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Rh-Catalyzed Asymmetric Hydrogenation of α-Substituted Vinyl Sulfones: An Efficient Approach to Chiral Sulfones

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Supporting Information

ABSTRACT: Rh/(*S*)-(+)-DTBM-Segphos complex catalyzed asymmetric hydrogenation of α-substituted vinyl sulfones has been achieved, furnishing the desired products in high yields and excellent enantioselectivities (>90% yield, up to 99% ee). This method provided an efficient approach to α-substituted chiral sulfones under mild conditions and has potential applications in organic synthesis.

The chiral sulfones have been identified as valuable molecules that play an important role in organic synthesis.[1] For example, sulfones can be readily transformed to acids,[2] alcohols,[3] carbohydrate derivatives,[4] and other functionalized compounds.[5] In addition, chiral sulfones display interesting biological properties as HIV-1 protease inhibitors,[6] protein tyrosine phosphatase inhibitors,[7] γ-secretase inhibitors,[8] and antisepsis agents.[9] Therefore, great efforts have been devoted to the development of new methodologies for the synthesis of chiral sulfones. Among them, the representative methods include Ni-catalyzed Negishi arylations and alkenylations of α-bromosulfones,[10] Rh-catalyzed asymmetric conjugate addition to unsaturated sulfones,[11] asymmetric Michael addition of nucleophiles to vinyl sulfones employing organocatalysts,[12] asymmetric catalytic radical additions,[13] asymmetric hydrogenation of functionalized sulfones,[14] and others.[15] However, most of the reported approaches are focused on the synthesis of β-substituted chiral sulfones; α-substituted chiral sulfones, an important chiral motif found in biologically active molecules and drugs (Figure 1a), received far less attention than β-substituted chiral sulfones. In fact, very few synthetic routes to α-substituted chiral sulfones have been reported.

In the past decades, transition-metal-catalyzed asymmetric hydrogenation has become a powerful route to chiral compounds.[16,17] In this context, asymmetric hydrogenation of β-ketosulfones,[14a] β-amido acrylosulfones,[14d] and vinyl/allyl/homoallylic sulfones[14b,c] have been reported by several groups, and excellent enantioselectivities have been achieved (Figure 1b). However, the chiral center of these products is far away from the sulfone groups. Highly enantioselective synthesis of chiral α-substituted sulfones via asymmetric hydrogenation is rarely reported. *Herein, we disclose an efficient approach to synthesize α-substituted chiral sulfones through Rh-catalyzed asymmetric hydrogenation of α-substituted vinyl sulfones* (Figure 1c).

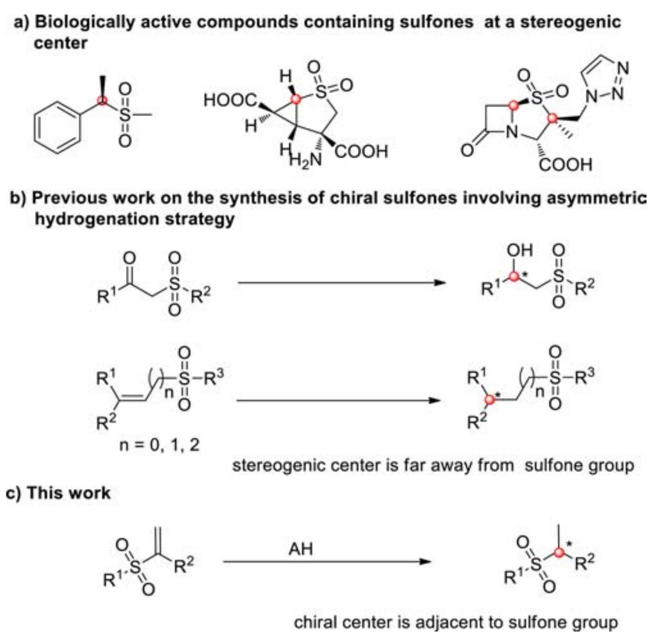

Figure 1. Examples of biologically active compounds containing chiral sulfone scaffolds and the synthesis of chiral sulfones involving asymmetric hydrogenation strategy.

