Chiral Ruthenium-Catalyzed Hydrogenation of β-Keto Sulfoxides

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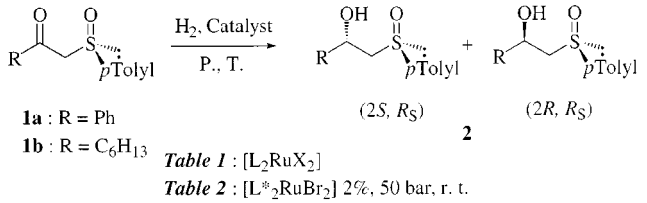
The diastereoselective catalytic hydrogenation of β-keto sulfoxides in the presence of ruthenium complexes was studied. Optically pure β-keto sulfoxides were hydrogenated in the presence of achiral catalysts leading to moderate yields and stereoselectivities. Using chiral ruthenium catalysts such as [(*R*)-MeO–BIPHEPRuBr$_2$] and [(*S*)-MeO–BIPHEPRuBr$_2$], the hydrogenation proceeded in good yields with very high diastereoselectivity. Chirality at the secondary centre of the β-hydroxy sulfoxides produced was controlled by the catalysts.

Introduction

Chiral sulfoxides are well-known in terms of their usefulness as chiral auxiliaries for asymmetric synthesis.[1] In particular, the reduction of the carbonyl group in a chiral β-keto sulfoxide has been shown to be potentially useful for the preparation of optically active alcohols and derivatives.[2] One of the most stereoselective reactions has been their reduction with *i*Bu$_2$AlH or ZnCl$_2$/*i*Bu$_2$AlH.[3] Recently, the stereoselective sulfoxide-directed reduction of 1,2-diketo- and γ-keto-derivatives was described.[4]

In conjunction with our studies on the stereoselective hydrogenation of functionalized ketones in the presence of a chiral metal catalyst,[5] we investigated the hydrogenation of β-keto sulfoxides catalyzed by ruthenium complexes. First, we examined the hydrogenation of an optically pure β-keto sulfoxide such as (*R*)-*p*-tolylsulfinylacetophenone **1a** with an achiral ruthenium catalyst generated in situ from commercially available Ru(COD)(2-methylallyl)$_2$.[6]



Scheme 1. Hydrogenation of optically pure β-keto sulfoxide

Working with [DPPERuBr$_2$] (DPPE = diphenylphosphanylethane) at atmospheric pressure, no conversion was observed and the starting β-keto sulfoxide **1a** was recovered. At higher pressures (50 or 80 bar), hydrogenation of the keto group proceeded: β-hydroxy sulfoxides were obtained in low yields and a large amount of degradation products was obtained.

The diastereomeric ratio was measured by ^{1}H NMR spectroscopy (250 MHz) and the major diastereomer was identified as (2*S*,*R*$_S$)-β-hydroxy sulfoxide **2a** in agreement with the published study on the reduction mechanism.[3b]

The best results were obtained using [(PPh$_3$)$_2$RuBr$_2$]; total conversion of the β-keto sulfoxide **1a** into β-hydroxy sulfoxide **2a** was observed at 50 bar. At a lower pressure, the yield decreased. The temperature influenced neither the yield nor the diastereomeric ratio: 80:20 in favour of the (2*S*,*R*$_S$)-β-hydroxy sulfoxide **2a** (Table 1).

To explain the diastereoselectivity, a chelated model could be envisaged in which the metal is chelated by both oxygens of the β-keto sulfoxide.[7] The substrate could adopt two conformations with the two chelated intermediates in equilibrium. The most favoured conformation of the substrate is that in which the smaller substituent of the sulfoxide occupies a pseudo-axial position. The conformer **B** should be favoured and the (2*S*,*R*$_S$) configuration is observed for the major hydrogenated product. In this case, the stereochemistry of the created hydroxylated centre is controlled by the chirality of the sulfoxide.

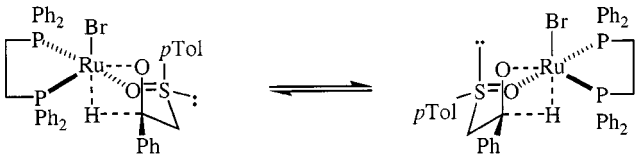


Figure 1. Ruthenium(II)-chelated intermediates

The hydrogenation of optically pure β-keto sulfoxides was then carried out in the presence of the chiral ruthenium catalysts [(*R*)-MeO–BIPHEPRuBr$_2$] and [(*S*)-MeO–BIPHEPRuBr$_2$] at room temperature and under pressure (50 bar).

