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Organocatalytic Asymmetric Sulfa-Michael Addition of Thiols to 4,4,4-Trifluorocrotonates

Xiu-Qin Dong,[†] Xin Fang,[†] and Chun-Jiang Wang*[,†,‡]

College of Chemistry and Molecular Sciences, Wuhan University, 430072, China, and State Key Laboratory of Elemento-organic Chemistry, Nankai University, 300071, China

cjwang@whu.edu.cn

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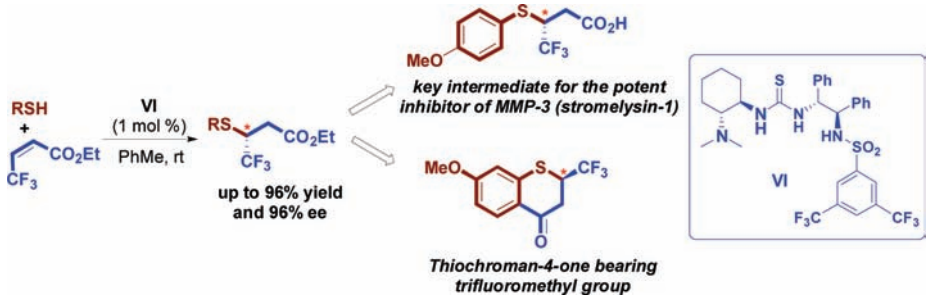
ABSTRACT



The first asymmetric sulfa-Michael addition of thiols to 4,4,4-trifluorocrotonates for the construction of a stereogenic center bearing a unique trifluoromethyl group and a sulfur atom has been achieved in high yields and excellent enantioselectivities with a 1 mol % bifunctional organocatalyst. Subsequent transformation led to the expedient preparation of enantioenriched thiochroman-4-one and the key intermediate of the potent inhibitor of MMP-3, (*R*)-γ-trifluoromethyl γ-sulfone hydroxamate.

The chemistry of organofluorine compounds is a rapidly developing area of research due to their wide range of applications in a number of important fields such as drug discovery and materials science.[1] Among organofluorine molecules, chiral trifluoromethylated compounds play a unique and significant role in agricultural and medicinal chemistry, as it often imparts enhanced biological activity, metabolic stability, binding interactions, or other desirable changes in physical properties to drug molecules.[2] One such example is (*R*)-γ-trifluoromethyl γ-sulfone hydroxamate (Figure 1), the potent inhibitor of MMP-3 (stromelysin-1), and the stereogenic carbon center bearing a unique CF_3 group plays a significant role in the structure–activity relationship.[3] Zanda and co-workers reported an approach to access both of the two enantiomerically pure γ-trifluoromethyl γ-sulfone hydroxamates by means of a sulfa-Michael addition of *p*-methoxythiophenol to chiral 4,4,4-trifluorocrotonamide as the key step, although the chiral-auxiliary-induced sulfa-Michael addition was not efficient and delivered the key intermediates as nearly equimolar mixtures of diastereomers.[3] Catalytic asymmetric sulfa-Michael addition (SMA) constitutes a direct and versatile approach toward optically active chiral sulfur

[†] Wuhan University.
[‡] Nankai University.

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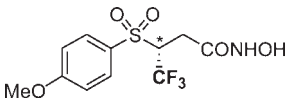

Figure 1. Potent inhibitor of MMP-3 (stromelysin-1): (*R*)-γ-trifluoromethyl γ-sulfone hydroxamate.

compounds,[4] and much attention has been paid to developing enantioselective catalytic protocols for this reaction over the past decades.[5−7] However, catalytic asymmetric sulfa-Michael addition to straightforwardly access the optically pure intermediates bearing a sulfur atom and a trifluoromethyl group at the stereogenic center remains a challenge and has met with little success. To the best of our knowledge, there was only one example of the asymmetric sulfa-Michael addition of thiols to 4,4,4-trifluorocrotonate promoted by an enzyme in moderate yield and enantioselectivity.[8] A catalytic asymmetric version of this transformation may not only diversify the existing asymmetric sulfa-Michael addition reaction but also be uniquely valuable in the efficient construction of building blocks bearing a trifluoromethyl group and a sulfur atom at the stereogenic carbon center.

