A Bis-Steroidal Phosphine as New Chiral Hydrogenation Ligand

V. Enev,[1] Ch. L. J. Ewers, M. Harre, K. Nickisch, and J. T. Mohr*

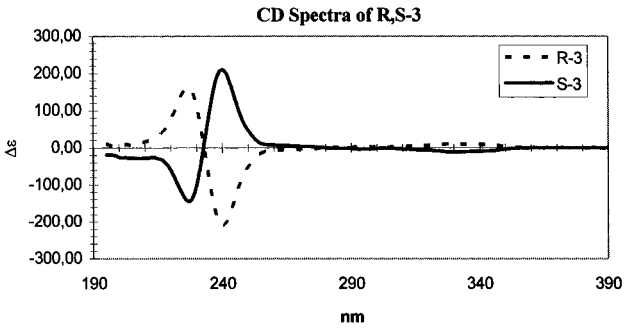
Process Research, Schering AG-Berlin, Müllerstrasse 170-178, D-13342 Berlin, Germany

Received August 4, 1997

Recently a significant improvement of the BINAP ligand synthesis was achieved by a nickel-mediated introduction of the diphenylphosphine residue.[2] Yet, the synthesis of this and similar atropisomeric ligands is still hampered by the fact that the chirality of the ligand is obtained from a chiral resolution of a racemic intermediate late in the synthesis.[3] We reasoned that a steroid as a precursor for an atropisomeric ligand should be attractive if (i) we could take advantage of the steroid local chirality for the separation of the ligands and (ii) the diastereomeric ligands would behave chemically as enantiomers due to the mirror image sterochemistry of the axis.

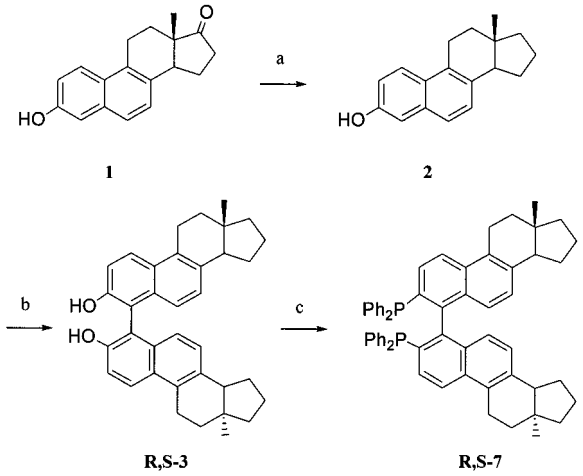
In this communication, we describe the synthesis of a new bis-steroidal phosphine based on the steroidal precursor equilenine (**1**), the incorporation of the ligand into a chiral ruthenium complex, and the first results from the enantioselective hydrogenation experiments with this ligand.

Equilenine[4] (**1**) was deoxygenated prior to the coupling reaction affording desoxy-equilenine **2** in 85% yield (Scheme 1). While our initial coupling attempts with Fe^{3+}salts[5] failed to give the desired bis-steroid, $Mn(acac)_3$ in acetonitrile at 60 °C afforded the bis-steroids **3** as a 1:1 mixture of diastereomers in 60% combined yield.[6] The yield could further be improved to 96% with Koga's copper catalyst at 0 °C.[7] The diastereoselectivity of the coupling showed a moderate temperature dependence ranging from 1:3 at room temperature to 3:1 at −20 °C. For practical reasons, the coupling step was usually carried out at 0 °C, affording a diastereomeric ratio of 1:1.5. As we had hoped, the diastereomeric mixture was separable by column chromatography and both ligands displayed mirror image CD spectra. Based on the CD spectra, the absolute configuration for the major diastereomer was assigned as *R* and the minor as *S*.[8]



