Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1767–1779

TETRAHEDRON: *ASYMMETRY*

Synthesis and evaluation of a new steroidal BINAP type phosphine

V. Enev,† M. Harre, K. Nickisch, M. Schneider and J. T. Mohr*

Process Research, Schering AG-Berlin, Müllerstrasse 170–178, D-13342 Berlin, Germany

Received 18 February 2000; accepted 30 March 2000

Abstract

The short and high yielding synthesis of a new *cis*-configured bissteroidal phosphine **7** is reported. The comparison of these new phosphines as ligands in ruthenium-based hydrogenation catalysts with the previously synthesized diastereomeric *trans*-configured phosphines **20** shows that the steroid backbone exerts only a minor influence on the enantioselection of the ruthenium catalysts and confirms that the bissteroidal phosphines behave as 'pseudo'-enantiomers in spite of their diastereomeric nature. Evidence is presented that the mode of catalyst preparation, i.e. catalyst structure, is the crucial reaction parameter which mainly determines the enantiomeric excess of the hydrogenation products.

1. Introduction

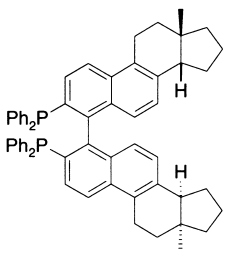
Recently, we reported the synthesis and application of a *trans*-configured bissteroidal phosphine as an axially chiral hydrogenation ligand.[1] In a first substrate screening our phosphines displayed higher activities relative to the benchmark phosphine BINAP in the hydrogenations of α-acetamidocinnamic and tiglic acid. Although the new ligand met our initial expectations, the success was somewhat compromized by the high price of the starting material equilenine, which endangered any further applications, for instance in hydrogenation catalysts.

We now report the economic synthesis of a new bissteroidal phosphine **7** and its application as a chiral ligand in ruthenium-based asymmetric hydrogenation catalysts.

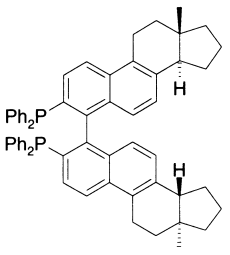
* Corresponding author. E-mail: joergtorsten.mohr@schering.de

† Postdoctoral Fellow on leave from the Bulgarian Academy of Science, Sofia, Bulgaria. Current address: University of Vienna, Austria.

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00127-0



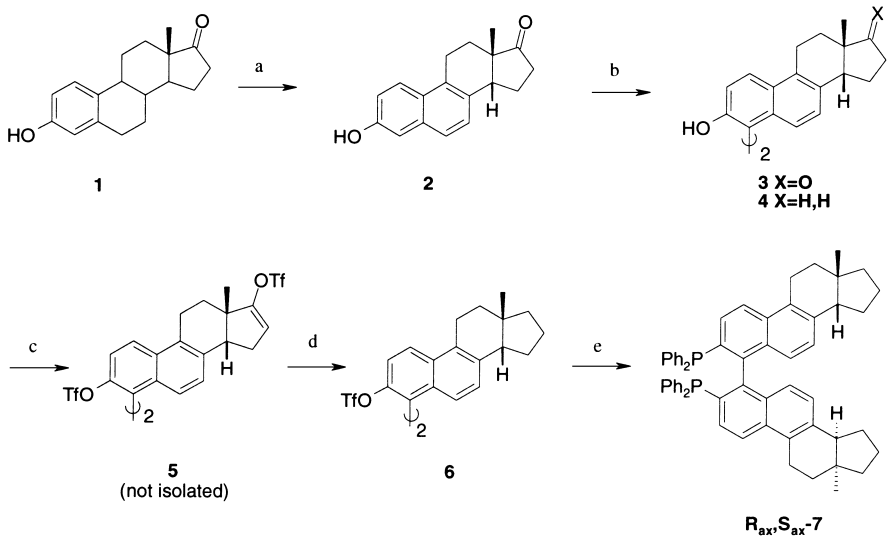
7



20

2. Results and discussion

Except for our previously applied starting material equilenine no other steroidal monomer is available which already has included an aromatic A- as well as an aromatic B-ring in its structure. Therefore, our first goal was to find a simple and high yielding method for the synthesis of these kinds of structures. We were intrigued by the idea of using estrone **1** as an economically attractive starting material, because the dehydrogenation of estrone over palladium charcoal is a well-known reaction in steroid chemistry.[2] Two problems were anticipated with this strategy: the first was the moderate yield of only 48% stated in the literature as well as the long dehydrogenation reaction time of 3 days which caused a bottleneck in the synthesis of the required larger amounts of the monomer. This problem could be solved by replacing the original solvent triethyleneglycol dimethylether with 1-methyl naphthalene which reduced the reaction time from 3 days to 3 h and allowed the synthesis of isoequilenine **2** in 1 kg batch sizes and high yields (92%) in the pilot plant (Scheme 1).



1 2 3 X=O 4 X=H,H 5 (not isolated) 6 R_{ax},S_{ax}-7

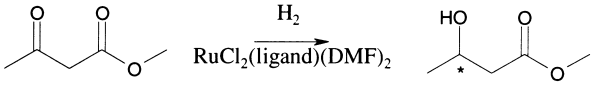
Scheme 1. Reagents and conditions: (a) cat. Pd/C (10%), 1-methyl naphthalene, 92%; (b) cat. CuCl(OH)–TMEDA, CH_2Cl_2, O_2, 95%; (c) Tf_2O, $^iPr_2NEt$, crude; (d) cat. PtO_2, H_2, 81% (two steps); (e) cat. $NiCl_2$dppe, Ph_2PH, DABCO, 89%

The second problem lay in the assessment of the isomerization of the proton at C-14 in the course of the dehydrogenation reaction of estrone. As this isomerization means a change of the C–D ring junction from *trans* to the thermodynamically more stable *cis* form we were confronted with the question of whether this structural modification would affect the properties of the final bissteroidal phosphine. Although this question could only be answered at the end of our studies, our initial hypothesis was along the lines of not expecting large differences regarding the degree of enantioselection which will be induced by the two phosphines, because the structural modification in the backbone is far away from the metal-binding site in the catalyst.

