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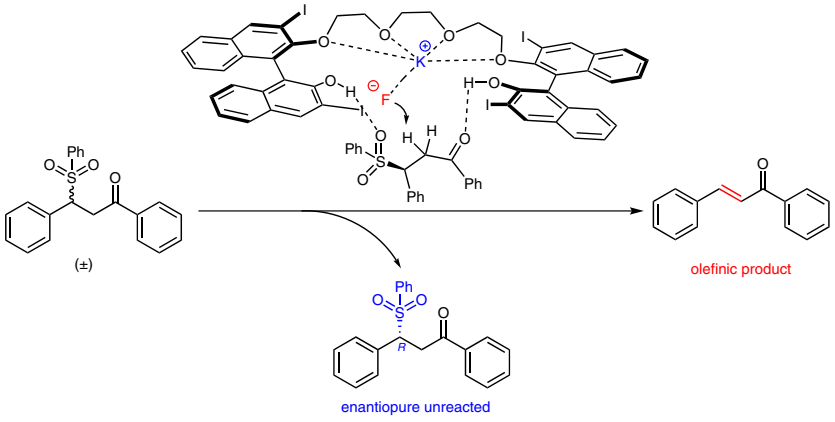
# Efficient Enrichment of Chiral β-Sulfonyl Ketones through Asymmetric β-Elimination

**Yidong Liu**
**Wenling Qin**
**Hailong Yan***

Innovative Drug Research Centre, Chongqing University, Chongqing 401331, P. R. of China
yhl198151@cqu.edu.cn

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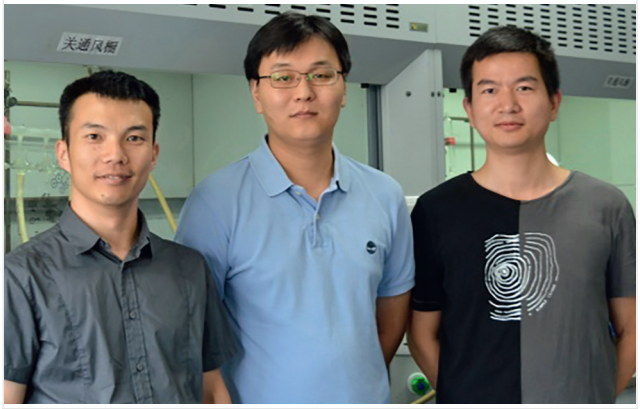
**Abstract** Chiral sulfones are important functionalities of various interesting organic compounds. Herein we reported a catalytic enantioselective β-elimination reaction for the first time and realized the kinetic resolution of racemic β-sulfonyl ketones. The resulted enones could be recovered to re-perform the catalytic resolution. This protocol overcame the yield limitation of 50% of resolution procedures. The resulting chiral β-sulfonyl ketones were successfully transformed into corresponding amide, hydrazine, and alcohols with good stereocontrol, demonstrating the application prospect of this reaction system.

**Key words** enantioselective β-elimination, chiral sulfone, kinetic resolution

Chiral sulfones exist in a wide range of bioactive compounds and have key functionalities, including anticancer, antibacterial activities, secretase inhibiting, and Alzheimer's Diseases treating.[1] (Figure 1) Many efforts have been devoted to the formation of chiral sulfones, including metal-catalyzed hydrogenation,[2] asymmetric substitution,[3] cycloaddition,[4] and carbon–hydrogen insertion.[5] In particular, Lewis acid mediated Diels–Alder reactions have been successfully applied in the preparation of chiral sulfones with a high enantioselectivity.[6]

More attractively, the research groups of Alexakis, Deng, Tian, Chen, and Chi successfully developed organocatalytic methods for this pattern.[7] Kinetic resolution[8] is a crucial tool for obtaining chiral products, but its application in the preparation of chiral sulfones has never been reported. Catalytic kinetic resolution has been widely used in organic chemistry to obtain chiral products with high enantioselectivity and chemical or enzymatic methods were well established and widely used even in industrial production.[9] Attracted by the prospect of kinetic resolution process, com-



