2/19.9 min (*R*), 27.7 min (*S*)
5	Chiralcel AD	*T*: 20°C, hexane/(hexane/^{i}PrOH/$HNEt_2$ 975:25:1) 70:30/8.7 min (1st enantiomer), 9.2 min (2nd enantiomer)

[4] Reduction of the P-chlorphosphines by $LiAlH_4$ afforded the corresponding sec.-phosphines.

5.2.1. Procedures A (with solvents)

Two solutions containing the substrate and the catalyst (generated from $[Ir(cod)Cl]_2$, the diphosphine, the tetrabutylammonium iodide and (if stated) acetic acid), respectively, were prepared under an argon atmosphere, for each using half of the total solvent volume. The two solutions were transferred via steel capillary into the autoclave, which was set under argon before. After sealing the autoclave the reaction was started immediately as described above.

5.2.2. Procedures B (without solvents)

The appropriate amount of imine **1** was placed in a 50 ml stainless steel autoclave. Then, $[Ir(cod)Cl]_2$, the diphosphine, the tetrabutylammonium iodide and acetic acid were added, and the autoclave was sealed and set under argon. The reaction was started immediately as described above.

5.3. Analytical procedures

The conversion of the crude reaction product was determined by glc (column: DB 17/30W, 15 m (JCW Scientific Inc.), temperature program: 60°C/1 min to 220°C, ΔT: 10° min^{-1}). The enantiomeric excess of the reaction product was determined by HPLC as summarized in Table 6.

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