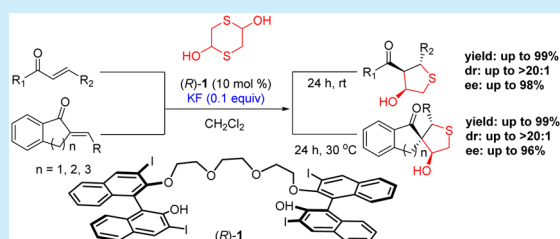


Asymmetric Synthesis of Trisubstituted Tetrahydrothiophenes via in Situ Generated Chiral Fluoride-Catalyzed Cascade Sulfa-Michael/Aldol Reaction of 1,4-Dithiane-2,5-diol and α,β -Unsaturated KetonesMengying Duan,^{†,§} Yidong Liu,^{†,§} Jun Ao,[†] Lu Xue,[†] Shilong Luo,[†] Yu Tan,[†] Wenling Qin,[†] Choong Eui Song,^{‡,Ⓜ} and Hailong Yan^{*,†,Ⓜ}[†]Innovative Drug Research Centre (IDRC), School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, China[‡]Department of Chemistry, Sungkyunkwan University, Suwon 440-746, Korea

Supporting Information

ABSTRACT: A chiral fluoride-catalyzed asymmetric cascade sulfa-Michael/aldol condensation reaction of 1,4-dithiane-2,5-diol and a series of α,β -unsaturated ketones is described to access chiral trisubstituted tetrahydrothiophene derivatives. The target products, including the spiro tetrahydrothiophene derivatives bearing a five-, six-, and seven-membered ring, were highly functionalized and showed high ee value. This established protocol realized a highly enantioselective reaction with a catalytic amount of KF and Song's chiral oligoEG via in situ generated chiral fluoride to construct useful heterocyclic skeletons with great complexity.



The in situ generation of chiral fluoride, which can serve as a catalyst for a variety of asymmetric reactions, is one of the most challenging problems in modern organic chemistry.¹ Inorganic fluoride salts such as alkali metal fluorides (MFs) are stable, easy to handle, and inexpensive. Therefore, they are strong candidates for fluoride sources in various catalytic reactions. However, their applications are limited due to their low solubilities in organic solvents. To increase the solubility of alkali metal salts in organic solvents, phase-transfer catalysts such as chiral crown ethers² and quaternary ammonium or phosphonium salts³ are used to reduce the Coulombic interactions of MFs and generate a “naked” fluoride ion. Many efforts have been made to develop efficient multifunctional organocatalysts, which enable cooperative catalysis involving chiral fluoride anion. Recently, Song and co-workers reported a new type of easily accessible 1,1'-bi-2-naphthol (BINOL)-based organocatalysts bearing phenols and polyether units for asymmetric cation-binding catalysis.⁴ This new type of cooperative cation-binding catalysis has been successfully applied in various chiral fluoride catalyzed asymmetric reactions including desilylative kinetic resolution of silyl-protected racemic alcohols and kinetic resolution of β -sulfonyl ketones through enantioselective β -elimination. Despite such significant achievements, the requirement of stoichiometric amount or excess of KF limits its application in asymmetric catalysis. The development of highly enantioselective reactions with catalytic amount of KF is therefore a challenging and interesting subject.

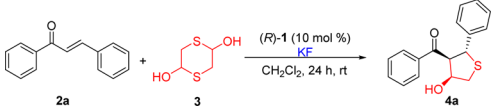
The stereocontrolled polysubstituted tetrahydrothiophenes are of particular interest for organic chemists owing to its potential toward further synthetically and biologically valuable elaboration.⁵ Asymmetric cascade sulfa-Michael/aldol and

Michael/Michael reactions have been used in the preparation of optically pure polysubstituted tetrahydrothiophenes through an organocatalytic manner between α,β -unsaturated compounds and mercaptoacetaldehyde analogues⁶ or 1,4-dithiane-2,5-diol.⁷ Furthermore, Feng reported a Ni(II)-catalyzed asymmetric domino thia-Michael/aldol reaction to form chiral spirocyclic oxindole-fused tetrahydrothiophenes.⁸ More recently, He developed an enzymatic asymmetric procedure for this reaction by using pepsin.⁹ Owing to the importance of polysubstituted tetrahydrothiophenes, during our studies, we became interested in the development of more versatile catalytic methods for the construction of these structural motifs. Herein, we described a chiral fluoride catalyzed highly enantioselective cascade sulfa-Michael/aldol reaction for construction of trisubstituted tetrahydrothiophenes; notably, the chiral fluoride was generated in situ from catalytic amount of KF binding with Song's oligoEG catalyst.