**Yidong Liu** (right) was born in Hubei, China, in 1988. He received his BSc degree from China Pharmaceutical University in 2012 and joined Dr. Hailong Yan's research group in Innovative Drug Research Centre at Chongqing University to pursue his PhD in 2013.
**Wenling Qin** (left) Dr. Wenling Qin obtained his PhD in organic chemistry in 2014 under the guidance of Prof. Mauro Panunzio and Ass. Prof. Daria Giacomini at University of Bologna. After that he awarded a fellowship from ISOF-CNR (Italy) for six months. And then he worked as the co-founder and R&D director of Cubane (Shanghai) Biological and pharmaceutical Co., Ltd. from March 2015 to May 2016. Meanwhile, he served as a technical consultant in China for Allecra Therapeutics SAS (Germany) and Novachemaromatici s.r.l. (Italy) until May 2016. He joined Dr. Yan's group as a lecture in July 2016.
**Hailong Yan** (middle) was born in Shandong Province, China. In 2011, he received his PhD from Sungkyunkwan University, Korea under the guidance of Prof. Choong Eui Song. After that he was a postdoctoral fellow with Prof. Song for one more year. From 2012 to 2013, he was a postdoctoral fellow with Prof. Yu Zhao at National University of Singapore. Since 2013, he joined Chongqing University, China, as a member of Plan of One-Hundred Young Talents.

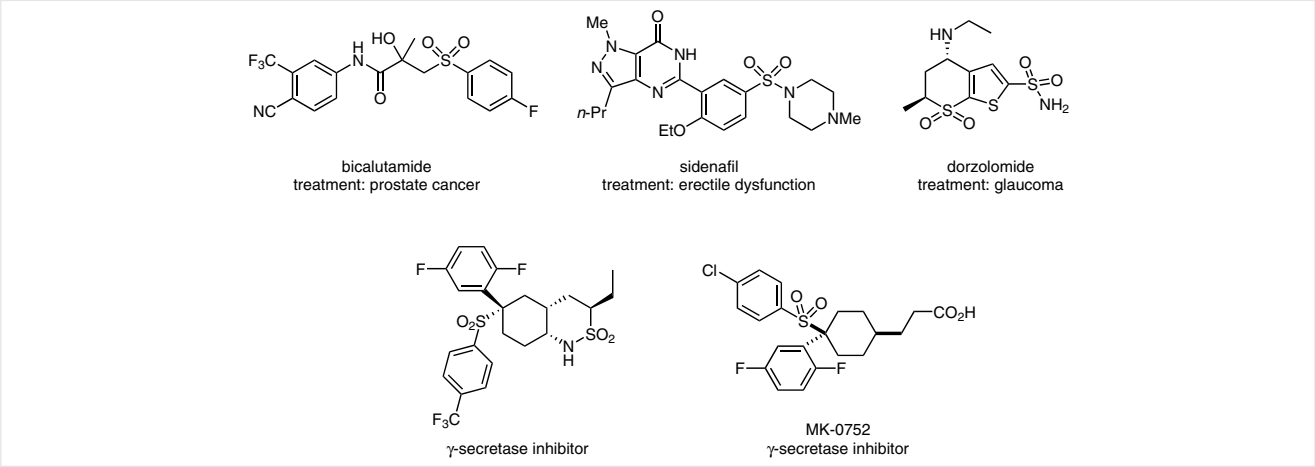
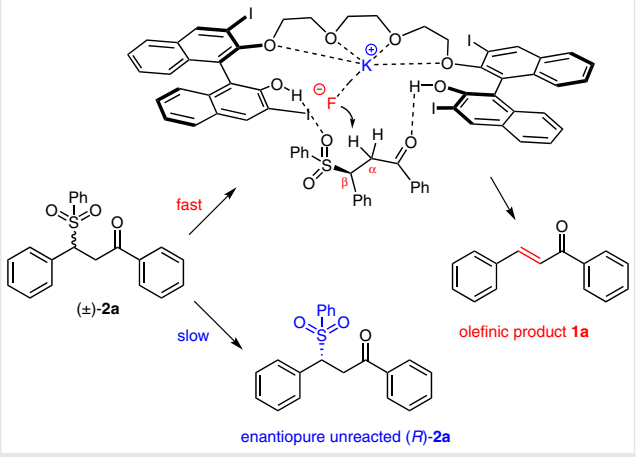



**Figure 1** Examples of bioactive sulfones

bined with our previous experiences on cation-binding catalysis, the study aims to develop a resolution protocol for the generation of highly enantiopure chiral sulfones as an attractive and complementary alternative (Scheme 1).

