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The First Highly Enantioselective Homogeneously Catalyzed Asymmetric Reductive Amination: Synthesis of α-*N*-Benzylamino Acids

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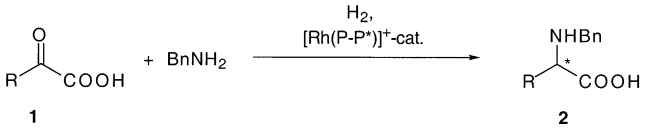
Abstract: High-throughput screening considering a library of 96 chiral *P*-ligands involved in two types of Rh^I complexes was used for the identification of homogeneous catalysts for the highly enantioselective reductive amination of α-keto acids with benzylamine. After optimization of the reaction conditions and scale-up with a cationic Rh-Deguphos catalyst, a range of chiral α-amino acids could be produced by this new reaction in good yield and by up to 98% ee.

The heterogeneously catalyzed one-pot reductive amination of ketones and aldehydes is an important method for the preparation of amines.[1] Interestingly, only a few homogeneous catalysts were tested for this reaction,[2] although the latter should provide the potential of an asymmetric version. With the exception of Blaser's work,[2c] all other investigations known up to now were focused upon the nonasymmetric versions of the reaction. We were especially interested in the asymmetric reductive amination of easily available keto acids,[3] which would afford a fast access to pharmaceutically important chiral α-amino acids.[4]

Recently, we reported the first reductive amination of aldehydes and ketones with Rh^I catalysts.[5] Chelating diphosphines revealed very promising results as ancillary ligands. We could show that even an asymmetric version of this reaction is possible by application of chiral diphosphine ligands. Unfortunately, only poor enantioselectivities were observed when a limited set of ligands were tested. The main obstacle of this approach consisted of the tedious individual screening of a series of ligands and reaction conditions. This was quite time-consuming and finally not very successful, since the reaction yielded poor ee.

Herein, we report that the application of a stepwise test methodology including high-throughput screening is a very effective approach in order to identify highly enantioselective homogeneous catalysts and reaction conditions for the reductive amination of α-keto acids **1** (eq 1) within a short time. In general, this approach may also be useful for related investigations in homogeneous asymmetric catalysis. As an amine benzylamine was chosen because the benzyl group can be easily removed from the products **2**. Moreover, N-protection is frequently required for further synthetic transformations of amino acids.



1 **2**

a: $PhCH_2$; **b:** Me; **c:** Ph; **d:** $HOOCCH_2CH_2$; **e:** $HOOCCH_2$; **f:** $PhCH_2CH_2$; **g:** Me_2CHCH_2; **h:** Me_3CCH_2

To identify most efficient ligands and reaction conditions in the first stage, a large library of P-ligands were tested in the asymmetric reductive amination of phenyl pyruvic acid (**1a**). The reactions were performed in an autoclave containing 96 microreactors. Precatalysts were generated in situ by the reaction of 96 chiral ligands with $[Rh(COD)_2]BF_4$ and $[Rh(COD)Cl]_2$, respectively.

The screening of our ligand library showed that ligands forming five-membered chelates and bearing diphenylphosphino groups gave the best results. Figure 1 shows a detail of results obtained. It is clear that catalysts based on (*R*,*R*)-Norphos,[6] (*S*,*S*)-Chiraphos,[7] and (*R*,*R*)-Deguphos[8] are superior. *N*-Benzylphenylalanine (**2a**) was obtained in up to 82% ee at the first level of testing. Other promising ligands were (*R*)-Prophos,[9] (*R*)-

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(1) (a) Tarasevich, V. A.; Kozlov, N. G. *Russ. Chem. Rev.* **1999**, *68*, 55−72. (b) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985; pp 82−93. (c) Emerson, W. S. *Org. React.* **1948**, *4*, 174−255.

(2) (a) Marko, L.; Bakos, J. *J. Organomet. Chem.* **1974**, *81*, 411−414. (b) Klyuev, M. V.; Khidekel, M. L. *Transition Met. Chem.* **1980**, *5*, 134−139. (c) Blaser, H.-U.; Buser, H.-P.; Jalett, H.-P.; Pugin, B.; Spindler, F. *Synlett* **1999**, 867−868. (d) Margalef-Catala, R.; Claver, C.; Salagre, P.; Fernandez, E. *Tetrahedron Lett.* **2000**, *41*, 6583−6588.

