Asymmetric Cleavage of Racemic 1,3-Oxazolidines – A New Dynamic Process in Homogeneous Rh(I)-Catalyzed Hydrogenation

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Abstract: The mechanism of the homogeneously catalyzed hydrogenation of 1,3-oxazolidines with a Rh(I) diphosphane catalyst affording tertiary hydroxyethyl-substituted amines was investigated with the help of D_2 labelling experiments. It was found that the reaction proceeds *via* prochiral intermediates with, preferentially, an iminium cation being in equilibrium with the 1,3-oxazolidine. This observation opened up the opportunity to run the reaction stereoselectively by employment of a racemic 1,3-oxazolidine and a chiral catalyst. By means of high-throughput screening considering 144 catalysts a cationic Rh(NORPHOS)-complex was identified as the most efficient catalyst, which afforded after optimization of solvent, temperature and H_2 pressure the corresponding chiral hydroxyethylamine in 95% yield and 80% ee.

Keywords: enantioselective hydrogenation; homogeneous catalysis; phosphanes; P-ligands; rhodium

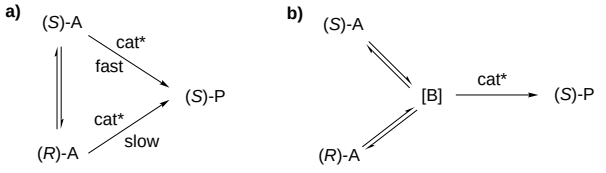
Introduction

Although significant progress in enantioselective synthesis has been achieved in the last decades the separation of enantiomers is still an important task.[1] Principally kinetic resolution can give both enantiomers but the maximum yield of one enantiomer does not exceed the theoretical yield of 50%.[2] Dynamic kinetic resolution is more advantageous since it can provide a quantitative yield of the desired enantiomer. Of particular interest are those dynamic processes which are assisted by a chiral metal catalyst.[3]

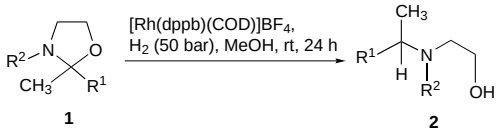
Among dynamic processes two general types can be distinguished (Scheme 1). The first type (**a**) known as "dynamic kinetic resolution" is associated with the fast preequilibrium of enantiomers.[3] In this case a chiral catalyst promotes selectively the conversion of one enantiomer into the chiral product. Processes of type **a** are well-documented for different types of organic reactions[4] and even examples of hydrogenation reactions are known.[5]

The second type (**b**) is characterized by the formation of a single prochiral intermediate (**B**) from both enantiomers and its subsequent enantioselective reaction in the presence of a chiral catalyst. Up to now type **b** processes are mainly restricted to the Pd-catalyzed asymmetric allylic substitution of racemic allyl acetates[6] and the alkylation of prochiral carbanions in the presence of chiral phase-transfer catalysts.[7] To the best of our knowledge there is no example for the latter type concerned with catalytic hydrogenation.

In recent reports we showed that under rather smooth reaction conditions acyclic and cyclic *N,O*-acetals can be cleanly and regioselectively reduced to amines by molecular hydrogen in the presence of a homogeneous



Scheme 1. Two types of dynamic processes.

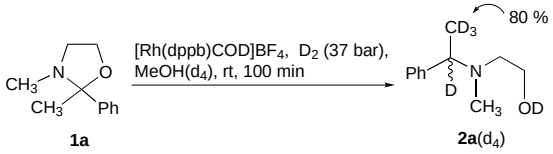


Scheme 2. Homogeneously catalyzed reductive cleavage of 1,3-oxazolidines.

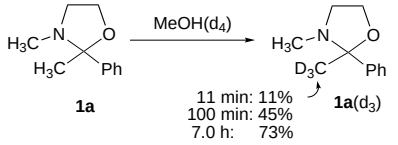
  1615-4150/03/3451+2-239–245 $ 17.50+.50/0

Rh(I) catalyst bearing a chelating phosphorus compound as ancillary ligand.[8,9] This finding could be advantageously employed for the hydrogenation of cyclic *N,O*-acetals **1** derived from non-symmetrical ketones giving rise to *N*-alkylaminoethanol derivatives **2** (Scheme 2). For this reaction [Rh(dppb)(COD)]BF_4 [dppb = 1,4-bis(diphenylphosphanyl)butane, COD = cyclooctadiene] was shown to be highly effective as a precatalyst.

