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Asymmetric Hydrogenation of Phenylthio Ketones with Chiral Ru(II) Catalysts

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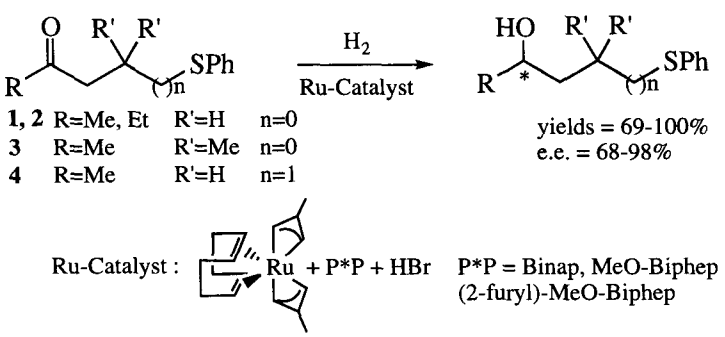
Abstract: *Asymmetric hydrogenation of phenylthio ketones using chiral Ru(II) catalysts is reported. Complete conversions and enantiomeric excesses up to 98% were obtained.*

Because organosulfur compounds are widely used in organic synthesis to bring about numerous selective transformations,[1] readily available alcohols of high enantiomeric purity, which also bear the phenylthio group, would be of considerable use in synthesis. Divalent sulfur is easily oxidized to sulfoxides or sulfones, functionalities having wide synthetic utility,[2] or it can be reductively replaced with lithium.[3] Recently, baker's yeast-mediated asymmetric reduction of ketones bearing a phenylthio group in the β or γ position has been reported and the corresponding alcohols have been prepared in high enantiomeric excess but moderate conversions.[4,5] These alcohols have been utilized for the synthesis of spiroacetal pheromones and several other cyclic compounds of high enantiomeric excess.[4,6] There is also a recent report of the microbial reduction of two sulfenyl-trifluoromethyl ketones with high diastereo and enantioselection depending on the microorganisms.[7] In our continuous interest in homogeneous catalytic asymmetric hydrogenation using chiral ruthenium complexes,[8,9] we now report enantioselective hydrogenation of some phenylthio ketones using our simple *in situ* preparation of Ru(II) catalysts (Scheme 1).[8e]



Scheme 1

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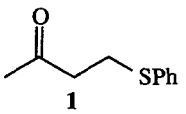
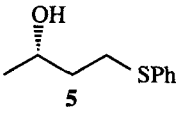
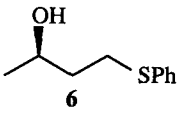
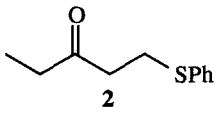
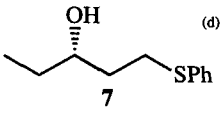
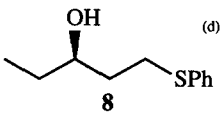
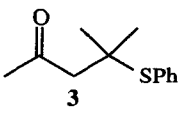
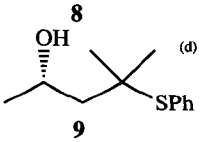
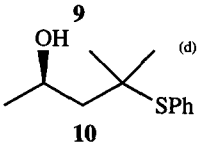
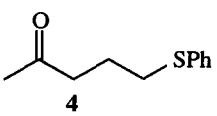
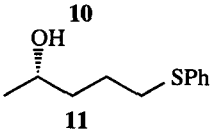
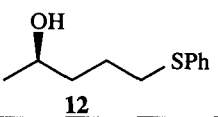
Our results are summarized in Table 1. The phenylthio ketones were easily prepared by conjugate addition of thiophenol or the cuprate derived from phenylthiomethyllithium to the appropriate enone.[4,10] All hydrogenation reactions were carried out in methanol at 30 bars and room temperature for 24 h (except entries 11, 12 and 13), using 2 mol.% of chiral ruthenium catalyst prepared *in situ*.[8e,11] Lower conversions were obtained with 1 mol.% or when the reaction was conducted in dichloromethane.

Asymmetric hydrogenation of 4-phenylthio-2-butanone **1** was performed for 24 hrs using (*S*)-Binap and (*S*)-MeO-Biphep leading to (*S*)-4-phenylthio-2-butanol **5** in 96% and 98% e.e. (entries 1 and 2). The (*R*)-isomer **6** was prepared using (*R*)-Binap and (*R*)-MeO-Biphep as ligands in 92% and 97% e.e., respectively (entries 3 and 4). The hydrogenation of 5-phenylthio-3-pentanone **2** was studied under the same reaction conditions leading to (*S*) or (*R*)-5-phenylthio-3-pentanol **7** and **8** in 81% e.e. using (*S*) and (*R*)-Binap (entries 5 and 7). Better enantiomeric excesses were obtained with (*S*) and (*R*)-MeO-Biphep (88 and 97% e.e., entries 6 and 8). 4-Methyl-4-phenylthio-2-pentanone **3** having a bulky end group was quantitatively reduced to **9** and **10** respectively with a 80% e.e. using (*S*)-Binap (entry 9) and better e.e. approaching 90% with (*R*)-MeO-Biphep and (*R*)-2-furyl-MeO-Biphep (entries 10 and 11). Finally, 5-phenylthio-2-pentanone **4** having a longer alkyl chain was hydrogenated to (*S*)-**11** and (*R*)-**12** in nearly 70% yield and e.e. (entries 12 and 13). In this particular case, high pressure and temperature were necessary to perform the reaction probably resulting from a difficult chelation of the ruthenium with the phenylthio ketone. The absolute configurations of the phenylthio alcohols **5**,**6**,**11**, and **12** were assigned by comparison of their specific rotations with those described in the literature.[4] Those of **7**-**10** were assumed based on the results of the other reductions.[12]

