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Highly Efficient Enantioselective Synthesis of Chiral Sulfones by Rh-Catalyzed Asymmetric Hydrogenation

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Asymmetric hydrogenation, *Unsaturated sulfones*, *Chiral sulfones*, *Rhodium catalysts*, *Enantioselectivity*, *f-spiroPhos.*

ABSTRACT: A highly efficient and enantioselective Rh-(*R*, *R*)-f-spiroPhos complex catalyzed hydrogenation of a series of unsaturated sulfones has been developed. With Rh-(*R*, *R*)-f-spiroPhos catalyst under mild conditions, not only the asymmetric hydrogenation of both the 3,3-diaryl and exocyclic α,β-unsaturated sulfones was first realized with up to 99.9% ee, but also 3-alkyl-3-aryl and benzo[*b*]thiophene 1,1-dioxides were successfully hydrogenated to the corresponding chiral sulfones with excellent enantioselectivities (up to 99.4% ee) regardless of the steric hindrance, electronic property and geometry of the substrates. Moreover, this reaction offers a route to (*S*)-(+)-*ar*-turmerone as a spice flavor, which is an important synthetic intermediate of pharmaceuticals.

1. INTRODUCTION

Chiral sulfones represent an important functional group prevalently found in many biologically active compounds and pharmaceutical intermediates to produce *ar*-turmerone,[1] (*R*)-curcuphenol,[1b] (*S*)-curcudiol,[1b] Remikiren,[2] *r*-secretase inhibitor,[3] and inflammatory cytokines inhibitor (Figure 1).[4] Sulfones serve as useful intermediates and can be converted into other chiral functional groups by alkylation, halogenation, oxidation, desulfonylation and Julia olefinations.[5]

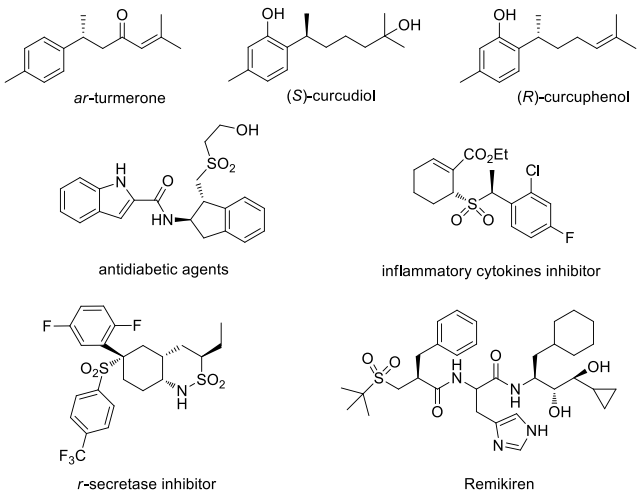


Figure 1. Key structural elements in chiral pharmaceuticals.

The synthesis of chiral sulfones has attracted increased attention due to their utility as intermediates. Previous reported methods for the synthesis of chiral sulfones have included asymmetric arylations/alkenylations of α-bromosulfones,[6] rhodium- and organo-catalyzed asymmetric conjugate addition to unsaturated sulfones,[7] asymmetric radical additions,[8] and asymmetric conjugate reduction of prochiral unsaturated sulfones.[9-11,13-16] Amongst the reported methods, metal-catalyzed asymmetric conjugate reduction of prochiral unsaturated sulfones is of interest as one of the most straightforward approaches for chiral sulfone synthesis. However, only a few efficient catalyst systems for the preparation of chiral sulfones have been reported so far.[10-11]

Catalytic asymmetric hydrogenation represents one of the most efficient, straightforward, and well-established approaches to chiral compounds.[12] To date, only a few examples of asymmetric hydrogenation of unsaturated sulfones have been reported.[13-17] Andersson and co-workers reported the efficient asymmetric hydrogenation of vinylic, allylic, homoallylic and cyclic sulfones catalyzed by a chiral Ir/N, P complex achieving good to high enantioselectivities.[13] Recently, Pfaltz and co-workers also developed two chiral iridium N, P-ligand complexes which exhibited good activity and enantioselectivity in the asymmetric hydrogenation of benzothiophene 1,1-dioxides. But only moderate to good enantioselectivities were achieved in the hydrogenation of the corresponding alkyl substituted substrates.[14] Zhang and co-workers developed Rh-catalyzed asymmetric hydrogenation of α-substituted vinyl sulfones and β-acetylamino acrylosulfones using DTBM-SegPhos and Tangphos, respectively, achieving high enantioselectivities for the (*Z*)-β-acetylamino acrylosulfones.[15, 16] But (*E*)-substrates only provided low to moderate enantioselectivities. Thus, the substrate scope of the asymmetric hydrogenation of sulfones remains limited.

