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Asymmetric catalysis

XL *. Enantioselective hydrosilylation of ketones by diphenylsilane with $[Rh(cod)Cl]_2$ / pyridinethiazolidine catalysts

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Abstract

Fiftyeight prochiral ketones have been used in enantioselective hydrosilylation with diphenylsilane promoted by in-situ catalysts consisting of $[Rh(cod)Cl]_2$ and the chiral ligands (4*S*)-2-methyl-2-(2-pyridyl)-4-carbomethoxy-1,3-thiazolidine (**A**) and (4*S*)-2-(2-pyridyl)-4-carbethoxy-1,3-thiazolidine (**B**). Hydrolysis of the silyl ethers gave the corresponding secondary alcohols. Aryl methyl ketones were reduced with ee's better than 80% irrespective of whether the substituents Me, Cl, F, OMe were in *o*-, *m*-, or *p*-position of the phenyl ring. The only exceptions were ketones containing the *p*-OMe substituent, for which a "*p*-methoxy effect" diminished the optical yields. Heterocyclic ketones were also hydrosilylated with high optical inductions, e.g. 2-acetylpyridine with 88.5% ee. Linear alkyl ketones with the CO group in the 2-position (methyl ketones) gave up to 50% ee *R*, in contrast to the corresponding ethyl ketones with the CO group in 3-position, which gave predominantely *S*-configurated products. In 35 cases the asymmetric inductions were higher with ligand **B** than with ligand **A**.

Introduction

We have previously demonstrated the efficiency of in-situ catalysts, consisting of $[Rh(cod)Cl]_2$ (cod = 1,5-cyclooctadiene) and optically active pyridinethiazolidines in the asymmetric hydrosilylation of acetophenone with diphenylsilane [2,3]. We describe here an extension of these studies to a series of 58 prochiral ketones, with the aim of ascertaining how variations in the structure of the ketones affect the optical purity of the products [4]. For this purpose the pyridinethiazolidines **A** and **B** were selected as chiral ligands. **A** and **B** are easily prepared by condensation of

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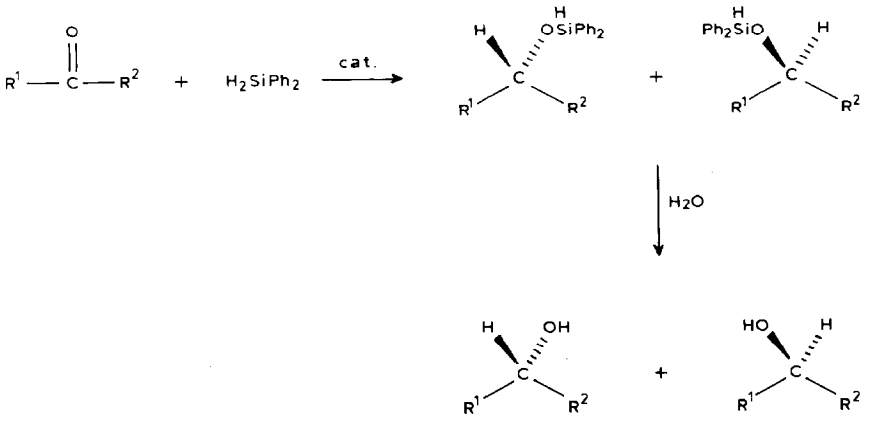
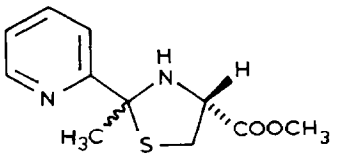
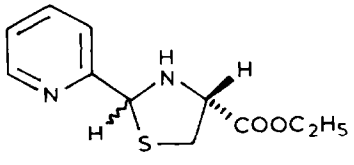


Scheme 1

2-acetylpyridine and 2-pyridinealdehyde with the corresponding cysteine esters [2–4]. In these syntheses, mixtures of two diastereomers are obtained, differing in the configuration at C(2) of the thiazolidine ring. From these oily mixtures the pure diastereomers **A** and **B**, both of which are white solids, can be isolated by fractional crystallization. **A** is commercially available from Merck-Schuchardt.



(**A**)



(**B**)

It has been shown previously that the pure diastereomers **A** and **B** gave the same enantioselectivities as the diastereomeric mixtures in hydrosilylation of ketones. This is a result of a rapid $[Rh(cod)Cl]_2$-catalysed epimerisation at C(2) in solution [3]. The present study represents a continuation of our efforts to modify enantioselective transition metal catalysts by replacing optically active phosphine ligands [5–7] that are expensive and difficult to synthesize by nitrogen ligands [7–9], with those that are inexpensive and easy to prepare.

