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Asymmetric catalysis. Part 153: Metal-catalysed enantioselective α-ketol rearrangement☆

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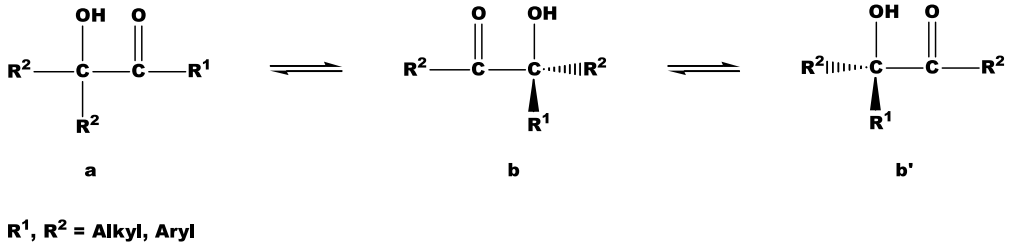
Abstract—Promoted by catalytic amounts of Ni complexes tertiary α-hydroxyketones **1a**, **3a**–**5a** undergo rearrangement, forming chiral isomers **1b**, **3b**–**5b**. The best enantioselection was obtained with the model system 1-benzoylcyclopentanol **4a**/2-hydroxy-2-phenylcyclohexanone **4b**. In a ligand screening 2-[4-(*S*)-*tert*-butyloxazolin-2-yl]pyridine gave the highest enantiomeric excess of 46% (*S*)-**4b**. The analogous isomerisation reactions of α-hydroxyimines **6a**, **7a** forming chiral α-aminoketones **6b**, **7b** were established.

1. Introduction

In the rearrangement of α-hydroxyketones, shown in Scheme 1, the carbon skeleton isomerises via migration of its alkyl or aryl substituents. Using achiral compounds of type **a** as substrate, optically active catalysts can lead to the preferred formation of one or the other enantiomer **b** or **b′** of the chiral product. Recently, we investigated reactions of this type.[1] The rearrangement is a reversible reaction. In the first step one of the substituents R^2 migrates from the hydroxy carbon atom in **a** to the carbonyl carbon atom. A proton shift completes the role change of the carbonyl and the hydroxy function. Subsequently, R^1 may also take part in the rearrangement.

In order to achieve enantiocontrol, the reaction has to be stopped before equilibrum is established and a compromise between high enantioselectivity and conversion has to be found.[1] Ideally, the first step should be much faster than the subsequent reaction steps. One possibility is to use the different migration tendency of aryl and alkyl substituents (model system **1**, Scheme 2). Another approach to avoid the problems associated with the back-reaction, is the use of strained ring systems as starting materials (model systems **2**–**5**, Schemes 3, 4 and 7).[2] When replacing the carbonyl oxygen of a hydroxyketone by N-CH_3, one arrives at hydroxyimines, which can rearrange to become aminoketones. Model systems **6** and **7** (Scheme 8) were also investigated.[3]



Scheme 1.

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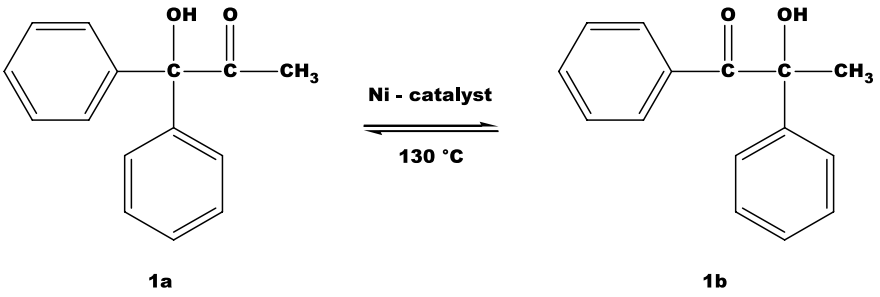
2. Results and discussion

2.1. Model systems 1–3

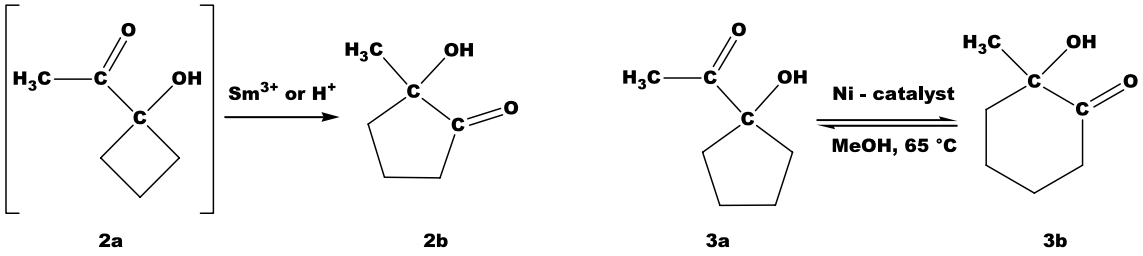
In order to investigate the influence of alkyl/aryl substituents on enantioselectivity during the rearrangement, a system carrying two phenyl rings at the hydroxy carbon atom and a methyl group at the carbonyl atom was tested. The achiral compound 1,1-diphenyl-1-hydroxypropane-2-one **1a** was prepared according to the literature.[4] In the isomerisation of **1a** the chiral isomer 1,2-diphenyl-2-hydroxypropane-1-one **1b** was formed (Scheme 2).

The isomer analysis was carried out by ^{1}H NMR spectroscopy. Enantiomeric analysis was possible by ^{1}H NMR using (*S*)-(+)-1-(9′-anthryl)-2,2,2-trifluoroethanol as a chiral shift reagent. To ensure comparability with the results obtained from other phenyl/alkyl-substituted systems,[1] the standard isomerisation procedure (no solvent, 130°C) was adopted for model system **1**. First, the rearrangement was carried out with $NiCl_2$ and the achiral ligand TMEDA (*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminoethane) in the ratio of 1:2 to determine the equilibrum composition of the system **1a**:**1b** = 22:78. Then, as a chiral catalyst, $NiCl_2$/**9a** 1:2, **9a** = pybox = 2,6-bis[4-(*S*)-isopropyloxazolin-2-yl]pyridine,[5] was chosen. This catalyst has given the best enantiomeric excess in the rearrangement of open-chain systems to date.[1] However, with 10 and 12% ee (*R*)-(+)-**1b**, respectively, after 16 h at 20% conversion in two parallel runs, lower enantioselectivities than in the open-chain model systems investigated before[1] were obtained.

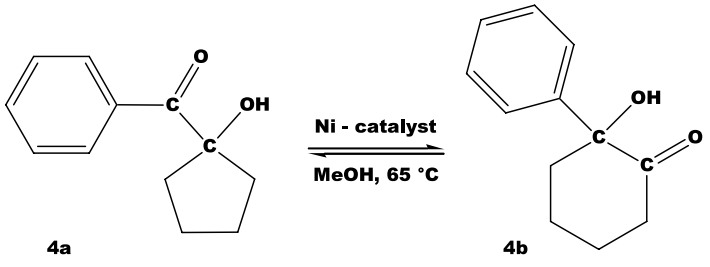
The synthesis of 1-acetylcyclobutanol, the starting material in model system **2** (Scheme 3), was attempted via SmI_2-mediated coupling of acetyl chloride and cyclobutanone.[6] However, due to the strain of the four-membered ring only the rearrangement product 2-hydroxy-2-methylcyclopentanone **2b** was isolated. Both the catalytic activity of the samarium species as well as the acidic work-up might favour the rearrangement of the intermediate product **2a**. However on the basis of these results it was not surprising that the synthesis of the corresponding three-membered ring system that could rearrange to a four-membered product failed.[3]



Scheme 2.



Scheme 3.



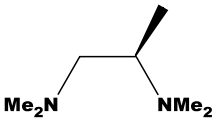
Scheme 4.