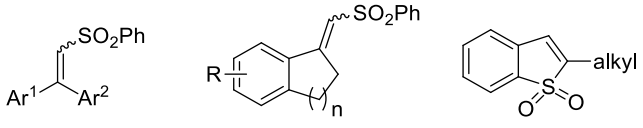


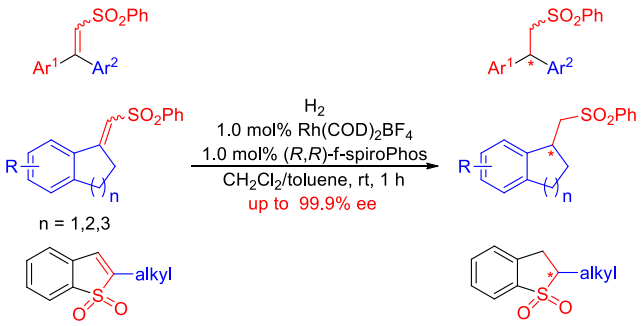
Figure 2. Some challenging substrates of unsaturated sulfones.

Representative challenging sulfone containing moieties for asymmetric hydrogenation are shown in Figure 2. The following sterically hindered substrates including 3,3-diaryl unsaturated sulfones and the cyclic unsaturated sulfones have so far

remain unexplored as substrates for asymmetric hydrogenation. It is not surprising because the bigger aromatic system and the bulkier steric hindrance in the substrates results in their inertness, which requires much higher catalytic activity. So far only a few successful examples of asymmetric hydrogenation of the substrates bearing diaryl substituents at the stereogenic center were reported.[18] In addition, most of present catalysts are only efficient for either of two isomers of unsaturated sulfones. Therefore, the development of efficient catalysts for asymmetric hydrogenation of unsaturated sulfones to afford chiral sulfones is still highly desirable.

Recently, we prepared and demonstrated the chiral diphosphine ligand, f-spiroPhos, containing the 1,1′-spirobiindane skeleton, as a highly efficient and enantioselective ligand in the hydrogenation of various substrates including unsaturated nitriles, carboxylic acids and imines.[19] Encouraged by the previous work, we decide to attempt to tackle the asymmetric hydrogenation of these challenging unsaturated sulfones. We herein report the first example of highly enantioselective Rh-catalyzed hydrogenation of 3,3-diaryl and exocyclic unsaturated sulfones with up to 99.9% ee. The reaction also showed high substrate scope, *E*- and *Z*-isomers of a wide range of substrates including 3,3-diaryl, 3-alkyl-3-aryl, exocyclic α, β-unsaturated sulfones and benzo[*b*]thiophene 1,1-dioxide can also be hydrogenated with excellent enantioselectivities under mild reaction conditions (Scheme 1).

Scheme 1



2. RESULTS AND DISCUSSION

2.1. Asymmetric Hydrogenation of Diaryl α,β-Unsaturated Sulfones.

Our initial investigation began with the hydrogenation of (*E*)-1-chloro-3-(1-phenyl-2-(phenylsulfonyl)vinyl)benzene **1a** as the model substrate under 80 atm of H_2 in CH_2Cl_2 at room temperature using 1.0 mol% the complex of $[Rh(COD)_2]BF_4$ and (*R*, *R*)-f-spiroPhos. Although only a moderate conversion was provided, a high enantioselectivity was achieved, 96% ee (Table 1, entry 1). To increase substrate conversion, we subsequently investigated the solvent effect. The role of solvent was found to play an important role in the asymmetric hydrogenation of chiral sulfones. Poor conversion was observed in most of the solvents such as MeOH, THF, DCE and 1,4-dioxane, (Table 1, entries 2–5). To our delight, performing reactions in toluene as the solvent, complete conversion and high enantioselectivity (98% ee) was achieved (Table 1, entry 6). Following solvent optimization, a screening of commercially available chiral phosphorus ligands (Figure 3) revealed that (*S*)-BINAP, electron-rich (*R*)-JosiPhos, (*S*, *S*)-Me-Duphos and (*R*, *R*)-Ph-BPE were ineffective in this transformation and only trace products were afforded (Table 1, entries 7–10). (*S*, *S*)-f-Binaphane gave higher conversion (29%) and ee value (68%). Thus demonstrating that the rigidity and bulkier steric hindrance of the spiro-backbone in f-spiroPhos had a significant positive effect on the conversion and enantioselectivity in this hydrogenation.