From the stereochemical point of view the stereogenic carbon atom at C-2 of oxazolidine **1** is transformed into another chiral center linked in compound **2** to the amine functionality. It was interesting to investigate if a suitable chiral catalyst is able to influence this reaction in an enantioselective manner when racemic oxazolidines are used as substrates.



Scheme 4. Deuteration of 1,3-oxazolidine **1a** in the presence of a precatalyst.



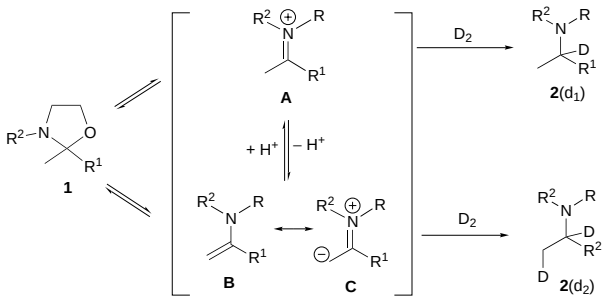
Scheme 5. Spontaneous H-D exchange in 1,3-oxazolidine **1a** in $MeOH(d_4)$.

Results and Discussion

Mechanistic investigations

In order to identify key intermediates in the hydrogenation of 1,3-oxazolidines, first, we tried to elucidate the mechanism of the process in more detail. It is reasonable to assume that the reduction proceeds *via* the formation of two species such as iminium cation **A** or enamine **B** as exemplarily depicted with a 2-methyl substituted 1,3-oxazolidine **1** in Scheme 3. In both cases an sp^2-configurated carbon atom is formed, which corresponds to the formation of a prochiral center. Both intermediates are produced from the same chiral precursor. These two species interconvert through the common zwitterionic intermediate **C** by abstraction of one proton from the solvent. Intermediate **C** represents a charged resonance structure of enamine **B**.

The following facts derived from the literature can be used as a support for Scheme 3. Thus, iminium cation **A** was detected in the hydrolysis of compounds of type **1**.[10] Zwitterionic intermediates of type **C** are usually suggested for the rationalization of the mechanism of the hydrolysis[11] and alkylation[12] of enamines. The related reductive amination using hydride agents is thought to involve the intermediacy of a highly reactive iminium ion.[13,14]



R = $CH_2CH_2O^-$ (for **A**); CH_2CH_2OH/D (for **B**, **C** and **2**)

Scheme 3. Possible key intermediates in the deuteration of a 1,3-oxazolidine.

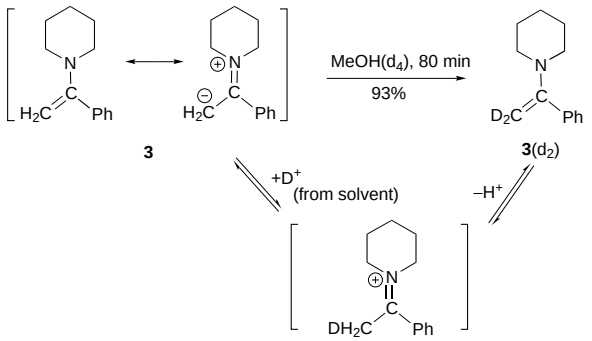
To distinguish between these two pathways labelling experiments with D_2 were carried out (Scheme 3). It is evident that in case of intermediacy of iminium cation **A** only one D atom should be found in the amine [**2**(d_1)].[15] However, if the reaction proceeds *via* enamine intermediate **B** incorporation of two vicinal D atoms can be expected [**2**(d_2)].