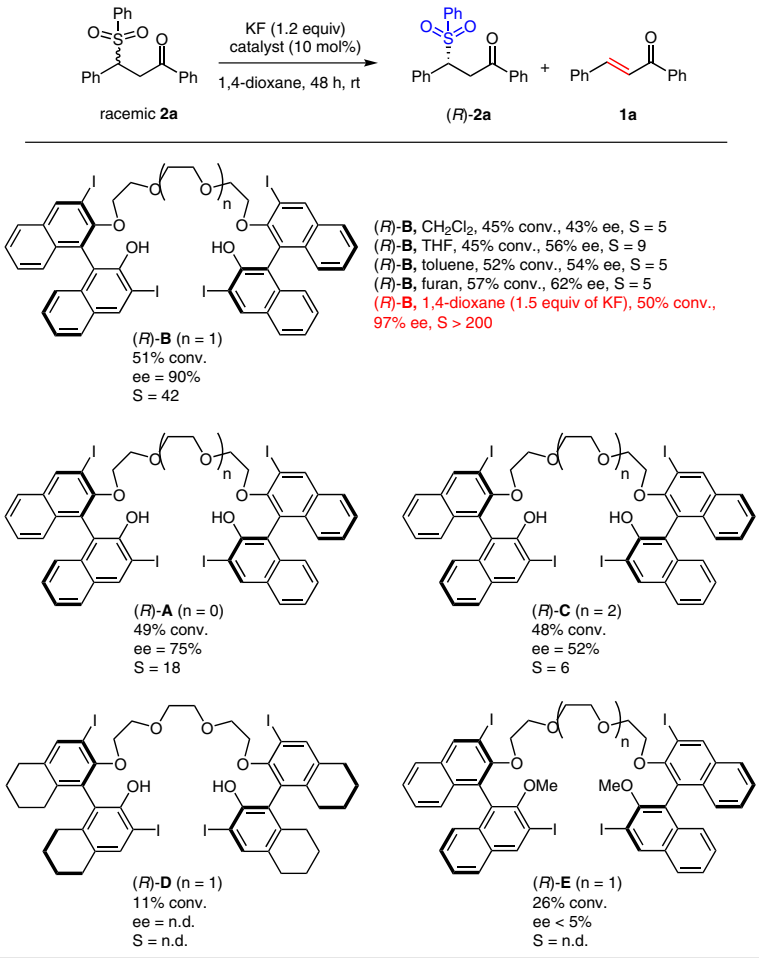



**Scheme 1** Proposed reaction pathway

In our strategy that takes advantage of a sulfonyl group as the leaving group, a catalytic enantioselective vicinal elimination reaction[10] is performed. Vicinal elimination is one of the most fundamental organic transformations for the construction of carbon–carbon double bonds and has been widely investigated and applied in the synthesis of nature products and medicines,[11] particularly the β-elimination of ketones to yield the corresponding enones. Enones have showed the potential as important functionalities and intermediates in organic synthesis. Various catalytic systems of β-elimination were successfully explored.[12] However, to the best of our knowledge, the field of enantioselective β-elimination reaction of β-functional ketones still remains unknown.[13] In theory, if a sulfonyl serves as the leaving group at the β-position of ketone, one single enantiomer is converted into enones through an enantioselective β-elimination process, while the counterpart remains stable, thus obtaining optically pure β-sulfonyl ketones. In other words, an efficient kinetic resolution of β-sulfonyl ketones can be realized.

Chiral polyethers have been successfully used as cation-binding catalysts in asymmetric synthesis.[14] Such BINOL-based chiral polyether can capture KF by a phase-transfer pathway. The Brønsted acidic moieties might be involved in secondary interactions with Lewis basic parties of sulfonyl ketones substrate through hydrogen bonding and the induced chiral environment could preferentially bind with one enantiomer rather than another. Furthermore, the activated fluoride anion could deprotonate the α-proton to form α,β-unsaturated ketones and realize a kinetic resolution of starting racemic sulfonyl ketones. On the basis of this deduction, we envisioned that an enantioselective β-elimination of ketones might occur, thus achieving a kinetic resolution of racemic β-sulfonyl ketones.

We firstly investigated a series of BINOL-based cation-binding catalysts. In the presence of KF and racemic substrate **2a**, a series of catalysts were examined with 10% loading in 1,4-dioxane at 25 °C. The results indicated that the length of polyether chain of the catalyst played a crucial role in the catalytic performance because the length of polyether chain was closely related to the formation of a suitable chiral coordinating cage for a potassium cation (Scheme 2). Meanwhile, the 3′,3-diiodo-substitution showed the highest reactivity and enantioselectivity. The possible explanation is that the strong coordination of iodine atoms to the potassium atom is benefited from the polarizability of iodine. Meanwhile, the large radius of iodine atom might influence stereoenvironments of the transition state and lead to an enhanced enantioselectivity. Furthermore, the catalyst derived from $H_8$-BINOL backbone (R-**D**) has demonstrated the poorer catalytic performance in both conversion and enantiomeric excess. In addition, the di-O-