(3) (a) Lin, Y.-S.; Yamamoto A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: Hoboken, 2002; pp 2399−2423. (b) Nikalje, M. D.; Ali, I. S.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett.* **2000**, *41*, 959−961. (c) Lower, E. S. *Riv. Ital. Sostanze Grasse* **1996**, *73*, 469−474. (d) Collin, J. *Bull. Soc. Chim. Fr.* **1988**, 976−781. (e) Chipens, G.; Slavinska, V.; Kreile, D.; Sile, D.; Krumina, L.; Strautina, A.; Karahanov, R. *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* **1988**, 515−535. (f) Cooper, A. J. L.; Ginos, J. Z.; Meister, A. *Chem. Rev.* **1983**, *83*, 321−358.

(4) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1988; pp 1−380.

(5) (a) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Börner, A. *Chem. Commun.* **2000**, 1867−1868. (b) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Börner, A. *Adv. Synth. Catal.* **2002**, *344*, 200−208.

(6) Brunner, H.; Pieronczyk, W.; Schönhammer, B.; Streng, K.; Bernal, I.; Korp, J. *Chem. Ber.* **1981**, *114*, 1137−1149.

(7) Bergens, S. H.; Whelan, J.; Bosnich, B. *Inorg. Synth.* **1997**, *31*, 131−138.

(8) Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326−3343.

(9) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491−5494.

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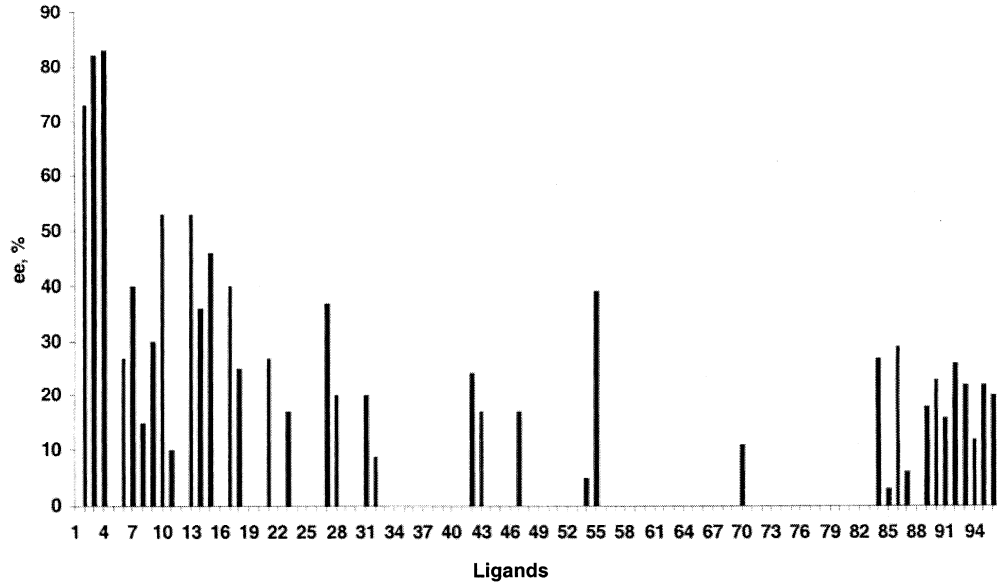
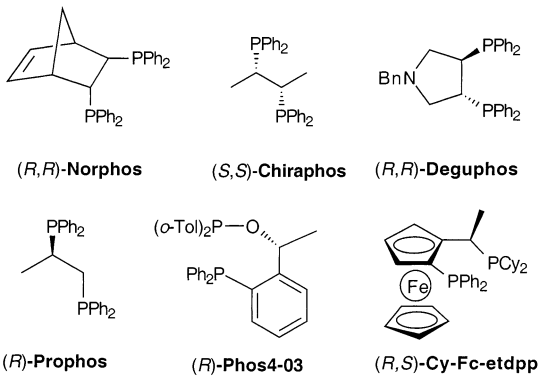


FIGURE 1. Enantioselectivities achieved in the reductive amination of of phenyl pyruvic acid (**1a**) with benzylamine. Depicted is a detail of the results obtained with a library of chiral *P*-ligands: ligand **2**, (*R*,*R*)-Norphos = (*R*,*R*)-2,3-bis(diphenylphosphino)-bicyclo[2.2.1]hept-5-ene; ligand **3**, (*S*,*S*)-Chiraphos = (*S*,*S*)-bis(diphenylphosphino)butane; ligand **4**, (*R*,*R*)-Deguphos = (*R*,*R*)-1-benzyl-3,4-bis(diphenylphosphino)pyrrolidine; ligand **13**, (*R*)-Prophos = (*R*)-1,2-bis(diphenylphosphino)propane; ligand **15**, (*R*)-Phos4-03 = (*R*)-1-[2′-(diphenylphosphino)phenyl]di(*o*-tolyl)phosphinyloxyethane; ligand **17**, (*R*,*S*)-Cy-Fc-etdpp = (*R*)-1-[(1*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldiphenylphosphine. Conditions: 0.1 mmol of phenylpyruvic acid **1a**, 0.15 mmol of benzylamine, 1 μmol of $[Rh(COD)_2]BF_4$ and 1.1 μmol of ligand, 0.5 mL of methanol, initial H_2 pressure 40 bar.