1-Acetylcyclopentanol **3a** (Scheme 3) was accessible from commercially available 1-ethynylcyclopentanol by Hg(II)-catalysed addition of water.[7] Isomer analysis was carried out by gas chromatography on a Restek Rt-βDEX column, which allowed determination of conversion and enantiomeric excess of 2-hydroxy-2-methylcyclohexanone **3b**. In order to compare the results to those obtained with the benzoyl compound (model system **4**), the isomerisation reaction was carried out under similar conditions (solvent methanol, 65°C). With the achiral catalyst system, $NiCl_2$/TMEDA 1:2, after 120 h, the equilibrum **3a**:**3b** = 5:95 was established (confirmed by methoxide-catalysed isomerisation). This equilibrum composition fitted that of model system **4** (**4a**:**4b** = 4:96). Repetition of the experiment with $NiCl_2$/**9a** 1:2, gave stereoselectivities of 10.1/13.7% ee (*S*)-(−)-**3b**, being unexpectedly low in comparison to model system **4**.

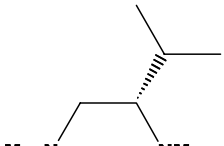
2.2. Ligand screening in model system 4

Model system **4** (Scheme 4) has already been investigated[2] with its reaction conditions and analytics being elaborated. Herein further ligands and catalysts were screened in order to optimise the enantioselectivity.

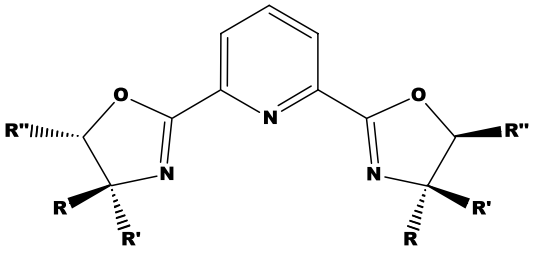
One concept to develop suitable ligands for Ni catalysts, was to introduce chirality into the ethylene backbone of TMEDA. As 1,2-disubstituted derivatives (*S*,*S*)- and (*R*,*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diamino-1,2-diphenylethane had shown only low catalytic activity in the rearrangement of open-chain systems,[1] we tested monosubstituted compounds. (*R*)-(+)-*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-diaminopropane **8a** was obtained by resolution of racemic 1,2-diaminopropane followed by Eschweiler–Clarke methylation (Scheme 5).[8–10] Conver-



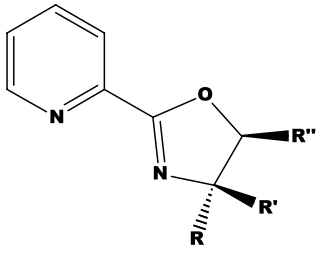
8a



8b

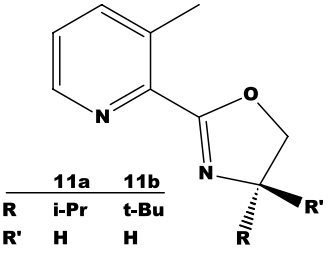


	9a	9b	9c	9d	9e	9f	9g	9h
R	i-Pr	H	t-Bu	*S*-s-Bu	i-Bu	Benzyl	Ph	Me
R'	H	Et	H	H	H	H	H	H
R''	H	H	H	H	H	H	H	Ph

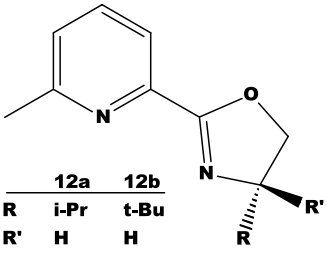


	10a	10b	10c	10d	10e	10f	10g	10h
R	Me	H	i-Pr	n-Pr	*S*-s-Bu	i-Bu	t-Bu	H
R'	H	Et	H	H	H	H	H	Cyhex
R''	H	H	H	H	H	H	H	H

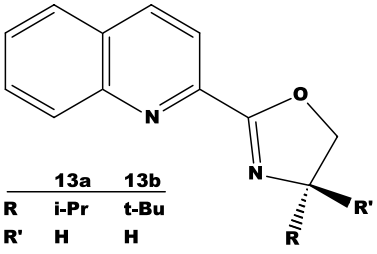
	10i	10j	10k	10l	10m	10n
R	H	Benzyl	$CH_2CH_2SCH_3$	H	Me	CH_2OH
R'	Ph	H	H	Me	H	H
R''	H	H	H	Ph	Ph	Ph



	11a	11b
R	i-Pr	t-Bu
R'	H	H



	12a	12b
R	i-Pr	t-Bu
R'	H	H



	13a	13b
R	i-Pr	t-Bu
R'	H	H

Scheme 5.

sion in model system **4** after 120 h (MeOH, 65°C, 5 mol% $NiCl_2$/**8a**) matched those results obtained with the parent ligand TMEDA. However, the enantiomeric excess (4.4% ee (*R*)-**4b**) was low (Table 1, entry 1).

Next, the isopropyl-substituted ligand (*S*)-(+)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diamino-3-methylbutane was synthesised (Scheme 5). Starting from the amino acid valine, the amino acid amide was formed and reduced with lithium aluminium hydride.[11] Reductive methylation yielded the new ligand **8b**. Due to the fact that conversion (48/49%) and enantioselectivity were low [3.2/3.3% ee (*S*)-**4b**], no further chiral TMEDA derivatives were investigated.

As $NiCl_2$/**9a** had afforded the best enantioselectivities to date,[2] the pyridinebisoxazoline system was regarded as a lead structure. From pyridinedicarboxylic acid and β-amino alcohols—mainly derived from natural amino acids—a variety of ligands with different steric demands were synthesised (Scheme 5). Using (*R*)-2-amino-1-butanol as the aminoalcohol component, 2,6-bis[4-(*R*)-ethyloxazolin-2-yl]pyridine[5] **9b** was prepared. Conversion (40%) and enantiomeric excess [1.2% (*R*)-**4b**] with **9b** were disappointing in comparison to **9a**. Thus, going from the isopropyl derivative **9a** to the smaller ethyl derivative **9b** resulted in an appreciable drop in enantioselectivity. Therefore, it was anticipated that a change from the isopropyl derivative **9a** to the larger *tert*-butyl derivative **9c** would increase enantiocontrol. However, while the steric demand of 2,6-bis[4-(*S*)-*tert*-butyloxazolin-2-yl]pyridine[5] **9c** explained the decreasing turnover (42/46%), the enantiomeric excess [10.1/9.4% ee (*R*)-**4b**] remained below expectations. Though carrying an additional stereocentre in its side chain, 2,6-bis{4-(*S*)-[1-(*S*)-methylpropyl]oxazolin-2-yl}pyridine[5] **9d**, a ligand most similar to the isopropyl derivative **9a**, resulted in almost identical enantioselectivity [35.9/35.3% ee (*R*)-**4b**] and only slightly diminished conversion (79/79%). On the other hand, 2,6-bis[4-(*S*)-(2-methylpropyl)oxazolin-2-yl]pyridine[12] **9e** gave only low conversion (33/35%) and enantiomeric excess [10.5/10.0% ee (*S*)-**4b**]. The benzyl derivative 2,6-bis[4-(*S*)-benzyloxazolin-2-yl]pyridine[13] **9f** showed

Table 1. Results of the ligand screening with model system **4**. Reaction conditions: solvent MeOH, 120 h, 65°C, 5 mol% catalyst, catalyst $NiCl_2$/ligand 1:2.[a]