As a model compound 1,3-oxazolidine **1a** (Scheme 4) was chosen which is easily prepared by condensation of acetophenone with *N*-methylethanolamine. The deuteration of **1a** at 37 bar initial D_2 pressure with 1 mol % of [Rh(dppb)(COD)]BF_4 as a precatalyst in 2 mL $MeOH(d_4)$ gave within 100 min amino alcohol **2a** in a yield of 80%. Noteworthy was the high D content measured in the product. NMR analyses revealed the incorporation of one D atom in the benzylic position. In the Me group of **2a** 80% of D was found.

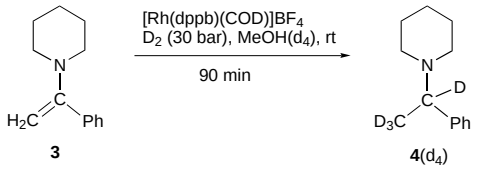
The unexpected high degree of D incorporation during the hydrogenation with D_2 can be rationalized by a spontaneous H-D exchange in the Me group of **1a** in $MeOH(d_4)$. Thus, by treatment of **1a** in $MeOH(d_4)$ in the absence of the precatalyst and D_2, the D content in the Me group of **1a**(d_3) was 11% after 11 min, 45% after 100 min and 73% after 7 h (Scheme 5).

Comparison of the degree of D-incorporation in the Me group of **1a** after 100 min (Schemes 4 and 5) shows that the spontaneous H-D exchange was enhanced during the hydrogenation with [Rh(dppb)(COD)]BF_4. This acceleration of H-D exchange might be a result of the coordination of the substrate to the Rh centre.

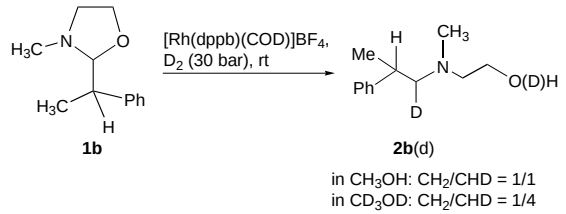
Spontaneous H-D exchange of methylene hydrogen atoms was also observed when enamine **3** derived from acetophenone and piperidine was treated in $MeOH(d_4)$ (Scheme 6). After 80 min 93% of D was found in the methylene group of the enamine. These facts are in



Scheme 6. H-D exchange in enamine **3** in $MeOH(d_4)$.



Scheme 7. Hydrogenation of an enamine with D_2.



Scheme 8. Hydrogenation of 1,3-oxazolidine **1b** with D_2.

agreement with Scheme 2 and the participation of species **A** and **C** in the H-D exchange.

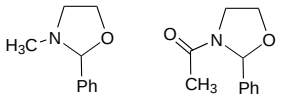
These data give the first direct evidence for the C-H acidity of *N,O*-acetals. It is also remarkable that spontaneous H-D exchange has never been studied with simple enamines.

Due to this fast spontaneous H-D exchange it is not surprising that the catalytic hydrogenation of enamine **3** in $MeOH(d_4)$ with D_2 gave exclusively the fully deuterated benzylamine derivative **4**(d_4) (Scheme 7).

Hence from the labelling experiments using substrate **1a** it was impossible to conclude which species **A** or **B** are responsible for the reduction of the oxazolidine **1a**. However, participation of iminium cation **A** became evident when deuteration of substrate **1b** was carried out (Scheme 8).

In this experiment only one deuterium atom was found in the product **2b**(d) at the carbon atom adjacent to nitrogen. No other D atoms were detected in **2b**(d) independent on the solvent used [MeOH or $MeOH(d_4)$]. In addition, no spontaneous H-D exchange in the initial substrate was observed. This result may be attributed to steric difficulties in the formation of relevant zwitterionic species of type **C** when the β-carbon atom is shielded by two substituents.[16]

Further indirect evidence for the participation of the iminium cation **A** as a common intermediate in the reduction of 1,3-oxazolidines could also be derived by consideration of 1,3-oxazolidines **1c** and **1d**.



Thus, the fast hydrogenation of 3-methyl-2-phenyl-1,3-oxazolidine (**1c**) observed can only be rationalized by assumption of an iminium cation. In contrast, the structurally related substrate **1d** resisted hydrogenation under the conditions described above. Obviously, the electron-withdrawing acetyl group prevents the intermediate formation of the iminium cation required for the hydrogenation.