Subsequent to the dehydrogenation of estrone **1** we planned to proceed in the synthesis of **7** with a Wolff–Kishner reduction of **2** followed by a copper-mediated coupling[3] of the deoxygenated isoequilenine (Scheme 1). Whereas the chemistry from isoequilenine **2** to the diastereomeric intermediates **4** proceeded uneventfully, we were not able to separate the deoxygenated ligands R_{ax},S_{ax}-**4** by column chromatography on a preparative scale.

Therefore, we decided to perform the coupling step prior to the reduction step and set out to find a racemization free method for the deoxygenation of **3**.[4] This goal was accomplished according to the following transformations: (i) copper mediated coupling of **2** (95% yield) yielding a 1:1 mixture of the diastereomeric compounds R_{ax}-**3** and S_{ax}-**3** which we were now able to separate via preparative HPLC even on a kilogram scale; (ii) conversion of the separated ligands R_{ax}-**3** and S_{ax}-**3** into R_{ax}-**5** and S_{ax}-**5** by reaction with triflic acid anhydride in the presence of diisopropylethylamine; (iii) selective hydrogenation of the crude tetra triflates R_{ax}-**5** and S_{ax}-**5** over 10 mol% PtO_2 at atmospheric pressure[5] yielding bistriflates R_{ax}-**6** and S_{ax}-**6** in 81% combined yield; and (iv) phosphinylation under previously established reaction conditions afforded the diastereomerically pure ligands R_{ax}-**7** and S_{ax}-**7** in 89% yield[1,6] (Scheme 1).

Having the new phosphines in hand methyl acetoacetate **8** was chosen as the first substrate to test our new phosphines. To this end ligands **7** and **20** (previously prepared from equilenine)[1] were incorporated into the oligomeric[7] ruthenium complexes $[RuCl_2(R_{ax}\text{-}\mathbf{7})(DMF)]_n$ **9a**, $[RuCl_2(S_{ax}\text{-}\mathbf{7})(DMF)]_n$ **9b**, $[RuCl_2(R_{ax}\text{-}\mathbf{20})(DMF)]_n$ **10a** and $[RuCl_2(S_{ax}\text{-}\mathbf{20})(DMF)]_n$ **10b**.[8] Under identical reaction conditions **9a**,**b** displayed similar activities as **10a**,**b** and afforded (*R*, resp. *S*)-3-hydroxybutanoate **11** in quantitative yield (Eq. 1).



8 **11** (1)

cat 9a:	s/c-1260, 100 % conversion, 95% ee (R)
cat 9b:	s/c-1260, 100 % conversion, 95% ee (S)
cat 10a:	s/c-1260, 100 % conversion, 99% ee (R)
cat 10b:	s/c-1260, 100 % conversion, 98% ee (S)

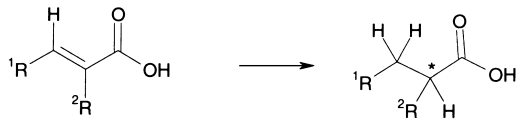
The asymmetric induction of catalysts **9a**,**b** was only slightly lower (95% ee) than the induction by catalysts **10a**,**b** (98–99% ee[1]) implying that the structure of the steroid backbone in the hydrogenation catalyst indeed affected the degree of enantioselection but only to a minor extent. No difference concerning the asymmetric induction between the two diastereomers R_{ax}-**7** and S_{ax}-**7** was observed.

In order to investigate the influence of the catalyst structure[9] on the enantioselection of the hydrogenation catalysts the following experiments were carried out in parallel runs of catalysts **9** and **10** and the dimeric catalysts $[RuCl_2(R_{ax}\text{-}\mathbf{7})]_2(NEt_3)$ **12a**, $[RuCl_2(S_{ax}\text{-}\mathbf{7})]_2(NEt_3)$ **12b**, $[RuCl_2(R_{ax}\text{-}\mathbf{20})]_2(NEt_3)$ **13a** and $[RuCl_2(S_{ax}\text{-}\mathbf{20})]_2(NEt_3)$ **13b**.[10]

An influence of the steroid backbone should be indicated by a difference in asymmetric induction of: (i) an S_{ax}-configured vs an R_{ax}-configured ligand; and (ii) ligands with a *cis* C–D ring junction vs a *trans* C–D ring junction. Similarly, an influence of the catalyst structure should be easily detectable by a difference in asymmetric induction of the oligomeric vs the dimeric catalyst with the same substrate.

Inspection of the results from the hydrogenation of compounds **14**–**16** with the different catalysts revealed again a small to moderate influence of the steroid backbone (Table 1). We observed in most cases a stereoreinforcing interaction of local and axial chirality in the R_{ax}- and a non-reinforcing interaction in the S_{ax}-diastereomers for both phosphines **7** and **20**. For the oligomeric catalysts the greatest difference in enantiomeric excess (ee) was 7% for the CD *cis*-configured (**9a** vs **9b**, substrate **15**) and 16% for the CD *trans*-configured phosphines (**10a** vs **10b**, substrate **14**). The dimeric catalysts showed a maximum difference in ee of 1% for the *cis*-series (**12a** vs **12b**, all substrates) and of 6% for the *trans*-series (**13a** vs **13b**, substrate **16**). The fact that the extent of this interaction was more pronounced in the case of the oligomeric catalysts **9** and **10** could be taken as a first hint of the importance of catalyst preparation for the success of the enantioselective hydrogenation reaction.

Table 1
Comparison of (R_{ax},S_{ax})-**7** and (R_{ax},S_{ax})-**20**[a]



^{1}R= Ph, ^{2}R= HNAc: **14** — **17**
^{1}R= H, ^{2}R= HNAc: **15** — **18**
^{1}R= CH_3, ^{2}R= CH_3: **16** — **19**

catalyst/	**9a**	**9b**	**10a**	**10b**	**12a**	**12b**	**13a**	**13b**
substrate	%ee[b]		%ee[b]		%ee[b]		%ee[b]	
	R_{ax}-**7**	S_{ax}-**7**	R_{ax}-**20**	S_{ax}-**20**	R_{ax}-**7**	S_{ax}-**7**	R_{ax}-**20**	S_{ax}-**20**
14	82	79	85	69	87	86	84	87
15	75	68	72	66	97	96	97	96
16	82	85	90	90	69[c]	68[c]	65[c]	71[c]

[a] >98% conversion in all cases except noted; [b] determined by chiral gas chromatography;
[c] 40% conversion.