Entry	Ligand	Configuration	Conversion (%)	Enantiomeric excess (% ee)
1	**8a**	(*R*)	94	4.4 (*R*)
2	**8b**	(*S*)	48/49	3.2/3.3 (*S*)
3	**9a**	(4*S*,4*S*)	91/91	35.2/36.0 (*R*)
4	**9b**	(4*R*,4*R*)	40	1.2 (*R*)
5	**9c**	(4*S*,4*S*)	42/45	10.1/9.4 (*R*)
6	**9d**	(4*S*,4*S*)	79/79	35.9/35.3 (*R*)
7	**9e**	(4*S*,4*S*)	33/35	10.5/10.0 (*S*)
8	**9f**	(4*S*,4*S*)	87	5.0 (*R*)
9	**9g**	(4*S*,4*S*)	39/38	rac. /1.1 (*S*)
10	**9h**	(4*S*,4*S*,5*S*,5*S*)	17/14	0.4 (R) /1.6 (*S*)
11	**10a**	(4*S*)	32/40	26.5/22.0 (*S*)
12	**10b**	(4*R*)	93/80	36.8/38.7 (*R*)
13	**10c**	(4*S*)	88/88	35.6/37.2 (*S*)
14	**10d**	(4*S*)	24/27	22.1/21.2 (*S*)
15	**10e**	(4*S*)[c]	93/93	33.8/33.0 (*S*)
16	**10f**	(4*S*)	91/79	40.2/40.9 (*S*)
17	**10g**	(4*S*)	91/90	45.9/45.8 (*S*)
18	**10g**[b]	(4*S*)	87	45.2 (*S*)
19	**10h**	(4*R*)	26	15.5 (*R*)
20	**10I**	(4*R*)	23/17	2.4/2.2 (*R*)
21	**10j**	(4*S*)	94	31.6 (*S*)
22	**10k**	(4*S*)	94/92	34.6/28.2 (*S*)
23	**10l**	(4*S*,5*S*)	39	12.9 (*R*)
24	**10m**	(4*R*,5*S*)	46	34.2 (*S*)
25	**10n**	(4*S*,5*S*)	16	0.8 (*R*)
26	**11a**	(4*S*)	86/87	40.9/42.8 (*S*)
27	**11b**	(4*S*)	58	41.9 (*S*)
28	**12a**	(4*S*)	94/65	24.0/30.0 (*S*)
29	**12b**	(4*S*)	94	13.2 (*S*)
30	**13a**	(4*S*)	82/92	41.3/47.3 (*S*)
31	**13b**	(4*S*)	92/89	29.1/32.9 (*S*)
32	**14**	(*S*)	23/32	25.2/17.9 (*S*)
33	**15**	(7*S*,7a*R*,14*S*,14a*S*)	86/78	1.8/0.3 (*R*)
34	**16**	(*S*)	30/24	2.7/4.4 (*R*)

[a] Reaction without catalyst yielded 4% conversion.
[b] 96 h, 20 mol% catalyst.
[c] Configuration in the side chain: (*S*).

good catalytic activity (87%), however, stereoselectivity was low [5.0% ee (*R*)-**4b**]. The commercially available ligand 2,6-bis[4-(*S*)-phenyloxazolin-2-yl]pyridine **9g** afforded low conversion (39/38%) with insignificant enantiocontrol [0/1.1% ee (*S*)-**4b**]. 2,6-Bis[4-(*S*)-methyl-5-(*S*)-phenyloxazolin-2-yl]pyridine **9h**, also commercially available, gave low catalytic activity (17/14%) with almost racemic product distribution (ee <2% ee). These results demonstrated that in model system **4**, results with pyridinebisoxazolines (Table 1, entries 3–10) reached optimum with isopropyl and *sec*-butyl substitution (entries 3 and 6).

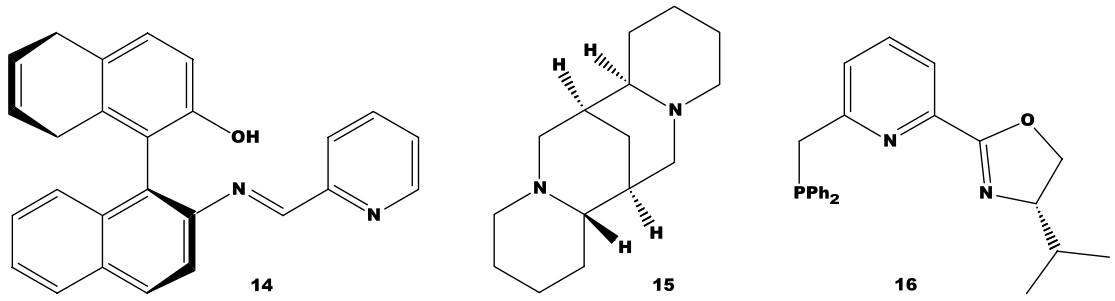
Pyridinemonoxazolines (Scheme 5), the first oxazoline ligands used in enantioselective catalysis,[14] were tested as chiral ligands for $NiCl_2$ catalysts in model system **4** (Table 1, entries 10–22). The most common ligand of the series, 2-[4-(*S*)-isopropyloxazolin-2-yl]pyridine **10c**,[15] gave conversion (88/88%) and enantiomeric excess [35.6/37.2% ee (*S*)-**4b**] comparable to the results of the corresponding bisoxazoline **9a** in magnitude, whereas the configuration of the preferentially formed product enantiomer changed to (*S*). This is surprising because ligand **10c**, abbreviated pymox,[16] is only a bidentate ligand compared to pybox **9a** which is a tridentate ligand coordinating meridionally.[5] Variation of the substituents connected to the oxazoline ring was started with the methyl derivative 2-[4-(*S*)-methyloxazolin-2-yl]pyridine[15] **10a**. The enantiomeric excess was a little lower than that with the isopropyl derivative **10c** [26.5/22.0% ee (*S*)-**4b**] but its turnover (32/40%) was much lower. The ethyl derivative 2-[4-(*R*)-ethyloxazolin-2-yl]pyridine[15] **10b** showed good conversion (93/80%) and enantioselectivity [36.8/38.7% (*R*)-**4b**], while the *n*-propyl derivative 2-[4-(*S*)-*n*-propyloxazolin-2-yl]pyridine[15] **10d** was of weaker catalytic activity (24/27%) and enantioselection [22.1/21.2% (*S*)-**4b**]. The *sec*-butyl derivative 2-{4-(*S*)-[1-(*S*)-methylpropyl]oxazolin-2-yl}pyridine[15] **10e** [93/93% conversion, 33.8/33.0% ee (*S*)-**4b**], and the *iso*-butyl derivative 2-[4-(*S*)-(2-methylpropyl)oxazolin-2-yl]pyridine[15] **10f** [91/79% conversion, 40.2/40.9% ee (*S*)-**4b**], structurally related to the 'reference' isopropyl compound **10c**, yielded comparable results. The best results were obtained with the ligand 2-[4-(*S*)-*tert*-butyloxazolin-2-yl]pyridine[15] **10g**. At conversions of 91/90%, the enantiomeric excess was 45.9/45.8% ee (*S*)-**4b** (entry 17). Repetition of the experiment with a catalyst concentration of 20 mol% gave 87% turnover after 96 h with 45.2% ee (*S*)-**4b** (entry 18). The ligand 2-[4-(*R*)-cyclohexyloxazolin-2-yl]pyridine[15] **10h**, carrying a cyclohexyl substituent considered to be similar to an isopropyl substituent, showed only low conversion (26%) and enantiomeric excess [15.5% (*R*)-**4b**]. Using the phenylated ligand 2-[4-(*R*)-phenyloxazolin-2-yl]pyridine[15] **10i**, low turnover numbers (23/17%) and enantioselectivities [2.4/2.2% ee (*R*)-**4b**] were observed. The ligands 2-[4-(*S*)-benzyloxazolin-2-yl]pyridine[15] **10j** [94% conversion, 31.6% ee (*S*)-**4b**] and 2-{4-(*S*)-[2-(methylthio)ethyl]-oxazolin-2-yl}pyridine[15] **10k** [94/92% conversion, 34.6/28.2% ee (*S*)-**4b**] provided good conversion rates and enantioselectivities. Unfortunately the methionine-derived ligand **10k** did not show a significant heteroatom-side chain effect on enantiomeric excess. In the series of pyridinemonoxazoline ligands no clear correlation of enantiomeric excess and turn over rates with the steric demand of the substituents located at the oxazoline ring, could be established. However, all (*S*)-configurated ligands gave the (*S*)-product **4b**, the (*R*)-ligands gave the (*R*)-product **4b** in excess.