Phos4-03,[10] and (*R*,*S*)-Cy-Fc-etdpp.[11] Noteworthy is that all successful ligands differ considerably in their structure. Therefore, there is no unique rationalization possible at the moment.



After the identification of the most promising ligands in the next stage, we confirmed the results obtained at a 0.1 mmol scale by running the reductive amination of **1a** in a larger scale. The reactions with 0.5 mmol of the substrate were performed in an array hosting eight closed 2 mL autoclaves. With catalysts based on (*R*,*R*)-Norphos, (*S*,*S*)-Chiraphos, and (*R*,*R*)-Deguphos nearly quantitative yields and high ee's were achieved within 24 h (Table 1).

TABLE 1. Yields and Enantioselectivities Achieved in the Reductive Amination of Phenylpyruvic Acid (1a) with Benzylamine Catalyzed by Rh(I) Complexes[a]

run	ligand	yield (%)	ee (%)
1	(*R*,*R*)-Norphos	99	95 (*S*)
2	(*S*,*S*)-Chiraphos	99	91 (*R*)
3	(*R*,*R*)-Deguphos	98	92 (*S*)
4	(*R*)-Prophos	24	27 (*R*)
5	(*R*)-Phos4-03	98	46 (*S*)
6	(*R*,*S*)-Cy-Fc-etdpp	55	42 (*S*)

[a] Conditions: 0.5 mmol of phenylpyruvic acid (**1a**), 0.75 mmol of benzylamine, 5 μmol of $[Rh(COD)_2]BF_4$, 5 μmol of ligand, 1.5 mL of MeOH, 24 h, room temperature, initial hydrogen pressure: 60 bar.

TABLE 2. Influence of Solvents and Additives upon Yield and Enantioselectivity of the Reductive Amination of Phenylpyruvic Acid (1a) with Benzylamine with [Rh[(*R*,*R*)-Deguphos](COD)]BF_4[a]

run	solvent	additive	yield[b] (%)	ee (%)
1	MeOH		44	98 (*S*)
2	EtOH		49	97 (*S*)
3	THF		*c*	
4	toluene		*c*	
5	MeOH	CF_3COOH	64	98 (*S*)
6	MeOH	HCl	67	98 (*S*)
7	MeOH	DMAP	*c*	
8	MeOH	*t*-BuOK	*c*	

[a] Conditions: 0.5 mmol of phenylpyruvic acid (**1a**), 0.75 mmol of benzylamine, 0.5 mmol of additive, 5 μmol of [Rh[(*R*,*R*)-Deguphos](COD)]BF_4, 1.5 mL of solvent, 4 h, room temperature, initial hydrogen pressure: 60 bar. [b] Yield of *N*-benzylphenylalanine (**2a**). [c] No product was formed.

To study the effect of solvents and additives upon rate and enantioselectivity in the third stage, the reaction with {Rh[(*R*,*R*)-Deguphos](COD)}BF_4 as precatalyst was studied more in detail. The results are summerized in

(10) Bosch, B. E.; Trauthwein, H.; Riermeier, T.; Dingerdissen, U.; Monsees, A. (Aventis Research & Technologies Gmbh & Co Kg, Germany). Ger. Patent. DE 19918420, 2000.

(11) Spindler, F.; Wirth-Tijani, A.; Landert, H. (Ciba-Geigy A.-G., Switz.) EP 612758 1994.

(12) (a) Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *46*, 327−333; b) Hassan, N. A.; Bayer, E.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3747−3758. (c) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539−4547.

