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Enantioselective Homogeneous Hydrogenation of Monosubstituted Pyridines and Furans

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Summary. The first case of an enantioselective hydrogenation of monosubstituted pyridines and furans with homogeneous rhodium diphosphine catalysts with low but significant enantioselectivities and catalyst activities is reported. Best enantioselectivities (*ee*s of 24–27%) were obtained for the hydrogenation of 2- and 3-pyridine carboxylic acid ethyl ester and 2-furan carboxylic acid with catalysts prepared *in situ* from $[Rh(nbd)_2]BF_4$ and the chiral ligands *diop*, *binap*, or ferrocenyl diphosphines of the *josiphos* type. Turnover numbers (*ton*) were in the order of 10–20, turnover frequencies (*tof*) usually 1–2 h^{-1}. Diphosphines giving 6- or 7-ring chelates led to higher *ee*s than 1,2-diphosphines; otherwise, no clear correlation between ligand properties and catalytic performance was found. In some experiments black precipitates were observed at the end of the reaction, indicating the decomposition of the homogeneous catalysts for certain ligand/metal/substrate combinations.

Keywords. Homogeneous catalysis; Enantioselective hydrogenation; Heterocyclic arenes; Rh diphosphine complexes.

Introduction

The enantioselective synthesis of chiral compounds containing substituted cyclohexanes, piperidines, or piperazines is of interest due to their biological activity. Classical ways to synthesizie such ring systems enantioselectively are asymmetric *Diels-Alder* reactions [1], the use of starting materials from the chiral pool [2], or enzymatic methods [3]. A catalytic two-step procedure for the synthesis of chiral piperazines starting from the corresponding pyrazine has been described by *Funchs* and *Roduit* [4] who reported on the enantioselective reduction of tetrahydropyrazine (prepared by Pd/C-catalyzed hydrogenation) by a homogeneous Rh diphosphine complex with *ee*s of 40–97%. We have described a similar approach for the enantioselective synthesis of ethyl nipecotinate using cinchona-modified heterogeneous Pt catalysts for the second step, but *ee*s were rather low [5]. A one-step stereoselective catalytic hydrogenation of the respective aromatic compound would be a very attractive method since many substituted arenes are readily available. However, up to now the hydrogenation of monosubstituted pyrazines is the

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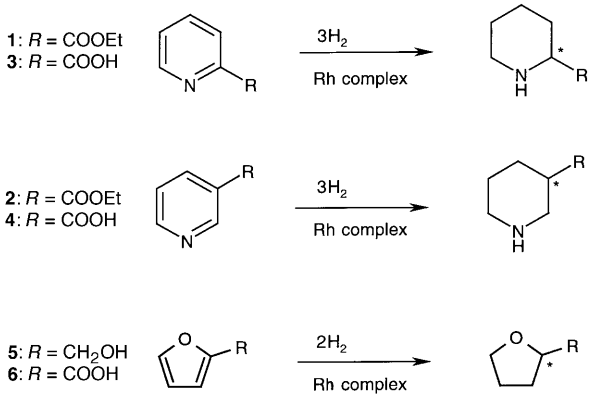
only example of such a reaction [6]. In a patent application, piperazine-2-carboxylic acid *t*-butylesters and *t*-butylamides have been claimed to give *ee*s up to 78% with homogeneous Rh complexes of ferrocenyl diphosphine ligands, whereas the corresponding methyl ester only gave 4% *ee*. All other efforts to hydrogenate aromatic rings enantioselectively have resulted in *ee*s below 6% [7–9]. A few cases of a diastereoselective hydrogenation of aromatic rings with chiral substituents have also been reported with moderate to good stereoselectivities [10–12]; in most cases, heterogeneous catalysts were used. In this paper we describe our attempts to develop homogeneous catalysts for the enantioselective hydrogenation of monosubstituted pyridines and furans.