Low conversion rates of the 4,5-disubstituted pyridinemonoxazoline derivatives 2-[4-(*S*)-methyl-5-(*S*)-phenyloxazolin-2-yl]pyridine[15] **10l** (39%), 2-[4-(*R*)-methyl-5-(*S*)-phenyloxazolin-2-yl]pyridine[15] **10m** (46%) and 2-[4-(*S*)-hydroxymethyl-5-(*S*)-phenyloxazolin-2-yl]-pyridine[15] **10n** (16%) were presumably due to increased steric hindrance because of the additional phenyl group in 5-position of the oxazoline system (Table 1, entries 23–25). Enantiomeric excess was good for **10m** [34.2% ee (*S*)-**4b**], lower for **10l** [12.9%ee (*R*)-**4b**], and negligible for **10n** [0.8% ee (*R*)-**4b**], a ligand containing a functionalised oxazoline substituent.

As pyridinemonoxazolines turned out to be interesting ligands for $NiCl_2$ catalysts in model system **4**, derivatives substituted at the pyridine nucleus were synthesised and tested (Scheme 5). The isopropyl substituted 3-methylpyridine derivative **11a**, a new ligand, was prepared as described for compounds **12** and **13**.[17] It gave good conversion (86/87%) and better enantioselectivities [40.9/42.8% ee (*S*)-**4b**] than the parent pyridine compound **10c**. However, with the *tert*-butyl substituted compound **11b**[18] it was just the other way round. The 6-methylpyridine ligands **12a**[17] and **12b**[17] both showed lower selectivities than their unsubstituted counterparts. In the quinoline series the isopropyl compound **13a**[17] led to a higher enantiomeric excess [41.3/47.3% ee (*S*)-**4b**] than the *tert*-butyl derivative **13b**[17] [29.1/32.9% ee (*S*)-**4b**]. In both cases conversions were high and as observed in the pyridinemonoxazoline series, the (*S*)-configured ligands **11**–**13** all gave (*S*)-**4b** in excess (Table 1, entries 26–31).

Besides the systematic variation of lead structures, other ligands (Scheme 6) were screened for use in the $NiCl_2$-catalysed model system **4** (Table 1, entries 32–34). Salicyl aldimines (derived from salicylaldehyde and the primary amines (*R*)-2-aminobutane-1-ol, (*R*)-1-phenylethylamine and 2-(*S*)-amino-1-(*S*)-phenylpropane-1,3-diol), (*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-2,2′-diamino-1,1′-binaphthyl[19] and 1,3-bis[4-(*S*)-isopropyloxazolin-2-yl]benzene, the benzene analogue of the successful ligand pybox **9a**, showed catalytic activity, but gave racemic product.[3] The axially chiral ligand (*S*)-2-(2-pyridinylmethyleneamino)-2′-hydroxy-1,1′-binaphthyl **14**,[20] an excellent ligand in the Ru-catalysed transfer hydrogenation of acetophenone, provided moderate enantioselectivity [17.9/25.2% ee (*S*)-**4b**].

The natural product (−)-sparteine **15** was a suitable ligand for $NiCl_2$ in model system **4** (78/86% conver-



Scheme 6.

sion), but only insignificant enantiomeric excess [0.3/1.8% ee (*S*)-**4b**] was achieved. Similar results were obtained with 2-[(diphenylphosphanyl)methyl]-6-[4-(*S*)-isopropyloxazolin-2-yl]pyridine **16**,[21] a tridentate ligand as pyridinebisoxazolines. This screening showed that it was easy to find ligands which gave high conversion in the $NiCl_2$-catalysed model system **4**, but difficult to identify ligands which afforded good enantioselectivity.

The variation of the central metal ion confirmed what earlier investigations with open-chain hydroxyketone systems had shown: Ni^{II} was the most suitable metal ion. Thus, $Co(acac)_2$/**9a** under standard conditions gave an enantiomeric excess of 15.3% ee (*R*)-**4b**, whereas $NiCl_2$/**9a** had achieved 34.2% ee (*R*)-**4b**. Neither $Pd(acac)_2$ nor $[Pd(COD)Cl]_2$ (COD = 1.5-cyclooctadiene) in combination with **9a** were found suitable catalysts for model system **4** (due to precipitation of Pd^0 during the isomerisation).

2.3. Enantioselectivity as a function of time in model system 4

Conversion and enantiomeric excess of the rearrangement of model system **4** were studied as a function of time using 2 mol% of $NiCl_2$/**9a** 1:2 as the catalyst under standard conditions. While conversion asymptotically approached the equilibrum composition **4a**:**4b** = 4:96, unexpectedly, enantiomeric excess increased during the reaction. A typical example is shown in the left part of Figure 1. After 24 h the ee of (*R*)-**4b** was 13.5%, after 48 h it was 23.8%, after 72 h it was 25.9%, and after 96 h it was 27.9%. If in a given reaction enantioselection increases with increasing conversion, frequently besides the ee itself the differential ee (Δee) is used to illustrate the change in enantioselection from data point to data point. Applied to the first catalytic cycle of Figure 1 the Δee between 0 and 24 h is 13.5%, between 24 and 48 h it is 54.1% and between 48–72 h and 72–96 h it rises to 81.0 and 78.0%, respectively, indicating a remarkable increase in enantioselection during catalysis.

A possible explanation is that besides the chiral reaction channel, an achiral channel is also working at the beginning of the reaction but disappearing after some time. This achiral channel may be due to a slow formation of the catalytically active chiral species from the components $NiCl_2$ and pybox **9a** of the in situ catalyst. Thus, we repeated the experiment stirring the components of the in situ catalyst 24 h in MeOH solution to form the catalytically active chiral species, before we added the substrate. Again, an increase in enantioselectivity during the reaction was observed.

Another explanation might be that the substrate and/or the product act as supporting ligands in the catalyti-

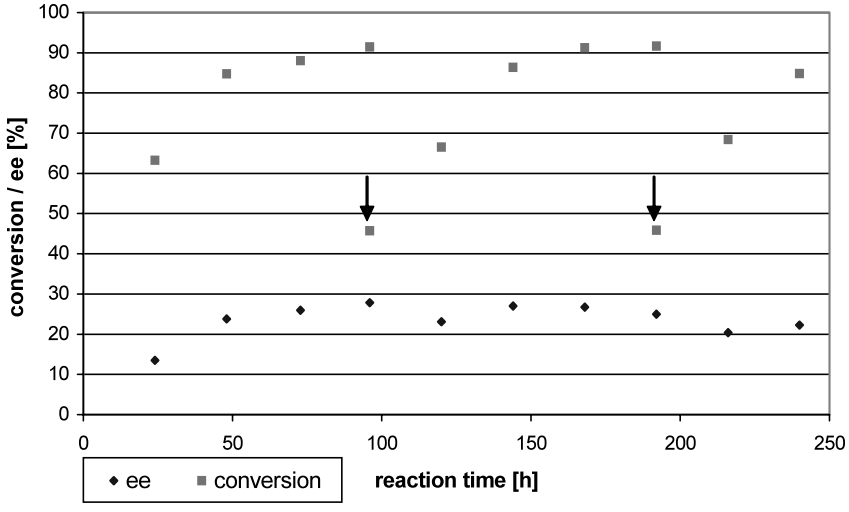


Figure 1. Model system **4** using $NiCl_2$/**9a** 1:2 as a catalyst. Arrows indicate addition of further substrate **4a**.

cally active species. This would lead to the interesting situation that the desired product enantiomer favours its own production.[22] A possible model for such a system is shown in Figure 2. In formula A the tridentate ligand pybox **9a** coordinates meridionally at the top, back and bottom positions of the octahedron shown. Arbitrarily, the sterically encumbering substituents of the C_2-symmetric ligand pybox are indicated by lobes pointing to the right (top) and to the left (bottom).

