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Asymmetric C=C - Hydrogenation of a Substrate With Sulfur Functionality. Influence of Solvent and Substrate Configuration on Enantioselectivity.

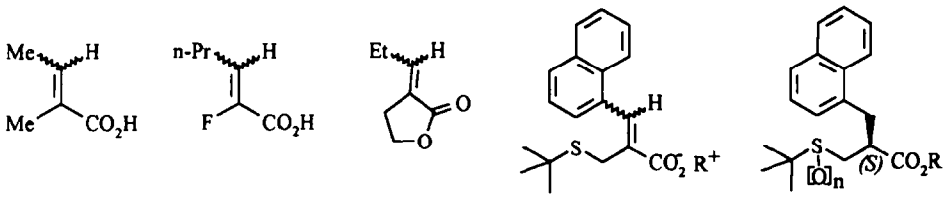
Heiner Jendralla

Hoechst AG, Allgemeine Pharma Forschung, Postfach 800320, 65926 Frankfurt / M. 80, Germany

Abstract : *In the presence of homochiral Rh^{I}- and Ru^{II}-diphosphine catalysts substrates 4 and 5 are asymmetrically hydrogenated to give 6 (up to 84% ee). Ru^{II}-binap catalyzed hydrogenation of (E) and (Z) isomers of 4 and 5 leads to product 6 of the same absolute configuration, however with opposite solvent effects. π-face selectivity is the same as reported for (E)-1, 2 and 3.*

Asymmetric hydrogenations with homochiral Rh^{I}- [1,2] or Ru^{II}-diphosphine catalysts [2,3] have been applied to a broad range of substrates with different functional groups.[4] However, examples of an asymmetric hydrogenation of a substrate with sulfur functionality are uncommon.[5] To the best of our knowledge, allylic sulphides as well as ruthenium complexes have not yet been used in such a reaction. The reluctance to apply the methodology to this kind of substrates may be due to the fact that many sulfur compounds are poisons for **heterogeneous** hydrogenation catalysts.[6] Indeed, a chelating chiral thioether was recently reported to induce efficient chiral poisoning of **homogeneous** Rh^{I}-diphosphine catalysts.[7]

The asymmetric hydrogenation of prochiral C=C bonds, utilizing Ru^{II}-binap catalysts, is further complicated by an inconsistency of the influence of substrate's configuration (*E/Z*-ratio) on the absolute configuration and the optical purity of the product: Ru-binap catalyzed hydrogenation of *(E)* and *(Z)* isomers of α,β-unsaturated acid **1** gives rise to the **antipodal** products with pronouncedly **different** enantioselectivities (91 *vs.* 57% ee).[8] In contrast, *(E)* and *(Z)* isomers of **2** lead to the saturated product of the **same** absolute configuration with nearly the **same** optical purity (83 - 90% ee).[9] Similarly, asymmetric hydrogenations of *(E)* and *(Z)* isomers of unsaturated lactone **3** produce the product of the **same** absolute configuration with the **same** enantioselectivity (95% ee).[10]



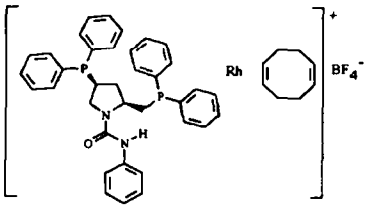
1 **2** **3**

R = H **4**
R = c-$C_6H_{11}NH_3$ **5**

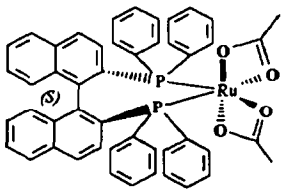
n = 0 **6**
n = 2, R = H **7**

In a process for large scale preparation of **7** we desired an enantioselective hydrogenation of *(Z/E)*-2-*tert*-butylthiomethyl-3-(1-naphthyl)-acrylic acid (**4**).[4d] In the presence of 1 mol % of [Rh(COD)(-) phenyl CAPP] BF_4 (I)[11], pure[12] acid *(Z)*-**4**[13] was hydrogenated to give **6** (>90% isolated yield, 42-45% ee, entries 1-3). The moderate enantioselectivity did not significantly depend on the reaction temperature (20 -120°C) and the