Results and Discussion

Selection of a suitable metal precursor

A homogeneous catalyst not sufficiently stabilized by its ligands and/or the substrate will decompose to give black precipitates that are often active with respect to ring hydrogenation resulting in racemic products, since the chiral ligand is no longer coordinated to the metal. Because the stability of a complex depends on the metal precursor, we first tested various precursor metal salts with the achiral diphosphine 1,2-*bis*(diphenylphosphino) *e*thane (*dppe*) in the hydrogenation of picolinic acid ethyl ester (**1**, Scheme 1). $[Rh(nbd)_2]BF_4$, $[Rh(nbd)_2Cl]_2$, $[Ir(cod)(py)_2]PF_6$, $RuCl_2$, $Pt(cod)Cl_2$, and $[Ir(cod)Cl]_2$ were chosen; the best activity and a homogenous solution at the end of the reaction was obtained with $[Rh(nbd)_2]BF_4$. $[Rh(nbd)_2Cl]_2$ used in Ref. [6] also gave high activity, but in most of the cases the mixtures were heterogeneous at the end of the reaction. All other precursors gave heterogeneous precipitates and/or were considerably less active. The successful combination $[Rh(nbd)_2]BF_4$/*dppe* showed also reasonable conversions and yields for substrates **2–6**; only for **4** and sometimes **2**, the mono-unsaturated intermediate was observed as a byproduct. For these reasons, **1** was chosen for our further experiments unless otherwise indicated.

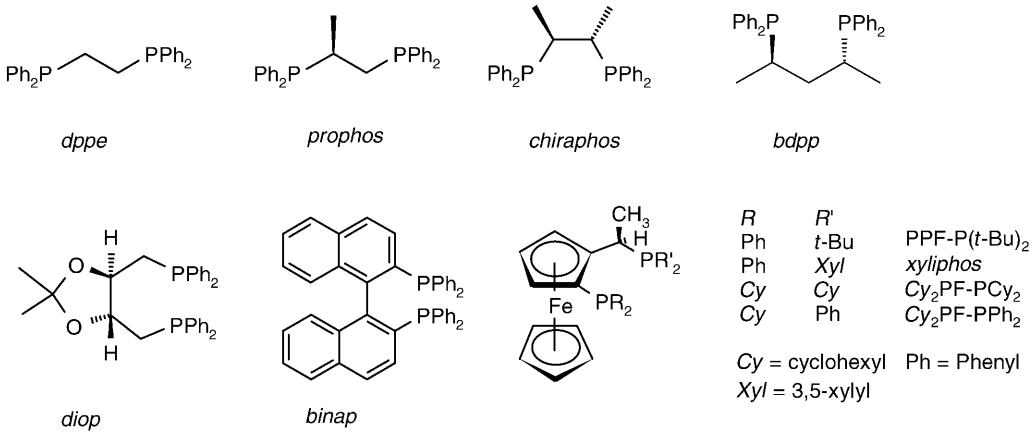


Scheme 1

Screening of ligands and reaction parameters

Representatives of important ligand families (Scheme 2) were selected for screening, using catalysts prepared *in situ* from $[Rh(nbd)_2]BF_4$ in the appropriate solvent. Selected results are presented in Tables 1–4 and Fig. 1. Since the test reactions with *dppe* had shown a rather low catalytic activity, the reactions were generally run at 60°C and 100 bar hydrogen pressure with 5 mol% of catalyst (s/c ratio = 20). The effect of these reaction parameters was investigated with **3** (Table 3).

The most extensive ligand and solvent testing was carried out with the 2- and 3-pyridinecarboxylic acid ethyl esters **1** and **2**. In 24 experiments with **1**, all ligands were investigated in several solvents (EtOH, MeOH, toluene, and *THF*); representative results are summarized in Table 1. Best *ee*s were obtained in ethanol with *binap*, *diop*, and *xyliphos* with moderate to high conversions and very high chemoselectivity. Results in MeOH were comparable; for all other ligand-solvent combinations, *ee*s and quite often also catalytic activities were much lower and/or metal precipitation was observed. For the 3-isomer **2** 14 experiments were carried