Considering the significant role of bifunctional catalysts played in the asymmetric catalysis,[9,10] we envisioned that an acid−base bifunctional catalyst could efficiently enhance the nucleophilicity of the thiols and simultaneously activate the conjugated double bond in 4,4,4-trifluorocrotonates through hydrogen bonding interactions with the ester group and, thereby, realize this challenging sulfa-Michael addition with high enantioselectivity. Herein, we report the first catalytic asymmetric sulfa-Michael addition of thiols to 4,4,4-trifluorocrotonates catalyzed by bifunctional amine-thiourea in high yields and excellent enantioselectivities with as low as a 1 mol % catalyst loading, and further demonstrate that application of the method allowed for facile access to enantioenriched thiochroman-4-one and the key intermediate for the asymmetric synthesis of the potent MMP-3 inhibitor, (*R*)-γ-trifluoromethyl γ-sulfone hydroxamate.

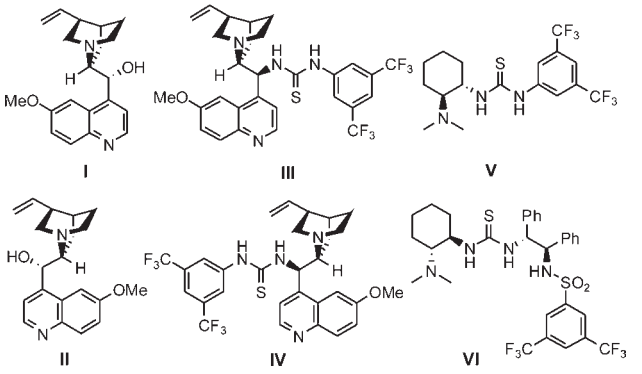

Figure 2. Structures of the screened bifunctional organocatalysts.

To explore the feasibility of the synergistic activation strategy for the proposed catalytic asymmetric sulfa-Michael addition process, reaction of thiophenol **1a** with an *E* isomer of ethyl 4,4,4-trifluorocrotonate **2a**[11] was carried out in dichloromethane at room temperature in the presence of several commonly used acid−base bifunctional organocatalysts. Two natural cinchona alkaloids and four amine-thioureas were screened since they had been demonstrated to be efficient for a variety of asymmetric

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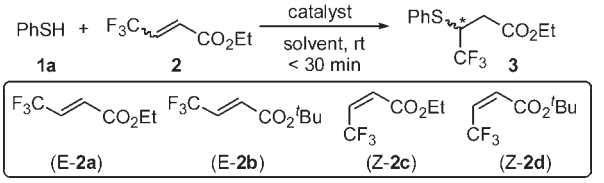
organocatalytic Michael addition, especially with nitroolefins as the corresponding Michael acceptors (Figure 2). The results of these reactions, summarized in Table 1, demonstrate that the SMA reaction proceeded efficiently in less than 30 min, affording the desired Michael adduct as a single isomer in high yields and with excellent ester-controlled regioselectivities (Table 1, entries 1–6). However, the enantioselectivities varied remarkably depending on the organocatalyst used. For example, natural cinchona alkaloids **I** and **II**, as the venerable and efficient catalysts for asymmetric sulfa-Michael addition of unsaturated enones,[12] exhibited good activities but with low enantioselectivities (Table 1, entries 1 and 2). Among several commonly used bifunctional amine-thioureas derived from 1,2-diaminocyclohexane[13] or cinchona alkaloids,[14] catalyst **VI**[15] developed in this lab recently proved to be the choice for further investigation (Table 1, entries 3–6). The change of solvents had a remarkable effect on the enantioselectivity. Less polar solvents such as dichloromethane, toluene, and ether were superior to polar and protic solvents (Table 1, entries 6–11). Toluene was the best solvent of choice and 74% ee was obtained (Table 1, entry 8). Interestingly, changing the double-bond geometry of 4,4,4-trifluorocrotonate from *E* to *Z*[16] led to the formation of the opposite enantiomer with remarkably higher enantioselectivity (Table 1, entry 8 vs 13). The observation of the opposite absolute configuration of **3aa** for (*E*)-**2** and (*Z*)-**2** indicated that the ester moiety on the 4,4,4-trifluorobutyrates played a key role in the enantioface selection of this sulfa-Michael addition and the nucleophilic attack occurred from the same face (*Si*) of C2 irrespective of the geometry of the double bond. Further examination of the ester moieties in (*E*)-4,4,4-trifluorocrotonate revealed that the bulkier *tert*-butyl ester afforded better enantioselectivity than the corresponding ethyl ester (Table 1, entry 8 vs 12). For 4,4,4-trifluorocrotonate with a *Z*-geometry, changing the ester group from ethyl to the bulkier *tert*-butyl group had little effect on the reaction and delivered the same enantioselectivity (95% ee) (Table 1, entry 13 vs 14). Reducing the reaction temperature from room temperature to 0 °C did not improve the enantioselectivity (Table 1, entry 15). Further optimization displayed that a high yield and enantioselectivity and fast reaction rate remained when the reaction was performed with as low as a 1 mol % catalyst loading (entry 17).