hydrogen pressure (30 - 150 bar). Hydrogenation was slow at 20°C (entry 4). Addition of triethylamine decelerated the hydrogenation and the enantioselectivity deteriorated (entries 5,6). Ru^{II}-binap catalysts with strongly electronegative anions (chloride, trifluoroacetate)[14] had no catalytic activity on *(Z)*-**4** under the conditions tested[15], but acetate $Ru(OAc)_2$(-)binap (**II**)[16] provided hydrogenation product **6** within a broad range of temperature and pressure (entries 7-16). The enantioselectivity of the catalyst was minimum at 50°C (entry 12) and maximum at 100-120°C (entries 8-9). Hydrogenation was considerably slower at lower temperature, but even at 25°C under only 5 bar of hydrogen formation of product **6** was largely attained (entry 15). In the presence of 1.05 equiv of triethylamine the enantioselectivity deteriorated at 50°C (entry 13) and the hydrogenation was completely inhibited at 25°C.[17] There was no significant influence of hydrogen pressure on the enantioselectivity.



(2*S*,4*S*)-**I**



(*S*)-**II**

Table 1. Asymmetric Hydrogenation of Acid *(Z)*-**4**[a]

Entry	Catalyst[b]	Temp. / °C	H_2 / bar	NEt_3	rct. / hr	Conv. / %[c]	ee / %[d]
1	*(2S,4S)*-**I**	120	150	0	24	100	44
2		50	150	0	24	100	45
3		50	30	0	24	100	42
4		20	100	0	24	20	49
5		40	150	1.05	24	60	29
6		50	5	1.05	24	15	9
7	*(S)*-**II**	150	150	0	1	100	61
8		120	150	0	2	100	68
9		100	150	0	3	100	68
10		100	5	0	24	100	65
11		80	150	0	6	100	66
12		50	150	0	48	100	38
13		50	150	1.05	48	100	< 5
14		25	150	0	96	100	51
15		25	5	0	48	85	59
16		25	5	1.05	48	0	--

a) Reaction conditions : substrate (1.0 mmol), catalyst (0.01 mmol), solvent methanol (50 mL). b) Catalyst : **I** = [Rh(COD)phenylCAPP]BF_4 ; **II** = $Ru(OAc)_2$(binap) ; *(S)* refers to the configuration of phenylCAPP and binap. c) HPLC, *cf.* lit. 4d. d) HPLC, *cf.* lit. 4d. Product **6** was preferentially formed with the *(S)*-configuration.

We optimized the enantioselectivity of the hydrogenation with $Ru^{II}(OAc)_2$(-)binap catalyst **II**, keeping the optimum reaction parameters (100°C, 150 bar H_2) constant, and exploring variations of solvent, *Z/E*-ratio and counterion (*i.e.* **4** *vs.* **5**). The optical purities of product *(S)*-**6** are summarized in Table 2.

Table 2. Asymmetric Hydrogenation of *(Z)*-**4**, *(E)*-**4**, and *(Z/E)*-**5** With Catalyst *(S)*-**II**[a]

	% ee of *(S)*-**6**		
Solvent	Substrate *(Z)*-**4**	Substrate *(E)*-**4**	Substrate **5** (*Z/E* = 57:43)
c-C_6H_{12}	84	9	
THF	80	10	48[b]
CH_2Cl_2/MeOH (50:1)	76	41	
C_6H_5Me	71		
MeOH	68	47	59
*t*BuOMe	65		
*i*PrOH	52		
CF_3CH_2OH	34, *(R)*-**6** !	62	51

a) Reaction conditions : substrate (1.0 mmol), catalyst (0.01 mmol), solvent (50 mL), 100°C, 150 bar H_2, 3 hr (for CH_2Cl_2/MeOH : 72 hr). HPLC[4d] indicated ≥ 95% of **6** and ≤ 1% of **4** in all cases. Optical purities determined by HPLC[4d]. b) Substrate **4** (*Z/E* = 57:43) was employed.