In the hydrosilylation, one of the Si–H bonds of diphenylsilane adds to the C=O bond of the ketone R^1–CO–R^2 to give a silyl ether, which on subsequent hydrolysis is converted into the corresponding secondary alcohol (Scheme 1).

Results and discussion

Hydrosilylation – standard conditions

All of the hydrosilylations of the ketones **1–58**, shown in Tables 1–4, were carried out under standard conditions. In each case 6 mmol of ketone and 6.6 mmol (1.1 ml) of diphenylsilane were used. The concentration of the procatalyst $[Rh(cod)Cl]_2$ was fixed at 0.66 mol%. The cocatalyst **A** or **B** was added in 8-fold excess with respect to Rh, because a ligand excess had been found to be beneficial for high optical inductions [2,3].

The in-situ catalyst was prepared by dissolving the procatalyst and cocatalyst in the ketone. No solvent was used for liquid ketones, but solid ketones were dissolved in 5 ml of benzene. The reaction was initiated by adding the diphenylsilane at 0 °C and the mixture was slowly warmed to room temperature. The extent of conversion of the ketone/diphenylsilane mixture into the corresponding silyl ether was monitored by ^{1}H NMR spectroscopy [4]. Normally the reaction times, given in Tables 1–4, allowed complete or almost complete turnover. However, in the cases of the less reactive ketones the hydrosilylations were interrupted after partial conversion. The amount of ketone remaining when the reaction was stopped by hydrolysis is given in Tables 1–4 in the first section of the turnover column. After hydrolysis, the product was distilled and weighed to give the yields shown in the second section of the turnover column. It was then again subjected to a ^{1}H NMR analysis. In some cases a higher ketone content was found in the distilled product than was expected from the amount of ketone present when the reaction mixture was hydrolyzed, the reason for this is that alkyl ketones can react with silanes to give silyl enol ethers which on hydrolysis regenerate the ketones [10,11]. The ratio of alcohol/ketone found in the isolated product is given in the third section of the turnover column. To determine the degree of optical induction in the catalytic enantioselective hydrosilylation, the secondary alcohol was converted into the corresponding urethane by treatement with t-butylisocyanate and the enantiomeric urethanes were baseline-resolved on a 50 m Chirasil-L-Val column, allowing determination of the ee to within ±1%. The assignment of the configurations given in Tables 1–4 is based on the assumption that *R*-enantiomers of the urethanes of secondary alcohols are eluted before *S*-enantiomers on a Chirasil-L-Val column [12].

It is surprising that both catalytic systems give approximately the same reaction rates and yields for all of the ketones **1–58** [4]. Thus the enantioselectivities obtained with ligand **A** and **B** refer to the same reaction times and turnovers. In some experiments, especially when **A** was used as a ligand, the reaction mixture was not homogenous. This is indicated by an appropriate footnote to Tables 1–4.

Aryl methyl ketones 1–17

Table 1 contains the results of the hydrosilylation of aryl methyl ketones with aryl = either phenyl or phenyl bearing one or more Me, Ph, Cl, F, NO_2 or OMe substituents.

Under standard conditions the hydrosilylation of acetophenone **1** gave 85.6% *R* with ligand **B** and 79.4% *R* with ligand **A**, in accord with values reported previously [3]. The asymmetric induction decreased when the procatalyst $[Rh(cod)Cl]_2$ was replaced by $[Rh(CO)_2Cl]_2$. Under standard conditions the rhodium/substrate ratio was 1/150. When it was raised to 1/4200 and again to 1/10000 there was no change in product ee, though the reaction time had to be increased. Naphthylphenylsilane, superior to diphenylsilane in the hydrosilylation of α-ketoesters [5–7,13,14], was less efficient in the hydrosilylation of acetophenone **1** than diphenylsilane [15].