The influence of the backbone configuration as measured by the difference in enantioselection between catalysts derived from the structurally different phosphines R_{ax}-**7** vs R_{ax}-**20** [maximum difference of 8% ee in the case of **9a** vs **10a** (substrate **16**) and of 4% ee in the case of **12a** vs **13a** (substrate **16**)] and S_{ax}-**7** vs S_{ax}-**20** [maximum difference of 10% ee in the case of **9b** vs **10b**

(substrate **14**) and of 3% ee in the case of **12b** vs **13b** (substrate **16**)] was of similar magnitude to the differences between the R_{ax},S_{ax}-diastereomers of phosphines **7** and **20**. These results led to the conclusion that the absolute configuration of the steroid backbone was not the primary factor influencing the degree of enantioselection of the catalysts.

A comparison of the results clearly showed that the ees of compounds **17**–**19** were mainly determined by the use of either a dimeric or an oligomeric catalyst. The effect brought about by the variation of the catalyst structure was always larger than the influence of the different steroidal structure of the ligands which were employed for the catalysts or the interaction effect of axial and local chirality in the steroid backbone. In the case of tiglic acid **16** catalysts **9** and **10** displayed a significantly higher asymmetric induction as well as a better conversion compared to catalysts **12** and **13** which were obviously not suited for this type of substrate. In contrast, catalysts **12** and **13** displayed higher enantioselections as well as smaller fluctuations of the degree of enantioselection compared to catalysts **9** and **10** in the hydrogenation of α-acetamidocinnamic acid **14** and α-acetamidoacrylic acid **15**. The most astonishing example of the influence of the catalyst structure came from the hydrogenation of **15** where catalysts **12** and **13** afforded *N*-acetylalanine **18** with ≥96% ee. To our knowledge, these are the highest ees which have ever been reported for the enantioselective hydrogenation of α-acetamidoacrylic acid **15** with bisaryl or bisnaphthyl derived phosphines.[11]

This influence of the catalyst preparation is obviously not a singularity observed with our steroidal phosphines, as a similar effect was noted while we were checking our catalyst preparations with BINAP as a reference ligand: when using $[RuCl_2(BINAP)(DMF)]_n$ in the hydrogenation of **15** an ee of 77% was found for *N*-acetylalanine **18** while catalyst $[RuCl_2(BINAP)]_2(NEt_3)$ afforded an ee of 83%.[12]

The dimeric catalysts **12** and **13** are surprisingly stable as exemplified by using material, stored for several month at –20°C under argon, which afforded *N*-acetylphenylalanine **17** with nearly the same degree of enantioselectivity [79% ee (**13a**) and 84% ee (**13b**)] as freshly prepared catalysts **12** and **13** did. The influence of the hydrogen pressure on the enantioselection of the hydrogenation was only investigated in the case of tiglic acid **16** with catalysts **9a**,**b**. Similar to the results described for the hydrogenation of **16** with BINAP–Ru dicarboxylate complexes,[13] an increase of hydrogen pressure from 4 to 7 atm resulted in a dramatic decrease of enantioselection: when using tiglic acid **16** as starting material and catalyst **9a** at 7 atm 2-methyl butyric acid **19** was obtained in only a 73% ee while tiglic acid **16** as starting material and catalyst **9b** at 7 atm afforded compound **19** with a moderate ee of only 68%.

In conclusion, we have presented a short and effective synthesis of a new bissteroidal phosphine which circumvents the previous synthetic limitations to this class of phosphines. The evaluation of the new phosphine **7** and of our previously prepared phosphine **20** supported our initial hypothesis that the influence of the steroidal backbone on the enantioselectivity of the ruthenium-based hydrogenation catalysts is only a minor one, thereby confirming that our bissteroidal phosphines behave as 'pseudo'-enantiomers in spite of their diastereomeric nature. The catalyst structure was identified as the important reaction parameter which mainly determined the ee of the hydrogenation products. The dimeric catalysts **12** and **13** displayed higher enantioselectivities in the hydrogenation of the dehydroamino acids **14** and **15**, while the oligomeric catalysts **9** and **10** were more suited for the hydrogenation of tiglic acid **16**. Based on the more consistent results from the investigation of catalysts **12** and **13** the CD *cis*-configured phosphines R_{ax},S_{ax}-**7** and the *trans*-configured phosphines R_{ax},S_{ax}-**20** have to be considered as ligands of similar activity. The observed activity differences between BINAP and our ligands in the hydrogenation of

compounds **14** and **15** cannot be ascribed to the chirality of the steroid backbone of our compounds. Different electronic properties of our bissteroidal ligands and BINAP may be the reason for the partly more effective asymmetric induction of their ruthenium complexes compared to the BINAP analogue.[14]

3. Experimental

3.1. General methods

All reactions were carried out under an argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was oven-dried (200°C). Tetrahydrofuran was distilled from sodium benzophenone ketyl, DMF and dimethyl acetamide from calcium hydride. Methanol was deoxygenated by a freeze–thaw cycle in which the solvent was first frozen in liquid N_2 and then warmed up in vacuo (0.1 mmHg). Flash column chromatography was performed on Merck silica gel (grade 60, 230–400 mesh); TLC was performed on Merck aluminium foils 60 F 254. Infrared (IR) spectra were recorded on a Nicolet 20 SBX spectrophotometer. Mass spectral analyses were recorded on a Micromass AutoSpec EQ mass spectrometer. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ using TMS or the solvent as internal standard. ^{31}P (121 MHz) NMR spectra were recorded in $CDCl_3$ using 80% phosphoric acid (external) as standard. All melting points were uncorrected. CD spectra were taken on an Instruments SA-CD6 spectrometer.