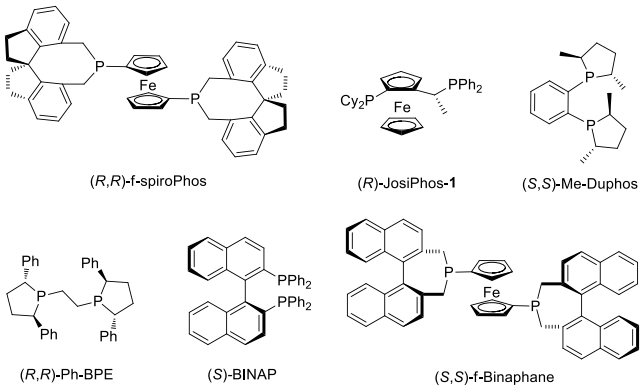
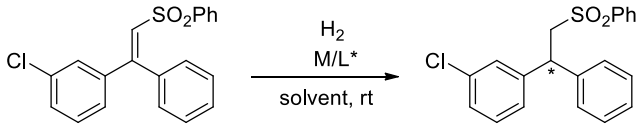


Figure 3. Structures of the phosphine ligands for hydrogenation of (*E*)-1-chloro-3-(1-phenyl-2-(phenylsulfonyl)vinyl)benzene **1a**.

Table 1. Asymmetric Hydrogenation of (*E*)-1-chloro-3-(1-phenyl-2-(phenylsulfonyl)vinyl)benzene 1a.[a]



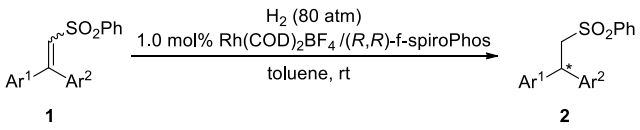
entry	ligand	solvent	conv.(%)[b]	ee(%)[c]
1	(*R*, *R*)-f-spiroPhos	CH_2Cl_2	60	96
2	(*R*, *R*)-f-spiroPhos	MeOH	5	ND
3	(*R*, *R*)-f-spiroPhos	THF	3	ND
4	(*R*, *R*)-f-spiroPhos	DCE	6	ND
5	(*R*, *R*)-f-spiroPhos	dioxane	3	ND
6	(*R*, *R*)-f-spiroPhos	toluene	99	98
7	(*R*)-BINAP	toluene	0.5	ND
8	(*R*)-JosiPhos-1	toluene	2	ND
9	(*R*, *R*)-Me-Duphos	toluene	1	ND
10	(*R*, *R*)-Ph-BPE	toluene	1	ND
11	(*S*, *S*)-f-Binaphane	toluene	29	68

[a] Reaction conditions: $Rh(COD)_2BF_4$/ligand/substrate ratio = 1.0 : 1.1 : 100, 80 atm H_2, 24 h, rt. [b] Determined by GC analysis. [c] Determined by chiral SFC using a chiral stationary phase Lux 5u Cellulose-3 (250 × 4.60 mm), MeOH : CO_2 = 30 : 70, 3.0 mL/min, 210 nm.

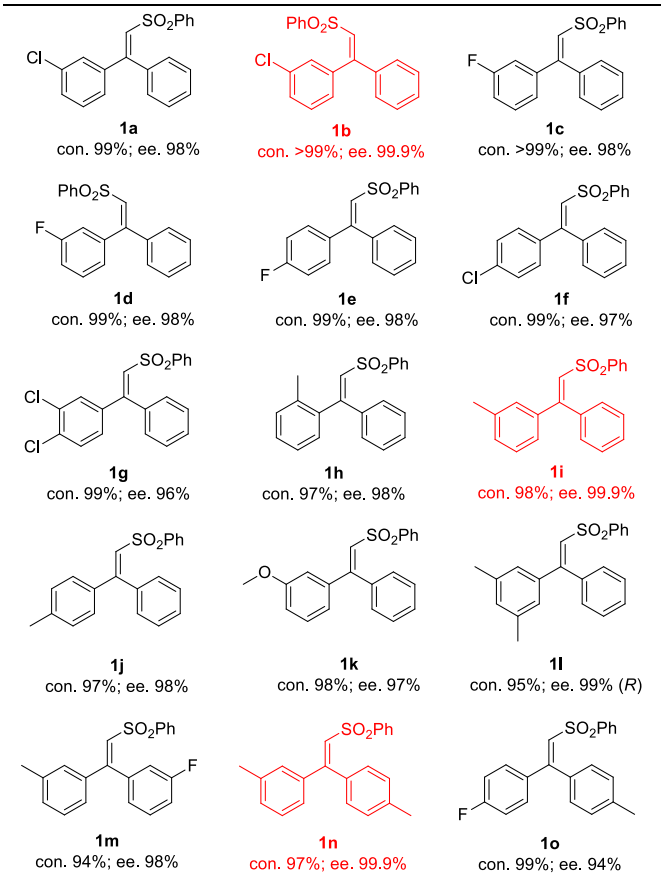
Encouraged by the promising results obtained by the asymmetric hydrogenation of (*E*)-1-chloro-3-(1-phenyl-2-(phenylsulfonyl)vinyl)benzene **1a**, we then prepared a variety of 3,3-diaryl unsaturated sulfones **1** and applied them to the hydrogenation in toluene under the catalyst loading of 1.0 mol% $[Rh(COD)_2]BF_4$/(*R*, *R*)-f-spiroPhos and 80 atm H_2 (Table 2). All of the substrates examined (**1a** – **1o**) could be successfully hydrogenated to produce the corresponding chiral sulfones in