In subsequent experiments the influence of various substituents in different ring positions of acetophenone on the enantiomeric excess was examined. Introduction of methyl or chloro substituents in *ortho* or *para* positions in ketones **2**, **3**, **6**, and **7** did not change the asymmetric induction. Similarly, the enantiomeric excess did not fall when the *p*-chloro substituent in ketone **6** was replaced by the *p*-fluorosub-

(Continued on p. 419)

Table 1

Hydrosilylation of the ketones **1–17** (6 mmol) with diphenylsilane (6.6 mmol); catalyst: $[Rh(cod)Cl]_2$ (0.04 mmol Rh) and ligand **A** or **B** (0.32 mmol); T 0 → 20 °C; the ketones **1–17** are aryl methyl ketones with aryl = either phenyl or phenyl bearing one or more Me, Ph, Cl, F, NO_2 or OCH_3 substituents in specified positions of the ring

Number	Ketone R^1–CO–R^2	Reaction time	Turnover			Ligand **A**		Ligand **B**	
	R^1 (R^2 = methyl)		Before hydrolysis: % ketone	After hydrolysis		Runs	% ee (*R*)	Runs	% ee (*R*)
				Isolated yield (%)	Ratio alcohol/ketone				
1 [a]	phenyl	18 h	0	90	100/0	2	78.9–79.9	4	84.8–86.7
1 [a,c]	phenyl	22 h	5	95	90/10	2	8.2; 11.2	2	13.4; 15.9
1 [a,d]	phenyl	21 d	0	95	100/0	–	–	1	83.3
1 [a,e]	phenyl	75 d	5	90	95/5	–	–	1	82.3
1 [a,f]	phenyl	7 d	50	95	45/55	2	51.0; 50.5	2	56.3; 57.3
2 [a]	4-methylphenyl	18 h	0	95	100/0	2	76.9; 77.1	2	85.6; 86.2
3 [a]	2-methylphenyl	20 h	5	90	90/10	2	72.5; 73.3	2	83.2; 84.4
4 [a]	2,4,6-trimethylphenyl	40 h	15	90	80/20	4 [i]	66.9–70.3	2	68.5; 68.7
5 [b]	4-phenylphenyl	18 h	15	90	80/20	4 [i]	70.4–73.8	2	60.6; 62.2
6 [a]	4-chlorophenyl	66 h	0	90	100/0	2	77.5; 77.7	2	88.3; 89.0
7 [a]	2-chlorophenyl	22 h	5	95	95/5	2	77.3; 78.7	2	82.9; 83.1
8 [a]	4-fluorophenyl	24 h	0	95	100/0	2	74.8; 75.4	3	86.8–88.8
9 [a,g]	4-nitrophenyl	12 d	50	75	45/55	2 [i]	53.5; 53.5	2	58.5; 61.2
10 [ag]	3-nitrophenyl	12 d	50	75	45/55	2 [i]	64.5; 64.5	2	51.8; 52.2
11 [a]	2-methoxyphenyl	24 h	0	95	100/0	2	60.1; 61.7	2	80.8; 81.8
12 [a]	3-methoxyphenyl	18 h	0	95	100/0	2	71.8; 74.0	2	89.9; 91.1
12 [a,h]	3-methoxyphenyl	8 d	0	95	100/0	–	–	1	93.3
13 [b]	4-methoxyphenyl	18 h	0	90	100/0	4	17.6–19.2	6	15.2–21.7
14 [b]	3,4-dimethoxyphenyl	18 h	0	90	100/0	4 [i]	20.8–22.9	4	13.0–15.3
15 [b]	2,5-dimethoxyphenyl	18 h	0	90	100/0	2	72.4; 72.6	2	81.7; 83.3
16 [b]	3,4,5-trimethoxyphenyl	40 h	0	85	100/0	2 [i]	74.8; 77.5	2	82.4; 83.2
17 [b]	2,3,4-trimethoxyphenyl	18 h	0	90	100/0	2	24.7; 25.3	2	32.2; 33.4

[a] Without solvent. [b] With 5 ml of benzene. [c] $[Rh(CO)_2Cl]_2$. [d] Ratio Rh/ketone = 1/4200. [e] Ratio Rh/ketone = 1/10000. [f] Naphthylphenylsilane. [g] T 50 °C. [h] T −15 °C. [i] Reaction mixture not homogeneous.

Table 2

Hydrosilylation of the ketones **18–35** (6 mmol) with diphenylsilane (6.6 mmol); catalyst: $[Rh(cod)Cl]_2$ (0.04 mmol Rh) and ligand **A** or **B** (0.32 mmol); T 0 → 20 °C; the ketones **18–35** are phenyl alkyl ketones, aryl alkyl ketones, and aryl phenyl ketones, aryl being substituted phenyl, naphthyl or a heterocyclic substituent