Scheme 2

Table 1. Ligand and solvent screening for the hydrogenation of **1**

Ligand	Solvent	Time h	Conv. %	Yield %	*ee* %	Comments
diop	EtOH	20	41	41	27	
binap	EtOH	21	100	96	25	
xyliphos	EtOH	20	23	22	20	
prophos	*THF*	20	100	100	13	With $[Rh(nbd)_2Cl]_2$
bdpp	EtOH	20	100	97	9	Precipitate
chiraphos	EtOH	20	92	90	9	Precipitate
PPF-P(*t*-Bu)$_2$	EtOH	20	29	28	6	
Cy$_2$PF-P*Cy*$_2$	EtOH	20	96	96	5	
PPF-P(*t*-Bu)$_2$	Toluene	4	100	100	4	Precipitate

Reaction conditions: $[Rh(nbd)_2]BF_4$, 60°C, 100 bar, s/c = 20

Table 2. Ligand screening for the hydrogenation of **2**

Ligand	Solvent	Time h	Conv. %	Yield %	Part.[a] %	*ee* %	Comments
bdpp	EtOH	19	85	45	40	17	
diop	EtOH	20	100	52	45	12	
binap	EtOH	17	100	44	56	9	Precipitate
chiraphos	EtOH	19	75	22	53	8	
prophos	*THF*	18	100	64	33	7	With $[Rh(nbd)_2Cl]_2$, precipitate
xyliphos	EtOH	20	64	31	33	6	

Reaction conditions: $[Rh(nbd)_2]BF_4$, 60°C, 100 bar s/c = 20; [a] Partially hydrogenated product

Table 3. Ligand screening and effect of *p*, *T*, and s/c for the hydrogenation of **3** and **4**

	Ligand	Solvent	Time h	Yield %	*ee* %	Comments
3	Cy_2PF-PPh_2	MeOH	20	14	26	s/c = 100
3	Cy_2PF-PPh_2	MeOH	19	52	25	
3	Cy_2PF-PPh_2	MeOH	20	100	25	sc = 5
3	Cy_2PF-PPh_2	MeOH	20	19	23	room temperature
3	Cy_2PF-PPh_2	MeOH	20	16	20	10 bar
3	Cy_2PF-PPh_2	MeOH	20	3.6	17	room temperature/10 bar
3	PPF-P(*t*-Bu)$_2$	MeOH	20	58	17	
3	*diop*	MeOH	20	28	15	
3	Cy_2PF-PCy_2	MeOH	19	100	10	
3	PPF-P(*t*-Bu)$_2$	MeOH/Toluene	20	54	10	With $[Rh(nbd)_2Cl]_2$, room temperature, precipitate
4	Cy_2PF-PCy_2	MeOH	20	8	17	
4	PPF-P(*t*-Bu)$_2$	MeOH	20	5	6	

Reaction conditions: $[Rh(nbd)]_2]BF_4$, 60°C, 100 bar, s/c = 20

out; the best results are shown in Table 2. Here, *ee*s were generally lower, and best *ee*s were observed with *bdpp* and *diop*, whereas *binap* and the ferrocenyl diphosphines were much less effective. In all cases, significant amounts of the stabilized 1,4,5,6-tetrahydro intermediate (column ''part.'' in Table 2) were observed.

For the 2-picolinic acid **3** fewer ligands were screened, but the effect of varying *p*, *T* and s/c as well as of some additives was investigated. *ee*s and activities were similar to those of the corresponding ester **1**. Quite surprisingly, Cy_2PF-PPh_2 turned out to be the most selective ligand by far. Changing the s/c ratio only affected the catalyst activity but not the *ee*, whereas lowering pressure and temperature lowered the activity strongly and the enantioselectivity somewhat. Addition of triethyl amine or trifluoroacetic acid significantly decreased the *ee*s without affecting activity very much (results not shown). The hydrogenation of nicotinic acid (**4**) turned out to be

Table 4. Ligand screening for the hydrogenation of **5** and **6**

	Ligand	Solvent	Time h	Yield %	*ee* %	Comments
5	*binap*	MeOH	19	91	7	Precipitate
5	*prophos*	MeOH	20	98	5	Precipitate
5	*chiraphos*	MeOH	20	98	4	Precipitate
5	*diop*	MeOH	20	93	1	
6	PPF-P(*t*-Bu)$_2$	MeOH	20	3	24	
6	*diop*	MeOH	20	4	4	
6	*Cy*$_2$PF-P*Cy*$_2$	MeOH	19	100	1	
6	*xyliphos*	MeOH	19	85	0	

Reaction conditions: [Rh(*nbd*)$_2$]BF$_4$, 60°C, 100 bar, s/c = 20

very difficult, and due to the formation of oligomeric side products, very low yields of nipecotinic acid resulted. In some cases, the tetrahydro intermediate was also observed. Best *ee*s (17%) were observed with *Cy*$_2$PF-P*Cy*$_2$.