TABLE 3. Yields and Enantioselectivities of the Reductive Amination of α-Keto Acids 1a−h with Benzylamine

	substrate						
run	no.	R	cond[a] (time (h))	precatalyst[b]	product[c]	yield (%)	ee[e] (%)
1	**1a**	$PhCH_2$	II (3)	A	*N*-Bn-Phe (**2a**)	99 (81)[d]	98 (97)[d] (*S*)
2	**1b**	Me	I	A	*N*-Bn-Ala (**2b**)	43	78 (*S*)
3	**1b**	Me	I	B	*N*-Bn-Ala (**2b**)	32	43 (*S*)
4	**1c**	Ph	I	A	*N*-Bn-Phg (**2c**)	27	19 (*R*)
5	**1c**	Ph	I	B	*N*-Bn-Phg (**2c**)	24	9 (*S*)
6	**1c**	Ph	II (20)	C	*N*-Bn-Phg (**2c**)	47	
7	**1d**	$HOOCCH_2CH_2$	I	A	*N*-Bn-Glu (**2d**)	19	60 (*S*)
8	**1d**	$HOOCCH_2CH_2$	I	B	*N*-Bn-Glu (**2d**)	31	13 (*S*)
9	**1d**	$HOOCCH_2CH_2$	II (3)	C	*N*-Bn-Glu (**2d**)	51	
10	**1e**	$HOOCCH_2$	I	A	*N*-Bn-Ala (**2b**)	38	73 (*S*)
11	**1e**	$HOOCCH_2$	I	B	*N*-Bn-Ala (**2b**)	86	39 (*S*)
12	**1f**	$PhCH_2CH_2$	I	A	*N*-Bn-Bn-Ala (**2f**)	79	81 (+)[f]
13	**1f**	$PhCH_2CH_2$	I	B	*N*-Bn-Bn-Ala (**2f**)	79	35 (+)
14	**1g**	Me_2CHCH_2	II (2)	A	*N*-Bn-Leu (**2g**)	99	90 (*S*)
15	**1g**	Me_2CHCH_2	I	B	*N*-Bn-Leu (**2g**)	46	61 (*S*)
16	**1h**	Me_3CCH_2	II (24)	A	*N*-Bn-*t*-Bu-Ala (**2h**)	94	86 (+)[g]
17	**1h**	Me_3CCH_2	I	B	*N*-Bn-*t*-Bu-Ala (**2h**)	32	60 (+)

[a] Conditions: (I) 1 mmol of keto acid, 1 mmol of benzylamine, 3 mL of methanol, 10 μmol of precatalyst in 100 μmol of CH_2Cl_2, 24 h, room temperature, initial hydrogen pressure: 60 bar; (II) 10 mmol of keto acid, 15 mmol of benzylamine, 50 μmol of precatalyst, 50 mL of methanol. [b] precatalysts: (A) {Rh[(*R*,*R*)-Deguphos](COD)}BF_4, (B) {Rh[(*R*,*R*)-Norphos](COD)}BF_4, (C) [Rh(dppb)(COD)]BF_4. [c] *N*-Bn-Phe = *N*-benzylphenylalanine, *N*-Bn-Ala = *N*-benzylalanine, *N*-Bn-Phg = *N*-benzylphenylglycine, *N*-Bn-Glu = *N*-benzylglutamic acid, *N*-Bn-Bn-Ala = *N*-benzylbenzylalanine, *N*-Bn-*t*-Bu-Ala = *N*-benzyl-*tert*-butylalanine. [d] After recrystallization from DMF. [e] In all cases with the exception of run 1, the ee values were determined by HPLC on chiral columns (Chirobiotic R). The absolute configuration was obtained by comparison of the optical rotation with values given in ref 12. [f] $[\alpha]^{27}_D = +32.2$ (*c* 1, AcOH). [g] $[\alpha]^{26}_D = +11.2$ (*c* 1, AcOH).

Table 2. To make the effects more visible in comparison to the first level of testing (Table 1), the time for the reaction was shortened to 4 h, which influenced the yields.

As clearly shown, maximum yield and highest ee values were obtained in alcohols as solvent. While the presence of an acid accelerated the reaction, strong bases and aprotic solvents had a disadvantageous effect.

On the basis of these preliminary results, the asymmetric reductive amination of phenylpyruvic acid (**1a**) with benzylamine applying the isolated precatalyst [Rh[(*R*,*R*)-Deguphos](COD)]BF_4 in a 10 mmol substrate scale was performed. (*S*)-*N*-Benzylphenylalanine (**2a**) was obtained in quantitative yield. The product crystallized from the reaction mixture in 98% ee. It is noteworthy that attempts to recrystallize this material diminished its optical purity.