Number	Ketone R^1–CO–R^2		Reaction time	Turnover			Ligand **A**		Ligand **B**	
	R^1	R^2		Before hydrolysis: % ketone	After hydrolysis		Runs	% ee (*R*)	Runs	% ee (*R*)
					Isolated yield (%)	Ratio alcohol/ketone				
18 [a]	phenyl	ethyl	18 h	0	90	100/0	2	61.1; 61.5	4	72.4–76.7
19 [a]	phenyl	n-propyl	40 h	5	85	95/5	2 [c]	54.5; 56.0	4	77.8–81.3
20 [a]	phenyl	i-propyl	5 d	0	90	95/5	3 [c]	14.5–16.1	3	6.8– 9.0
20 [a]	phenyl	i-propyl	14 d	0	90	95/5	2 [c]	15.3; 15.5	–	–
21 [a]	phenyl	c-propyl	18 h	0	95	100/0	4 [c]	0.0 ± 0.4	4	0.0 ± 0.3
22 [a]	4-chlorophenyl	n-propyl	18 h	5	95	95/5	2 [c]	58.7; 61.2	2	64.2; 65.1
23 [a]	4-bromophenyl	3-chloro-n-propyl	40 h	10	90	90/10	2 [c]	60.6; 61.5	4	59.3–64.3
24 [b]	4-methoxyphenyl	ethyl	40 h	0	95	100/0	2 [c]	34.1; 34.6	3	58.5–61.0
25 [a]	1-naphthyl	methyl	18 h	0	95	100/0	2	75.7; 76.1	2	81.5; 83.3
26 [b]	2-naphthyl	methyl	18 h	0	90	100/0	2 [c]	78.2; 79.4	2	77.9; 77.9
27 [a]	2-pyridyl	methyl	18 h	5	90	90/10	2	72.2; 72.7	2	87.6; 89.6
28 [a]	3-pyridyl	methyl	18 h	50	35	40/60	1 [c]	21.3	2	48.6; 49.2
29 [a]	4-pyridyl	methyl	18 h	50	35	40/60	2 [c]	18.4; 19.0	3	31.6–33.2
30 [a]	2-furyl	methyl	18 h	5	90	95/5	2	20.4; 20.8	2	15.4; 16.6
31 [a]	2-thienyl	methyl	18 h	0	95	100/0	2	6.8; 7.8	2	33.8; 34.0
32 [b]	3,4-methylendioxyphenyl	methyl	18 h	15	90	80/20	2 [c]	58.5; 59.7	2	60.8; 62.2
33 [b]	3,4-ethylendioxyphenyl	methyl	18 h	0	95	100/0	2 [c]	60.9; 62.1	4	63.9–66.4
34 [b]	2-methylphenyl	phenyl	10 d	25	70	75/25	2 [c]	22.4; 24.7	2	15.5; 16.9
35 [b]	2,4-dimethylphenyl	phenyl	14 d	25	60	75/25	2 [c]	36.7; 37.7	2	17.6; 18.8

[a] Without solvent. [b] With 5 ml of benzene. [c] Reaction mixture not homogeneous.

Table 3

Hydrosilylation of the ketones **36–40** (6 mmol) with diphenylsilane (6.6 mmol); catalyst: $[Rh(cod)Cl]_2$ (0.04 mmol Rh) and ligand **A** or **B** (0.32 mmol); T 0 → 20 °C; the ketones **36–40** are cyclic ketones

Number	Ketone	Reaction time (h)	Turnover			Ligand **A**		Ligand **B**	
			Before hydrolysis: % ketone	After hydrolysis		Runs	% ee	Runs	% ee
				Isolated yield (%)	Ratio alcohol/ketone				
36 [a]	1-indanone	18	0	90	100/0	2 [c]	46.3; 47.6 (*R*)	2	58.1; 58.5 (*R*)
37 [a]	1-tetralone	18	5	85	95/5	4 [c]	69.1–72.3 (*R*)	3	79.1–82.6 (*R*)
38 [b]	6-methoxy-1-tetralone	18	5	75	95/5	3 [c]	1.3–3.2 (*S*)	2	1.6; 2.8 (*S*)
39 [b]	4-chroman-1-one	18	10	80	85/15	3	70.0–71.2 (*R*)	2	81.2; 81.5 (*R*)
40 [b]	4-thiochroman-1-one	18	10	80	85/15	2	60.2; 62.1 (*R*)	4	58.9–63.5 (*R*)

[a] Without solvent. [b] With 5 ml of benzene. [c] Reaction mixture not homogeneous.

stituent in **8**. For the mesitylene ketone **4** and the 4-biphenyl ketone **5** the optical induction fell to 68.6% *R* and 61.4% *R*, respectively when **B** was used as ligand. The nitro ketones **9** and **10** were found to react very slowly with diphenylsilane; reaction times of 12 d were required for 50% conversion, accompanied by a decrease in the optical inducation to 50–65% ee.