In the model of Figure 2 the substrate to be rearranged is bonded as a chelate to the positions to the right and to the front. In the remaining sixth position to the left of the octahedron another substrate or product molecule can bind with its keto group. Its hydroxy group can then form a hydrogen bond to the keto group of the substrate to be processed, as indicated in formulas A–C, supporting catalysis. At the beginning of the reaction only the substrate acts as supporting ligand. Species A has a certain catalytic activity and a given maybe low enantioselectivity. During the reaction the achiral substrate disappears and the product isomers form and act as supporting ligands. Species B with the less favoured product enantiomer suffers from steric hindrance (mismatched combination) resulting in a low concentration (and maybe low catalytic activity). Species C, the matched combination, then takes over during catalysis. If species C gives a higher stereoselectivity than species A, the increase in enantioselection during catalysis is understandable and, interestingly enough, in such a model, the product enantiomer favours its own production.

To test model system A–C, catalysis was performed under standard conditions in an enlarged run with 2 mol% $NiCl_2$/**9a** as the catalyst. Samples were taken every 24 h as shown in Fig. 1. After 96 h the first 'normal' catalytic cycle **4a**→**4b** with increasing enantioselectivity had reached 92% conversion (left side of Fig. 1). At this point the same amount of substrate **4a** as used in the beginning was added keeping the system under standard conditions. This brought the conversion down to calculated 46% as indicated by the first arrow. After another 24 h (from 96 to 120 h) conversion had increased to 67%, the enantioselectivity dropping to 23% (Fig. 1, middle part). In the next 24, 48 and 72 h the conversion increased as did the enantioselectivity. The right part of Figure 1 shows that a third cycle can be started similarly. The drop in the enantioselectivity observed after 120 h (and after 216 h) is in agreement with the assumption that on addition of the new substrate **4a**, species A, containing the substrate as supporting ligand, is re-formed with its relatively low enantioselectivity. On increasing conversion, species C takes over reaching the plateau-selectivity for the given system with close to 30% ee. Thus, with the postulates, indicated, the data of Fig. 1 is in agreement with catalyst model A–C in Fig. 2. Repeating the experiment with addition of both starting material **4a** and catalyst $NiCl_2$/**9a** to keep the substrate/catalyst ratio constant gave similar results.[3]

2.4. Model system 5

In model system **5** (Scheme 7) the starting material **5a** was synthesised in moderate yields from fluorenone.

Conversion and enantiomeric excess had to be monitored by HPLC analysis, as isomer analysis by ^{1}H NMR was not possible due to the absence of suitable signals, both in **5b** as well as in its $OSiMe_3$ derivative.[3] Using $NiCl_2$/TMEDA 1:2 as a catalyst, no isomerisation was observed under reaction conditions used for the other five-membered ring systems (solvent MeOH, 65°C, 5 mol% catalyst, 120 h). Repetition of the experiment under the reaction conditions of the open-chain systems such as **1** (solution of 5 mol% catalyst in the molten substrate, 130°C, 240 h) yielded the rearrangement product **5b** containing only traces of starting material **5a**. The chiral catalyst system $NiCl_2$/**9a** 1:2 (solution of 5 mol% catalyst in molten **5a**, 130°C, 240

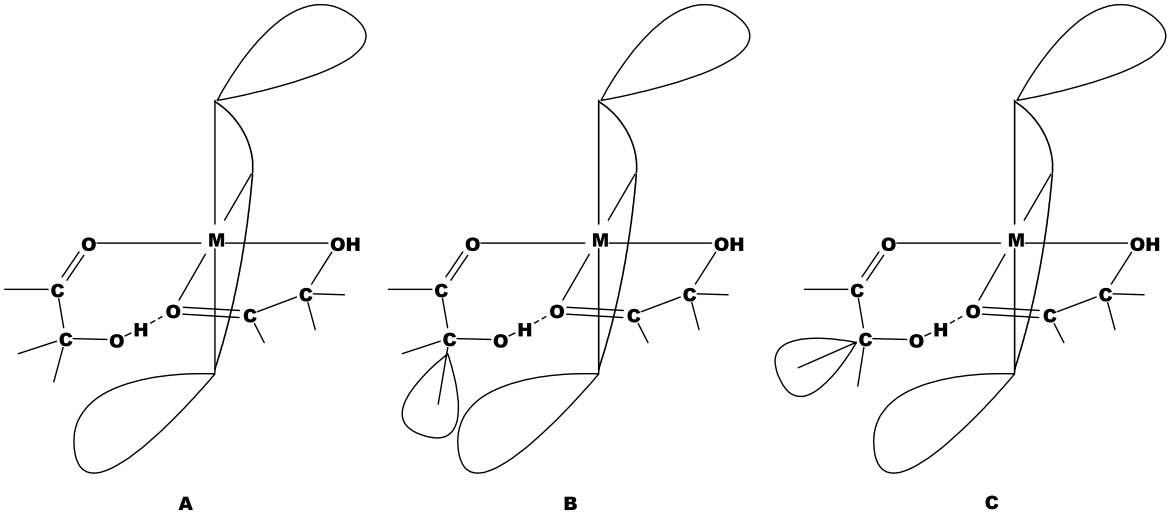
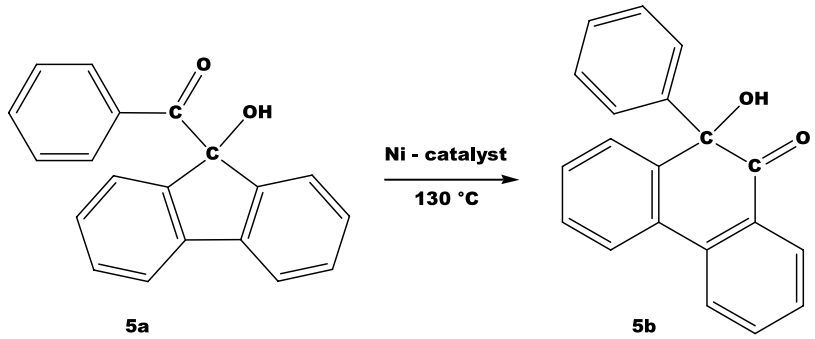


Figure 2. Species A: At the beginning of catalysis achiral starting material acts as supporting ligand. Species B, C: During catalysis the product enantiomers act as supporting ligand. Species C, the matched combination, favours its own formation.



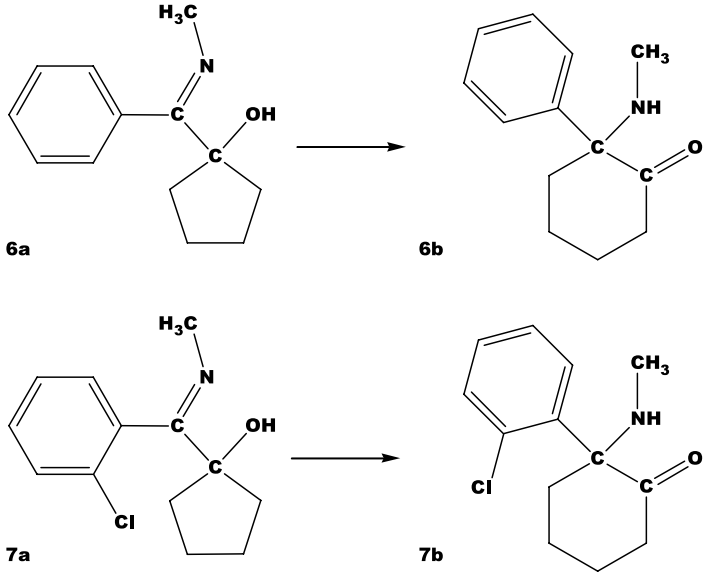
Scheme 7.

h) generated only insignificant enantioselectivities of 2.6% ee at 18% conversion. The harsh reaction conditions necessary for rearrangement as well as the low stereoselectivities likely are due to the inflexible skeleton of model system **5**.