Thus with substrate *(Z)*-**4** the *(S)*-enantioselectivity is supported by the non-polar character and low steric demand of the solvent : in the non-polar solvent cyclohexane 84% ee of *(S)*-**6** was attained ; in the highly polar solvent 2,2,2-trifluoroethanol the catalyst had reversed π-face selectivity and led preferentially to *(R)*-**6**. Much to our surprise, the **opposite** order of *(S)*-enantioselectivity was observed, when the configurational isomer *(E)*-**4** was hydrogenated under exactly the same conditions. In cyclohexane *(S)*-**6** was formed with the exceedingly low enantioselectivity of 9% ee ; in trifluoroethanol *(S)*-**6** was provided with 62% ee.

The optical purities of products **6**, obtained by hydrogenations of cyclohexylammonium salts **5**, did not significantly differ from those obtained from the corresponding carboxylic acids **4**. This contrasts the influence of triethylamine on Rh^{I}- and Ru^{II}-catalyzed hydrogenations of **4** *(vide supra)*. Because of the divergent solvent effects for configurational isomers of **4** and **5**, the optical purities of products **6** from *(Z/E)*-**4** or *(Z/E)*-**5** were only slightly influenced by the solvent.[18]

The hydrogen addition in the presence of $Ru^{II}(OAc)_2$-*(S)*(-)-binap catalyst occurs preferentially to the *Re* face at C(2), regardless of *(Z)* or *(E)* configuration of **4** (or **5**), to give *(S)*-**6**. This is the same π-face selectivity as reported for *(E)*-**1**[8], **2**[9], and **3**[10], suggesting that the hydrogenation proceeds by the conventional coordination of Ru^{II} to the carboxylate group[19] and not by chelate formation with the sulfur atom and C=C. In summary, we have shown that substrates **4** and **5** can be asymmetrically hydrogenated in the presence of Rh^{I}- and Ru^{II}-diphosphine complexes without poisoning these catalysts. Similar to **2** and **3**, Ru^{II}-binap catalyzed hydrogenation of *(Z)* and *(E)* isomers of **4** (or **5**) leads to product **6** (up to 84% ee) of the **same** absolute configuration, however with pronouncedly different enantioselectivities. An unprecedented influence of solvent polarity on the enantioselectivity of Ru^{II}-binap is found to be opposite for *(Z)*- and *(E)*-substrate.