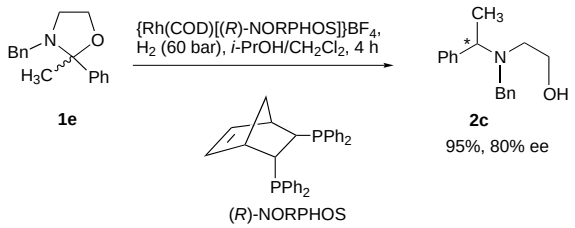
The intermediate formation of iminium cations of type **A**, as evidenced herein is important for a wide range of reductive amination or reductive alkylation reactions in which half-aminals and iminium species were postulated as intermediates but no experimental evidence was given up to now.[17]

Enantioselective Hydrogenation

As shown above there are several pieces of evidence that the reduction of chiral *N,O*-acetals proceeds *via* a prochiral iminium cation. A suitable chiral catalyst should be able to differentiate between both enantiotopic faces of this intermediate.

In order to verify this hypothesis, 3-benzyl-2-methyl-2-phenyl-1,3-oxazolidine **1e** was chosen as substrate. The product of the hydrogenation, hydroxyethylamine **2c**, in turn might be easily debenzylated and used for the synthesis of compounds of pharmaceutical relevance. Substrate **1e** is chiral, but due to the non-stereoselective synthesis it is racemic.

The enantioselective reduction of this 1,3-oxazolidine was investigated in a parallel reactor allowing at once the screening of 48 catalysts. The reactions were carried out in 1 mL glass vials filled with 0.5 mL of methanol as solvent and placed in a rack. Precatalysts were generated *in situ* by mixing equimolar amounts of the relevant phosphorus ligands derived from a ligand library with $[Rh(COD)]_2BF_4$, $[Rh(COD)]_2OTf$ and $[Rh(COD)Cl_2]_2$, respectively. Simultaneously, the 1,3-oxazolidine was added in a substrate:precatalyst ratio of 100:1. The reactions were run at 50 bar hydrogen pressure for 24 h. After identification of the most promising catalysts by HPLC analysis of the reaction products the results were confirmed by upscaling and performance of the hydro-



Scheme 9. Enantioselective hydrogenation of racemic 1,3-oxazolidine **1e.**

genation in individual trials. Among 48 ligands tested Prophos[18] and DeguPHOS[19] were superior and induced enantioselectivities of 40 – 60% ee in the product. The most efficient reaction was achieved by application of a catalyst which was obtained from $[Rh(COD)_2]OTf$ and (*R*)-NORPHOS.[20,21] This catalytic system gave in the parallel screening the desired amino alcohol in 95% yield and 72% ee (Scheme 9). Confirmation of this result was achieved by use of the opposite enantiomer of NORPHOS. With the (*S*)-NORPHOS catalyst amino alcohol **2a** was obtained in 98% yield and 74% ee.

We examined the effect of the solvent and found that alcohols were best suited for the hydrogenation (Table 1).

The reaction was sluggish in aprotic solvents (THF, DMF and CH_2Cl_2) giving either very low conversion or no product at all. We observed an increase of the enantioselectivity when methanol was replaced by 2-propanol. In addition the influence of the hydrogen pressure was also investigated. Higher pressures clearly led to an increase of the reaction rate. There was no obvious pressure effect on the degree of enantioselection. It is noteworthy that quantitative yield but only 50% ee was obtained when the reaction was carried out in a large-scale in pure 2-propanol or methanol under those reaction conditions optimized in a small-scale. Careful studies of large-scale reactions showed that the presence of dichloromethane is essential for high enantioselectivity. In the presence of 6% dichloromethane hydrogen uptake ceased after 4 hours affording quantitatively 2-[benzyl(1-phenylethyl)amino]ethanol **2c** in 80% ee (Scheme 9). Interestingly, the activity of the catalytic system dropped dramatically when alkylammonium halides (benzyl and tetrabutylammonium chloride or iodide) were added even in small amounts.

