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An Efficient Synthesis of Chiral β-Hydroxy Sulfones via Ru-Catalyzed Enantioselective Hydrogenation in the Presence of Iodine

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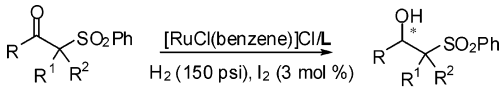
ABSTRACT



ee: up to >99%, TON: up to 1000

Ru-SUNPHOS catalyzed asymmetric hydrogenation of a variety of sulfonyl ketones (R = alkyl, aryl) in the presence of iodine gave enantioenriched hydroxyl sulfones with good catalytic efficiency. Further investigation revealed that the in situ generated anhydrous HI is the operating additive.

The increasing demand for enantiomerically pure pharmaceuticals, agrochemicals, flavors, and other fine chemicals has greatly stimulated the research in the field of asymmetric catalytic technologies.[1,2] Among these, asymmetric hydrogenation, which utilizes molecular hydrogen to reduce prochiral olefins, ketones, and imines, has become one of the most efficient methods for constructing chiral compounds.[3] It is well-known that asymmetric catalytic systems are often very sensitive to small variations in substrate, catalyst, and reaction conditions. Frequently, small amounts of achiral or chiral additives have been attributed to remarkable change in conversion rate, yield, enantioselectivity, and even reaction pathway.[4] This effect is not only significant in academic reasearch[4b] but also serves a pivotal role in some industrial applications.[4c]

Optically active β-hydroxy aryl sulfones are useful chiral synthons in organic synthesis, as the α-carbon among these compounds can be further functionalized and, moreover, the sulfonyl groups can be easily removed from the skeleton

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without racemization[5,6] They have been successfully applied to synthesis of biologically active molecules such as γ-butenolides,[6a−c] γ-butyrolactones,[6d] 5-disubstituted tetrahydrofuran and δ-valeractones,[6e] etc. As a result, many methods have been developed for the enantioselective synthesis of optically active β-hydroxy sulfones, including kinetic resolution,[7] and/or kinetically controlled oxidation of racemic substrates by biocatalysts,[8] baker's yeast or fungus[9] mediated reduction and chiral oxazaborolidine[10] or polymer-supported sulfonamide[11]-catalyzed borane reduction of β-keto sulfone. Genêt et al. reported an enantioselective hydrogenation of β-keto sulfones with chiral Ru(II) catalyst,[12] and Hou and co-workers reported Rh-catalyzed enantioselective hydrogenation of β-keto sulfones using a bisferrocenyl diphosphine ligand with planar chirality;[13] however, reduction of aromatic analogues required drastic reaction conditions to obtain high optical purity or more expensive Rh catalyst.

Recently we have been focusing on the design and application of new biaryl phosphine ligands. Initial work in this area has resulted in the identification of a series of bidentate ligands **L1**−**L4** (Figure 1) highly effective at enantioselective hydrogenation of ketoesters.[14] We also reported the significant improvement on catalyst stability and enantioselectivity by Lewis acid additives in the asymmetric hydrogenation of α-ketoesters.[14c] In this paper, we report a highly enantioselective hydrogenation of β-keto sulfones in the presence of iodine.

The chiral Ru(II) catalyst was readily prepared from [Ru(benzene)Cl_2]$_2$ and diphosphine ligand by refluxing them in degassed ethanol/benzene for 1 h.[15] The chiral bidentate ligands **L1**−**L4** and two commercially available chiral bidentate phosphines, (*R*)-BINAP and (*S*)-SEGPhos, were also tested for the asymmetric hydrogenation of 1-phenyl-2-(phenylsulfonyl)ethanone **(1a)** under 150 psi of H_2, at 70 °C in EtOH for 20 h with 1 mol % of Ru(II) catalyst. The β-ketosulfone **1a** was successfully reduced with complete conversion and good ee. We found the enantioselectivities were greatly dependent on ligands, ee increasing in the following order: (*R*)-BINAP (73.0%), **L4** (89.7%), **L2** (90.3%), (*S*)-SEGPhos (92.5%), **L1** (94.5%), **L3** (95.2%) (Table 1).