high yields with excellent enantioselectivities, 94 – 99.9% ee. Neither the electron property nor position of the substituents at the two aryl rings of the substrates had an apparent effect on the enantioselectivity. In general, the substrates with electron-donating substituents including Me, MeO group exhibited relatively lower reactivity compared with those bearing electron-withdrawing substituents. For instance, the fluro- or chloro-substituted substrates **1a** – **1g** were hydrogenated in full conversions with 96 – 99.9% ee, while the substrates bearing electron-donating substituents Me, MeO **1h** – **1l** provided 94 – 97% conversions. Notably, even if the substrate contained the same substituent present at different position of the two phenyl ring (*i.e meta* and *para*), excellent enantioselectivity was achieved. This is shown in the following example (substrates **1i** and **1n**) substituted by a methyl group at *meta*-position of one phenyl ring or both *meta*- and *para*-position of the two phenyl rings respectively provided the highest enantioselectivity, 99.9% ee. Remarkably, this catalyst could also exhibited the comparable activity and enantioselectivity in the hydrogenation of the corresponding (*Z*)-isomers to afford the products with an opposite absolute configuration compared with that obtained by (*E*)-isomers. For example, the substrates (*Z*)-**1b** and (*Z*)-**1d** were hydrogenated providing the desired products **2b** and **2d** with 99.9% and 98% ee respectively. It was found that the (*Z*)-substrates provided the hydrogenation products with an opposite absolute configuration compared with that afforded by (*E*)-isomers by comparison with the sign of the specific rotation and order of elution for major and minor enantiomers from the chiral column. The absolute configuration of hydrogenation product **2l** was determined and assigned to be (*R*) configuration by X-ray crystallographic analysis of the corresponding single-crystal structure (Figure 4). It was demonstrated that this method could produce chiral sulfones with either desired configuration, (*S*) or (*R*)-enantiomer in excellent enantioselectivities by the asymmetric hydrogenation of (*E*)- or (*Z*)-α,β-unsaturated sulfones.

Table 2. Rh-Catalyzed Asymmetric Hydrogenation of 3,3-Diaryl α,β-Unsaturated Sulfones 1.[a]



1 **2**



[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(COD)_2]BF_4$/(*R*,*R*)-f-spiroPhos/substrate ratio of 1.0 : 1.1 : 100, toluene, 80 atm H_2, rt, 24 h. The conversion was determined by ^1H NMR spectroscopy or GC analysis; the enantioselectivity was determined by SFC analysis using a chiral stationary phase.