2.5. Model system 6 and 7

Formally replacing the carbonyl oxygen in **4a** by N-CH_3 gives model system **6** 1-methyliminophenylmethylcyclopentanol **6a**/2-methylamino-2-phenylcyclohexanone **6b** (Scheme 8). The rearrangement of **6a** leading to the isomeric aminoketone **6b** is known as a thermal reaction,[23] which has not yet been investigated under enantiodiscriminating conditions. The product 2-methylamino-2-phenylcyclohexanone **6b** was described in the patent literature for the treatment of various infection diseases.[23] **6a** was prepared from benzonitrile via a reaction with the Grignard derived from bromocyclopentane. Treatment of the product obtained with bromine yielded 1-bromocyclopentylphenylketone,[24] which when reacted with water-free methylamine (reagent, base and solvent in one) at −30°C, provided 1-methyliminophenylmethylcyclopentanol **6a**.[23] A racemic sample of **6b** was synthesised according to the literature procedure[23] in order to establish conditions for enantiomer analysis. Baseline separation via gas chromatography was achieved with long retention times. Formation of diastereomeric salts with (*R*)-(−)-mandelic acid allowed differentiation of the two enantiomers by ^{1}H NMR spectroscopy (solvent $CDCl_3$). Although the relevant NCH_3 signals overlapped with a CH_2 multiplet, quantification was possible with the deconvolution function of the Bruker WinNMR software. The rearrangement of **6a** was catalysed with 2 mol% $NiCl_2$/TMEDA 1:2 at 130°C in 1-butanol. After 72 h the rearrangement was complete. Repetition of the experiment with 2 mol% $NiCl_2$/**9a** 1:2 also gave complete conversion. However, racemic **6b** was obtained.

Isomerisation of 1-(2-chlorophenylmethyliminomethyl)-cyclopentanol **7a** yields 2-chlorophenyl-2-methylaminocyclohexanone **7b** (model system **7**). The compound is known since 1963 and used as the short term injection narcotics cetamine®.[25] However, the (*R*)-enantiomer can cause hallucinations during the wake-up phase,[26] while (*S*)-(+)-cetamine® is four times as effective in its anaesthetic effects as the (*R*)-enantiomer. Therefore, the enantiomerically pure drug was intro-



Scheme 8.

duced into the market as Ketanest S®. At the moment the enantiopure compound is obtained via resolution of its tartaric acid salt, recently optimised with respect to solvent and base/tartaric acid ratio.[27,28] The undesired (*R*)-enantiomer must be disposed of. Therefore, it is desirable to develop an enantioselective synthesis for the (*S*)-isomer. Synthesis of **7a** was performed starting from 2-chlorobenzonitrile (Aldrich). The isomerisation **7a**→**7b** under various conditions is described in the patent literature.[29] It was our approach to render the reaction enantioselective in the presence of metal complexes with chiral ligands.

To establish enantiomer analysis, a racemic sample of **7b** was prepared from **7a** in decalin (190°C). Differentiation of the enantiomers was possible by ^{1}H NMR spectroscopy of the (*R*)-(−)-mandelic acid salt of **7b**. In $CDCl_3$, diastereomeric adducts were formed and a splitting of the NCH_3 singlet was observed.

Using 5 mol% $NiCl_2$/**9a** 1:2, rearrangement of **7a** did not occur in boiling methanol, ethanol or in 1-butanol at 110°C. Isomerisation in 1-butanol started at 130°C (Table 2, entry 1) and was complete in 1-octanol at 150°C after 24 h using $NiCl_2$/**9a** as a catalyst (entry 2). As reported in the literature for the thermal rearrangement using alcohols as solvents, in addition to **7b** decomposition products were formed in the rearrangement of **7a**.[29] Therefore, the reaction was carried out in either *p*-xylene (entry 3) or without a solvent to form a cloudy reaction mixture (entries 4–10). Under these reaction conditions $NiCl_2$/pybox catalysts proved to be less effective than lanthanoid catalysts, which afforded high or complete conversion. Unfortunately, all the chiral catalysts so far, $La(acac)_3$/pybox, $LaCl_3$/pybox, $Pr(tfc)_3$ and $Eu(hfc)_3$ only gave racemic mixtures of **7b**.[3]

3. Experimental

3.1. General remarks

NMR spectra: Bruker AC 250, Bruker Avance 300 and Bruker ARX 400 (internal or external TMS).—EI mass spectra: Finnigan MAT 311 A, CI mass spectra: Finnigan MAT 95.—Infra red spectra: Beckman IR 4240.—Optical rotations: Perkin-Elmer polarimeter 241 (1 dm cell).—Melting points: Büchi SMP 20 (uncorrected).

3.2. Model system 1: isomerisation 1a/1b starting from 1,1-diphenyl-1-hydroxypropane-2-one 1a

1,1-Diphenyl-1-hydroxypropane-2-one **1a** (2.26 g, 10.0 mmol),[4] 13.0 mg (0.1 mmol) of $NiCl_2$ and 0.2 mmol of the ligand were put in a Schlenk tube together with a stirring bar (without solvent) and kept in a thermostated oil bath at 130°C. Aliquots were taken for analysis. The samples were cooled to rt and dissolved in CH_2Cl_2. Metal salt and ligand were removed by filtration using a Pasteur pipette filled with silica (5 cm). After removal of the solvent, the samples were ready for analysis. During and after catalysis a mixture of 1,1-diphenyl-1-hydroxypropane-2-one **1a** and 1,2-diphenyl-2-hydroxypropane-1-one **1b** was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.90$ (s, <3H, CH_3, **1b**), 2.27 (s, <3H, CH_3, **1a**), 4.74 (sb, <1H, OH, **1b**), 4.84 (sb, <1H, OH, **1a**), 7.27–7.41/7.43–7.48/7.66–7.69 (m, 10H, CH_{arom}, **1a**/**1b**). ^{1}H NMR (300 MHz, 4 equiv. (*S*)-(+)-1-(9′-anthryl)-2,2,2-trifluoroethanol, $CDCl_3$): $\delta = 1.87$ (s, <3H, CH_3, (*S*)-(−)-**1b**), 1.88 (s, <3H, CH_3, (*R*)-(+)-**1b**), 2.26 (s, <3H, CH_3, **1a**), 3.06 (sb, 4H, anthryl-OH), 4.90 (sb, 1H, OH, **1a**/**1b**), 6.62 (dd, $J =$ 16.0 Hz, $J = 8.0$ Hz, 4H, anthryl-H), 7.28–7.68 (m, 26H, CH_{arom}, **1a**/**1b**, anthryl-H), 8.00–8.20 (m, 12H, anthryl-H), 8.53 (s, 4H, anthryl-H), 8.97 (sb, 4H, anthryl-H).

3.3. Model system 2: synthesis of 2-hydroxy-2-methyl-cyclopentanone 2b

A mixture of 157 mg (143 μL, 2.0 mmol) of acetyl chloride and 140 mg (151 μL, 2.0 mmol) of cyclobutanone (Merck) in 5 mL of THF was rapidly dropped into 42 mL of a solution of SmI_2 (0.1 M) in THF. The solution was treated with 0.1 M HCl and extracted with diethyl ether. The organic layer was washed with water and brine. After drying with Na_2SO_4 removal of the solvent yielded the crude product. Purification by bulb-to-bulb distillation (95°C/5 mmHg). Colourless oil; 56 mg, 25% yield; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.26$ (s, 3H, CH_3), 1.80–2.60 (m, 6H, CH_2).

Table 2. Catalysis with model system **7** starting from **7a**

Entry	Solvent	Temperature (°C)	Reaction time (h)	Catalyst system	Conversion (%)
1	1-Butanol	130	24	$NiCl_2$/pybox	32
2	1-Octanol	150	24	$NiCl_2$/pybox	100
3	*p*-Xylene	130	24	$NiCl_2$/pybox	32
4	Neat	130	24	$NiCl_2$/pybox	23
5	Neat	130	24	$NiCl_2$/pybox/K_2CO_3	23
6	Neat	130	96	$La(acac)_3$	100
7	Neat	130	24	$La(acac)_3$/pybox	89
8	Neat	130	24	$LaCl_3$/pybox	85
9	Neat	130	24	$Pr(tfc)_3$[a]	100
10	Neat	130	24	$Eu(hfc)_3$[b]	100

[a] Praseodymium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate].
[b] Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].