While the CD spectra supported our initial assumption that the chiroptical properties of the ligands are mainly determined by the bis-steroidal axis, we wanted to examine whether this also applied to the chemical properties of the diastereomeric ligands. Therefore, a Noyori-type asymmetric reduction of acetophenone **4** was performed with a chiral lithium aluminum hydride reagent prepared from $LiAlH_4$, ligand **3**, and EtOH.[9] The reduction with (*R*)-**3** at −70° C afforded (*R*)-phenyl ethanol **5** with an enantiomeric excess of 92.8%. With ligand (*S*)-**3** it had to be carried out at −50° C due to its decreased solubility in THF at lower temperature and afforded (*S*)-phenyl ethanol **5** with an ee of 63%. At this point of the investigation we were not interested in the improvement of the asymmetric reduction of **4**. More important to us was that the opposite absolute configuration of the reduction products confirmed the assignment from CD and proved that both ligands behaved chemically as enantiomers.

Scheme 1



(a) hydrazine hydrate, diethyleneglycol, NaOH, 85%;
(b) CuCl(OH)·TMEDA, CH_2Cl_2, O_2, 96%;
(c) 1. Tf_2O, Py, 90%, 2. $NiCl_2$dppe, Ph_2PH, DABCO, 70%.

The syntheses of the phosphines (*R,S*)-**7** were accomplished according to the protocol for BINAP.[2] Ligands (*R,S*)-**3** were converted into the triflates (*R,S*)-**6** in 90% yield, which were subsequently treated with diphenylphosphine under nickel catalysis affording ligand (*R,S*)-**7** in 70% yield. The target phosphines (*R,S*)-**7** were thus available in a short and efficient synthesis from equilenine (**1**) in 58% overall yield (Scheme 1).

Next, we turned our attention to the application of our ligands (*R,S*)-**7** and decided to investigate the asymmetric hydrogenation of methyl acetoacetate **8** with $RuCl_2$-

* Corresponding author. E-mail: JOERGTORSTEN.MOHR@SCHERING.DE.

(1) Postdoctoral Fellow on leave from the Bulgarian Academy of Science, Sofia, Bulgaria.

(2) Cai, D.; Payack, J. F.; Verhoeven, T. R. US Patent 5,399,771. Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 7180.

(3) Separation of a racemic BIFUB ligand on a chiral stationary phase was reported: Sirges, W.; Albach, R. W. *Proceedings of the Chiral Europe '96 Symposium*, 14−15 Oct 1996, Strasbourg, France; p 9.

(4) (a) Djerassi, C. *J. Am. Chem. Soc.* **1950**, *72*, 4531. *Ibid.* 4534. *Ibid.* 4540. (b) Alder, K.; Schumacher, M. *Ann.* **1951**, *571*, 134.

(5) (a) Pummerer, R.; Prell, E.; Rieche, A. *Chem. Ber.* **1926**, *59*, 2159. (b) Toda, F.; Tanaka, K.; Iwata, S. *J. Org. Chem.* **1989**, *54*, 3007.

(6) Feringa, B.; Wynberg, H. J. *J. Org. Chem.* **1981**, *46*, 2547.

(7) Noji, M.; Nakajima, M. Koga, K. *Tetrahedron Lett.* **1994**, *43*, 7983.

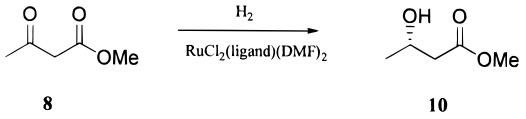
(8) (a) IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry. In *J. Org. Chem.* **1970**, *35*, 2849. (b) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy-Exiton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

(9) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

(10) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163.

S0022-3263(97)01444-8 CCC: $14.00

(ligand)$(DMF)_2$ **9**[10] (eq 1). We were pleased to see that under the described conditions (100 bar, 100 °C, 1 h)



(1)

8 **10**

S-BINAP: s/c-1150, 100% conversion, 99 % ee (S)

S-7: s/c-1260, 100 % conversion, 99% ee (S)

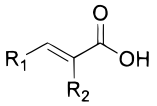
R-7: s/c-1260, 100 % conversion, 97% ee (R)

ligand (*S*)-**7** turned out to be as active as BINAP. The diastereomeric ligand (*R*)-**7** afforded (*R*)-3-hydroxybutanoate with a slightly lower enantiomeric excess of 97%, confirming again that the diastereomeric ligands induce enantiomeric sterochemistry in the products.