We initiated our investigation by studying the KF loading amount with the model reaction of **3** and **2a** with catalyst (*R*)-**1** in CH_2Cl_2 to form **4a**. From an excess amount (2 equiv, Table 1, entry 5) to a catalytic amount (0.1 equiv, Table 1, entry 1) of KF, the decrease in KF loading did not influence the catalytic performance dramatically, and product **4a** was formed with a high ee value (93% ee) and diastereomer ratio (dr >20:1). Notably, without the loading of KF, the reaction did not take place (Table 1, entry 6). It is obvious that a catalytic amount of KF is necessary and sufficient for cooperation with Song's chiral

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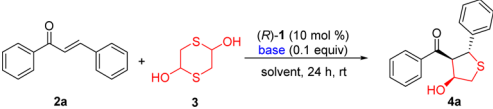
Table 1. Optimization of the Loading Amount of KF^a


entry	KF (equiv)	yield ^b (%)	ee ^c (%)
1	0.1	95	93
2	0.2	98	89
3	0.5	95	90
4	1	95	93
5	2	90	93
6	0	-	-

^aReaction conditions: **2a** (0.2 mmol), **3** (0.15 mmol), (*R*)-**1** (0.02 mmol) in solvent (2.0 mL) at room temperature for 24 h unless otherwise specified. ^bIsolated yield. ^cDetermined by chiral HPLC analysis.

oligoEG catalyst in this asymmetric cascade sulfa-Michael/aldol condensation reaction.

We then screened a series of solvents with catalyst (*R*)-**1** and a catalytic amount of KF as base. Dichloromethane gave the best results in the aspects of yield and ee value (Table 2, entry

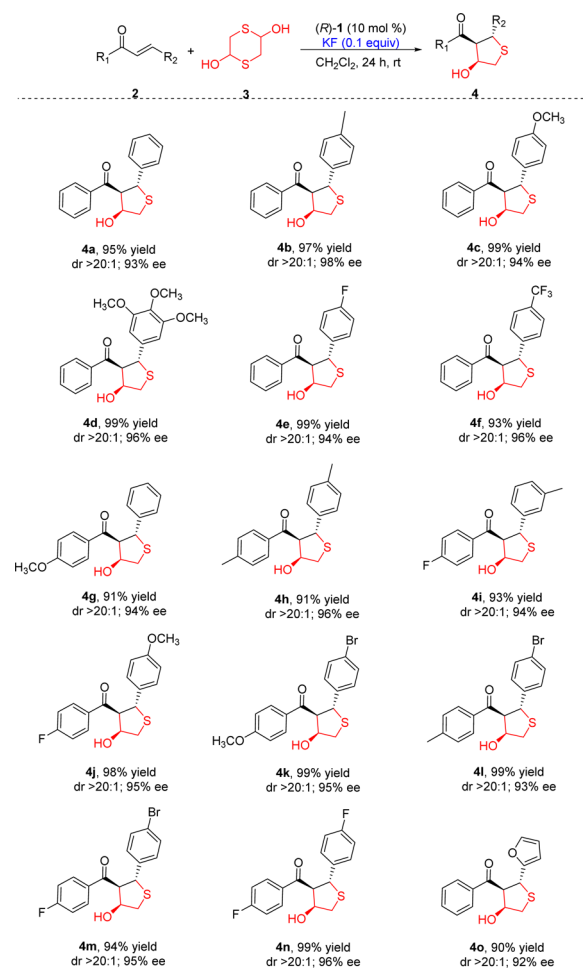
Table 2. Optimization of the Reaction Conditions^a


entry	base	solvent	yield ^b (%)	ee ^c (%)
1	KF	CH ₂ Cl ₂	90	91
2	KF	toluene	84	70
3	KF	CHCl ₃	85	88
4	KF	CCl ₄	76	63
5	KF	1,4-dioxane	83	5
6	KF	DCE	86	90
7 ^d	KF	CH ₂ Cl ₂	95	93
8	KSCN	CH ₂ Cl ₂	47	88
9	phthalimide potassium	CH ₂ Cl ₂	78	71

^aReaction conditions: **2a** (0.2 mmol), **3** (0.15 mmol), base (0.02 mmol), (*R*)-**1** (0.02 mmol) in solvent (1.0 mL) at room temperature for 24 h unless otherwise specified. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. ^dThe reaction was performed in solvent (2.0 mL).

1). After screening the reaction solvents, we investigated the reaction concentration regarding solvent and substrate loading. The combination of 0.2 mmol of substrate **2a** and 2.0 mL of solvent gave the best results. We then turned our attention to various potassium salts such as potassium thiocyanate and phthalimide potassium, but their performances were much poorer than that of KF. On the basis of the preceding results, the best parameters were obtained with the reaction performed at ambient temperature with 0.2 mmol of substrate **2a** and 2.0 mL of solvent as well as the catalyst (*R*)-**1**, KF loading of 10 mol % (95% yield, 93% ee) (Table 2, entry 7).