REFERENCES and NOTES

1. Reviews : a) Brunner, H. *Top. Stereochem.* **1988**, *18*, 129-247. b) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901-6916. c) Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett* **1992**, 169-178.
2. Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051-1069.
3. Reviews : a) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187-208. b) Takaya, H.; Ohta, T.; Mashima, K.; Noyori, R. *Pure & Appl. Chem.* **1990**, *62*, 1135-1138.
4. We used this technology to prepare optically pure building blocks of human renin- and HIV-protease-inhibitors on large scale : a) Jendralla, H. *Tetrahedron Lett.* **1991**, *32*, 3671-3672. b) Jendralla, H.; Henning, R.; Seuring, B.; Herchen, J.; Kulitzscher, B.; Wunner, J *Synlett* **1993**, 155-157. c) Jendralla, H. *Synthesis* **1994**, in press. d) Beck, G.; Jendralla, H.; Kammermeier, B. *Tetrahedron* **1994**, *50*, 4691-4698.
5. a) Ando, D. ; Bevan, C. ; Brown, J.M. ; Price, D.W. *J. Chem. Soc., Chem. Commun.* **1992**, 592-594 applied chiral and non-chiral cationic Rh^{I}-diphosphine complexes for the homogeneous hydrogenation of vinyl sulfones and vinyl sulfides. b) Ojima, I. ; Yoda, N. ; Yatabe, M. ; Tanaka, T. ; Kogure, T. *Tetrahedron* **1984**, *40*, 1255-1268 applied a chiral cationic Rh^{I}-diphosphine complex for the asymmetric hydrogenation of an N-acetyl-dehydroaminoacid derivative with **remote** sulfur functionality. c) Vineyard, B.D. ; Knowles, W.S. ; Sabacky, M.J. ; Bachman, G.L. ; Weinkauff, D.J. *J. Am. Chem. Soc.* **1977**, *99*, 5946-5952 used a cationic Rh^{I}-diphosphine complex for the asymmetric hydrogenation of a thiocarbonylamino-dehydroaminoacid ester. d) Zhang, X. ; Taketomi, T.; Yoshizumi, T. ; Kumobayashi, H. ; Akutagawa, S. ; Mashima, K. ; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 3318-3319 utilized cationic Ir^{I}-binap catalysts for the enantioselective carbonyl-hydrogenation of β-thiacycloalkanones.
6. Zymalkowski, F. in *Houben-Weyl, Methoden der Organischen Chemie* ; Kropf, H. Ed.; Georg Thieme Verlag : Stuttgart **1980**, Vol. *IV/1c* ; pp 26-28.
7. Faller, J.W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804-805.
8. Ohta, T. ; Takaya, H. ; Kitamura, M. ; Nagai, K. ; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174-3176.
9. Saburi, M. ; Shao, L. ; Sakurai, T. ; Uchida, Y. *Tetrahedron Lett.* **1992**, *33*, 7877-7880.
10. Ohta, T. ; Miyake, T. ; Seido, N. ; Kumobayashi, H. ; Akutagawa, S. ; Takaya, H. *Tetrahedron Lett.* **1992**, *33*, 635-638.
11. Ojima, I. ; Yoda, N. *Tetrahedron Lett.* **1980**, *21*, 1051-1054.
12. Attempts to hydrogenate **crude** *(Z/E)*-**4**, employing different Rh^{I}- and Ru^{II}-catalysts, did not lead to any formation of product **6**, indicating the inhibition of hydrogenation by efficient catalyst poisons.
13. Detailed procedures for the preparation of pure *(Z)*-**4**, *(E)*-**4**, and *(Z/E)*-**5** are given in ref. 4d.
14. $[RuCl(C_6H_6)(-)binap]Cl$; *cf.* Kitamura, M. ; Tokunaga, M. ; Ohkuma, T. ; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163-4166. $[RuCl_2(-)binap]$ and $[Ru(O_2CCF_3)_2(-)binap]$; *cf.* Heiser, B. ; Broger, E.A. ; Crameri, Y. *Tetrahedron : Asymmetry* **1991**, *2*, 51-62.
15. S/C = 200 - 1000, CH_3OH, 40°C, 150 bar H_2, 1d.
16. Kitamura, M. ; Tokunaga, M. ; Noyori, R *J. Org. Chem.* **1992**, *57*, 4053-4054.
17. Inhibition of Ru^{II}-binap catalyzed C=O hydrogenation of β-ketoesters by traces of NEt_3 was reported: King, S.A. ; Thompson, A.S. ; King, A.O. ; Verhoeven, T.R. *J. Org. Chem.* **1992**, *57*, 6689-6691.
18. Competition of hydrogenation and *(E/Z)*-isomerization was evident from HPLC of some incompletely hydrogenated reaction solution : *e.g.* hydrogenation of *(E)*-**5** (S/C = 100, MeOH, 100°C, 5 bar H_2, 24hr) gave 81% *(S)*-**6** (44% ee), 17% *(Z)*-**5** and < 1% of unreacted *(E)*-**5**.
19. Ashby, M.T. ; Halpern, J. *J. Am. Chem. Soc.* **1991**, *113*, 589-594.

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