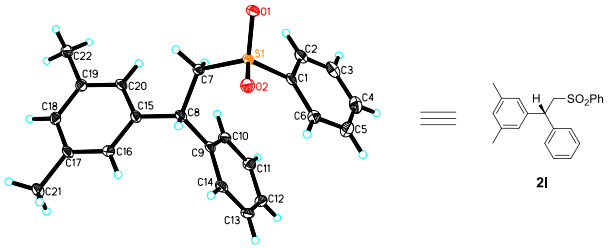


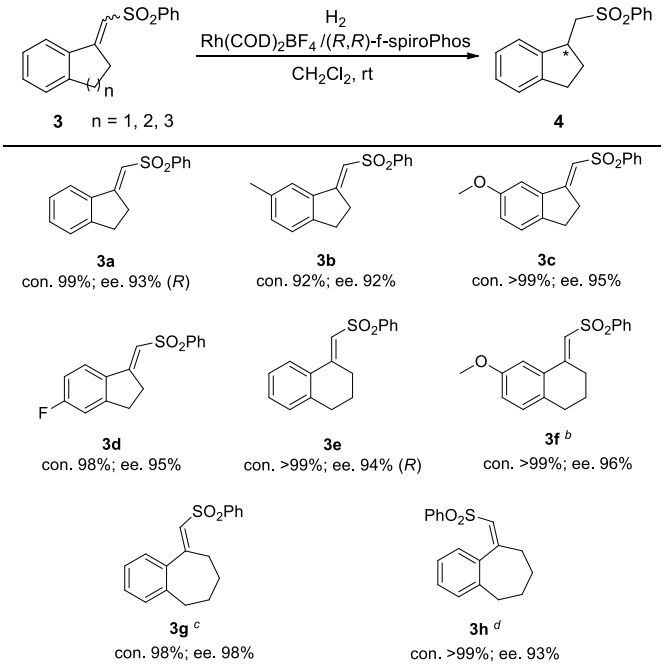
Figure 4. X-ray crystal structure of the product (*R*)-**2l**.

2.2. Asymmetric Hydrogenation of Cyclic α,β-Unsaturated Sulfones.

Previously, Charette and co-workers reported the copper-DuPhos(O) catalyzed enantioselective hydrosilylation of vinyl phenyl sulfones including two cyclic sulfones and achieved excellent enantioselectivities.[11] Surprisingly, the asymmetric hydrogenation of cyclic unsaturated sulfones (substrate **3)** has not been reported. To develop the asymmetric hydrogenation of this class of substrates and extend the substrate scope of the catalyst, we decided to evaluated the cyclic α,β-unsaturated sulfone **3a** under the previously optimized reaction conditions

in the hydrogenation of 3,3-diaryl α, β-unsaturated sulfones **1**, a conversion of 76% conversion and 90% ee was obtained. After further solvent optimization, dichloromethane was found to result in full conversion and better enantioselectivity (93% ee). Lowering the hydrogen pressure from 80 atm to 10 atm still resulted in complete substrate conversion while preserving high enantioselectivity. The effect of different electronic substitutes on the ring was investigated and all resulted in full conversions and excellent enantioselectivities (> 92% ee). It was revealed that ring size in the substrates (*i.e.* cyclopentyl, cyclohexyl or cycloheptyl) had no apparent influence on the enantioselectivity (substrates **3a** – **3h**) and excellent enantioselectivities were observed. However, the reactivity was affected by the ring size of substrates. The substrates with five-membered ring **3a** – **3d** could be hydrogenated to obtain the corresponding products in satisfactory conversions under 10 atm of H_2 at room temperature for 1 h, whereas the substrate with a six- or seven-membered ring required higher catalyst loadings and increased hydrogen pressure for complete conversion. The substrate (*E*)-**3f** could be fully hydrogenated under 80 atm of hydrogen pressure in 24 h, while (*E*)-**3g** with a seven-membered ring required 2 mol% catalyst loading. The catalyst system was also suitable for the (*Z*) isomer of the cyclic unsaturated sulfones, such as the (*Z*)-**3h**, providing the corresponding product **4h** with excellent enantioselectivities (93% ee), with a reversal of the absolute configuration as discussed above.

Table 3. Rh-Catalyzed Asymmetric Hydrogenation of Cyclic α,β-Unsaturated Sulfones 3.[a]