Conclusions

In summary, with the help of labelling experiments we have shown for the first time that reductive cleavage of racemic 1,3-oxazolidines with homogeneous Rh(I) catalysts proceeds *via* prochial intermediates, most probably iminium cations. Therefore, this process can be considered as a dynamic process of type **b** (Scheme 1). This feature allows the complete conversion of racemic *N,O*-acetals derived from non-symmetrical ketones into enantiomerically enriched hydroxyethylamines by means of an appropriate chiral Rh-diphosphane catalyst. By parallel screening considering 48 diphosphane ligands incorporated in three different catalyst precursors a cationic Rh-NORPHOS complex was found to be superior. Subsequent scale-up and optimization of solvent, temperature and H_2 pressure improved the enantioselectivity in the product by up to 80% ee.

Experimental Section

Solvents were distilled under argon using standard procedures. The compounds in the ligand library were obtained from commercial sources or synthesized according to literature procedures. The complex $\{Rh[(R)\text{-NORPHOS}](COD)\}BF_4$ was prepared from commercially available Rh(acac)(COD) and (2*R*,3*R*)-(−)-2,3-bis(diphenylphosphanyl)-bicyclo[2.2.1]-hept-5-ene.

Table 1. Enantioselective hydrogenation of racemic 2-methyl-2-phenyl-3-benzyl-1,3-oxazolidine **1e** using $[Rh(R)\text{-NORPHOS})(COD)]BF_4$ as a precatalyst (S:C = 100:1).[a]

Run	Solvent	H_2 Pressure [bar]	Time [h]	Temperature [°C]	Yield [%][b]	ee [%][b, c]
1	MeOH	60	12	20	99	74
2	EtOH	60	12	20	99	76
3	*i*-PrOH	60	12	20	99	82
4	*i*-PrOH	60	3	35	97	72
5	*i*-PrOH	40	3	35	98	67
6	*i*-PrOH	20	3	35	93	71
7	*i*-PrOH	10	3	35	74	71
8	*i*-PrOH	5	3	35	46	69

[a] See experimental section for details.
[b] Determined by HPLC analysis (ChiralPak AD, hexane:*i*-PrOH 98:2).
[c] Absolute configuration was not determined.

High-Throughput Screening of the Ligand Library

Preparation of reaction solutions for initial screening was performed on a Hamilton automated workstation in a glovebox under an argon atmosphere. In a typical procedure, each sample was prepared by adding 100 μL of an $[Rh(COD)_2]BF_4$ solution (0.01 M) in CH_2Cl_2 and 110 μL of the ligand solution (0.01 M) in CH_2Cl_2 to 1 mL glass vials equipped with stirring bars. Subsequently, the solvent was removed from all vials and 500 μL of a 0.2 M solution of 3-benzyl-2-methyl-2-phenyl-1,3-oxazolidine **1e** in methanol were added. A rack containing 48 vials was placed in a 1 L flat stainless autoclave and pressurized with 40 bar of hydrogen. At the end of the run the hydrogen was released, each reaction solution was concentrated by purging with a nitrogen gas stream, extracted with 0.4 mL of toluene and diluted with 0.6 mL of heptane. The mixtures were passed through a short Al_2O_3 plug and analyzed by HPLC (ChiralPak AD, hexane:*i*-PrOH = 98:2).

Individual Runs in a Small-Scale

The samples were prepared in a glovebox by mixing 200 μL of a {Rh[(*R*)-NORPHOS](COD)}BF_4 solution (0.01 M) in CH_2Cl_2

Table 2. Hydrogenation of 2-methyl-2-phenyl-3-benzyl-1,3-oxazolidine **1e** using catalysts prepared *in situ* from catalyst precursors and ligand (1:1.1).[a]