The activity of the different Rh-ligand complexes for the hydrogenation of the two furan derivatives **5** and **6** was investigated only briefly. Whereas **5** was reduced with high conversions with most ligands, this was mainly due to decomposition of the catalysts to black, heterogeneous Rh metal deposits and subsequent heterogeneous hydrogenation with low *ee*s. In contrast, results were just the opposite with **6** where very low conversions but *ee*s up to 24% were obtained using PPF-P(*t*-Bu)$_2$, whereas-somewhat surprisingly-other ferrocenyl diphosphines gave high conversion but no induction, despite the fact that the reaction mixture remained homogeneous.

Comparison of Results

Generally, heterogeneous catalysts are much better suited for the hydrogenation of aromatic rings [13], but as already pointed out, up to now *ee*s with chirally modified heterogeneous catalysts were below 6% [7–9]. For the homogenous hydrogenation of aromatic compounds only very few results have been reported and so far none of the catalytic systems has turned out useful for preparative applications [14–19] because of low activity and productivity. Of particular importance are catalysts based on allyl-cobalt complexes developed by *Mutterties* [14, 15], the C_5Me_5-Rh catalysts of *Maitlis* [19], and – for our purposes – Rh-*dppe*$^+$ complexes as studied by *Halpern* [17]. The patent results with the homogeneous Rh complexes described by *Fuchs* [6] had not yet appeared when we began our study. Since homogeneous catalysts are generally more promising for enantioselective transformations than heterogeneous catalysts [20], we decided to investigate the enantioselective hydrogenation of heteroaromatic compounds. The reason for this choice was that these are usually easier to reduce than the analogous homoaromatic derivatives [13]. As catalysts we chose compounds formed *in situ* from several noble metal precursors and a series of chiral diphosphines (see Scheme 2) with a good track record for the enantioselective hydrogenation of C=C, C=O, and C=N bonds [21]. These ligands cover a broad

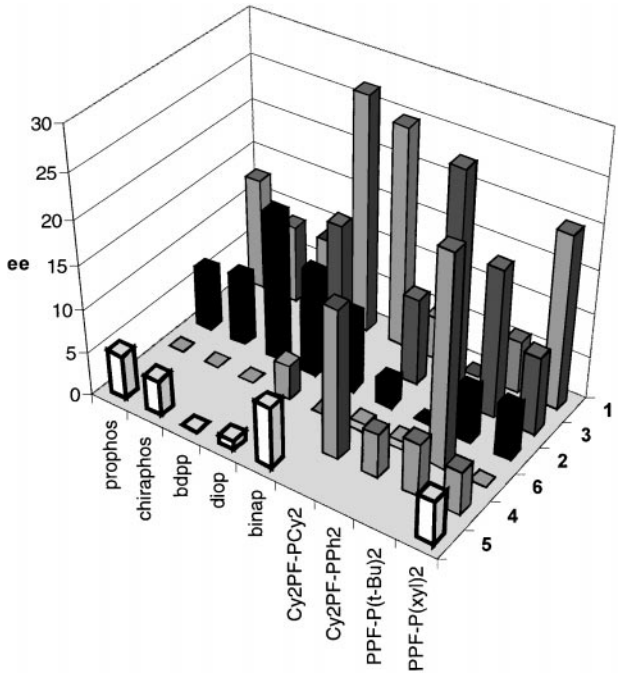


Fig. 1. Best *ee*s for various ligand-substrate combinations; ligands are sorted by increasing chelate size and decreasing basicity

range of properties concerning chelate size (5–7), flexibility (*diop vs*. *binap*), and steric and electronic properties (ferrocenyl diphosphines [22]).