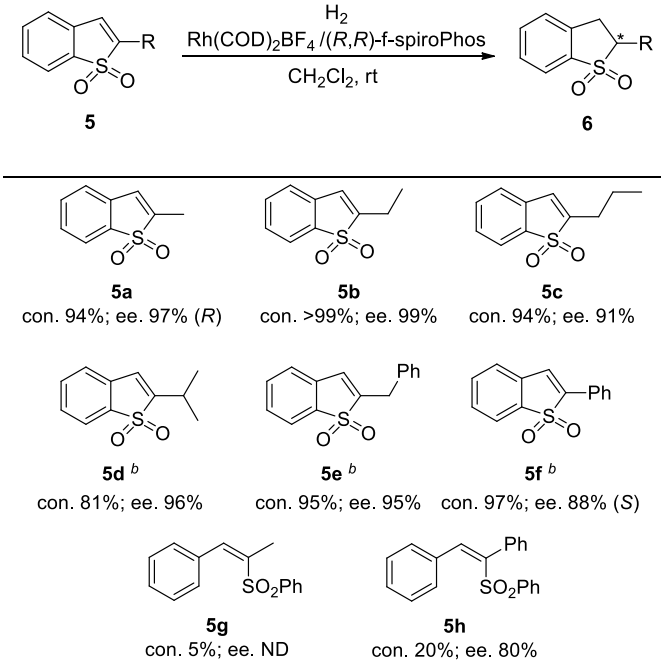


[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(COD)_2]BF_4$/(*R*,*R*)-f-spiroPhos/substrate ratio of 1.0 : 1.1 : 100, CH_2Cl_2, 10 atm H_2, rt, 1 h. The conversion was determined by ^1H NMR spectroscopy; the enantioselectivity was determined by HPLC analysis using a chiral stationary. [b] 80 atm H_2, 24 h. [c] $[Rh(COD)_2]BF_4$ (2.0 mol%), 80 atm H_2, 24 h. [d] $[Rh(COD)_2]BF_4$ (3 mol%), 80 atm H_2, 24 h.

2.3. Asymmetric Hydrogenation of Benzo[*b*]thiophene 1,1-dioxides.

Recently, Pfaltz's group reported Ir-P, N complex catalyzed asymmetric hydrogenation of benzo[*b*]thiophene 1,1-dioxides, and the 2- and 3-aryl substituted substrates were hydrogenated with high conversions and excellent enantioselectivities (up to 99% ee).[14] However, poor conversions or moderate to good enantioselectivities were observed for the 2-alkyl substituted substrates. The application of the catalyst/ligand investigated reported herein, Rh-(*R*, *R*)-f-spiroPhos, for the hydrogenation of 2-alkyl-substituted benzo[*b*]thiophene 1,1-dioxides yielded excellent enantioselectivities (up to 99% ee) for a wide range of 2-alkyl-substituted substrates **5** (Table 4). The 2-methyl-, 2-ethyl- and 2-*n*propyl-substituted substrates **5a** – **5c** were hydrogenated under 10 atm hydrogen pressure in an hour to provide the products with high enantioselectivities and conversions. Replacing the alkyl substituent at 2-position with an isopropyl group ((*E*)-**5d**) still maintained the excellent enantioselectivity of 96% ee, but led to a decreased conversion to 81%, and was attributed to the increased steric hindrance. The 2-phenyl substituted substrate (*E*)-**5f** also exhibited lower reactivity but higher hydrogen pressure and longer reaction time for the satisfactory conversion were required. Inspired by these exciting results obtained by this cyclic substrates, we also investigated the hydrogenation of linear α-methyl or phenyl substituted substrate **5g** and **5h**, but very poor conversions (5% and 20% conversion, respectively) were observed.

Table 4. Rh-Catalyzed Asymmetric Hydrogenation of Benzo[*b*]thiophene 1,1-Dioxides 5.[a]



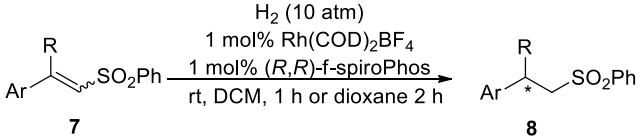
[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(COD)_2]BF_4$/(*R*,*R*)-f-spiroPhos/substrate ratio of 1.0 : 1.1 : 100, CH_2Cl_2, 10 atm H_2, rt, 1 h. The conversion was determined by ^1H NMR spectroscopy; the enantioselectivity was determined by HPLC analysis using a chiral stationary. [b] 80 atm H_2, 24 h.

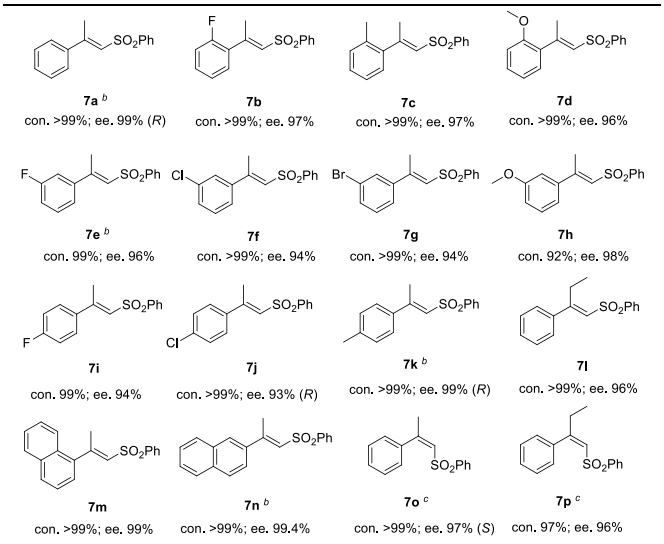
2.4. Asymmetric Hydrogenation of 3-Alkyl-3-aryl α,β-Unsaturated Sulfones.