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Table 1. Hydrogenation of (*R*)-*p*-tolylsulfinylautophenone **1a** with achiral ruthenium(II) catalysts

Catalyst (%)	*p* (bar)	*T* (°C)	*t* (h)	Isolated yield of **2** (%)	(2*S*,*R*$_S$)/(2*R*,*R*$_S$)
Ru DPPE Br_2	1	50	16	0	–
(2)	50	50	24	12	78/22
	80	50	4	20	79/21
Ru $Br_2(PPh_3)_2$	50	20	64	99	80/20
(1)	10	20	50	30	79/21
	50	40	50	95	81/19

Table 2. Hydrogenation of β-keto sulfoxides with chiral ruthenium(II) catalysts

Substrate	L*$_2$	*t* (h)	Isolated yield of **2** (%)	(2*S*,*R*$_S$)/(2*R*,*R*$_S$)
1a	(*S*)-MeO–BIPHEP	63	70	>99/1
1a	(*R*)-MeO–BIPHEP	63	95	10/90
1b	(*S*)-MeO–BIPHEP[8]	25	82	>99/1
1b	(*R*)-MeO–BIPHEP[8]	23	74	6/94

Under these experimental conditions, no degradation product was observed and the β-hydroxy sulfoxides were isolated in good yield. The diastereoselectivity was excellent: with (*S*)-MeO–BIPHEP as the chiral ligand on the ruthenium catalyst, only the (2*S*,*R*$_S$) diastereomer was detected; with (*R*)-MeO–BIPHEP, the other diastereomer (2*R*,*R*$_S$) was obtained as the major β-hydroxy sulfoxide with good selectivity (> 80%).

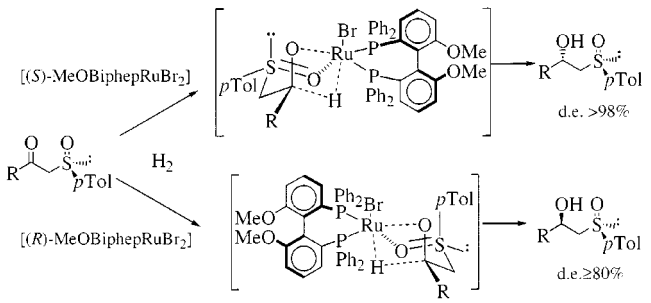


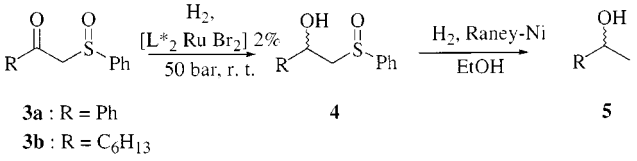
Figure 2. Ruthenium hydrogenation of β-keto sulfoxides with (*R*) and (*S*) atropisomeric ligands

With a chiral ruthenium catalyst, the approach of the substrate is controlled by the configuration of the diphosphane ligand. With [(*S*)-MeO–BIPHEPRuBr$_2$], the β-keto sulfoxide adopts a conformation in which the *p*-tolyl substituent on the sulfur atom has a pseudoequatorial position and the lone pair of electrons a pseudoaxial position. This conformation is totally favoured and an excellent diastereoselectivity is observed (>98%) leading to a single (2*S*,*R*$_S$) diastereomer. However, with [(*R*)-MeO–BIPHEPRuBr$_2$], the conformation of the β-keto sulfoxide is less favoured. We also noticed a small decrease in the diastereoselectivity (>80%), the major diastereomer having the (2*R*,*R*$_S$) configuration. These results are in agreement with matched and mismatched effects of the two chiral reagents: the use of an (*S*) atropisomer ligand on the catalyst with an optically pure (*R*)-sulfoxide afforded the (2*S*,*R*$_S$)-β-hydroxy sulfoxide as the only diastereomer. However, the (2*R*,*R*$_S$)-β-hydroxy sulfoxide was obtained as the major diastereomer using a ruthenium catalyst bearing the (*R*) antipode (Table 2).