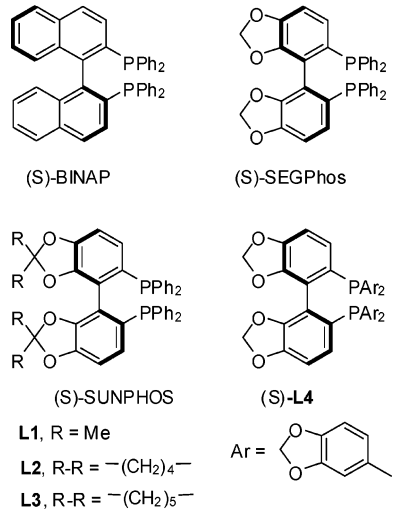
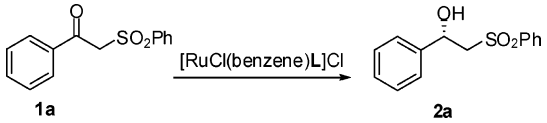


Figure 1. Structure of ligands.

Table 1. Catalytic Asymmetric Hydrogenation of **1a** with [RuCl(benzene)**L**]Cl[a]



1a **2a**

entry	L	ee (%)[b]
1	(*R*)-BINAP	73.0
2	(*S*)-SEGPhos	92.5
3	**L1**	94.5
4	**L2**	90.3
5	**L3**	95.2
6	**L4**	89.7

[a] All reactions were carried out under 150 psi of hydrogen with a substrate (1 mmol) concentration of 0.25 M in EtOH at 70 °C for 20 h. Substrate/[Ru(benzene)Cl_2]$_2$/ligand = 100/0.5/1.1, Conversion: 100%. [b] Ee values were determined by HPLC on a Chiralpak AD-H column.

It has been reported that catalytic additives play a crucial role in improving the reactivity and enantioselectivity of

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many asymmetric reactions.[4] Accordingly, we evaluated a number of additives for asymmetric hydrogenation of **1a** by using 1 mol % of Ru(II)-**L3** complex as catalyst and 3 mol % of the additive in an attempt to promote the enantioselectivity. As shown in Table 2, a series of sulfonic acids

Table 2. Optimization Studies of Catalytic Asymmetric Hydrogenation of **1a**[a]

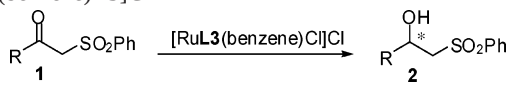
entry	additives	convn (%)	ee (%)[c]
1	CSA[d]	100	96.6
2	CF_3SO_3H	100	96.2
3	CH_3SO_3H	100	95.6
4	H_2SO_4	100	95.7
5	$TsOH·H_2O$	100	95.9
6	HCl aq	100	96.1
7	HBr aq	100	97.0
8	HI aq	100	98.9
9	K_2CO_3	23[b]	60.1
10	Et_3N	15[b]	27.6
11	I_2	100	99.2
12[e]	I_2	100	99.1
13[f]	I_2	90[b]	99.0

[a] All reactions were carried out under 150 psi of hydrogen with a substrate (1 mmol) concentration of 0.25 M in EtOH at 70 °C for 20 h. Substrate/[Ru(benzene)Cl_2]$_2$/**L3**/additives = 100/0.5/1.1/3.0. [b] Determined by ^{1}H NMR. [c] Ee values were determined by HPLC on a Chiralpak AD-H column. [d] Camphor sulfonic acid. [e] Methanol was used as solvent. [f] Isopropanol was used as solvent.

(Table 2, entries 1−5) slightly increased the ee values of the β-hydroxy sulfone **2a**. Aqueous HX also enhanced enantioselectivities in the following order: HCl aq (ee 96.1%, entry 6), HBr aq (ee 97.0%, entry 7), HI aq (ee 98.9%, entry 8). In contrast to acidic additives, the addition of organic or inorganic bases decreased both the enatioselectivities and conversion rates (entries 9 and 10). Interestingly, when iodine was applied to the asymmetric hydrogenation of β-ketosulfone **1a**, an unprecedentedly high enantioselectivity was obtained (ee 99.2%, entry 11). Similar results were obtained when methanol or isopropanol was employed as solvent, although a lower conversion of starting material was observed when isopropanol was employed (Table 2, entries 12 and 13).