**Scheme 2** Optimization of the reaction conditions

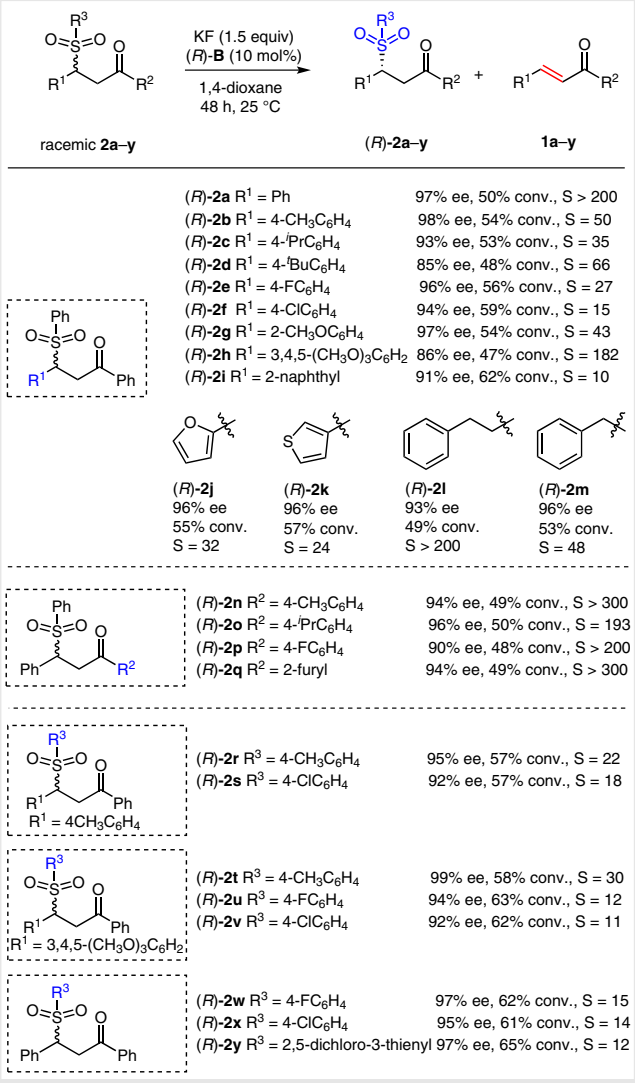
protected catalyst (R-**E**) was completely inactive, revealing that the existence of terminal hydroxyl group at the 2,2′-position of BINOL backbone was crucial for the catalytic performance of the multifunctional catalyst.

With the most efficient catalyst, we started to investigate the influences of other reaction conditions, including solvents and the amount of additives. Among various solvents, 1,4-dioxane showed the best catalytic performance compared to dichloromethane, toluene, furan, and THF. Furthermore, 1.5 equivalents of KF as additive and the concentration of starting substrate (0.1 mmol/mL) were identified as the best reaction conditions.

The substrate scope of this catalytic protocol has been extensively investigated (Scheme 3). First, a variety of substituents on the aromatic $R^1$ (**2a–i**) were investigated, different substituted functional groups on $R^1$, including those bearing electrodonating or electron-withdrawing groups, were well tolerated to our catalytic system. The position of substituents did not affect the enantioselectivity of the reaction. Moreover, heteroaryl sulfones (**2j**,**k**) were also excellent substrates. In addition to the aryl and heteroaryl substrates, the aliphatic sulfones were also investigated. However, generality with respect to aliphatic substrates was limited, only the primary alkyl substrate could be resolved with good selectivity (**2l–m**).

Substrates bearing different $R^2$ groups (**2n–q**) were shown to be excellent substrates for this elimination reaction, giving the corresponding unreacted sulfones with higher selectivity. Finally, different functional groups ($R^3$) on the sulfone were also investigated. Substrates bearing both electron-donating and electron-withdrawing groups underwent β-elimination smoothly to give the unreacted sulfones in high enantioselectivity (**2r–x**). In addition, a heteroaryl sulfone substrate (**2y**) was also well tolerated.