With the optimal reaction conditions in hand, the in situ generated chiral fluoride-catalyzed cascade sulfa-Michael/aldol reactions of 1,4-dithiane-2,5-diol with a variety of chalcone analogues bearing different electronic and steric properties were investigated (Scheme 1). Substrates with electron-donating (Scheme 1, **4b–d**) and electron-withdrawing (Scheme 1, **4e,f**)

Scheme 1. Asymmetric Cascade Sulfa-Michael/Aldol Condensation Reactions between Chalcone Analogues and 1,4-Dithiane-2,5-diol^a

groups on R₂ gave the desired products with excellent yield and high ee value. Meanwhile, different substitution groups on both R₁ and R₂ were also well tolerant to the reaction conditions and showed no significant change, indicating that the nature or the position of the substituents on chalcone had no obvious influence on the chiral induction and productivity (Scheme 1, **4h–n**). It is worth noting that satisfactory results with respect to yield and enantioselectivity were also achieved with α,β -unsaturated ketone bearing a heterocyclic ring (Scheme 1, **4o**).¹⁰

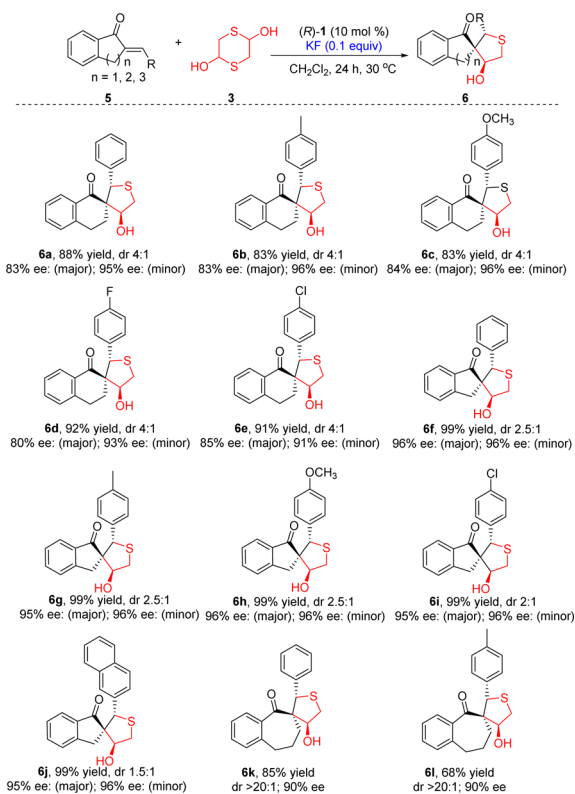
After the reaction scope exploration of chalcone analogues, we were interested in expanding the reaction applications to more complicated and challenging substrates. We envisioned that α,β -unsaturated benzocyclic ketones might be a suitable object for the further application of our reaction system, to react with 1,4-dithiane-2,5-diol to form chiral spirocyclic tetrahydrothiophene derivatives, which represented a challenging topic in organic synthesis because it involves the construction of spirocyclic compounds and generation of a highly optically pure quaternary carbon center.¹¹ Recently,

groups on R₂ gave the desired products with excellent yield and high ee value. Meanwhile, different substitution groups on both R₁ and R₂ were also well tolerant to the reaction conditions and showed no significant change, indicating that the nature or the position of the substituents on chalcone had no obvious influence on the chiral induction and productivity (Scheme 1, **4h–n**). It is worth noting that satisfactory results with respect to yield and enantioselectivity were also achieved with α,β -unsaturated ketone bearing a heterocyclic ring (Scheme 1, **4o**).¹⁰

some progress has been reported in α,β -unsaturated benzocyclic ketones and benzofuran-containing spiro heterocycles from 1,4-dithiane-2,5-diol and the corresponding α,β -unsaturated ketones via a cascade sulfa-Michael/aldol condensation reaction in a one-pot manner.^{7g,h,8,12} However, highly enantioselective procedures are still required for this reaction.