A different set of compounds was thus required to elucidate possible differences between BINAP and our ligand. We chose α-acetamidocinnamic acid (**11**) and tiglic acid (**12**) (Table 1) as substrates as there were so far only moderate ee's reported for their enantioselective hydrogenations with BINAP containing chiral ruthenium or rhodium catalysts.[11] Moreover, we decided to apply the *in situ* prepared ruthenium catalyst **9** here as well, because of the appealing simplicity of its preparation. To the best of our knowledge it is the first time that this *in situ* prepared catalyst is applied to the hydrogenation of alkenes. For simplicity reasons only the results for (*R*)-**7** are shown in Table 1, as the deviation for (*S*)-**7** was in the range of 1−2% enantiomeric excess for all compounds.

The comparison of our ligand and BINAP showed that ligand **7** leads to a chiral ruthenium hydrogenation catalyst of higher activity than the corresponding BINAP-derived catalyst. The hydrogenation of α-acetamidocinnamic acid (**11**) with ligand (*R*)-**7** and BINAP showed an important difference between both ligands: While similar conversions were achieved in both reactions, ligand (*R*)-**7** afforded *N*-acyl-(*R*)-phenylalanine **13** with a notably higher enantiomeric excess than BINAP. Moreover, the hydrogenation with this ligand was faster and required only half of the amount of the chiral catalyst. A similar result was achieved in the hydrogenation of tiglic acid (**12**), as (*R*)-**7** again afforded (*R*)-2-methylbutyric acid (**14**) with a higher enantiomeric excess. Yet, while our ligand afforded the product with complete conversion, the BINAP-containing catalyst was less active, affording the product only with about 40% conversion under these conditions.

Table 1. Comparison of Ligand 7 and BINAP



11 R_1=Ph, R_2=HNAc
12 R_1=R_2=Me

substrate	ligand	*s/c*	pressure (atm)	time (h)	conv[a] (%)	ee[b] (%)
11	BINAP	340	7	72	90	77[c]
11	(*R*)-**7**	605	7	48	>98	85.7
12	BINAP	200	4	24	44	87.5[d]
12	(*R*)-**7**	200	4	24	>98	90.4

[a] Determined by NMR analysis of the crude mixture. [b] Determined by chiral gas chromatography of the corresponding methyl ester. [c] Best result with ruthenium catalyst: 86% ee.[11] [d] est result with ruthenium catalyst: 91% ee.[11]

In conclusion, we have presented the short and high-yielding synthesis of the first representative of a bis-steroidal phosphine. The results corroborate that both of our initial criteria are successfully met, as our ligands turned out to be separable and afforded the formation of enantiomers in all reactions tested so far. Moreover, the results from the hydrogenation of α-acetamidocinnamic acid (**11**) and tiglic acid (**12**) show that the new bis-steroid ligand is in part more active than BINAP and that the application of the *in situ* prepared chiral ruthenium catalyst **9** is not limited to the enantioselective hydrogenation of β-keto esters. So far, we do not have enough experimental evidence to explain the difference between BINAP and our ligand. Further experiments will be directed to extend the scope of the catalyst application as well as to investigate structurally modified ligands.

Acknowledgment. We thank Drs. Depke and Michl for CD and NMR and F. Igogeit for chiral GC measurements. Financial support for V.E. by Schering's Unternehmenforschungsprogramm is gratefully acknowledged.

Supporting Information Available: Procedures, analytical and physical data for compounds **2**, **3**, **7**, and general procedures for the reduction of compound **4**, preparation of catalyst **9**, and hydrogenation of compounds **11** and **12** (6 pages).

JO971444P

(11) (a) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245. (b) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922. (c) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3176.