When comparing the present results of reductions of **1** and **4** with those using baker's yeast reductions, the following conclusions can be drawn. In the case of **1**, better conversion to **5** and a marginally better enantiomeric excess are obtained by asymmetric hydrogenation and this is thus the method of choice. In the case of **4**, enzymatic reduction gives more satisfactory e.e. values for **11** and that is the preferred method. However, in contrast with baker's yeast mediated reduction, both enriched enantiomers are available by asymmetric hydrogenation with equal ease and in high yields. As previously reported for substituted ketones bearing a heteroatom,[9] a general orientation of the enantioselectivity is observed with these sulfur containing ketones, allowing a general prediction of the absolute configuration of the alcohols by the appropriate choice of axial biphenyl ligands.[12]

In conclusion, asymmetric syntheses of phenylthio alcohols by Ru-catalyzed hydrogenation were achieved with good conversions and enantiomeric excesses. The presently reported hydrogenation is compatible with a divalent sulfur. Further applications of this ruthenium mediated asymmetric hydrogenation to optically active alcohols containing sulfones and sulfoxides are in progress. This approach constitutes a rapid access to enantiomerically enriched phenylthio alcohols which are interesting building blocks for natural product synthesis.

Table 1: Asymmetric hydrogenation of phenylthio ketones with (P*P)$RuBr_2$

Entry	Substrate	Ligand[a]	Alcohol	Yield[b]	e.e.[c]
1	 **1**	(*S*)-Binap	 **5**	100	96
2		(*S*)-MeO-Biphep		100	98
3	"	(*R*)-Binap	 **6**	100	92
4	"	(*R*)-MeO-Biphep		100	97
5	 **2**	(*S*)-Binap	 **7**	90[e]	81
6		(*S*)-MeO-Biphep		100	88
7	"	(*R*)-Binap	 **8**	100	81
8	"	(*R*)-MeO-Biphep		100	97
9	 **3**	(*S*)-Binap	 **9**	100	80
10	"	(*R*)-MeO-Biphep	 **10**	100	90
11	"	(*R*)-2-furyl-MeO-Biphep		100	88[f]
12	 **4**	(*S*)-Binap	 **11**	70	70[g]
13	"	(*R*)-Binap	 **12**	69	68[g]

(a) Chiral Ru (II) catalyst (2% mol). (b) Yields are determined by ^1H NMR. (c) E. e. were determined by GC analysis (Megadex 5 column, dimethylpentyl-β-cyclodextrin, 25 m x 0.25 mm, fused capillary, df 0.25 μm) except for **11** and **12**. (d) The absolute configuration is inferred by analogy with the other results in the table. (e) Reaction times: 22 h. (f) 50 bars, room temp., 43h. (g) 115 bars, 80 °C, 70 h; enantiomeric excesses were determined by ^1H NMR of the corresponding MTPA esters.

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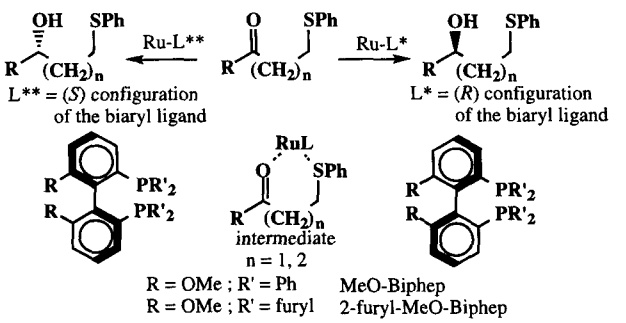
10. Cherkauskas, J. P.; Cohen, T. *J. Org. Chem.*, **1992**, *57*, 6-8.
11. Preparation of the (P*P)$RuBr_2$ complexes and typical procedure for asymmetric hydrogenation : (*S*)-Binap (7.5 mg) and $CODRu(2\text{-methylallyl})_2$ (3.2 mg, commercially available from Acros), were placed in a Schlenk tube and purged three times with vacuum/argon and dissolved with 1 mL of acetone (degassed by 3 cycles of vacuum/argon at r.t.). To this suspension was added 2.2 eq. of methanolic HBr (48% aq HBr in a methanolic solution) and the suspension was stirred at room temperature for 30 min. A yellow solid precipitated. The solvent was evaporated under vacuum and the phenylthio ketone (0.5 mM) dissolved in 2 mL of degassed MeOH was added to the Ru(II)-catalyst. The resulting mixture was placed under argon in a 250 mL stainless steel autoclave. The argon atmosphere was replaced by hydrogen by three cycles of pressurizing and the reaction was carried out until complete conversion.
12. Specific relationship between chiral atropoisomeric ligands (e.g. MeO-Biphep, 2-furyl-MeO-Biphep, Binap) and alcohol absolute configuration.



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