Finally, we turned our attention to the asymmetric hydrogenation of 3-alkyl-3-aryl α,β-unsaturated sulfones. Initially, we chose (*E*)-((2-phenylprop-1-en-1-yl)sulfonyl)benzene **7a** as the model substrate under 80 atm of H_2 in CH_2Cl_2. Both full conversion and high enantioselectivity of 94% ee were obtained. For comparison, other electron-rich ligands including (*R*)-JosiPhos-1, (*S, S*)-Me-Duphos, (*R, R*)-Ph-BPE and (*S, S*)-f-Binaphane were also evaluated, but only poor conversions and enantioselectivities were obtained except the ligand (*S,S*)-f-Binaphane achieving relatively better results, 71% conversion and 77% ee.[20] As shown above, the hydrogen pressure can be lowered to 10 atm without any deleterious effects on enantioselectivity or reaction time (1 hour). Further lowering the hydrogen pressure to 5 atm, high conversion (97%) and high enantioselectivity were achieved. In addition to CH_2Cl_2, 1,4-dioxane was also proved as the suitable solvent for this hydrogenation and an extremely high enantioselectivity of 99% ee with full conversion could be achieved.

It was revealed that a variety of (*E*)-3-alkyl-3-aryl α,β-unsaturated sulfones **7** could be successfully hydrogenated to produce the corresponding chiral sulfones with 93 – 99.4% ee (Table 5) using the catalyst system. The electron property and position of the substituents at the phenyl ring of the substrates had no obvious influence on both the reactivity and enantioselectivity. Generally, the substrates with electron-donating substituents on the phenyl ring gave higher enantioselectivities than those with electron-withdrawing substituents. For example, the substrate (*E*)-**7i** and (*E*)-**7j** with a *para*-fluoro or chloro substituent gave 93 – 94% ee, while the substrate (*E*)-**7k** with a *para*-methyl substituent yielded **8k** with as high as 99% ee. The substrates with a larger 3-alkyl substituent such as ethyl group ((*E*)-**7l**) could also give comparable enantioselectivity with substrate (*E*)-**7a**. Both the 1-naphthyl substrate (*E*)-**7m** and 2-naphthyl (*E*)-**7n** exhibited higher enantioselectivity, and (*E*)-**7n** provided product **8n** with the highest 99.4% ee value. The hydrogenation of the (*Z*)-isomers such as the substrates (*Z*)-**7o** and (*Z*)-**7p** could also be performed smoothly providing the desired products **8o** and **8p** with 97% and 96% ee respectively, which was the highest enantioselectivity in the hydrogenation of the (*Z*)-isomers of 3-alkyl-3-aryl α,β-unsaturated sulfones so far. It was also found that the products obtained by the (*E*)- and (*Z*)-isomers were opposite enantiomers.

Table 5. Rh-Catalyzed Asymmetric Hydrogenation of (*E*)-3-alkyl-3-aryl α,β-Unsaturated Sulfones 7.[a]





[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(COD)_2]BF_4$/(*R,R*)-f-spiroPhos/substrate ratio of 1.0 : 1.1 : 100, CH_2Cl_2, 10 atm H_2, rt, 1 h. The conversion was determined by ^1H NMR spectroscopy or GC analysis; the enantioselectivity was determined by HPLC analysis using a chiral stationary phase. [b] 10 atm H_2, 2 h, 1,4-dioxane. [c] $Rh(COD)_2PF_6$ (2 mol%), 80 atm H_2, 24 h.

2.5. Preparative Asymmetric Hydrogenation on a Larger Scale of Unsaturated Sulfones.

Under the optimal reaction conditions, we carried out the preparative hydrogenation of the following substrates in Figure 5 on a large scale (1.0 mmol). The desired products were obtained with maintained high conversions and excellent enantioselectivities.