Initially, α-Ts-substituted styrene **1a** was selected as a model substrate to optimize the reaction conditions. A variety of diphosphine ligands were examined (Figure 2), and the results are summarized in Table 1. When P-chiral ligands, such as Me-DuPhos, Binapine, and TangPhos, were employed in this reaction, all of them exhibited excellent activity and gave the product with high yields, albeit with poor to moderate

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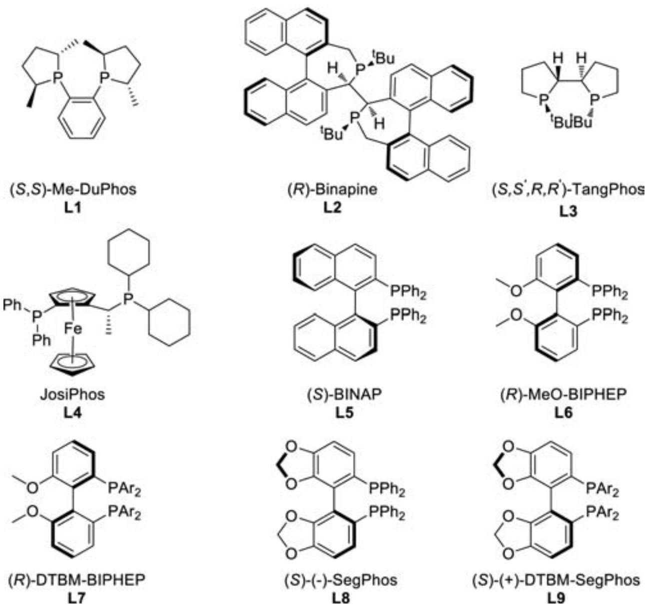
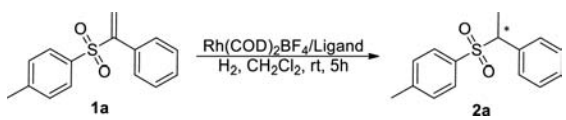


Figure 2. Ligands screening in Rh-catalyzed hydrogenation of **1a**.

Table 1. Ligand Screening for Rh-Catalyzed Asymmetric Hydrogenation of 1a[a]



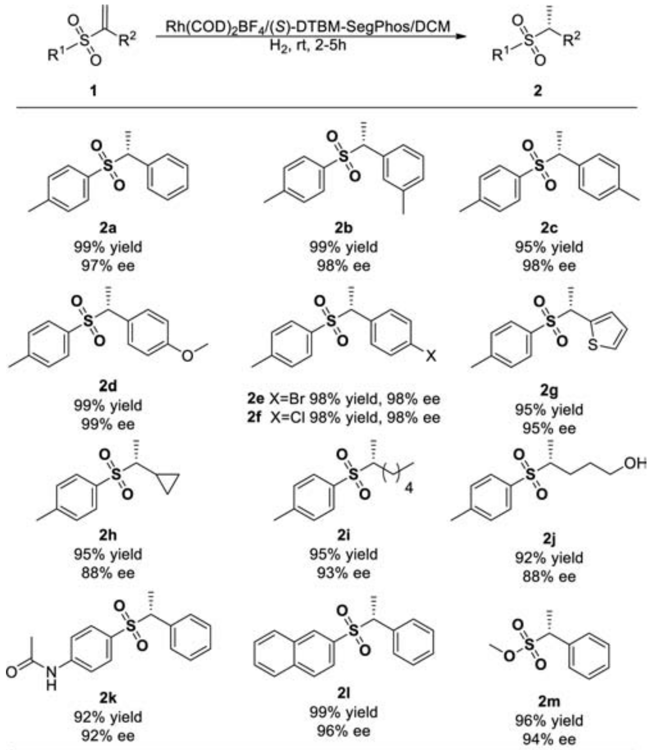
entry	ligand	solvent	yield[b] (%)	ee[c] (%)
1	**L1**	DCM	98	15
2	**L2**	DCM	99	65
3	**L3**	DCM	99	20
4	**L4**	DCM	99	27
5	**L5**	DCM	95	93
6	**L6**	DCM	95	94
7	**L7**	DCM	97	95
8	**L8**	DCM	99	93
9	**L9**	DCM	99	97
10	**L9**	MeOH	trace	
11	**L9**	THF	trace	
12	**L9**	1,4-dioxane	trace	
13	**L9**	CF_3CH_2OH	trace	
14	**L9**	CH_3CN	trace	