The results presented in the preceding section and summarized in Fig. 1 show that none of the 9 ligands gave more than 24–27% *ee* in our attempts to hydrogenate **1**–**6**. This compares well to the methyl ester of piperazine-2-carboxylic acid which gave an *ee* of only 3.6% [6]. It remains to be seen if the corresponding *t*-butyl esters and amides of pyridines **1** and **2** give much higher *ee*s as claimed for the corresponding pyrazines (78% *ee* for the corresponding *t*-butyl ester [6]). In addition to the low *ee*s, *ton*s and *tof*s were also rather low, similar to those reported in Ref. [6]. In short, we have by no means developed a synthetically useful method. On the other hand, we have shown that Rh diphosphine complexes are indeed able to hydrogenate monosubstituted pyridines and furans at relatively low temperatures. In addition, moderate but significant and reproducible *ee*s have been observed for most of the substrates tested. The chiral induction indicates that the main reaction path is indeed homogeneous. A more detailed comparison of *ee*s and conversions for the 9 ligands tested is presented in Fig. 2. Ligands are grouped for increasing chelate size (*prophos*, *chiraphos*, *bdpp*, *diop*, and *binap*) and decreasing basicity for the 4 *josiphos* type ligands [22]. Our results indicate that chelate sizes of 6 or 7 are preferable. A comparison of the results for *binap* and *diop* shows that ligand flexibility is not an issue. The same holds for ligand basicity: Each of the 4 ferrocenyl diphosphines led to the highest *ee* for a particular substrate.

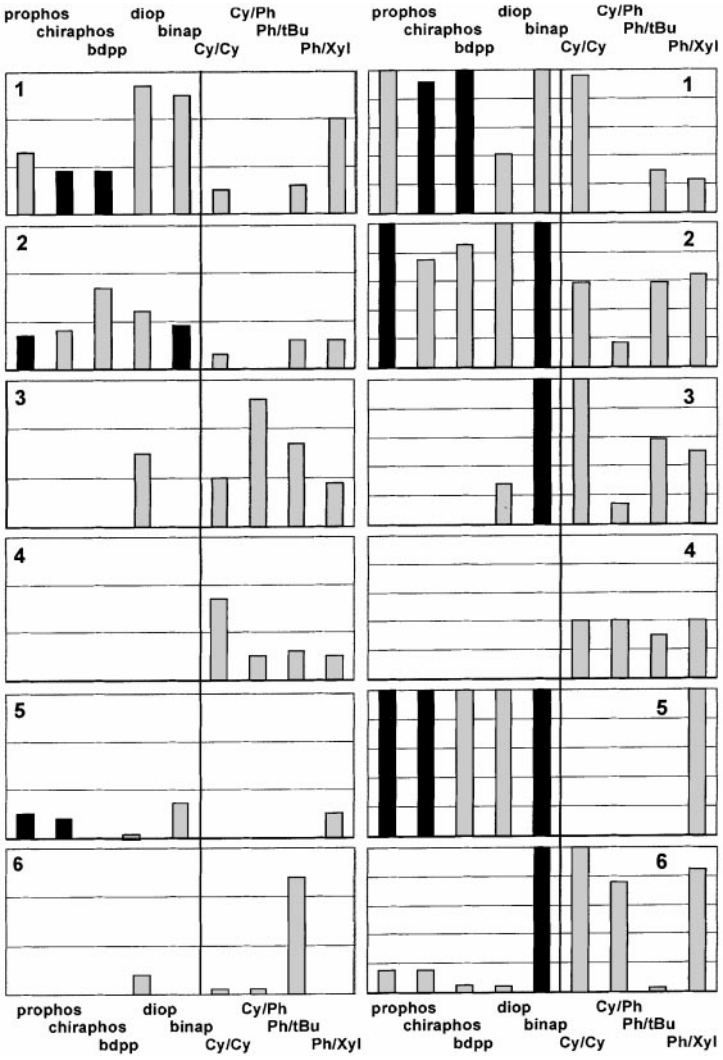


Fig. 2. Best *ee*s (first row, scale 30%) and conversions (second row, scale 100%) for various ligand-substrate combinations; ligands are sorted by increasing chelate size and decreasing basicity; black columns indicate Rh precipitate

Experimental

All regents and solvents were obtained from commerical suppliers and used without further purification. All products showed ^{1}H and ^{13}C NMR results corresponding to literature values.