The diastereoselectivity of the hydrogenation of the chiral β-keto sulfoxide with chiral ruthenium catalysts was completely controlled by the chirality of the diphosphane ligand in the ruthenium complex.

In order to confirm this observation, we decided to hydrogenate racemic β-keto sulfoxides with [(*R*)-MeO–BIPHEPRuBr$_2$] and [(*S*)-MeO–BIPHEPRuBr$_2$] as chiral catalysts. The four stereoisomers of the β-hydroxy sulfoxides were obtained in this reaction. The diastereomeric ratio, measured by ^{1}H NMR spectroscopy, indicated the proportion of the major diastereomer (2*R*,*S*$_S$) + the minor (2*S*,*R*$_S$) compared to the major (2*R*,*R*$_S$) + the minor (2*S*,*S*$_S$) approaching 50:50. We could not calculate the stereoselectivity and the major absolute configuration of the hydroxyl centre could not be determined at this stage.

The β-hydroxy sulfoxides **4** were desulfurized using Raney Ni under classical conditions and the corresponding methyl carbinols were obtained as a mixture of enantiomers (*R*)-**5** + (*S*)-**5**.



Scheme 2. Asymmetric hydrogenation of racemic β-keto sulfoxides

Table 3. Asymmetric hydrogenation of racemic β-keto sulfoxides

Substrate	L*$_2$	Isolated yields (%) of **4** and **5**		(*R*)-**5**/(*S*)-**5**
3a	(*S*)-MeO–BIPHEP	78	95	80/20
3a	(*R*)-MeO–BIPHEP	60	95	5/95
3b	(*S*)-MeO–BIPHEP	94	95	95/5
3b	(*R*)-MeO–BIPHEP	94	95	4/96

The optical purities of the obtained methylcarbinols **5a** and **5b** were measured by gas chromatography. The **5a** enantiomeric mixtures were converted into their Mosher esters and the diastereomeric ratio were obtained using an achiral GC column (*T* = 95 to 180 °C, gradient = 3 °C/min., flow = 1 mL/min.). For **5b**, the *ee* was determined using a chiral Lipodex G.C. column (T = 75 °C, flow = 1 mL/min.). The absolute configuration of the major enantiomer was determined by optical rotation. The diastereoselectivity of the hydrogenation of racemic β-keto sulfoxides is the same as that observed for the optically pure substrates. The [(*S*)-MeO–BIPHEPRuBr$_2$] catalyst induced the major (*S*) absolute configuration for the created hydroxyl centre of the β-hydroxy sulfoxide and the (*R*)-**5** methylcarbinol was obtained as the major enantiomer after the cleavage of the sulfoxide group. The (*R*) ligand leads to the major (2*R*)-β-hydroxy sulfoxide and to the (*S*)-**5** alcohol. There-

fore we have shown here that the chirality of the sulfur centre is not essential for a good diastereoselection.

In conclusion, we have proposed here the first study of the hydrogenation of β-keto sulfoxides using a ruthenium catalyst. With achiral ruthenium complexes and optically pure β-keto sulfoxides the diastereoselectivity of this reaction did not exceed 60%. On the other hand, in the presence of chiral ruthenium complexes, the diastereoselectivity was very high and the chirality of the created hydroxyl centre was controlled by the catalyst, starting from either optically pure or racemic β-keto sulfoxides.

Experimental Section

General: Infrared spectra (IR) were measured with a Bruker 45 FTIR instrument. – ^{1}H NMR spectra were recorded on a Bruker AC200 spectrometer at 200 MHz with $CDCl_3$ as solvent. – Column chromatographic separations were carried out over Merck silica gel 60 (0.040–0.063 mm); analytical thin layer chromatography (TLC) experiments were performed on Merck silica gel TLC plates F254. – Elemental analyses were performed by the Service Régional de Microanalyses de l'Université Pierre et Marie Curie.

General Procedure of Hydrogenation of β-Keto Sulfoxides: A β-keto sulfoxide (5 mmol) was diluted under argon in degassed methanol (1 mL). This solution was transferred with a canula into a 10 mL Schlenk tube containing the ruthenium complex (2 mol-%). The reaction mixture was immediately placed in an autoclave which was purged three times with hydrogen and pressurized. The autoclave was heated and magnetic stirring was started as soon as the required temperature was reached. Stirring was stopped (see Table 2) and the autoclave was cooled to room temperature. The brownish solution obtained was concentrated under vacuum. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy on the crude product. The product was purified by flash chromatography (hexane/ether).