3.2. Procedures

3.2.1. Synthesis of R_{ax},S_{ax}-*3*

To a suspension of isoequilenine **2** (10 g, 38 mmol) in CH_2Cl_2 (300 ml) was added CuCl(OH)–TMEDA[3] (0.800 g, 0.35 mmol) and the solution was stirred at 0°C for 10–15 min while bubbling oxygen through the mixture. The reaction was monitored by TLC. At the end of the reaction HCl (10%, 5 ml) was added to the mixture and stirred for an additional 15 min (the colour changed from blue to yellow). The organic layer was washed with brine and dried, and the solvent was evaporated. The crude mixture (9.9 g) was separated by column chromatography using ethyl acetate/toluene as eluent to give: compound R_{ax}-**3** (5.2 g, 52%), m.p. 293°C decomp.; $[\alpha]_{365}=+139.5$ ($c=2.4$ in THF); ^{1}H NMR: 8.17 (1H, d, J = 9.3 Hz), 7.40 (1H, d, J = 9.3 Hz), 7.17 (1H, d, J = 8.5 Hz), 7.08 (1H, d, J = 8.5 Hz), 4.85 (1H, s, OH), 1.19 (3H, s); ^{13}C NMR: 222.6 (s), 152.3 (s), 134.1 (s), 133.1 (s), 130.5 (s), 129.1 (d), 127.9 (s), 126.4 (d), 123.0 (d), 117.5 (d), 112.2 (s), 47.5 (s), 46.8 (d), 37.0 (t), 28.9 (t), 26.4 (t), 22.3 (t), 19.9 (q); MS-CI: 548 (100, M^++1+NH_3), 531 (20, M^++1); MS-EI: 530 (100, M^+), 474 (15), 209 (20), 181 (25), 165 (20); HRMS: 530.246399 (100, M^+); calcd for $C_{36}H_{34}O_4$: 530.245709. Compound S_{ax}-**3** (4.3 g, 43%), m.p. 180°C decomp. (hexane); $[\alpha]_{365}=+154.0$ ($c=2.0$ in THF); ^{1}H NMR: 8.17 (1H, d, J = 9.3 Hz), 7.42 (1H, d, J = 9.3 Hz), 7.15 (1H, d, J = 8.5 Hz), 7.05 (1H, d, J = 8.5 Hz), 5.15 (1H, s, OH), 1.20 (3H, s); ^{13}C NMR: 222.7 (s), 152.3 (s), 134.1 (s), 133.2 (s), 130.6 (s), 129.1 (d), 127.9 (s), 126.5 (d), 122.9 (d), 117.6 (d), 112.0 (s), 47.7 (d), 46.9 (s), 37.0 (t), 29.0 (t), 26.4 (t), 22.1 (t), 20.1 (q); MS-CI: 548 (100, M^++1+NH_3), 531 (25, M^++1); MS-EI: 530 (100, M^+), 474 (15), 209 (25), 181 (65), 165 (20); HRMS: 530.246399 (100, M^+); calcd for $C_{36}H_{34}O_4$: 530.245709.

3.2.2. Synthesis of S_{ax}-**6**

To a solution of S_{ax}-**3** (2.2 g, 4.16 mmol) and *N*-ethyldiisopropylamine (4 ml, 23.5 mmol) in toluene (60 ml) was added over a period of 30 min dropwise triflic anhydride (3.6 ml, 21.94 mmol). The mixture was stirred for 30 min at room temperature and then heated to 60°C and kept at this temperature for 3 h. At the end of the reaction the mixture was cooled down and the upper (toluene) layer was separated. The organic phase was washed with water, 2N HCl and brine, dried with Na_2SO_4 and the solvent was evaporated. The residue was filtered through SiO_2 (hexane:ethyl ether, 15:1, to give the crude S_{ax}-**5** (3.8 g, 3.59 mmol, 86%) which was dissolved in ethanol:methylene chloride (30 ml, 10:1) and exposed to hydrogen (1 atm) in the presence of PtO_2 (0.2 g) for 2 h. The mixture was filtered through a pad of Celite, the solvent was evaporated and the crude product was dissolved in ethyl acetate. The solution was washed with $NaHCO_3$ and brine, and dried with Na_2SO_4. The solvent was evaporated and the crude product was purified on SiO_2 to yield (S_a)-4,4′-bis(14-*epi*-3-trifluoromethylsulfonyloxyestra-1,3,5(10),6,8-pentaene) S_{ax}-**6**: (2.6 g, 3.39 mmol, 81.5%), m.p. 115–116°C; $[\alpha]_D = +128.8$ ($c = 0.1$ in THF); ^{1}H NMR: 8.28 (1H, d, J = 10.0 Hz), 7.60 (1H, d, J = 10.0 Hz), 7.12 (1H, d, J = 9.0 Hz), 6.98 (1H, d, J = 9.0 Hz), 1.10 (3H, s); ^{13}C NMR: 144.8 (s), 139.2 (s), 132.0 (s), 131.4 (s), 130.7 (d), 130.4 (s), 126.6 (d), 124.5 (d), 120.3 (s), 118.5 (d), 50.7 (d), 40.7 (t), 39.3 (s), 35.4 (t), 31.4 (t), 25.7 (q), 23.2 (t), 22.7 (t); MS-CI: 784 (100, M^++1+NH_3); MS-EI: 766 (80, M^+), 633 (17) 483 (100), 387 (21), 308 (17); HRMS: 766.185682; calcd for $C_{38}H_{36}F_6O_6S_2$: 766.185752.

3.2.3. Synthesis of R_{ax}-**6**

The compound was synthesized according to the same procedure as for S_{ax}-**6**: m.p. 204–204.5°C; $[\alpha]_D = -23.9$ ($c = 0.1$ in THF); ^{1}H NMR: 8.28 (1H, d, J = 10.0 Hz), 7.60 (1H, d, J = 10.0 Hz), 7.11 (1H, d, J = 9.0 Hz), 7.01 (1H, d, J = 9.0 Hz), 1.10 (3H, s); ^{13}C NMR: 144.3 (s), 139.2 (s), 132.0 (s), 131.4 (s), 130.8 (d), 130.5 (s), 127.0 (d), 124.6 (d), 124.9 (s), 118.5 (d), 50.6 (d), 40.6 (t), 39.6 (s), 35.4 (t), 31.5 (t), 25.7 (q), 23.3 (t), 22.8 (t); MS-CI: 784 (88, M^++1+NH_3); MS-EI: 766 (100, M^+), 633 (17), 483 (75), 389 (26), 309 (7); HRMS: 766.185685; calcd for $C_{38}H_{36}F_6O_6S_2$: 766.185752.