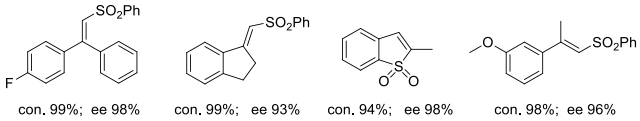
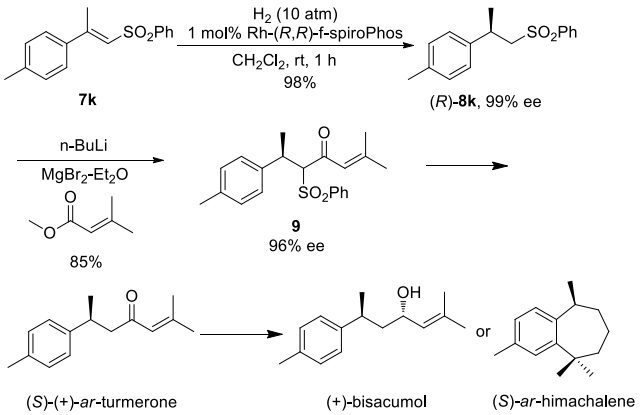


Figure 5. Substrates evaluated on a large scale.

2.6. Application of the Rh-(*R,R*)-f-spiroPhos Catalyst to the Synthesis of Biologically Active Compounds and Pharmaceuticals.

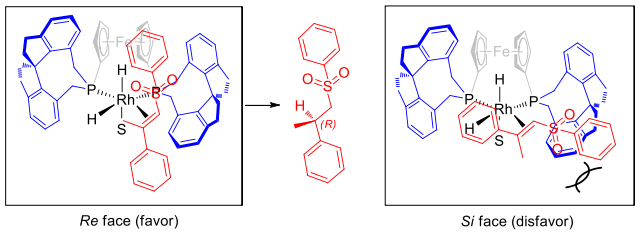
The optical active chiral sulfones are versatile synthetic intermediates that can be easily converted to various derivatives. To illustrate this point, we performed a short synthesis of the precursor of (*S*)-(+)-*ar*-turmerone and (+)-bisacumol (Scheme 2). Product (*R*)-**8k** obtained by asymmetric hydrogenation could be transformed by acylation reaction with 3,3-dimethylacrylic acid methyl ester and $MgBr_2$-Et_2O to the intermediate **9**. In the following step, intermediate **9** was converted to (*S*)-(+)-*ar*-turmerone as a spice flavor of turmeric. (*S*)-(+)-*ar*-turmerone could also be used to the asymmetric synthesis of (*S*)-*ar*-himachalene, which is a pheromone component of the flea beetle and (+)-bisacumol, as a member of the aromatic bisabolane sesquiterpene family isolated from the rhizome of Curcuma Xanthorrhiza.[1b]

Scheme 2



Based on the configurations of hydrogenation products and the reported mechanism of rhodium and iridium catalyzed asymmetric hydrogenation reactions,[21] we proposed the transition model determining the enantioselectivity (Scheme 3). The ferrocenyl group of the ligand blocked one side of the complex and prevented the coordination of the substrate from this orientation. The substrate could only coordinate with rhodium from the opposing face of the catalyst. The repulsive steric interaction of the ligand with the larger sulfonyl group led to the coordination of the (*E*)-substrate with rhodium more favorable from the *Re*-face than *Si*-face of the α, β-unsaturated sulfones, predictably resulting in the (*R*) product. By X-ray crystallographic analysis of the corresponding single-crystal structure or comparison with the sign of the specific rotation reported, the stereochemistry of some other products was determined. It was demonstrated to be in good agreement with the predicted stereochemical outcome of the hydrogenation products.

Scheme 3. Proposed enantio-determining transition model for Rh-catalyzed asymmetric hydrogenation of α,β-unsaturated sulfones.



CONCLUSION

In conclusion, we have developed a highly efficient method for enantioselective synthesis of various optical active chiral sulfones. By employing a Rh-(*R*,*R*)-f-spiroPhos complex, a wide range of α,β-unsaturated sulfones including the (*E*)- and (*Z*)-isomers of 3,3-diaryl, cyclic, 3-alkyl-3-aryl α,β-unsaturated sulfones as well as 2-alkyl substituted benzo[*b*]thiophene 1,1-dioxides were successfully hydrogenated to the corresponding chiral sulfones with excellent enantioselectivities (up to 99.9% ee). Hydrogen pressure can be as low as 10 atm in certain cases with reactions completion in an hour. Moreover, this method was also applied to the asymmetric synthesis of a spice flavor, (*S*)-(+)-*ar*-turmerone, an important synthetic intermediate of pharmaceuticals. We envision in this method to allow for the broad screening of chiral sulfones for a wide variety of industries including pharmaceuticals, pesticides or chiral polymers.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization data, analysis of enantioselectivities of products and crystal parameters for compound **2l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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SYNOPSIS TOC