Rh-Catalyzed Asymmetric Hydrogenation of $\alpha$-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 $\alpha$-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 $\alpha$-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. For example, sulfones can be readily transformed to acids, alcohols, carbohydrate derivatives, and other functionalized compounds. In addition, chiral sulfones display interesting biological properties as HIV-1 protease inhibitors, protein tyrosine phosphatase inhibitors, $\gamma$-secretase inhibitors, and antiseptic agents. 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 $\alpha$-bromosulfones, Rh-catalyzed asymmetric conjugate addition to unsaturated sulfones, asymmetric Michael addition of nucleophiles to vinyl sulfones employing organocatalysts, asymmetric catalytic radical additions, asymmetric hydrogenation of functionalized sulfones, and others. However, most of the reported approaches are focused on the synthesis of $\beta$-substituted chiral sulfones; $\alpha$-substituted chiral sulfones, an important chiral motif found in biologically active molecules and drugs (Figure 1a), received far less attention than $\beta$-substituted chiral sulfones. In fact, very few synthetic routes to $\alpha$-substituted chiral sulfones have been reported.

In the past decades, transition-metal-catalyzed asymmetric hydrogenation has become a powerful route to chiral compounds. In this context, asymmetric hydrogenation of $\beta$-ketosulfones, $\beta$-amido acrylosulfones, and vinyl/allyl/homoallylic sulfones 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 $\alpha$-substituted sulfones via asymmetric hydrogenation is rarely reported. Herein, we disclose an efficient approach to synthesize $\alpha$-substituted chiral sulfones through Rh-catalyzed asymmetric hydrogenation of $\alpha$-substituted vinyl sulfones (Figure 1c).

Initially, $\alpha$-Ts-substituted styrene 1a was selected as a model substrate to optimize the reaction conditions. A variety of diphenylphosphine 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...
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,S′,R,R)-TangPhos 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 exhibited good substrate tolerance. When R² 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). 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 R² was replaced by alkyl groups (>90% yields, 88−95% ee; Scheme 1, 2h−j). In addition, when R¹ 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.
furnishing the desired product with 97% yield and 95% ee (Scheme 2).

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 its applications in organic synthesis are underway in our laboratory.

**REFERENCES**


The Absolute configuration of compound 2m was confirmed to be R by comparison with literature data (for R-2m in ref 18: $\alpha$D 2m = 25.6 (c = 1.0, CHCl3, 98% ee); our experiment result for 2m: $\alpha$D 2m = 22.0 (c = 1.0, CHCl3, 94% ee)). All of the other configurations are uncertain and based on the assumption that the configuration follows that of 2m.