3.2.4. Synthesis of S_{ax}-**7**

To a solution of $NiCl_2$–dppe (0.070 g, 0.13 mmol) in dimethyl acetamide (2 ml) was added diphenylphosphine (0.13 ml, 0.139 g, 0.75 mmol) at room temperature, and the solution was heated to 100°C. After 45 min a solution of triflate S_{ax}-**6** (1 g, 1.3 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.62 g, 5.5 mmol) in dimethyl acetamide (4 ml) was added at once, the resulting green solution was kept at 100°C and three additional portions of diphenylphosphine (0.13 ml each) were added after 1, 3 and 5 h, respectively. The reaction was kept at 100°C for 6 days and then the dark brown solution was diluted with MeOH. The desired product was filtered and the filter cake was washed with MeOH and dried under vacuum. The crude product (1.1 g) was recrystallized from MeOH:toluene, 10:1, to give pure S_{ax}-**7** (0.97g, 1.156 mmol, 89%); the m.p. of the compound was not determined due to air sensitivity: $[\alpha]_D = -79.3$ ($c = 0.13$ in THF); ^{1}H NMR: 7.98 (1H, d, J = 10.0 Hz), 7.36 (1H, brd, J = 10.0 Hz), 7.3–6.9 (10H, m), 6.52 (2H, s), 3.12 (1H, dt, J = 3.2, 21.0 Hz), 2.95 (1H, m), 2.52 (1H, t, J = 7.5 Hz), 2.1 (2H, m), 1.7 (1H, m), 1.9–1.3 (5H, m), 0.98 (3H, s); ^{13}C NMR: 146.4 (s), 146.0 (s), 138.2 (s), 133.1 (s), 132.8 (s), 132.0 (s), 129.5 (s), 129.9 (s), 130.3, 128.8, 128.3, 127.9, 127.4, 125.6, 123.2, 50.0 (each d), 40.3 (s), 38.7 (t), 35.8 (t), 25.0 (t), 24.6 (t), 20.8 (t), 16.4 (q); ^{31}P NMR: –15.2 (s); MS-HRFAB: 839.3927 (50, M^++1); calcd for $C_{60}H_{57}P_2$: 839.3936.

3.2.5. Synthesis of R_{ax}-7

The compound was synthesized according to the same procedure as for S_{ax}-**7**; the m.p. of the compound was not determined due to air sensitivity: $[\alpha]_D = +160.8$ ($c = 0.16$ in THF); ^{1}H NMR: 8.08 (1H, d, J = 10.0 Hz), 7.46 (1H, brd, J = 10.0 Hz), 7.3–7.0 (10H, m), 6.62 (2H, ABq, J = 12Hz), 3.12 (2H, m), 2.62 (1H, t, 7.5 Hz), 2.1 (2H, m), 1.7 (1H, m), 1.9–1.3 (5H, m), 1.10 (3H, s); ^{13}C NMR: 146.4 (s), 146.0 (s), 138.2 (s), 133.1 (s), 132.6 (s), 132.0 (s), 130.1 (s), 129.9 (s), 130.3, 128.8, 128.3, 127.9, 127.4, 125.6, 123.2, 50.0 (each d), 40.8 (t), 39.2 (s), 35.3 (t), 31.6 (t), 25.7 (q), 23.2 (t), 22.8 (t); ^{31}P NMR: –15.2 (s); MS-HRFAB: 839.3919 (50, M^++1); calcd for $C_{60}H_{57}P_2$: 839.3936.

3.2.6. Hydrogenation of methyl acetoacetate ***8*** *in the presence of* $RuCl_2(S_{ax}$-7$)(DMF)_n$ ***9b***

A dry 50 ml Schlenk tube containing a Teflon® coated stirring bar was charged with $[RuCl_2$(benzene)$]_2$ (0.018 g, 0.036 mmol), S_{ax}-**7** (0.06 g, 0.072 mmol) and DMF (1 ml). The resulting brown suspension was heated at 100°C under argon for 30 min to give a clear reddish-brown solution. The reaction mixture was allowed to cool at 50°C during which it was concentrated at 1 mmHg and then at 0.05 mmHg for 1 h to give $RuCl_2(S_{ax}$-**7**$)(DMF)_n$ **9b**. To the resulting reddish-brown solid of **9b** was added under argon a solution of methyl acetoacetate **8** (7.3 g, 63 mmol) in degassed methanol (40 ml) and the mixture was stirred for 5 min. Then the solution was transferred to a 125 ml stainless steel autoclave and kept for 1 h at 100°C under hydrogen (100 atm) followed by 10 h at room temperature at 100 atm. After the excess hydrogen had been blown off, the apparatus was disassembled. The content was concentrated. Distillation (110°C, 46 mmHg) afforded methyl (*S*)-3-hydroxybutanoate **11** (7.2 g, 98%): $[\alpha]_D = +49.4$ ($c = 1.5$, in $CHCl_3$), in 95% ee assayed as MTPA ester; lit. (Fluka), $[\alpha]_D = +50.5$ ($c = 1.4$ in $CHCl_3$).

3.2.7. Hydrogenation of methyl acetoacetate ***8*** *in the presence of* $RuCl_2(R_{ax}$-7$)(DMF)_n$ ***9a***

According to the same procedure hydrogenation of **8** (7.3 g) with **9a** (from $[RuCl_2$(benzene)$]_2$ (0.018 g, 0,036 mmol) and R_{ax}-**7** (0.06 g, 0.072 mmol)) afforded (*R*)-3-hydroxybutanoate **11** (7.20 g, 98%): $[\alpha]_D = -49.6$ ($c = 1.5$, in $CHCl_3$), in 95% ee assayed as MTPA ester.