Under the optimized reaction conditions, a variety of substrates were hydrogenated with use of [RuCl(benzene)-**L3**]Cl/I_2 as catalyst (Table 3). A series of β-keto sulfones bearing a different substituent at the para position on the phenyl group were studied (entries 2−6). The results show that the electron density of the aromatic ring has little effect on the enantioselectivities (ee 98.7−99.4%, entries 2−6), even *p*-methoxy (strong electron-donating substituent) substituted aryl β-keto sulfone (ee 98.2%, entry 6). When *m*-Cl was employed as the substrate, high enantioselectivity was also obtained comparable to those of the para-substituted substrates (98.3%, ee, entry 7). For the ortho-substituted β-keto sulfones, the hydrogenation results are depending on the substituents on the aromatic ring: for a noncoordinating ortho-substituted substrate, the ee drops slightly (ee 97.1%,

Table 3. The Asymmetric Hydrogenation of **1** with [RuCl(benzene)**L3**]Cl[a]



entry	R	ee (%)[b]
1	Ph (**1a**)	99.2
2	4-F-C_6H_4 (**1b**)	98.9
3	4-Cl-C_6H_4 (**1c**)	98.7[c]
4	4-Br-C_6H_4 (**1d**)	98.8[c]
5	4-Me-C_6H_4 (**1e**)	99.4
6	4-MeO-C_6H_4 (**1f**)	98.2
7	3-Cl-C_6H_4 (**1g**)	98.3
8	2-Me-C_6H_4 (**1h**)	97.1
9	2-Cl-C_6H_4 (**1i**)	89.8
10	Me (**1j**)	99.4
11	*i*-Pr (**1k**)	97.0
12	Cy (**1l**)	99.3
13[d]	Ph (**1a**)	99.1

[a] All the reactions were carried out under 150 psi of hydrogen gas with a substrate (1 mmol) concentration of 0.25 M in EtOH at 70 °C for 20 h. Substrate/[Ru(benzene)Cl_2]/**L3**/I_2 = 200/0.5/1.1/3.0. Conversion: 100%.[b] Ee values were determined by HPLC on a Chiralpak AD-H column. [c] Ee values were determined by HPLC on a Chiralcel OJ-H column. [d] S/C = 1000/1. Conversion: >95% (NMR).

entry 8); for a coordinating ortho-substituted substrate, the ee drops dramatically (ee 89.8%, entry 9).

Hydrogenation of an aliphatic analogue also gave excellent enatioselectivity (R = Me, ee 99.4%, entry 11), even for the more hindered carbonyl groups (R = *i*-Pr, ee 97.0%, entry 12 and R = Cy, ee 99.3%, entry 13).

When the substrate/catalyst ratio increased from 200 to 1000, the hydrogenation of **1a** still proceeded smoothly, keeping the enantioselectivity (ee 99.2%, entry 1, vs ee 99.1%, entry 13).

Several groups have recently applied iodine or iodide salts in Ir-catalyzed asymmetric hydrogenation.[4c,16] To our best knowledge, there has been no report on the effect of iodine on Ru-catalyzed reactions. To investigate the role of iodine in the hydrogenation reactions, we have run three experiements: first, we mixed [RuCl(cymene)**L3**]Cl with 3 equiv of iodine in the presence or absence of **1a** in EtOH under 150 psi of hydrogen gas at room temperature for 2 h, and we found that the purple-red color of both solutions disappeared; second, we dissolved substrate **1a** and 1 equiv of iodine in EtOH, and evaporated EtOH to afford an α-iodinated product 2-iodo-1-phenyl-2-(phenylsulfonyl)ethanone (**4a**); third, when we terminated the hydrogenation reaction of **4a** halfway, we noticed complete deiodation (^{1}H NMR

