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General Synthesis of Chiral β-Hydroxy Sulfones *via* Enantioselective Ruthenium-Catalyzed Hydrogenation

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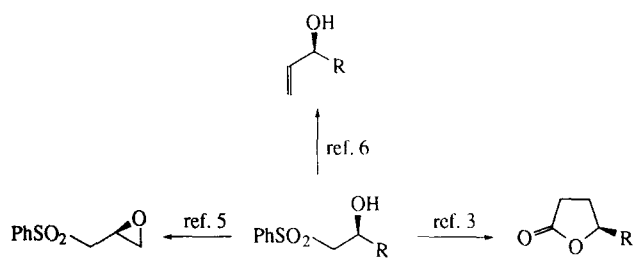
Abstract: *A new ruthenium-promoted hydrogenation of β-keto sulfones using MeO-BIPHEP as ligand is reported with complete conversions and enantiomeric excesses over 95%.*

Hydroxy sulfones are useful chiral synthons in organic synthesis. Their preparation in enantiomerically pure form has attracted a considerable interest.[1,2] They have been successfully used in the synthesis of optically active lactones such as (*R*)-hexanolide or (*R*)-umbelactone[3] and γ-lactones.[4] They are also useful synthetic intermediates to obtain enantiomerically pure 2,5-disubstituted tetrahydrofuran units found in many natural products or chiral epoxides containing an electron-withdrawing sulfonyl group at the β-position.[5] Alkylation of the dianions of 1-(phenylsulfonyl) alkan-2-ols with electrophilic reagents has also been studied (Scheme 1).[6]



Scheme 1

Baker's yeast-mediated reduction of β-keto sulfones to the corresponding β-hydroxy sulfones has been reported.[7] Enantiomeric excesses were highly dependent on the substrate and especially on the size of the groups adjacent to the carbonyl. For example, 1-(phenylsulfonyl) propan-2-one was reduced to the (*S*)-alcohol in 98% yield and 95% e.e. If instead, the pentyl or phenyl analogues were submitted to microbial transformation, the corresponding hydroxy sulfones were obtained respectively in 10% and 15% e.e. (Scheme 1, R=*n*-C_5H_{11} or Ph).

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This is one critical limitation of this reduction which resides in the substitution pattern of the carbonyl group of the β-keto sulfones.[7,8] The kinetic resolution of β-hydroxy sulfones has been achieved with porcine pancreatic lipase (PPL) with moderate selectivities.[9] Chemical methods for such reductions[10] have been also described which employed tartaric acid modified Raney nickel reagent leading to hydroxy sulfones in moderate 70% optical yield.[11]

The chiral Ru(II)-catalysts, readily prepared *in situ* from the commercially available CODRu(methylallyl)$_2$ and the chiral diphosphine by addition of methanolic HBr, are highly effective catalysts for the enantioselective hydrogenation of functionalized ketones to chiral alcohols. This method is advantageous for several reasons : wide scope, predictable absolute configurations, ready availability of the chiral Ru(II)-catalyst in either enantiomeric forms, simple process and high yields. Synthetic applications of this process include efficient syntheses of natural products or intermediates of biological interest.[12,13] We report here on a new application of the ruthenium-catalyzed asymmetric hydrogenation of β-keto sulfones using our simple *in situ* preparation of chiral Ru(II)-catalysts.[12]

All β-hydroxy sulfones were conveniently prepared through (*S*)-BINAP or (*S*)-MeO-BIPHEP /ruthenium catalyzed hydrogenations of the corresponding β-keto sulfones **1-6** easily accessible by condensation of the dianion of the methylphenylsulfone on various acid chlorides or esters.[14] We have found that the functionalized β-keto sulfones **1-4** were smoothly reduced at atmospheric pressure under optimized conditions (solvent, catalyst ratio, ligand) using 1 mol% of chiral ruthenium(II) catalyst in refluxing methanol. Our results are summarized in Table 1. Hydrogenation of the 1-(phenylsulfonyl) propan-2-one **1** to the (*R*)-1-(phenylsulfonyl)-propan-2-ol **7** proceeded with more satisfactory results using (*R*)-MeO-BIPHEP than (*R*)-BINAP (entries 1 and 2). Both enantiomers (*R*)-**7** and (*S*)-**8** were synthesized in enantiomerically pure forms respectively with (*R*) and (*S*)-MeO-BIPHEP (entries 2 and 3). The 1-(phenylsulfonyl) butan-2-one **2** was hydrogenated to the pure (*S*)-1-(phenylsulfonyl) butan-2-ol **9** again with (*S*)-MeO-BIPHEP (entry 4). In the hydrogenation reaction of 1-(phenylsulfonyl) heptan-2-one **3** promoted by ruthenium-BINAP complexes, both the activity and enantiomeric excess were moderate (entry 5, 82% e.e.). In contrast, excellent enantiofacial discrimination and complete conversion were observed with (*R*)-MeO-BIPHEP (entry 6, >95% e.e.) compared to baker's yeast-mediated reduction.[7] The asymmetric hydrogenation of β-keto sulfone **4** bearing a cyclohexyl ring proceeded smoothly in excellent e.e. affording (*R*)-1-(phenylsulfonyl)-2-cyclohexyl-ethan-2-ol **12**[15] with (*R*)-MeO-BIPHEP (entry 7, >95% e.e.). The ruthenium-mediated hydrogenation of β-keto sulfones **5** and **6** bearing respectively an alkyl long chain or an aromatic substituent required higher pressure : 1-(phenylsulfonyl) tridecan-2-one **5** and 1-(phenylsulfonyl)-2-acetophenone **6** were not completely hydrogenated at atmospheric pressure. When increasing the pressure to 10bar at 80°C, (*S*)-1-(phenylsulfonyl) tridecan-2-ol **13** was obtained with very high e.e. (entry 8, >95%,). Finally, the hydrogenation of 1-(phenylsulfonyl)-2-acetophenone **6** at 75bar and 80°C led to the corresponding β-hydroxy sulfone **14** in 89% e.e. (entry 9). In decreasing the temperature to 40°C, **14** was synthesized in an optically pure form (over 95%, entry 10).