In the series of the methoxy-substituted acetophenones the *ortho* and *meta* derivatives **11** and **12** gave the expected high enantiomeric excess, and for **12** this increased to 93.3% ee when the temperature was lowered to −15°C. In contrast, *p*-methoxyacetophenone (**13**) yielded only 15–20% *R*. Such a "*p*-methoxy-effect" on the selectivity was also observed for **1** and **13** in the $[Rh(cod)Cl]_2/(-)$DIOP-catalysed hydrosilylation [16] and in the reduction of **1** and **13** with baker's yeast [17]. The results for the di- and tri-methoxy-ketones **14–17** confirmed this "*p*-methoxy-effect". The optical inductions were low for ketones **14** and **17**, having a *p*-methoxy group, and high for **15**, having no *p*-methoxy group. The only exception is 3,4,5-trimethoxyacetophenone, which in spite of having a *p*-methoxy substituent gave 75–83% ee.

*Phenyl alkyl ketones, aryl alkyl ketones, and aryl phenyl ketones **18–35***

Table 2 shows the results of the hydrosilylation of phenyl alkyl ketones, aryl alkyl ketones, and aryl phenyl ketones with aryl = substituted phenyl, naphthyl, or a heterocyclic group.

In ketones **18** and **19** the methyl group of acetophenone **1** has been replaced by an ethyl and a n-propyl group. This change caused a slight decrease in the asymmetric induction when ligand **B** was used, and for ligand **A** the decrease was larger. The ee decreased from the n-propyl derivative **19** to the i-propyl and the cyclopropyl derivatives 20 and 21 with virtually no optical induction in the latter case. The possibility that the low optical induction of the i-propyl derivative **20** is the result of a slow racemisation of the silyl ether formed in the hydrosilylation can be ruled out [18], since a reaction time of 14 d gave the same results as one of 5 d. The presence of *p*-Cl and *p*-Br substituents in the phenyl ring in **22** and **23** did not change the optical induction relative to the unsubstituted phenyl n-propyl ketone **19** even when a Cl substituent was also present in the ω-position of the n-propyl group. Surprisingly, the *p*-methoxyphenyl ethyl ketone **24** gave a much higher optical yield than *p*-methoxyacetophenone **13**. For the enantiomeric excess in the case of the naphthyl methyl ketones **25** and **26** it was unimportant whether the naphthyl group was acylated in α or β position. The hydrosilylation of the acetylpyridines, however, was strongly dependent on the position of the acetyl group relative to the nitrogen atom; thus 2-acetyl-pyridine (**27**) was reduced by the $[Rh(cod)Cl]_2$/**B** catalyst with 88% *R*, whereas its stoichiometric reduction with $LiBH_4$ modified by *N,N'*-dibenzoylcystine gave only 56% ee [19]. Evidently, the substrate 2-acetylpyridine, although present in large excess, cannot efficiently compete with the cocatalysts **A** and **B**, which are also pyridine derivatives, for the metal coordination sites. In the case of the 3- and 4-acetylpyridines **28** and **29**, smaller optical inductions were observed in slow hydrosilylations, probably because **28** and **29**, contrary to **27**, cannot chelate to the metal atom in the rhodium/substrate complex. Although chelation would be possible for the 2-furyl and 2-thienyl ketones **30** and **31**, only small optical inductions were observed. The optical induction for the substrates **1–27** and **30** were similar for the two catalyst systems. However, for the ketones **28**, **29**, and **31** there

Table 4

Hydrosilylation of the ketones **41–58** (6 mmol) with diphenylsilane (6.6 mmol); catalyst: $[Rh(cod)Cl]_2$ (0.04 mmol Rh) and ligand **A** or **B** (0.32 mmol); T 0 → 20 °C; the ketones **41–58** are alkyl alkyl ketones and alkyl alkenyl ketones