Typical hydrogenation experiment

200 mg **1** (1.3 mmol) were degassed in a *Schlenk* tube at high vacuum and put under argon. After the addition of 10 cm^3 freshly distilled absolute ethanol, the substrate solution was transferred under argon to a 50 cm^3 autoclave (magnetically stirred, equipped with baffles, thermostated, 60°C). 24.7 mg $[Rh(nbd)_2BF_4$ (0.066 mmol) and a diphosphine ligand (0.066 mmol) were dissolved in 10 cm^3 EtOH with the same technique and transferred to the autoclave (20 cm^3 total EtOH volume).

The hydrogenation was run at 60°C and 100 bar hydrogen pressure for 22 h. With *dppe* as ligand, 100% conversion was obtained. The reaction product contained 96% of the pipecolic acid ethyl ester. The conversion was determined by GLC (see below), and the *ee* was determined by NMR after derivatization with *Mosher*'s acid chloride (see below). All other substrates were hydrogenated in the same apparatus under similar conditions.

Conversion was determined by ^{1}H NMR (**2**, **3**, **4**, and **6**) or GLC analysis (**1**, **2** [5], and **5**, Varian Star 3700 with a packed OV 101 column (2 m) and a FID detector, injector temperature 250°C, detector temperature 280°C). For **1**, the temperature program was 100–250°C, 10°C/min, and the retention times were 6.5 min for **1** and 5.0 min for the product. For **5**, the temperature program was 80–200°C, 5°C/min, and the retention times were 3.7 min for **5** and 4.5 min for the product. The *ee*s for the hydrogenation products of **1–4** were always determined after conversion to the corresponding *Mosher* amides (see Ref. [5] for details with **2** and **4**).

ee determination for the hydrogenation product of **1** [23]

10 mg hydrogenation product (0.064 mmol) were dissolved in 1 cm^3 absolute CH_2Cl_2 and treated with 26 mm^3 Et_3N (0.19 mmol) and 14.5 mm^3 (*R*)-(–)-*Mosher's* acid chloride (0.076 mmol). After 12 h at room temperature the mixture was filtered over cotton, evaporated, and analyzed by ^{1}H NMR spectroscopy. The two diastereomic protons at C-2 of the ester showed doublets at 5.55 (*L*-ester) and 5.35 ppm (*D*-ester). The *ee* of the hydrogenation product of **3** was determined with the same method after esterification with EtOH.

ee determination for the hydrogenation product of **5**

210 mg hydrogenation product (0.098 mmol) were dissolved in 1 cm^3 absolute CH_2Cl_2. After the addition of 40.0 mm^3 Et_3N (0.29 mmol), 1 crystal of N,N-dimethylaminopyridine, and 11.1 mm^3 Ac_2O (0.12 mmol), the mixture was reacted 3 h at room temperature and analyzed by GLC (Carlo Erba GC 6000 with an FID detector and a 30 m β-Dex 110 column supplied by Supelco, helium carrier, 95°C isotherm, injector temperature 250°C, detector temperature 270°C). Enantiomer **a** was observed after 19.3 min, enantiomer **b** after 19.7 min.

ee determination for the hydrogenation product of **6**

10 cm^3 absolute MeOH were cooled with an ice bath to 4°C. 1 cm^3 thionyl chloride (12.8 mmol) was added dropwise under stirring. The ice bath was removed, and the mixture was stirred for 15 min and then cooled to 4°C again. After the addition of 100 mg of the hydrogenation product (0.79 mmol), the ice bath was removed, and the reaction mixtures was stirred for 12 h at room temperature. The *ee* of the methyl ester was determined on the same system as for **5**. Enantiomer **a** was observed after 9.9 min, enantiomer **b** after 10.2 min.

Acknowledgments

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