Precursor	$[Rh(COD)_2]BF_4$		$[Rh(COD)_2]OTf$		$[Rh(COD)Cl]_2$	
Ligand No.[b]	Yield [%]	ee [%]	Yield [%]	ee [%]	Yield [%]	ee [%]
1	21	8	3	0	88	9
2	43	52	87	62	28	55
3	0	0	0	0	0	0
4	79	52	44	58	90	60
5	2	0	7	0	2	0
6	7	0	17	0	7	0
7	0	0	7	0	17	0
8	19	4	1,5	0	2	0
9	18	0	13	0	21	0
10	25	8	72	2	73	15
11	41	42	93	45	99	41
12	0	0	0	0	0	0
13	21	0	7	0	5	0
14	0	0	33	0	9	0
15	0	0	4	0	3	0
16	0	0	2	0	1,5	0
17	9	0	3	0	1,5	0
18	0	0	10	0	11	10
19	3	0	2	0	7	0
20	1	0	6	0	15	11
21	0.4	0	0,8	0	2	0
22	0,3	0	5	0	9	0
23	0	0	0,6	0	0,3	0
24	8	0	64	3	6	0
25	6	0	37	0	13	0
26	8	5	70	0	37	0
27	19	4	41	9	99	5
28	9	8	21	0	20	9
29	1	0	10	0	2	0
30	2	6	9	0	4	0
31	4	0	61	0	69	0
32	0	0	0	0	0	0
33	27	0	6	0	9	0
34	2	0	65	0	21	0
35	26	0	1	0	1	0
36	2	0	9	0	85	0
37	0,1	0	6	0	59	2
38	0	0	100	10	63	0
39	22	0	100	11	100	8
40	1	0	12	12	7	0
41	0	0	0,2	0	0,8	0
42	0	0	0	0	0	0
43	0	0	5	0	0,4	0

Table 2 (cont.)

Precursor	$[Rh(COD)_2]BF_4$		$[Rh(COD)_2]OTf$		$[Rh(COD)Cl]_2$	
Ligand No.[b]	Yield [%]	ee [%]	Yield [%]	ee [%]	Yield [%]	ee [%]
44	0	0	0	0	68	0
45	0	0	4	0	51	0
46	0	0	2	0	42	0
47	0	0	34	0	68	0
48	0	0	10	0	0,5	0

[a] See experimental section for details. Yields and enantioselectivities were determined by HPLC analysis (ChiralPak AD, hexane:*i*-PrOH = 98:2).

[b] Ligands:

1. *R,R*-DIPAMP = (1*R*,2*R*)-bis[(2-methoxyphenyl)phenylphosphanyl]ethane;
2. *R*-NORPHOS = (2*R*,3*R*)-(−)-2,3-bis(diphenylphosphanyl)-bicyclo[2.2.1]hept-5-ene;
3. *R,R*-CHIRAPHOS = (2*R*,3*R*)-(−)-bis(diphenylphosphanyl)butane;
4. *R,R*-DEGUPHOS = (3*R*,4*R*)-(+)-1-benzyl-3,4-bis(diphenylphosphanyl)pyrrolidine;
5. *R*-CyGanterPhos = (*R*)-[3,4-dimethylphosphaferrocen-2-yl)methyl]dicyclohexylphosphane;
6. *R,R*-Me-DUPHOS = (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholanyl]benzene;
7. *R,R*-Et-DUPHOS = (−)-1,2-bis[(2*R*,5*R*)-2,5-diethylphospholanyl]benzene;
8. *R,R*-Me-BPE = (+)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholanyl]ethane;
9. *R,R*-Et-BPE = (+)-1,2-bis[(2*R*,5*R*)-2,5-diethylphospholano]ethane;
10. *R,R*-Bis(MePhP)benzol = (1*R*,2*R*)-(+)-bis(methylphenylphosphanyl)benzene;
11. *R*-PROPHOS = (2*R*)-1,2-bis(diphenylphosphanyl)propane;
12. *R,R*-SKEWPHOS = (2*R*,4*R*)-(−)-bis(diphenylphosphanyl)pentane;
13. *S*-Phos4 = (*S*)-1-[2′-(diphenylphosphanyl)phenyl]diphenyl-phosphanylethane;
14. *R,S*-Cy-Fc-etdpp = (*R*)-1-{(1*S*)-2-(dicyclohexylphosphanyl)ferrocenyl}ethyldiphenylphosphane;
15. *R,S*-Cy-Fc-etdCyP = (*R*)-1-{(1*S*)-2-(dicyclohexylphosphanyl)ferrocenyl}ethyldicyclohexylphosphane;
16. *R,S*-Ph-Fc-etdtBuP = (*R*)-1-[(1*S*)-2-(diphenylphosphanyl)-ferrocenyl]ethyl-di-*tert*-butylphosphane;
17. *R,S*-JOSIPHOS = (*R*)-1-[(1*S*)-2-(diphenylphosphanyl)ferrocenyl]ethyldicyclohexylphosphane;
18. *R*-BINAP = (*R*)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl;
19. *R*-Carboxybutyl-BINAP = (*R*)-(+)-7-carboxybutyl-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl;
20. *R*-Tol-BINAP = (*R*)-2,2′-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl;
21. *R*-MeO-BIPHEP = (*R*)-(−)-(6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphane);
22. *R*-Tol-MeO-BIPHEP = (*R*)-(6,6′-dimethoxybiphenyl-2,2′-diyl)bis(di-*p*-tolylphosphane);
23. *R,R*-MeAAPHOS = (2*R*,3*R*,5*R*,6*R*)-2,3-dimethoxy-2,3-dimethyl-5,6-bis(diphenylphosphanylmethyl)-1,4-dioxane;
24. *R,S*-Phos3 = (3*R*,4*S*)-3-diphenylphosphanyloxy-4-[4-(di(4-fluorophenyl)phosphanyl-2,5-dimethyl-3-thienyl]tetrahydrofuran;
25. *S,S*-1,2-(BDPPmethyl)-cyclohexane = (1*S*,2*S*)-(+)-*trans*-1,2-bis(diphenylphosphanylmethyl)cyclohexane;
26. *S,S*-DIOP = (4*S*,5*S*)-(+)-4,5-bis(diphenylphosphanylmyrthyl)-2,2-dimethyl-1,3-dioxolane;
27. *S,S*-MOD-DIOP (4*S*,5*S*)-(+)-1,4-bis[bis(3,5-dimethyl-4-methoxyphenyl)phosphanylmyrthyl]-2,2-dimethyl-1,3-dioxolane;
28. *S,S*-BPPM-H = (2*S*,4*S*)-(−)-4-diphenylphosphanyl-2-(diphenylphosphanylmethyl)pyrrolidine;
29. *S,S*-BPPM = (2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-(diphenylphosphanyl)-2-(diphenylphosphanylmethyl)pyrrolidine;
30. *R,R*-Phenyl-CAPP = (2*R*,4*R*)-*N*-anilidooxy-4-(diphenylphosphanyl)-2-(diphenylphosphanylmethyl)pyrrolidine;
31. *R,R*-bdpch = (1*R*,2*R*)-(*trans*)-1,2-bis(diphenylphosphanyloxy)cyclohexane;
32. *R,R*-CYLOPP-2-Me = (1*R*,2*R*)-(*trans*)-1,2-bis(di-(2-methylphenyl)phosphanyloxy)cyclohexane;
33. *R,R*-CYCLOPP-4-CF_3 = (1*R*,2*R*)-(*trans*)-1,2-bis(di-(4-trifluoromethylphenyl)phosphanyloxy)cyclohexane;
34. *R,R*-CYCLOPP-3,5-Cl = (1*R*,2*R*)-(*trans*)-1,2-bis(di-(3,5-dichlorphenyl)phosphanyloxy)cyclohexane;
35. *R,R*-CYCLOPP-3,5-CF_3 (1*R*,2*R*)-(*trans*)-1,2-bis{[(di-(3,5-bis-trifluormethyl)phenyl]phosphanyloxy}cyclohexane;
36. *R,R*-CYCLOPP-3,5-F = (1*R*,2*R*)-(*trans*)-1,2-bis[di-(3,5-difluorphenyl)phosphanyloxy]cyclohexane;
37. CARBOPHOS-3,5-Me_2Ph = methyl 2,6-*O*-dibenzoyl-3,4-*O*-bis[bis-3,5-dimethylphenyl)phosphanyl]-α-D-glucopyranoside;
38. GLUCOPHOS-Ph-3,5-Me = phenyl 4,6-*O*-benzylidene-2,3-*O*-bis[bis-(3,5-dimethylphenyl)phosphanyl]-β-D-glucopyranoside;
39. Ph-β-Glup = phenyl 4,6-*O*-benzylidene-2,3-bis(*O*-diphenylphosphanyl)-β-D-glucopyranoside;
40. *R*-PROPRAPHOS = (*R*)-2-(*N*-isopropyl-*N*-diphenylphosphanyl)amino-1-(diphenylphosphanyloxy)propane;
41. *S*-CyCy-OxoPRONOP = (*S*)-1-(dicyclohexylphosphanyl)-2-(dicyclohexylphosphanyloxymethyl)pyrrolid-5-one;
42. *S*-Cy,Cy-PRONOP = (*S*)-1-(dicyclohexylphosphanyl)-2-(dicyclohexylphosphanyloxymethyl)pyrrolidine;
43. *S*-CyCyisoALANOP = (*S*)-2-(*N*-methyl-*N*-dicyclohexylphosphanyl)amino-1-(dicyclohexylphosphanyloxy)propane;
44. *R*-NAPHOS = (*R*)-(+)-2,2′-bis(diphenylphosphanylmethyl)-1,1′-binaphthyl;
45. *S*-PN-iPr = (*S*)-(+)-2-[2-(diphenylphosphanyl)-phenyl]-4-isopropyl-1,3-oxazoline;
46. *S*-PN-tBu = (*S*)-(+)-2-[2-(diphenylphosphanyl)phenyl]-4-(2-methyl)-isopropyl-1,3-oxazoline;
47. *R*-QUINAP = (*R*)-(+)-1-(2-diphenylphosphanyl-1-naphthyl)isoquinoline;
48. (*R,R*)-(*S,S*)-EtTRAP = (*R,R*)-2,2″-bis[(*S*)-1-(diethylphosphanyl)ethyl]-1,1″-biferrocene.