3.4. Model system 3: isomerisation 3a/3b starting from 1-acetylcyclopentanol 3a

$NiCl_2$ (13.0 mg, 0.1 mmol) and 0.2 mmol of the ligand were put in a Schlenk tube under a nitrogen atmosphere. After addition of the solvent (40 mL MeOH) the mixture was heated to reflux and 1-acetylcyclopentanol **3a**[7] (256 mg, 2.0 mmol) was added. For taking samples/work-up, the reaction was stopped by cooling in an ice bath and the solvent removed in vacuo. The residue was dissolved in CH_2Cl_2 and the catalyst removed by filtration through silica. After purification by bulb-to-bulb distillation (90°C/5 mmHg) the samples were analysed by GC. During and after catalysis a mixture of 1-acetylcyclopentanol **3a** and 2-hydroxy-2-methylcyclohexanone **3b** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (s, <3H, CH_3, **3b**), 1.55–2.17 (m, <8H, CH_2, **3a**/**3b**), 2.43–2.60 (m, <2H, CH_2, **3b**). GC analysis: Hewlett Packard 5890 A, split injector (260°C), FID detector (260°C), Spectra-Physics SP 4270 integrator, oven temperature 80°C, hydrogen as carrier gas, solvent CH_2Cl_2. Baseline separation was observed with a Rt-βDEX cst column (length 30 m, lumen 0.32 mm, film thickness 0.25 μm). Retention times: 26.3 min **3a**, 31.2 min (*S*)-(−)-**3b**, 33.7 min (*R*)-(+)-**3b.** The assignment of specific rotation/configuration is based on enantiomerically enriched samples.

3.5. Model system 4: isomerisation 4a/4b starting from 1-benzoylcyclopentanol 4a

$NiCl_2$ (13.0 mg, 0.1 mmol) and 0.2 mmol of the ligand were put in a Schlenk tube under a nitrogen atmosphere. After addition of the solvent (40 mL MeOH), the mixture was heated to reflux and 1-benzoylcyclopentanol **4a**[30] (380 mg, 2.0 mmol) added. For taking samples/work-up the reaction was stopped by cooling in an ice bath and the solvent removed in vacuo. The residue was dissolved in CH_2Cl_2 and the catalyst removed by filtration through silica. After purification by bulb-to-bulb distillation the samples were analysed by GC. During and after catalysis a mixture of 1-benzoylcyclopentanol **4a** and 2-hydroxy-2-phenylcyclohexanone **4b** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.63$–2.10 (m, <6H, CH_2, **4a**/**4b**), 2.30–2.57 (m, <2H, CH_2, **4a**/**4b**), 2.96–3.04 (m, <1H, CH_2, **4b**), 3.75 (s, <1H, OH, **4a**), 4.50 (s, <1H, OH, **4b**), 7.26–7.43 (m, <5H, CH_{arom}, **4a**/**4b**), 7.90–8.20 (m, <2H, CH_{arom}, **4a**). GC analysis: Hewlett Packard 5890 A, split injector (230°C), FID detector (260°C), Spectra-Physics SP 4270 integrator, oven temperature 130°C, hydrogen as carrier gas, solvent CH_2Cl_2. Baseline separation was observed with a Rt-βDEX cst column (length 30 m, lumen 0.32 mm, film thickness 0.25 μm). Retention times: 27.5 min (*R*)-(−)-**4b**, 28.8 min (*S*)-(+)-**4b**, 37.0 min **4a**. The assignment of specific rotation/configuration is based on enantiomerically enriched samples. GC results were confirmed by ^{1}H NMR.[2]

3.6. Model system 5: synthesis of 10-hydroxy-10-phenyl-10*H*-phenanthrene-9-one 5b starting from 9-benzoylfluorene-9-ol 5a

9-Benzoylfluorene-9-ol **5a** (2.86 g, 10.0 mmol), synthesised in a similar manner as **4a**,[30] 13.0 mg (0.1 mmol) of $NiCl_2$ and 0.2 mmol of the ligand were put in a Schlenk tube together with a stirring bar and kept in a thermostated oil bath at 130°C. Aliquots were taken for analysis. The samples were cooled to rt. They were then dissolved in CH_2Cl_2 and the metal salt and ligand removed by filtration using a Pasteur pipette filled with silica (5 cm). After removal of the solvent, the samples were ready for analysis. After 240 h complete conversion to obtain **5b** was achieved. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.93$ (s, 1H, OH), 7.14–7.22 (m, 5H, CH_{arom}), 7.30–7.36 (m, 1H, CH_{arom}), 7.42–7.52 (m, 2H, CH_{arom}), 7.61–7.68 (m, 1H, CH_{arom}), 7.76–7.85 (m, 2H, CH_{arom}), 7.90–7.98 (m, 2H, CH_{arom}). HPLC analysis: Hewlett Packard 1090 M, column: Daicel Chiralcel OD-H cellulose/250 mm/0.46/5μm, column temperature 15°C, injection volume 5 μL (~3.5 mg/mL, solvent = eluent), eluent: *n*-hexane/2-propanol = 9:1, flow rate 0.80 mL/min. Retention times: 22.5 min and 24.9 min **5b** (enantiomer assignment not possible due to low enantiomeric excess), 51.0 min **5a**.

3.7. Model system 6: isomerisation 6a/6b starting from 1-methyliminophenylmethylcyclopentanol 6a

1-Methyliminophenylmethylcyclopentanol **6a** was heated to 130°C in 1-butanol together with 2 mol% of the catalyst system. After 24 h the reaction mixture was cooled to rt and the solvent removed. The residue was chromatographed on a short silica gel column to remove the catalyst and decomposition products (eluent CH_2Cl_2). After removal of the solvent further purification was made possible by the recrystallisation of the hydrochloride from 2-propanol/diethylether (1:1). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.48$–2.00 (m, <8H, CH_2, **6a**/**6b**), 2.04 (s, <3H, NCH_3, **6b**), 2.23–2.45 (m, <3H, CH_2/NH, **6b**), 2.86–2.95 (m, <1H, CH_2, **6b**), 2.96 (s, <3H, NCH_3, **6a**), 5.63 (s, <1H, OH, **6a**), 7.00–7.05 (m, <2H, CH_{arom}, **6a**), 7.19–7.45 (m, 5H, CH_{arom}, **6a**/**6b**). ^{1}H NMR of **6b** (250 MHz, 1 equiv. (*R*)-(−)-mandelic acid, $CDCl_3$. The NCH_3 singlets overlapped a CH_2 multiplet. Nevertheless, integration possible with the deconvolution function of Bruker WinNMR software): $\delta = 1.49$–1.97 (m, 4H, CH_2), 1.98–2.20 (m, 4H, CH_2/NCH_3), 2.23–2.47 (m, 2H, CH_2), 2.77–2.89 (m, 1H, CH_2), 4.91 (s, 1H, CH), 7.17–7.80 (m, 13H, NH/OH/COOH/CH_{arom}). GC analysis: Fisons 8160 A, split injector (250°C), FID detector (240°C), Spectra-Physics SP 4270 integrator, oven temperature 50°C (5 min), heat rate 15°C/min to 140°C (200 min), helium as carrier gas, solvent CH_2Cl_2. Baseline separation was observed with a Lipodex E column (Macherey-Nagel, length 50 m, lumen 0.25 mm, film thickness 0.25 μm). Retention times: 23.1 min **6a**; 117.5 min and 121.9 min **6b**.