Number	Ketone R^1–CO–R^2		Reaction time (h)	Turnover			Ligand **A**		Ligand **B**	
	R^1	R^2		Before hydrolysis: % ketone	After hydrolysis		Runs	% ee	Runs	% ee
					Isolated yield %	Ratio alcohol/ketone				
41 [a]	butyl	methyl	18	15	80	80/20	4 [c]	43.0–45.5 (*R*)	2	51.0; 52.2 (*R*)
42 [a]	propyl	ethyl	18	10	85	90/10	2 [c]	10.6; 11.4 (*S*)	2	13.5; 13.6 (*S*)
43 [a]	pentyl	methyl	18	15	80	80/20	3 [c]	41.0–43.2 (*R*)	2	45.5; 46.5 (*R*)
44 [a]	butyl	ethyl	18	10	90	85/15	3 [c]	14.2–15.7 (*S*)	4	24.1–25.6 (*S*)
45 [a]	hexyl	methyl	40	5	90	90/10	2 [c]	21.8; 22.2 (*R*)	3	36.4–38.5 (*R*)
46 [a]	pentyl	ethyl	40	15	85	80/20	4 [c]	9.8–12.7 (*S*)	2	17.6; 19.2 (*S*)
47 [a]	heptyl	methyl	18	10	90	85/15	4 [c]	37.7–39.8 (*R*)	5	34.6–39.2 (*R*)
48 [a]	hexyl	ethyl	18	10	90	85/15	2 [c]	13.0; 14.2 (*S*)	2	17.8; 18.8 (*S*)
49 [a]	octyl	methyl	40	15	80	80/20	2 [c]	33.8; 34.2 (*R*)	4	38.0–40.3 (*R*)
50 [a]	heptyl	ethyl	40	10	85	90/10	2 [c]	10.4; 11.4 (*S*)	2	18.8; 20.0 (*S*)
51 [a]	hexyl	propyl	40	15	85	80/20	2 [c]	3.5; 4.5 (*S*)	2	2.8; 3.2 (*S*)
52 [a]	2-methyl-propyl	methyl	18	0	90	95/5	2 [c]	41.2; 41.6 (*R*)	2	55.2; 55.8 (*R*)
53 [a]	3-methyl-butyl	methyl	18	0	95	95/5	3 [c]	35.8–37.4 (*R*)	2	33.8; 34.2 (*R*)
54 [a]	2-methyl-butyl	ethyl	18	0	95	95/5	3 [c]	18.2–19.4 (*R*)	4	44.2–45.9 (*R*)
55 [a]	benzyl	ethyl	40	0	90	95/5	2 [c]	9.6; 9.6 (*R*)	2	23.0; 23.2 (*R*)
56 [a]	methoxy-methyl	methyl	18	0	85	65/35	2 [c]	2.8; 3.0 (*R*)	2	4.8; 5.0 (*R*)
57 [b]	trans-phenylvinyl	methyl	18	20	70	75/25	2 [c]	6.3; 8.1 (*R*)	4	12.1–13.8 (*R*)
58 [a]	*trans*-(2,6,6-trimethyl-2-cyclohexen-1-yl)-vinyl	methyl	40	20	80	75/25	2	35.5; 37.5 (*R*) [d]	2	40.1; 40.3 (*R*) [d]

[a] Without solvent. [b] With 5 ml of benzene. [c] Reaction mixture not homogeneous. [d] Diastereomeric excess.

were distinct differences in the asymmetric inductions for $[Rh(cod)Cl]_2$/**A** and $[Rh(cod)Cl]_2$/**B**. Ketones **32** and **33** gave an enantiomeric excess of about 60% even though they contain a *p*-alkoxy substituent, which normally lowers the optical induction (see above). The hydrosilylation of the unsymmetrical benzophenone derivatives **34** and **35** was slow, and occurred with low ee.

*Cyclic ketones **36–40***

Table 3 shows the results of the hydrosilylation of cyclic five- and six-membered ketones. For tetralone **37** the optical induction was much higher than for indanone **36** in both catalyst systems. In the hydrosilylation of 6-methoxy-1-tetralone **38**, the "*p*-methoxy effect" came into play, decreasing the enantiomeric excess for ligand **B** to about 2.1% *S* compared to about 80% *R* for the unsubstituted tetralone **37**. Replacement of the C-atom in the 4-position of 1-tetralone by oxygen (ketone **39**) had no effect on the ee. However, replacement by sulfur (ketone **40**) lowered the asymmetric induction.