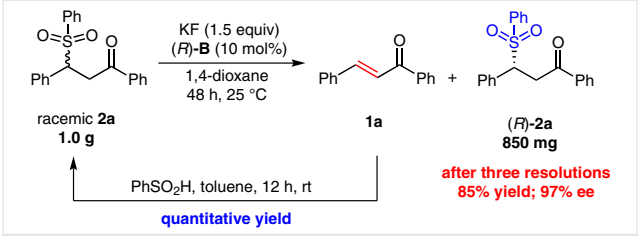
So far, we successfully developed a catalytic system for the preparation of chiral β-sulfonyl ketones with a wide range of substrate scope and high enantioselectivity. However, due to the inherent limitation of kinetic resolution, the yield of this reaction was lower than 50%. To overcome this limitation, the recovered α-,β-unsaturated ketones were further transformed into racemic β-sulfonyl ketones




**Scheme 3** Substrate scope

by the addition of sulfinic acid. Taking Substrate **2a** as an example, this multirecycle process was performed (Scheme 4). After the first kinetic resolution of racemic **2a**, the generated enone was successfully quantitatively converted into starting material (racemic **2a**), and then another catalytic kinetic resolution of regenerated racemic **2a** were performed to give the same product as fresh (*R*)-**2a**. After three cycles, chiral (*R*)-**2a** was enriched to obtain the absolute yield of 85% with 97% ee.

In order to acquire an insight into the reaction mechanism, we made an effort to capture the substrate–catalyst chelating complex. It is believed that the complex is composed of the sulfone substrate and a chiral ion pair which is formed by chelating of catalyst with potassium ion of KF. The HRMS observation results confirmed this complex and strongly supported our proposed reaction pathway (Figure 2). In this mechanism, fluoride anion deprotonated the α-




**Scheme 4** Recycling experiment with **2a**

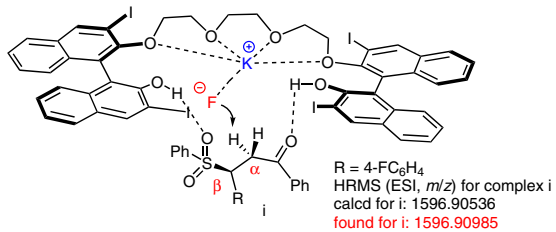
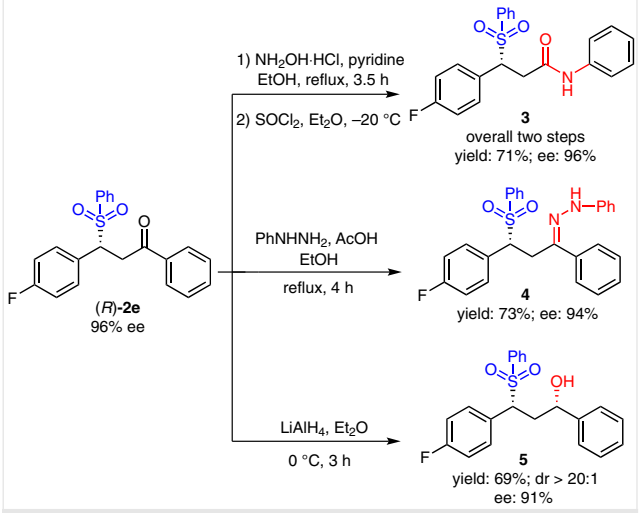



**Figure 2** Proposed transition state

proton, meanwhile the elimination of the $PhSO_2$ group from β-position leads to the generation of olefin, potassium salt. Simultaneously, the catalyst was regenerated.

To investigate the application prospect of our catalytic reaction system, we further expanded the utility of our reaction toward the functional-group transformation of target products. It was demonstrated that the produced chiral β-sulfonyl ketones could tolerate various transformation conditions. In other words, the formed chiral C–S bond remained stable under the conditions of various reaction, such as Beckmann rearrangement reaction, hydrazone formation reaction with hydrazine, and reduction reaction of ketones into alcohol (Scheme 5). Moreover, the newly produced chiral center showed the high stereocontrol performance. This versatile transformation of chiral β-sulfonyl ketones reveals a diversified application of our protocol in the preparation of various potential bioproducts.[15]




**Scheme 5** Functional-group transformation of target product

In conclusion, we developed an efficient catalytic β-elimination reaction and efficiently realized the resolution of racemic β-sulfonyl ketone. The resulted chiral β-sulfonyl ketones can be enriched to obtain the yield of 85% through multiple cycles of resolution and enone addition reaction. Meanwhile, the formed chiral β-sulfonyl ketones demonstrated the better tolerance to various transformation conditions for affording diversified products. Further efforts of our group will be focused on the reaction mechanism.

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