3.8. Model system 7: isomerisation 7a/7b starting from 1-(2-chlorophenyl-methyliminomethyl)cyclopentanol 7a

1-(2-Chlorophenylmethyliminomethyl)cyclopentanol **7a** was heated to 130°C in the absence of a solvent together with 5 mol% of the catalyst system. After 24 h

the reaction mixture was cooled to rt and chromatographed with CH_2Cl_2 on a short silica gel column to remove the catalyst and decomposition products. After removal of the solvent, further purification was made possible by recrystallisation from hexane. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.50$–2.06 (m, <8H, CH_2, **7a**/**7b**), 2.09 (s, <3H, NCH_3, **7b**), 2.29 (sb, <1H, NH, **7b**), 2.39–2.55 (m, <2H, CH_2, **7b**), 2.70–2.84 (m, 1H, CH_2, **7b**), 3.00 (s, <3H, NCH_3, **7a**), 5.50 (s, <1H, OH, **7a**), 7.02–7.10 (m, <1H, CH_{arom}, **7a**), 7.19–7.38 (m, <3H, CH_{arom}, **7a**/**7b**), 7.40–7.48 (m, <1H, CH_{arom}, **7a**), 7.54 (dd, $J = 7.8$ Hz, $J = 1.8$ Hz, <1H, CH_{arom}, **7b**). ^{1}H NMR of **7b** (250 MHz, 1 equiv. (*R*)-(−)-mandelic acid, $CDCl_3$, NCH_3 signal splits enabling enantiomeric analysis): $\delta = 1.37$–2.10 (m, 5H, CH_2), 2.23/2.25 (2s, 2×1.5H, NCH_3), 2.42–2.66 (m, 2H, CH_2), 2.86–3.06 (m, 1H, CH_2), 5.00 (s, 1H, CHOH), 6.10 (sb, 3H, NH/OH/COOH), 7.20–7.51 (m, 9H, CH_{arom}).

3.9. Synthesis of new ligands used in catalysis

3.9.1. (*S*)-(+)-*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-diamino-3-methylbutane. (*S*)-(+)-1,2-Diamino-3-methylbutane (1.13 g, 11.1 mmol) was methylated by Eschweiler–Clarke methylation according to literature.[9] Colourless liquid; 0.28 g, 15% yield; bp 120°C/5 mm Hg; $[\alpha]_D = 178$ ($c = 2.61$, $CHCl_3$); IR (film): 2980 (s, νCH), 2840 (s, νCH), 2800 cm^{-1} (s, νNCH_3); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (d, $J = 6.4$ Hz, 3H, CH_3), 0.91 (d, $J = 6.4$ Hz, 3H, CH_3), 1.73–1.85 (m, 1H, $CH(CH_3)$), 2.02 (dd, $J = 12.8$ Hz, $J = 4.2$ Hz, 1H, CH_2), 2.14–2.22 (m, 1H, CH), 2.17 (s, 6H, NCH_3), 2.23 (s, 6H, NCH_3), 2.39 (dd, $J = 12.8$ Hz, $J = 7.2$ Hz, 1H, CH_2); ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 19.32$ (1C, CH_3), 21.43 (1C, CH_3), 28.53 (1C, CH), 41.69 (2C, NCH_3), 45.94 (2C, NCH_3), 58.00 (1C, CH_2), 66.46 (1C, CH); MS (CIMS, NH_3): m/z (%) 159.1 (100.0) [MH].

3.9.2. 2-[4-(*S*)-Isopropyloxazolin-2-yl]-3-methylpyridine. Synthesis starting from 2-cyano-3-methylpyridine according to the literature procedure[17] with the amino alcohol (*S*)-(+)-2-amino-3-methyl-1-butanol obtained from (*S*)-(+)-valine.[31] Colourless crystals; 1.07 g, 52% yield; mp 58°C; $[\alpha]_D = -82$ ($c = 0.93$, $CHCl_3$); IR (KBr): 3040 (w, νCH_{arom}), 2960 (s, νCH), 1640 cm^{-1} (s, νC=N); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (d, $J = 6.8$ Hz, 3H, CH_3), 1.03 (d, $J = 6.8$ Hz, 3H, CH_3), 1.76–1.90 (m, 1H, $CH(CH_3)_2$), 2.59 (s, 3H, CH_3), 4.08–4.21 (m, 2H, $CHCH_2$), 4.35–4.49 (m, 1H, $CHCH_2$), 7.22 (dd, $J = 7.8$ Hz, $J = 4.7$ Hz, 1H, CH_{arom}), 7.53–7.57 (m, 1H, CH_{arom}), 8.47–8.51 (m, 1H, CH_{arom}); ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta =$ 18.42 (1C, $CH(CH_3)_2$), 18.95 (1C, $CH(CH_3)_2$), 20.52 (1C, CH_3), 32.92 (1C, $CH(CH_3)_2$), 69.75 (1C, CH_2), 73.54 (1C, CH), 124.64 (1C, CH_{arom}), 134.93 (1C, C_{arom}), 139.18 (1C, CH_{arom}), 145.82 (1C, C_{arom}), 146.78 (1C, CH_{arom}), 162.20 (1C, C=N); MS (EIMS): m/z (%) 204.1 (51.4) [M]; HRMS: found 204.1268; $C_{12}H_{16}N_2O$ (204.1): calcd C, 70.56; H, 7.90; N, 13.71; found C, 70.49; H, 8.79; N, 13.76.

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References

1. Brunner, H.; Stöhr, F. *Eur. J. Org. Chem.* **2000**, 2777 related literature cited therein.
2. Brunner, H.; Kagan, H. B.; Kreutzer, G. *Tetrahedron: Asymmetry* **2001**, *12*, 497.
3. Kreutzer, G. Ph.D. Thesis, Universität Regensburg, 2003.
4. Honzl, J.; Lövy, J. *Tetrahedron* **1984**, *40*, 1885.
5. Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500.
6. Collin, J.; Namy, J.-L.; Dallemer, F.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 3118.
7. *Organikum*, 20. Auflage, Wiley-VCH: Weinheim, 1999, 286.
8. Dwyer, F. P.; Garvan, F. L.; Shulman, A. *J. Am. Chem. Soc.* **1959**, *81*, 290.
9. Clarke, H. T.; Gillespie, H. B.; Weisshaus, Z. *J. Am. Chem. Soc.* **1933**, *55*, 4571.
10. Kurganov, A. A.; Davankov, V. A.; Ya. Zhuchkova, L.; Ponomaryova, T. M. *Inorg. Chim. Acta* **1980**, *39*, 237.
11. Brunner, H.; Schmidt, M.; Unger, G. *Eur. J. Med. Chem.—Chim. Ther.* **1985**, *20*, 509.
12. Howarth, J.; Gillespie, K. *Molecules* **2000**, *5*, 993.
13. Nishiyama, H.; Tomonori, T.; Takayama, M.; Itoh, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1461.
14. Brunner, H.; Obermann, U.; Wimmer, P. *J. Organomet. Chem.* **1986**, *316*, C1.
15. Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499.
16. Brunner, H.; Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed. Asymmetric Hydrosilylation; VCH: New York, 1993; p. 303.
17. Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 543.
18. Cheng, J.; Deming, T. J. *Macromolecules* **1999**, *32*, 4745.
19. Benson, S. C.; Cai, P.; Haiza, M. A.; Tokles, M.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 5335.
20. Brunner, H.; Henning, F.; Weber, M. *Tetrahedron: Asymmetry* **2002**, *13*, 37.
21. Brunner, H.; Zettler, C. *Chem. Monthly*, in press.
22. Bolm, C.; Bienewald, F.; Seger, A. *Angew. Chem.* **1996**, *108*, 1767; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1657.
23. Preiss, D. Patent DE 44 09 671 C1, 1995.
24. Menhart, V.; Mitinko, V. Patent CS 277268, 1992.
25. Klose, R.; Hoppe, U. (*S*)-*Ketamin*; Springer Verlag: Berlin, Heidelberg, New York, 2002.
26. Heinz, T. W. *Deutsches Ärzteblatt* **1999**, *96*, 2724.
27. Steiner, K. Patent WO 97/43244, 1997.
28. Russo, T.; Freire, V. Patent WO 01/98265 A2, 2001.
29. Menzer, M.; Kazmirowski, H.-G. Möller, G.; Laban, G. Patent DD 217 511 A1, 1985.
30. Creary, X.; Inocencio, P. A.; Underiner, T. L.; Kostromin, R. *J. Org. Chem.* **1985**, *50*, 1932.
31. Vogl, O.; Pöhm, M. *Monatsh. Chem.* **1952**, *83*, 541.