*Alkyl alkyl ketones and alkyl alkenyl ketones **41–58***

Table 4 shows the results of the hydrosilylation of alkyl alkyl ketones and alkyl alkenyl ketones. The enantiomeric excess in the hydrosilylation of alkyl alkyl ketones is strongly dependent on the position of the carbonyl group in the alkyl chain. The methyl ketones **41, 43, 45, 47**, and **49** with the C=O group in 2-position gave optical inductions of about 40–50%; with the *R* configuration predominating. The ethyl ketones **42, 44, 46, 48**, and **50** with the carbonyl group in 3-position gave predominately *S*-configurated products of 10–25% optical yield. As expected the stereoselectivity in the reduction of n-hexyl n-propyl ketone **51** is very low. The configurations of the secondary alcohols derived from ketones **41–51** were determined by comparing their optical rotations with literature values [20]. Without exception, this assignment agreed with that based on the assumption that *R*-enantiomers of secondary alcohols are eluted before *S*-enantiomers on a Chirasil-L-Val column [12]. Surprisingly, the methyl ketones **52** and **53** and the ethyl ketone **54**, which contain branched alkyl chains, gave relatively high optical inductions. For the methyl benzyl ketone **55** and the methoxymethyl ketone **56** only small optical yields were obtained.

In the hydrosilylation with diphenylsilane, the α,β-unsaturated ketones **57** and **58** gave the 1,2-adducts, in agreement with established rules [21–23]. The ee of the α,β-unsaturated alcohol was higher for **58** than for **57**. Whereas the chromatograms obtained by GLC for the urethanes derived from ketones **1–57** exhibited only two peaks, that of the urethane of ketone **58** contained four peaks. This is because ketone **58** has an asymmetric carbon atom in its *trans*-(2,6,6-trimethyl-2-cyclohexan-1-yl)-vinyl substituent. Since the ketone **58** was a racemic mixture, the sum of the peak areas of the *RR* + *RS* isomers and of the *SS* + *SR* isomers must have the same value, the first letter designating the configuration of the asymmetric carbon atom already present in the ketone and the second letter the configuration of the chiral center formed in the enantioselective hydrosilylation. This condition was fulfilled when the areas of the first and the fourth peak and the areas of the second and the third peak were added together. On the assumption that *R*-enantiomers were eluted before *S*-enantiomers on the Chirasil-L-Val column, the four peaks in order of

increasing retention times were assigned to the configurations *RR*, *SR*, *SS*, and *RS*.

Scope and limitations

As shown for the ketones **1–58**, the new methodology described in the present report offers an attractive alternative to other methods for the enantioselective conversion of prochiral ketones into secondary alcohols, e.g. catalytic hydrogenation [5–7] or stoichiometric reduction [24]. However, during our studies we encountered some ketones to which the new methodology could not be applied successfully. Benzoin, α-chloro- and α-bromoacetophenone, and some sterically hindered ketones, such as (−)-fenchone, (+)-camphor, and (+)-pulegone, failed to react with diphenylsilane in the presence of the catalyst $[Rh(cod)Cl]_2$/**A** or $[Rh(cod)Cl]_2$/**B** under the standard conditions [4]. The turnover in the hydrosilylation of α- and β-ketoesters was only 50% after 4 days at about 50 °C. Measurement of the optical rotation showed that only low optical inductions were achieved under these conditions [4].

For the following ketones the urethanes of the secondary alcohols, obtained by hydrosilylation, hydrolysis and derivatization, could not be resolved on a 50 m capillary Chirasil-L-Val column even though methyl-, isopropyl-, t-butyl-, phenyl-, 1-naphthylisocyanate, and (−)-*N*-trifluoroacetylpyrolyl-chloride were tried as derivatizing reagents [4]: butan-2-one, pentan-2-one, 1-buten-3-one, 1-chloropropan-2-one, cyclopropyl methyl ketone, cyclohexyl methyl ketone, benzyl methyl ketone, 2-hydroxyacetophenone, 3-aminoacetophenone, cyclohexyl phenyl ketone, 1,1-diphenylpropan-2-one, 9-acetylanthracene, 2-chlorobenzophenone, phenyl pyridyl ketone, benzanthrone, flavanone.

An observation which we made at the end of our experiments should be briefly noted. Knowing that in a catalysed reaction even the sequence of addition of the reactants could change the selectivity, we inverted the usual order of addition of ketone and diphenylsilane. For acetophenone **1** this reversed order of addition led to an increase in ee from 85.6 to 87.8%, and so this inverted addition was also used for ketones **4, 12, 18, 20, 25, 50**, and **58**., for both the catalysts $[Rh(cod)Cl]_2$/**A** and $[Rh(cod)Cl_2]$/**B**, i.e., for a total of 16 systems. In three the ee fell by between 3 and 5% compared to those obtained by the standard procedure, in one it remained constant, and in twelve it increased by up to 15% [4]. It thus appears to be possible to raise the enantioselectivities for most of the systems reported in the present paper by reversing the order of addition of ketone and diphenylsilane from that used in the standard procedure.