[a]Unless otherwise noted, all reactions were carried out with a $Rh(COD)_2BF_4$/ligand/substrate(0.1 mmol) ratio of 1:1.1:100 in 1.5 mL of solvent at room temperature under H_2 (10 bar) for 5 h. [b]Yield of purified product. [c]Determined by HPLC analysis using a chiral stationary phase.

enantioselectivities (Table 1, entries 1−3). Josiphos, a typical planar chiral ligand, also afforded excellent yield but with a poor ee (Table 1, entry 4). To our delight, excellent yield and enantioselectivity were obtained when (*S*)-BINAP was used as the ligand (Table 1, entry 5). Therefore, a series of chiral biphosphine ligands with axial chirality were screened to further improve the yield and enantioselectivity. It was found that substrate **1a** can be hydrogenated smoothly by Rh/(*S*)-(+)-DTBM-SegPhos complex, affording the desired product with the best yield and ee (Table 1, entry 9). Subsequently, the exploration of various solvents showed that DCM is the best solvent for this reaction.

The substrate scope of asymmetric hydrogenation of *α*-substituted vinyl sulfones was investigated under the optimal reaction conditions. As shown in Scheme 1, this reaction

Scheme 1. Rh-Catalyzed Asymmetric Hydrogenation of *α*-Substituted Vinyl Sulfones[a]



[a]Unless otherwise noted, all reactions were carried out with a $Rh(COD)_2BF_4$/ligand/substrate(0.1 mmol) ratio of 1:1.1:100 in 1.5 mL DCM at room temperature under H_2 (10 bar) for 2−5 h. Isolated yields. Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

exhibited good substrate tolerance. When R^2 was substituted with different aryl groups, *α*-substituted vinyl sulfones were efficiently hydrogenated and gave the desired products with excellent yields (>95%) and enantioselectivities (97−99% ee, Scheme 1, **2a**−**f**) regardless of whether the substituents on the phenyl ring were electron donating (Scheme 1, **2b**−**d**) or electron withdrawing (Scheme 1, **2e** and **2f**). Moreover, the substitution positions on the phenyl ring did not influence the reaction activity and enantioselectivity (Scheme 1, **2b** and **2c**). Heteroaromatic groups, such as *α*-thienyl vinyl sulfone, were also well tolerated in this reaction (Scheme 1, **2g**). Excellent yields and good enantioselectivities were obtained when R^2 was replaced by alkyl groups (>90% yields, 88−95% ee; Scheme 1, **2h**−**j**). In addition, when R^1 was changed to a *p*-acetamidophenyl or 2-naphthalenyl group, this reaction also worked smoothly. It is worth noting that *α*-substituted sulfonate **1m** was a good substrate for this reaction and afforded chiral sulfonic acid esters with 96% yield and 94% ee, which can be readily transferred to chiral phenylethanesulfonic acid ((−)-PES), an efficient resolving agent for the optical resolution of DL-leucine.[18]

To further illustrate the potential utility of this method, the asymmetric hydrogenation of *α*-Ts substituted styrene **1a** was carried out on a 0.88 g scale with 0.3% catalyst loading,

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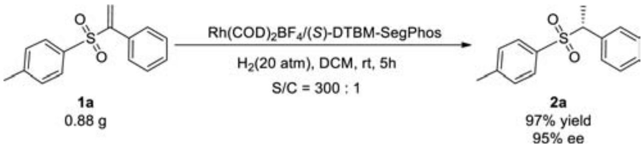
furnishing the desired product with 97% yield and 95% ee (Scheme 2).

Scheme 2. Gram-Scale Reaction for AH of 1a



In summary, we have developed an efficient strategy for highly enantioselective synthesis of α-substituted chiral sulfones through Rh-catalyzed asymmetric hydrogenation. This reaction features high reaction activity (>90% yield), excellent enantioselectivity (up to 99% ee), wide substrate scope, mild reaction conditions, and simple operation. It can serve as a practical method for the synthesis of chiral sulfones. Studies on the substrate scope of this reaction and it applications in organic synthesis are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03845.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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