In conclusion, the ruthenium-promoted hydrogenation reactions of β-keto sulfones have a wider scope and give in most cases higher e.e. values and yields than procedures using baker's yeast.[7] These reactions have been extended to preparative amounts (4 grams) of the starting β-keto sulfones. Furthermore, this process provides a practical and efficient route to both enriched enantiomeric forms of a wide range of β-hydroxy sulfones and this is the method of choice.

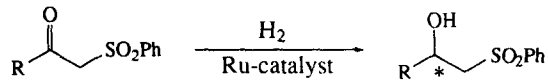
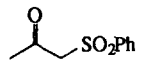
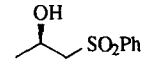
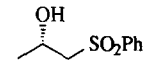
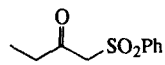
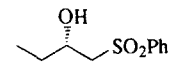
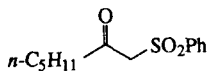
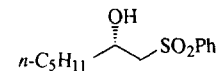
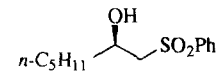
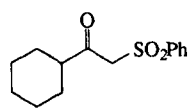
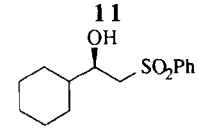
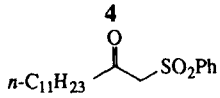
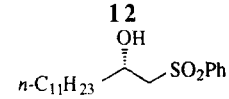
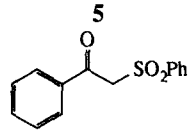
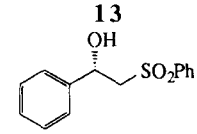


Table 1: Ruthenium-catalyzed hydrogenation of β-keto sulfones with (P*P)$RuBr_2$[a]

Entry	Substrate	Ligand (P*P)	Product[b,c]	Conv.[d]	e.e.[e]
1		(*R*)-BINAP		90	91
2	**1**	(*R*)-MeO-BIPHEP	**7**	100	>95[f]
3	**1**	(*S*)-MeO-BIPHEP	 **8**	100	>95[f]
4	 **2**	(*S*)-MeO-BIPHEP	 **9**	100	>95[f]
5	 **3**	(*S*)-BINAP	 **10**	67	82
6	**3**	(*R*)-MeO-BIPHEP	 **11**	100	>95[f]
7	 **4**	(*R*)-MeO-BIPHEP	 **12**	100	>95[f]
8	 **5**	(*S*)-MeO-BIPHEP[g]	 **13**	100	>95[f]
	 **6**		 **14**		
9	**6**	(*S*)-MeO-BIPHEP[h]	**14**	100	89
10	**6**	(*S*)-MeO-BIPHEP[i]	**14**	100	>95[f]

(a) Chiral Ru (II) catalyst (1% mol). (b) The absolute configurations of the β-hydroxy sulfones were assigned by comparison of their specific rotations with those described in the literature[7,17] except for compound **9**.[4a,16](c) Reaction times:18 to 65 h. (d) Conversions were determined by ^1H NMR. (e) e.e. were determined by ^1H NMR (250MHz) with $Eu(Tfc)_3$. (f) Only one enantiomer was detectable by ^1H NMR (250MHz or 400MHz) with $Eu(Tfc)_3$. (g) Hydrogenation conducted at 10bar and 80°C for 18h using 2% mol catalyst. (h) Hydrogenation conducted at 75bar and 80°C for 48h. (i) Hydrogenation conducted at 75bar and 40°C for 48h.

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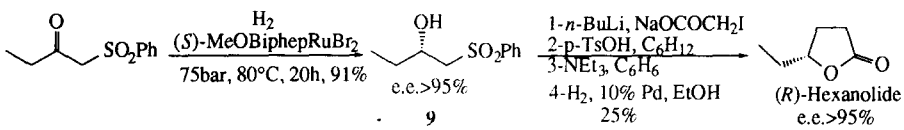
15. Characteristic data for compound **12** : ^{1}H NMR (250MHz, $CDCl_3$) : δ = 0.95-1.90 (11H, m), 3.20-3.30 (2H, m), 3.91-3.98 (1H, m), 7.55-7.73 (3H, m), 7.91-7.96 (2H, m). ^{13}C NMR (50MHz, $CDCl_3$) : δ = 25.8, 25.9, 26.1, 27.4, 28.4, 43.1, 60.2, 69.7, 127.8, 129.4, 133.9, 139.2. M.S. (E. I.) m/e = 269 (5, $M\text{-}H^+$), 185 (100), 141 (55). $[\alpha]_D$ = -20 (c=1, $CHCl_3$).
16. The absolute configuration of **9** was established by correlation with (*R*)-hexanolide, a component of the pheromone secreted by the female dermisted beetle *Trogoderma glabrum* using the following sequence. The e.e. of (*R*)-hexanolide was measured by chiral GC (Megadex 5 column) with an optical rotation in accord with literature data.[3]



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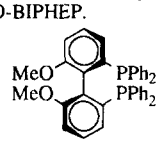
18. We are grateful to Dr. R. Schmid (Hoffmann La Roche) for samples of (*R*)-MeO-BIPHEP = (*R*)-(+)-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl and (*S*)-MeO-BIPHEP.



(*R*)-MeO-BIPHEP