3.2.8. Hydrogenation of α-acetamidocinnamic acid ***14*** *in the presence of* ***9b***

To the reddish-brown solid of **9b** (from $[RuCl_2$(benzene)$]_2$ (0.018 g, 0.036 mmol), S_{ax}-**7** (0.06 g, 0.072 mmol)) was added a solution of α-acetamidocinnamic acid **14** (3.6 g, 17.6 mmol) in degassed methanol (40 ml) and the mixture was stirred for 5 min. Then the solution was transferred to a 125 ml stainless steel autoclave and kept for 48 h at room temperature under hydrogen (7 atm). After the excess hydrogen had been blown off, the apparatus was disassembled. The content was concentrated to give 3.5 g crude product. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, t° detector = 280°C, t° column = 280°C) of this ester shows an ee of 79.5% and no trace of the starting material. The rest of the product was dissolved in hot water (200 ml) and washed with toluene (2×30 ml). The water was evaporated and the residue was dried under vacuum to give 3.5 g (97%) *N*-acetyl-(*S*)-phenylalanine **17**: $[\alpha]_D = +30.5$ ($c = 1.2$, in methanol).

3.2.9. Hydrogenation of α-acetamidocinnamic acid ***14*** *in the presence* ***9a***

According to the same procedure, hydrogenation of **14** (3.0 g, 14.6 mmol) with **9a** (from $[RuCl_2$(benzene)$]_2$ (0.01 g, 0.020 mmol), R_{ax}-**7** (0.035 g, 0.042 mmol)) gave 3 g crude product. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution

in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, $t°$ detector = 280°C, $t°$ column = 280°C) of this ester shows an ee of 82% and no trace of the starting material. The rest of the product was dissolved in hot water (200 ml) and washed twice with toluene (30 ml each). The water was evaporated and the residue was dried under vacuum to give 2.9 g (96%) *N*-acetyl-(*R*)-phenylalanine **17**: $[\alpha]_D = -32.1$ ($c = 1.0$, in methanol).

*3.2.10. Hydrogenation of α-acetamidoacrylic acid **15** with $RuCl_2(R_{ax}$-**20**$)(DMF)_n$ **10a***

To the solution of α-acetamidoacrylic acid **15** (1.4 g, 10.8 mmol) in degassed methanol (40 ml) was added **10a** (from $[RuCl_2(benzene)]_2$ (0.007 g, 0.014 mmol), R_{ax}-**20** (0.02 g, 0.024 mmol)) and the mixture was stirred for 5 min. Then the solution was transferred to a 125 ml stainless steel autoclave and kept for 48 h under hydrogen (7 atm). After the excess hydrogen had been blown off, the apparatus was disassembled. The content was concentrated to give 1.3 g crude product **18**. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (50 m FS-LIPODEX-E N° 211, 145° isoterm, 1 bar hydrogen, $t°$ detector = 280°C, $t°$ column = 280°C) of this ester shows an ee of 72% and >98% conversion.

*3.2.11. Hydrogenation of α-acetamidoacrylic acid **15** with $RuCl_2(S_{ax}$-**20**$)(DMF)_n$ **10b***

According to the same procedure, hydrogenation of **15** (1.25 g, 9.7 mmol) in degassed methanol (50 ml) with **10b** (from $[RuCl_2(benzene)]_2$ (0.007 g, 0.014 mmol), S_{ax}-**20** (0.02 g, 0.024 mmol)) gave 1.2 g crude product **18**. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (50 m FS-LIPODEX-E N° 211, 145° isoterm, 1 bar hydrogen, $t°$ detector = 280°C, $t°$ column = 280°C) of this ester shows an ee of 66% and >98% conversion.

*3.2.12. Hydrogenation of α-acetamidoacrylic acid **15** with **9a***

According to the same procedure, hydrogenation of **15** (1.4 g, 10.8 mmol) in degassed methanol (50 ml) with **9a** (from $[RuCl_2(benzene)]_2$ (0.012 g, 0.024 mmol), R_{ax}-**7** (0.035 g, 0.042 mmol)) gave 1.2 g crude product **18**. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (50 m FS-LIPODEX-E N° 211, 145° isoterm, 1 bar hydrogen, $t°$ detector = 280°C, $t°$ column = 280°C) of this ester shows an ee of 75% and >98% conversion.

*3.2.13. Hydrogenation of α-acetamidoacrylic acid **15** with **9b***

According to the same procedure, hydrogenation of **15** (1.2 g, 9.3 mmol) in degassed methanol (40 ml) with **9b** (from $[RuCl_2(benzene)]_2$ (0.014 g, 0.028 mmol), S_{ax}-**7** (0.04 g, 0.048 mmol)) gave 1.15 g crude product **18**. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (50 m FS-LIPODEX-E N° 211, 145° isoterm, 1 bar hydrogen, $t°$ detector = 280°C, $t°$ column = 280°C) of this ester shows an ee of 68% and >98% conversion.

*3.2.14. Hydrogenation of tiglic acid **16** in the presence of **9a***

To the reddish-brown solid of **9a** (from $[RuCl_2(benzene)]_2$ (0.015 g, 0.030 mmol), R_{ax}-**7** (0.045 g, 0.054 mmol)) was added a solution of tiglic acid **16** (0.83 g, 8.3 mmol) in degassed methanol (35

ml) and the mixture was stirred for 5 min. Then the solution was transferred to a 125 ml stainless steel autoclave and kept for 24 h at room temperature under hydrogen (4 atm). After the excess hydrogen had been blown off, the apparatus was disassembled. The content was concentrated to give 0.8 g crude product. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether). GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, t° detector = 280°C, t° column = 280°C) of this solution shows 82% ee and no trace of the starting material. Distillation of the crude product (78°C, 24 mmHg) afforded (*R*)-2-methylbutyric acid **19** (0.7 g, 84%, $[\alpha]_D = -13.9$ (neat)).

3.2.15. Hydrogenation of tiglic acid **16** in the presence of **9b**

According to the same procedure, hydrogenation of tiglic acid **16** (1.0 g, 10 mmol) in degassed methanol (40 ml) with **9b** (from $[RuCl_2(benzene)]_2$ (0.018 g, 0.036 mmol), S_{ax}-**7** (0.055 g, 0.066 mmol)) gave 1.0 g crude product. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether). GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, t° detector = 280°C, t° column = 280°C) of this solution shows an ee of 85% and no trace of the starting material. Distillation of the crude product (78°C, 24 mmHg) afforded (*S*)-2-methylbutyric acid **19** (0.9 g, 90%, $[\alpha]_D = +12.9$ (neat)).