To broaden the scope of this reaction, next we employed also other α-keto acids as substrate. On the basis of a parallel screening as discussed above in the reaction with pyruvic acid (**1b**), again the Rh(I) catalyst based on (*R*,*R*)-Deguphos was revealed to be superior at the first level of testing and gave the desired product in 62% ee. After optimization of the reaction, (*S*)-*N*-benzylalanine (**2b**) was obtained in 78% ee. In Table 3, all results including also those obtained with other catalysts and substrates are listed. Unfortunately, when phenylglyoxylic acid (**1c**) was used as substrate *N*-benzylphenylglycine (**2c**) was formed in poor yields and low ee independent of the catalyst used (runs 4 and 5). The reductive amination of 2-oxoglutaric acid (**1d**) with [Rh[(*R*,*R*)-Deguphos](COD)]BF_4 gave amino acid **2d** in low yield, but with 60% ee (run 7). Application of the Norphos catalyst (run 8) improved the yield but lowered the enantioselectivity. Interestingly, the achiral precatalyst [Rh(dppb)(COD)]BF_4 (dppb = 1,4-bis(diphenylphosphino)butane) converted substrates **1c**,**d** faster into the product than the chiral catalysts (runs 6, 9). It is noteworthy that under the standard conditions applied with oxaloacetic acid (**1e**) as substrate with both precatalysts decarboxylation took place (runs 10, 11). The product (*S*)-*N*-benzylalanine (**2b**) was obtained in moderate yield. Good results were achieved with 2-oxo-4-phenylbutyric acid (**1f**), 4-methyl-2-oxovaleric acid (**1g**), and 4,4-dimethyl-2-oxovaleric acid (**1h**) as substrates in the presence of [Rh[(*R*,*R*)-Deguphos](COD)]BF_4. Even after the amount of precatalysts was reduced to 0.5 mol %, N-benzylated amino acids were formed with good and excellent yields and ee's within 2−3 h. Only the sterically more hindered substrate **1h** required a longer reaction time (run 16). In all cases, the effect of the Norphos-catalyst was inferior (runs 13, 15, and 17). Unfortunately, due to the high complexity of the mechanism of the reductive amination[5b] conclusions about the chemoselectivity (formation of the nondesired alcohol) and the stereoselectivity cannot be drawn at the moment.

In conclusion, the stepwise approach including high-throughput screening represents an promising method for the fast discovery of new homogeneously catalyzed enantioselective reactions and the identification of most efficient catalysts. The high synthetic importance of this approach could be clearly demonstrated in the first highly enantioselective reductive amination of α-keto acids using a cationic Rh-Deguphos catalyst, where several chiral α-amino acids could be produced in good yield and by up to 98% ee.

Experimental Section

The screening of the members of the ligand library was performed in a reactor hosting 96 glass vials. In a glovebox under argon successively in each vessel 100 μL of CH_2Cl_2, 1 μmol of [$Rh(COD)_2$]BF_4 (100 μL 0.01 M in CH_2Cl_2), or 0.5 μmol [Rh(COD)Cl]$_2$ (50 μL 0.01 M in CH_2Cl_2) and 1.1 μmol of ligand (110 μL 0.01 M in CH_2Cl_2) were mixed. Then the solvent was evaporated. To each vessel was added 0.5 mL of a freshly prepared solution of 0.1 mmol of α-keto acid and 0.15 mmol of benzylamine in MeOH. The reactor was placed in an autoclave. Hydrogen with an initial pressure of 40 bar was added, and the

vessels were stirred for 24 h. After expansion, the amino acids were reacted with TMSCl in MeOH and subsequently acylated with pentafluoropropionic anhydride. The products were analyzed by GC (CP Chirasil DEX-CB).

The reactions in the 2 mL autoclaves were run in a similar manner at a 0.5 mmol scale. After expansion of the reactor the reaction mixture was diluted with ether. The product which precipated was filtrated, washed with ether, and dried. The determination of the ee was performed with HPLC using a chiral column (Chirobitic R, MeOH/0.5% TFA, pH 4.0) or after derivatization by means of GC.

Trials in the 100 mL autoclave: A solution of 10 mmol of keto acid and 37 mg (0.05 mmol) of [Rh[(*R*,*R*)-Deguphos](COD)]BF_4 in 50 mL of methanol was transferred under argon into the autoclave. Under ice cooling, 1.6 mL (15 mmol) of benzylamine was added. The autoclave was flushed with hydrogen. The reaction was run at an initial pressure of 60 bar at room temperature. The reaction mixture was diluted with ether. The product precipitated was filtrated, washed with ether, and dried.

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Supporting Information Available: A list of selected members of the ligand library, tables of hydrogenation data, and analytical data of *N*-benzylamino acids. This material is available free of charge via the Internet at http://pubs.acs.org.

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