(2*S*,*R*$_S$)-1-Phenyl-2-*p*-tolylsulfinylethanol (2a): (2*S*,*R*$_S$) diastereomer obtained by hydrogenation of **1a** in the presence of [(*S*)-MeO–BIPHEPRuBr$_2$]: diastereomeric ratio (2*S*,*R*$_S$)/(2*R*,*R*$_S$) > 99:1, m.p. 73 °C – $[\alpha]_D^{20}$ = +200 (*c* = 1, $CHCl_3$), {ref.[8] $[\alpha]_D^{20}$ = +202 (*c* = 1, $CHCl_3$)}. – IR (CCl_4): $\tilde{\nu}$ = 3350 cm^{-1} (OH), 1070 (SO). – ^{1}H NMR ($CDCl_3$): δ = 2.44 (s, 3 H, C*H*$_3$), 3.04 (ABX, *J* = 10.2, 2, 13.6 Hz, 2 H, C*H*$_2$), 5.25 (dd, *J* = 10.2, 2 Hz, 1 H, C*H*OH), 7.29–7.59 (m, 9 H, aromatic H).

(2*R*,*R*$_S$)-1-Phenyl-2-*p*-tolylsulfinylethanol (2a): (2*R*,*R*$_S$) diastereomer obtained by hydrogenation of **1a** in the presence of [(*R*)-MeO–BIPHEPRuBr$_2$]: diastereomeric ratio (2*R*,*R*$_S$)/(2*S*,*R*$_S$) = 90:10. – IR (CCl_4): $\tilde{\nu}$ = 3350 cm^{-1} (OH), 1070 (SO). – ^{1}H NMR ($CDCl_3$): δ = 2.44 (s, 3 H, C*H*$_3$), 3.07 (ABX, *J* = 10, 2, 13.5 Hz, 2 H, C*H*$_2$), 5.40 (dd, *J* = 10, 2 Hz, 1 H, C*H*OH), 7.28–7.60 (m, 9 H, aromatic H).

(2*S*,*R*$_S$)-1-*p*-Tolylsulfinyloctan-2-ol (2b): (2*S*,*R*$_S$) diastereomer obtained by hydrogenation of **1b** in the presence of [(*S*)-MeO–BIPHEPRuBr$_2$]: diastereomeric ratio (2*S*,*R*$_S$)/(2*R*/*R*$_S$) >99:1, m.p. 77 °C – $[\alpha]_D^{20}$ = +224 (*c* = 1, $CHCl_3$) – IR (CCl_4): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 1080 (SO). – ^{1}H NMR ($CDCl_3$): δ = 0.87–1.52 (m, 13 H, C_6H_{13}), 2.43 (s, 3 H, C*H*$_3$), 2.83 (ABX, *J* = 9.2, 2, 13.2 Hz, 2 H, C*H*$_2$), 4.20 (m, 1 H, C*H*OH), 7.40 (A_2B_2, *J* = 8 Hz, 4 H, aromatic H). – $C_{15}H_{24}O_2S$ (268.4): calcd. C 67.12, H 9.01; found C 66.77, H 8.85.

(2*R*,*R*$_S$)-1-*p*-Tolylsulfinyloctan-2-ol (2b): (2*R*,*R*$_S$) diastereomer obtained by hydrogenation of **1b** in the presence of [(*R*)-MeO–BIPHEPRuBr$_2$]: diastereomeric ratio (2*R*,*R*$_S$)/(2*S*,*R*$_S$) = 94:6. – IR (CCl_4): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 1080 (SO). – ^{1}H NMR ($CDCl_3$): δ = 0.87–1.52 (m, 13 H, C_6H_{13}), 2.43 (s, 3 H, C*H*$_3$), 2.84 (ABX, *J* = 9, 2, 13.2 Hz, 2 H, C*H*$_2$), 4.29 (m, 1 H, C*H*OH), 7.55 (AA′BB′, *J* = 8 Hz, 4 H, aromatic H).

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