3.2.16. General procedure for the synthesis of $[RuCl_2(ligand)]_2$TEA

To a suspension of phosphine (1 g, 1.2 mmol) and $[RuCl_2COD]_2$ (0.33 g, 1.2 mmol) in degassed xylene (25 ml) was added TEA (2.8 ml, 20 mmol) and the mixture was heated at 140°C in a closed vessel. After 4 h the apparatus was allowed to cool to room temperature and the solvent was evaporated under vacuum. The crude red product was recrystallized from hot MTB (10 ml) to give the desired catalyst as orange crystals (0.28 g). A crystalline product (0.42 g) was isolated additionally from the solution after cooling. The product was identical (from ^{31}P NMR) with the first one.

$[RuCl_2(R_{ax}$-**20**$)]_2$TEA **13a**: ^{31}P NMR, two isomers in a 3:1 ratio: 54.3 (d, J = 42.5 Hz), 50.8 (d, J = 42.5 Hz), 45.1 (d, J = 42 Hz), 40.0 (d, J = 42 Hz).

$[RuCl_2(S_{ax}$-**20**$)]_2$TEA **13b**: ^{31}P NMR, one isomer: 54.8 (d, J = 42.5 Hz), 51.3 (d, J = 42.5 Hz).

$[RuCl_2(R_{ax}$-**7**$)]_2$TEA **12a**: (0.8 g) ^{31}P NMR, one isomer: 52.8 (d, J = 42.5 Hz), 50.3 (d, J = 42.5 Hz).

$[RuCl_2(S_{ax}$-**7**$)]_2$TEA **12b**: (0.7 g) ^{31}P NMR, shows three isomers in a 2:1:0.5 ratio: 54.5 (d, J = 42.0 Hz), 51.1 (d, J = 42.0 Hz), 49.3 (d, J = 42.5 Hz), 44.9 (d, J = 42.5 Hz), 44.9 (d, J = 40.0 Hz), 39.7 (d, J = 40.0 Hz).

3.2.17. Hydrogenation of α-acetamidocinnamic acid **14** with **13a**

To the solution of α-acetamidocinnamic acid **14** (1.0 g, 4.87 mmol) in degassed EtOH:THF, 1:1 (50 ml), was added **13a** (0.05 g, 0.024 mmol) and the mixture was stirred for 5 min. Then the solution was transferred to a 125 ml stainless steel autoclave and kept for 24 h at 35°C under hydrogen (2 atm). After the excess hydrogen had been blown off, the apparatus was disassembled. The content was concentrated to give 0.98 g crude product. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, t° detector = 280°C, t° column = 280°C) of this ester shows an ee of 84% and no trace of the starting material. The rest of the product was dissolved in hot water (200 ml) and washed

twice with toluene (30 ml each). The water was evaporated and the residue was dried under vacuum to give 0.9 g (90%) *N*-acetyl-(*R*)-phenylalanine **17**: $[\alpha]_D = -31.8$ ($c = 1.0$, in methanol).

*3.2.18. Hydrogenation of α-acetamidocinnamic acid **14** with **13b***

According to the same procedure, hydrogenation of **14** (0.9 g, 4.39 mmol) in degassed EtOH:THF, 1:1 (50 ml), with **13b** (0.05 g, 0.024 mmol) gave 0.88 g crude product. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, t° detector = 280°C, t° column = 280°C) of this ester shows an ee of 87% and >98% conversion. The rest of the product was dissolved in hot water (200 ml) and washed twice with toluene (30 ml each). The water was evaporated and the residue was dried under vacuum to give 0.8 g (88%) *N*-acetyl-(*S*)-phenylalanine **17**: $[\alpha]_D = +33.5$ ($c = 1.0$, in methanol).

*3.2.19. Hydrogenation of α-acetamidocinnamic acid **14** with **12a***

According to the same procedure, hydrogenation of **14** (0.9 g, 4.39 mmol) in degassed EtOH:THF, 1:1 (50 ml), with **12a** (0.05 g, 0.024 mmol) gave 0.88 g crude product. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, t° detector = 280°C, t° column = 280°C) of this ester shows an ee of 87% and >98% conversion. The rest of the product was dissolved in hot water (200 ml) and washed with toluene (2×30 ml). The water was evaporated and the residue was dried under vacuum to give 0.8 g (88%) *N*-acetyl-(*R*)-phenylalanine **17**: $[\alpha]_D = -33.9$ ($c = 1.0$, in methanol).

*3.2.20. Hydrogenation of α-acetamidocinnamic acid **14** with **12b***

According to the same procedure, hydrogenation of **14** (0.9 g, 4.39 mmol) in degassed EtOH:THF, 1:1 (50 ml), with **12b** (0.05 g, 0.024 mmol) gave 0.88 g crude product. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, t° detector = 280°C, t° column = 280°C) of this ester shows an ee of 86% and >98% conversion. The rest of the product was dissolved in hot water (200 ml) and extracted twice with toluene (30 ml each). The water was evaporated and the residue was dried under vacuum to give 0.8 g (88%) *N*-acetyl-(*S*)-phenylalanine **17**: $[\alpha]_D = +33.2$ ($c = 1.0$, in methanol).

*3.2.21. Hydrogenation of α-acetamidoacrylic acid **15** with **13a***

To the solution of α-acetamidoacrylic acid **15** (1.0 g, 7.7 mmol) in degassed EtOH:THF, 1:1 (50 ml), was added **13a** (0.089 g, 0.042 mmol) and the mixture was stirred for 5 min. Then the solution was transferred to a 125 ml stainless steel autoclave and kept for 24 h at 35°C under hydrogen (2 atm). After the excess hydrogen had been blown off, the apparatus was disassembled. The content was concentrated to give 0.98 g crude product **18**. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (50 m FS-LIPODEX-E N° 211, 145° isoterm, 1 bar hydrogen, t° detector = 280°C, t° column = 280°C) of this ester shows an ee of 97% and >98% conversion.