Experimental section

Materials

The ketones (Aldrich, Fluka, Janssen, Merck) were purified by distillation and stored under nitrogen. Diphenylsilane was used as a reducing reagent, and was prepared by treatment of diphenyldichlorosilane with $LiAlH_4$ [15]. The procatalyst $[Rh(cod)Cl]_2$ can be obtained by reaction of $RhCl_3$ with 1,5-cyclooctadiene [26].

Ligand A = 2-methyl-2-(2-pyridyl)-4-carbomethoxy-1,3-thiazolidine

A mixture of L-methyl cysteinate hydrochloride (8.6 g, 50 mmol) (Serva), 2-acetylpyridine (5.5 ml, 49 mmol) and triethylamine (6.7 ml, 49 mmol) in 200 ml of absolute benzene was refluxed for 40 h with the refluent solvent percolating through $CaSO_4$ in a Soxhlet apparatus. The precipitated triethylammonium chloride was filtered off, and the solvent evaporated. The residue was stirred with 10 ml of petroleum ether to give a yellow solid. Repeated recrystallisation from $CHCl_3/EtO_2$ (1/1) gave the pure diastereomer **A**. White plates, m.p. 93°C, yield 6.5 g (55%). ^1H NMR (250 MHz, $CDCl_3$, internal TMS, 297 K): δ 1.94 (s, 3H), 3.04 and 3.48 (dd, 2H), 3.83 (s, 3H), 4.26 (m, 1H), 4.74 (s, 1H), 7.23, 7.47, 7.70 and 8.70 (m, 4H).

Ligand B: 2-(2-pyridyl)-4-carboethoxy-1,3-thiazolidine

L-Ethyl cysteinate hydrochloride (10 g, 54 mmol) (Fluka) were dissolved in methanol/benzene 20 ml/40 ml. 2-Pyridinealdehyde (4.9 ml, 52 mmol), triethylamine (7.2 ml, 52 mmol) and 5 g anhydrous Na_2SO_4 were added. After 15 h stirring at room temperature the solvent was evaporated and the residue was treated with 150 ml of ether. The triethylammonium chloride was filtered off and the solution was dried over Na_2SO_4. Evaporation of the solvent left an oily product that solidified on stirring with ether/petroleum ether (2/1) (10 ml). Repeated recrystallisation from $CHCl_3/EtO_2$ (1/1) gave the pure diastereomer **B**. White solid, m.p. 82°C, yield 2.6 g (20%). ^1H NMR (250 MHz, C_6D_6, internal TMS, 297 K): δ 0.9 (t, 3H), 2.96–4.20 (m, 4H), 3.93 (q, 2H), 6.03 (s, 1H), 6.51–8.37 (m, 4H).

Hydrosilylation – standard procedure

The in-situ catalysts were prepared by dissolving the procatalyst $[Rh(cod)Cl]_2$ (10 mg, 0.04 mmol Rh) and the thiazolidines **A** or **B** (80 mg, 0.34 mmol) in the ketone (6 mmol). When the ketone was a solid, benzene (5 ml) was used as a solvent. The hydrosilylation was started by adding diphenylsilane (1.1 ml, 6.6 mmol) at 0°C. The deep red mixture was slowly warmed to room temperature then stirred for the time indicated in Tables 1–4. For work-up, it was cooled in an ice bath and hydrolyzed by adding 10 ml of acetone, 2.5 ml of 10% HCl, and as much acetone as was necessary to give a homogeneous solution. After 2 h stirring at 0°C and 0.5 h at room temperature the mixture was neutralized by adding 5 ml saturated Na_2CO_3 solution and extracted twice with 30 ml portions of ether. The combined ethereal layers were dried over $MgSO_4$. After removal of the solvent and distillation of the crude product, its purity and the ratio secondary alcohol/ketone were checked by ^1H NMR spectroscopy [4] and its yield determined by weighing.

GLC-Determination of the optical purity

For measuring the enantiomeric excess, approximately 20 mg of pure product were mixed with t-butylisocyanate (0.3 ml) and one drop of triethylamine in a Reacti-Vial. After 12 h at 60°C the Reacti-Vial was cooled to room temperature and the excess of isocyanate was carried off in a stream of nitrogen. The remaining urethane was dissolved in approximately 1 ml of CH_2Cl_2 and this solution was used for the GLC-determination of the enantiomeric excess on a 50 m capillary Chirasil-L-Val column. The peaks were resolved for all the urethanes derived from ketones **1–58** when column temperatures between 60 and 160°C were used [4].

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