As shown in Scheme 2, a variety of functionalized spiro tetrahydrothiophene derivatives have been formed, and the

Scheme 2. Asymmetric Cascade Sulfa-Michael/Aldol Condensation Reactions between α,β -Unsaturated Benzocyclic Ketones and 1,4-Dithiane-2,5-diol^a

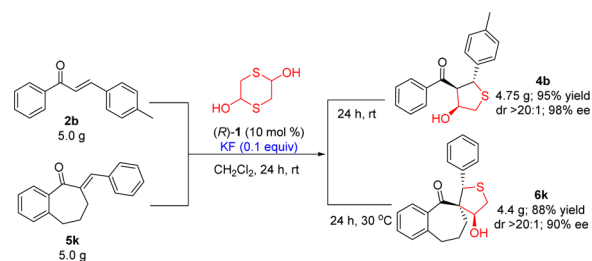


^aReaction conditions: **5** (0.2 mmol), **3** (0.15 mmol), KF (0.02 mmol), (*R*)-**1** (0.02 mmol) in CH₂Cl₂ (1.5 mL) at 30 °C for 24 h unless otherwise specified. The yield was determined after chromatographic purification, and the ee value was determined by HPLC analysis. Diastereomeric ratio (dr) was determined by ¹H NMR.

enantioselectivity of quaternary carbon center was well controlled. Moreover, the products displayed good structural diversity, including the spiro tetrahydrothiophene derivatives bearing a five- (Scheme 2, **6f–j**), six- (Scheme 2, **6a–e**), or seven-membered ring (Scheme 2, **6k,l**). This procedure required a higher reaction temperature than chalcone reactions to accelerate the reaction rate and increase the yield. Although the diastereoselectivity of the reaction decreased, the enantioselectivity of the reaction was satisfied. The absolute configurations of **6e** was unambiguously established by X-ray crystallographic analysis (see the Supporting Information).

In order to further evaluate the application prospect of the catalytic system, the gram-scale reactions were performed with substrates **2b** and **5k**. As shown in Scheme 3, the diastereoselectivity and enantioselectivity of trisubstituted tetrahydrothiophene **4b** (>20:1 dr, 98% ee) and spiro tetrahydrothiophene **6k** (>20:1 dr, 90% ee) remain untouched under the

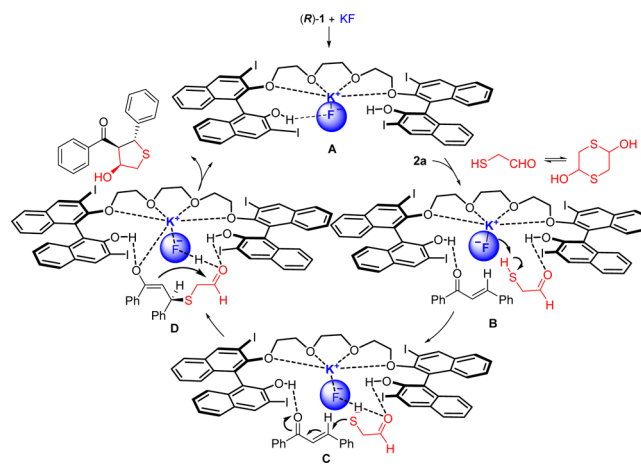
Scheme 3. Gram-Scale Experiment



conditions of a catalytic amount of KF (0.1 equiv) and Song's chiral oligoEG (*R*)-**1**.

Based on the comprehensive of in situ generated chiral fluoride from KF and Song's chiral oligoEG catalyzed enantioselective cascade reactions for construction of heterocyclic compounds, combined with a catalytic amount of KF loading, we proposed the reaction pathway outlined in Scheme 4. First, chiral fluoride was generated via the binding of catalyst

Scheme 4. Plausible Reaction Mechanism



(*R*)-**1** to KF and then formed the complex **A**. Meanwhile, 1,4-dithiane-2,5-diol was converted into mercaptoacetaldehyde under the reaction conditions. The obtained mercaptoacetaldehyde reacted with complex **A** and chalcone to lead to complex **B**. Then the active proton of thiol was captured by the fluoride anion to give complex **C**. Next, through an enantioselective sulfa-Michael addition reaction, complex **C** was converted into complex **D**, which was provided target product via stereocontrolled aldol reaction, followed by the regeneration of complex **A**. As shown in Scheme 4, the chiral fluoride generated from the KF binding to the Song's chiral oligoEG catalyst is critical to induce high reactivity and high enantioselectivity of this cascade sulfa-Michael/aldol reaction.

In conclusion, we described an asymmetric cascade sulfa-Michael/aldol condensation reaction between 1,4-dithiane-2,5-diol and a series of structural diversities α,β -unsaturated ketones to access enantiopure trisubstituted tetrahydrothiophene derivatives with a Song's chiral oligoEG as a cation-binding catalyst and catalytic amount of KF. The target products, including the spiro tetrahydrothiophene derivatives bearing a five-, six-, and seven-membered ring, were highly functionalized and showed high optical purity. This established protocol expanded the application field of the precedent Song's chiral oligoEG catalytic system in the enantioselective

construction of useful heterocyclic skeletons with great complexity. In particular, a highly enantioselective reaction with catalytic amount of KF was achieved. Moreover, this catalytic system can be applicable to the gram-scale reaction without any loss of diastereoselectivity or enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.7b00813](https://doi.org/10.1021/acs.orglett.7b00813).

Experimental procedure and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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