*3.2.22. Hydrogenation α-acetamidoacrylic acid **15** with **13b***

According to the same procedure, hydrogenation of **15** (0.8 g, 6.2 mmol) in degassed EtOH:THF, 1:1 (50 ml), with **13b** (0.062 g, 0.029 mmol) gave 0.8 g crude product **18**. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (50 m FS-LIPODEX-E N° 211, 145° isoterm, 1 bar hydrogen, $t°$ detector = 280°C, $t°$ column = 280°C) of this ester shows an ee of 96% and > 98% conversion.

*3.2.23. Hydrogenation of α-acetamidoacrylic acid **15** with **12a***

According to the same procedure, hydrogenation of **15** (0.8 g, 6.2 mmol) in degassed EtOH:THF, 1:1 (50 ml), with **12a** (0.068 g, 0.032 mmol) gave 0.8 g crude product **18**. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (50 m FS-LIPODEX-E N° 211, 145° isoterm, 1 bar hydrogen, $t°$ detector = 280°C, $t°$ column = 280°C) of this ester shows an ee of 97% and > 98% conversion.

*3.2.24. Hydrogenation of α-acetamidoacrylic acid **15** with **12b***

According to the same procedure, hydrogenation of **15** (0.8 g, 6.2 mmol) in degassed EtOH:THF, 1:1 (50 ml), with **12b** (0.064 g, 0.030 mmol) gave 0.8 g crude product **18**. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (50 m FS-LIPODEX-E N° 211, 145° isoterm, 1 bar hydrogen, $t°$ detector = 280°C, $t°$ column = 280°C) of this ester shows an ee of 96% and > 98% conversion.

*3.2.25. Hydrogenation of tiglic acid **16** with **13a***

To the solution of tiglic acid **16** (1.0 g, 10 mmol) in degassed EtOH:THF, 1:1 (50 ml), was added **13a** (0.089 g, 0.042 mmol) and the mixture was stirred for 5 min. Then the solution was transferred to a 125 ml stainless steel autoclave and kept for 24 h at 35°C under hydrogen (2 atm). After the excess hydrogen had been blown off, the apparatus was disassembled. The content was concentrated to give 1.0 g crude product **19**. A small amount of the crude product (0.05 g) was treated with excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, $t°$ detector = 280°C, $t°$ column = 280°C) of this ester shows an ee of 65% and about 40% conversion.

*3.2.26. Hydrogenation of tiglic acid **16** with **13b***

According to the same procedure, hydrogenation of **16** (1.0 g, 10 mmol) in degassed EtOH:THF, 1:1 (50 ml), with **13b** (0.070 g, 0.033 mmol) gave 1 g of crude product **19**. A small amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, $t°$ detector = 280°C, $t°$ column = 280°C) of this ester shows an ee of 71% and about 40% conversion.

*3.2.27. Hydrogenation of tiglic acid **16** with **12a***

According to the same procedure, hydrogenation of **16** (1.18 g, 11.8 mmol) in degassed EtOH:THF, 1:1 (50 ml), with **12a** (0.082 g, 0.039 mmol) gave 1.1 crude product **19**. A small

amount of the crude product (0.05 g) was treated with an excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, t° detector = 280°C, t° column = 280°C) of this ester shows an ee of 69% and about 40% conversion.

*3.2.28. Hydrogenation of tiglic acid **16** with **12b***

According to the same procedure, hydrogenation of tiglic acid **16** (1.2 g, 12 mmol) in degassed EtOH:THF, 1:1 (50 ml), with **12b** (0.089 g, 0.042 mmol) gave 1.1 g of crude product **19**. A small amount of the crude product (0.05 g) was treated with excess of diazomethane (solution in ethyl ether) to yield the corresponding methyl ester for determination of the ee. GC analysis (25 m Chiralsil-DEX, 150° isoterm, 1 bar hydrogen, t° detector = 280°C, t° column = 280°C) of this ester shows an ee of 68% and about 40% conversion.

Acknowledgements

Financial support for V.E. by Schering's Unternehmenforschungsprogramm is gratefully acknowledged. We thank Th. Hilsmann, C. Pieper and M. Stoppa for experimental assistance and H. Igogeit for GC measurements.

References

1. Enev, V.; Ewers, Ch. L. J.; Harre, M.; Nickisch, K.; Mohr, J. T. *J. Org. Chem.* **1997**, *62*, 7092.
2. Pelletier, S. H.; Ichinohe, Y.; Herald, D. L. *Tetrahedron Lett.* **1971**, 4179.
3. Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1994**, *43*, 7983.
4. The exposure of pure diastereomers R_{ax},S_{ax}-**3** as well as methoxy methyl-protected R_{ax},S_{ax}-**3** to the conditions of a Wolff–Kishner reduction afforded a fully racemized starting material as well as a fully racemized product.
5. Jigajinni, V. B.; Wightman, R. H. *Tetrahedron Lett.* **1982**, *23*, 117.
6. (a) Cai, D.; Payack, J. F.; Verhoeven, T. R. US Patent 5,399,771. (b) Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 7180.
7. Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327.
8. Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163.
9. Catalyst structure refers to the different modes of catalyst preparation, as the structures of the active catalysts are not known. ^{31}P NMR spectroscopic investigations of $[RuCl_2(ligand)]_2(NEt_3)$ with S_{ax}-**20** and R_{ax}-**7** hinted at a single species, while compound mixtures were found for R_{ax}-**20** and S_{ax}-**7**.
10. (a) King, A.; Thompson, A.; Verhoeven, T. *J. Org. Chem.* **1992**, *57*, 6689. (b) King, S. A.; DiMichele, L. In *Catalysis of Organic Reactions*; Dekker: New York, 1995; pp. 157–166. This assignment was arbitrarily chosen as we could not distinguish between the possible catalyst structures $[RuCl_2(ligand)]_2(NEt_3)$ and $[Ru_2Cl_5(ligand)_2](NH_2Et_2)$ due to overlapping signals in the ^{1}H NMR.
11. Genet, J.-P. In *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Chapman & Hall, 1996.
12. see:Ikariya, T. et. al. *Chem. Commun.* **1985**, 922: Ikariya reported 86% ee for the hydrogenation of **14** and 76% ee for the hydrogenation of **15** with $[RuCl_2(BINAP)]_2(NEt_3)$.
13. Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3176.
14. See, for instance, the comparison of BINAP and H_8-BINAP in: Takaya et al. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2309.