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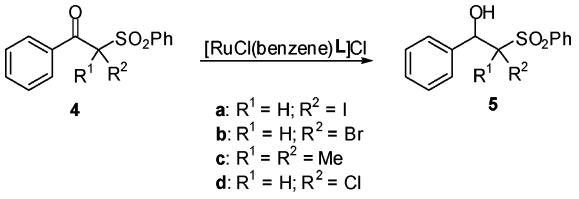
detection) prior to the complete conversion to the final compound. It is clear that the iodine or the iodated ketone was reduced to give hydrogen iodide under the hydrogenation conditions. So we further carried out a series of hydrogenation reactions to investigate the mechanism of the iodine effect. As shown in Table 4, asymmetric hydrogenation of **1a** with [RuI(cymene)**L3**]I as catalyst gave the same results as with [RuCl(benzene)**L3**]Cl as catalyst with or without the iodine (entries 1 and 2), revealing that the halogen atom bound to ruthenium has no obvious effect on the enantioselectivity. Asymmetric hydrogenation of **4a** yielded **2a** as the sole product with excellent enantioselectivity (ee 98.8% entry 3), comparable to asymmetric hydrogenation of **1a** with addition of iodine (ee 99.2%, Table 2, entry 11). Asymmetric hydrogenation of **1a** with **4a** as the additive also gave the same result as with the addition of iodine (ee 99.2%, entry 4), but NaI was found to exert no positive effect (ee 95.2%, entry 5). Hydrogenation of 2-bromo-1-phenyl-2-(phenylsulfonyl)ethanone (**4b**) also gave **2a** as the product of excellent enantioselectivity (ee 98.6%, entry 7). These results implicated the active role of hydroiodic acid generated in situ rather than I_2 itself. The Brønsted acids HX (X = I, Br) generated in situ promote the enatioselectivity and serve better than their aqueous conuterparts (X = I, Br, Cl; Table 2, entries 6, 7, and 8). The reaction of the α,α′-dimethylated β-ketosulfone, 2-methyl-1-phenyl-2-(phenylsulfonyl)propan-1-one (**4**c), proceeded equally well with or without additives (entry 7−9), indicating that the hydrogenation can occur in the keto form, if not exclusively.[17] Hydrogenation of 2-chloro-1-phenyl-2-(phenylsulfonyl)ethanone (**4d**) gave the mixture of **5d** (79%) and **2a** (21%) with moderate enatioselectivity (syn: 68.4% ee; anti: 89.3% ee) (entry 10).

Table 4. Effects of the Additives under Controlled Conditions[a]



entry	substrate	additives	product	ee (%)[b]
1[c]	**1a**	none	**2a**	95.3
2[c]	**1a**	I_2	**2a**	99.1
3	**4a**	none	**2a**	98.8
4	**1a**	**4a**	**2a**	99.2
5	**1a**	NaI	**2a**	95.2
6	**4b**	none	**2a**	98.6
7	**4c**	none	**5c**	98.2
8	**4c**	HI aq	**5c**	98.1
9	**4c**	I_2	**5c**	97.7
10	**4d**	none	**5d**, **2a**	68.4/89.3

[a] All the reactions were carried out under 150 psi of hydrogen gas with a substrate (1 mmol) concentration of 0.25 M in EtOH at 70 °C for 20 h. Substrate/[Ru(benzene)Cl_2]$_2$/**L3**/additives = 100/0.5/1.1/3.0. [b] Ee values were determined by HPLC on a Chiralpak AD-H column. [c] Substrate/[Ru(cymene)I_2]$_2$/**L3**/additives = 100/0.5/1.1/3.0.

In conclusion, we have developed a novel catalytic system for the enantioselective hydrogenation of a variety of β-keto sulfones using iodine as the additive; excellent enantioselectivity was obtained. Work is in progress to develop a deeper understanding into the mechanism and to apply this methodology to asymmetric hydrogenation of other prochiral ketones and olefins.

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Supporting Information Available: NMR and/or HPLC data of compounds **1**, **2**, **3**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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