and 1 mL of a 0.2 M solution of 3-benzyl-2-methyl-2-phenyl-1,3-oxzolidine **1e** in 2 mL glass vials. The vials were sealed with septa. Then these samples were transferred *via* a syringe into stainless 2 mL autoclaves equipped with stirring bars and flushed with hydrogen in order to replace the argon. When the reaction was finished the reaction mixtures were worked up and analyzed as described in the previous section.

Large-Scale Synthesis of 2-[Benzyl(1-phenylethyl)amino]ethanol 2c

A solution of {Rh[(*R*)-NORPHOS](COD)}BF_4 (114 mg, 0.15 mmol) in 3 mL of dichloromethane was placed in a 50 mL stainless steel autoclave under argon. Then a solution of 3-benzyl-2-methyl-2-phenyl-1,3-oxzolidine **1e** (3.81 g, 15 mmol) in 30 mL of 2-propanol was added *via* a syringe and the autoclave pressurized with hydrogen to an initial pressure of 60 bar. After 4 h the calculated amount of hydrogen was consumed and the hydrogen uptake ceased. A conversion of 99% was estimated by HPLC analysis of the crude reaction mixture. The solvent was evaporated and the residue was distilled under vacuum to give 2-[benzyl(1-phenylethyl)amino]ethanol; yield: 3.28 g (86%); 80% ee; bp 125–127 °C/5 $\times 10^{-4}$ mbar; ^{1}H NMR ($CDCl_3$): $\delta = 1.42$ (d, $J =$ 6.8 Hz, 3H), 2.53 (ddd, $J = 13.2$, 6.8, 4.4 Hz, 1H), 2.73 (ddd, $J =$ 13.3, 6.0, 4.4 Hz, 1H), 3.43 (ddd, $J = 10.8$, 6.1, 4.6 Hz, 1H), 3.50 (ddd, $J = 10.9$, 6.8, 4.3 Hz, 1H), 3.54 (AB, $J = 13.9$ Hz, 1H), 3.62 (AB, $J = 13.9$ Hz, 1H), 3.96 (q, $J = 6.9$ Hz, 1H), 7.22–7.35 (m, 10H).

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References and Notes

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[21] Since the parallel screening is known as a methodology giving only preliminary hits also other ligands might be useful. However, is was not possible to identify them under our high-throughput conditions.