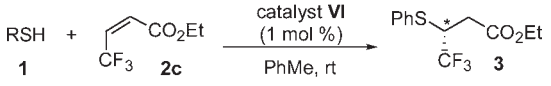
Table 1. Screening Studies of Sulfa-Michael Addition of Thiophenol **1a** and 4,4,4-Trifluorocrotonates **2** Catalyzed by Bifunctional Catalysts[a]



entry	catalyst	2	solvent	3	yield[b] (%)	ee[c] (%)
1	**I** (10 mol %)	**2a**	DCM	**3aa**	98	2 (*S*)
2	**II** (10 mol %)	**2a**	DCM	**3aa**	93	10 (*R*)
3	**III** (10 mol %)	**2a**	DCM	**3aa**	92	52 (*R*)
4	**IV** (10 mol %)	**2a**	DCM	**3aa**	91	17 (*S*)
5	**V** (10 mol %)	**2a**	DCM	**3aa**	95	45 (*S*)
6	**VI** (10 mol %)	**2a**	DCM	**3aa**	96	62 (*S*)
7	**VI** (10 mol %)	**2a**	THF	**3aa**	94	37 (*S*)
8	**VI** (10 mol %)	**2a**	PhMe	**3aa**	94	74 (*S*)
9	**VI** (10 mol %)	**2a**	MeCN	**3aa**	93	6 (*S*)
10	**VI** (10 mol %)	**2a**	Ether	**3aa**	90	57 (*S*)
11	**VI** (10 mol %)	**2a**	MeOH	**3aa**	97	0
12	**VI** (10 mol %)	**2b**	PhMe	**3ab**	95	86 (*S*)
13	**VI** (10 mol %)	**2c**	PhMe	**3ac**	95	95 (*R*)
14	**VI** (10 mol %)	**2d**	PhMe	**3ad**	90	95 (*R*)
15[d]	**VI** (10 mol %)	**2c**	PhMe	**3ac**	96	95 (*R*)
16	**VI** (5 mol %)	**2c**	PhMe	**3ac**	95	95 (*R*)
17	**VI** (1 mol %)	**2c**	PhMe	**3ac**	95	95 (*R*)

[a] All reactions were carried out with 0.22 mmol of **1a**, 0.20 mmol of **2** in 0.8 mL of solvent. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Carried out at 0 °C.

Table 2. Asymmetric Sulfa-Michael Addition of Thiols **1** to (*Z*)-Ethyl 4,4,4-Trifluorocrotonate **2c** with Organocatalyst **VI**[a]



entry	R	Prod.	yield[b] (%)	ee[c] (%)
1	Ph (**1a**)	**3ac**	95	95
2	*o*-Me-Ph (**1b**)	**3bc**	92	91
3	*m*-Me-Ph (**1c**)	**3cc**	89	93
4	*p*-Me-Ph (**1d**)	**3dc**	88	95
5	*o*-MeO-Ph (**1e**)	**3ec**	91	96
6	*m*-MeO-Ph (**1f**)	**3 fc**	90	93
7	*p*-MeO-Ph (**1g**)	**3gc**	90	94
8	*p*-tBu-Ph(**1h**)	**3hc**	93	96
9	*p*-F-Ph(**1i**)	**3ic**	90	90
10	*p*-Cl-Ph (**1j**)	**3jc**	92	90
11	2-Naphthyl (**1k**)	**3kc**	96	91
12	Bn (**1l**)	**3lc**	83	57

[a] All reactions were carried out with 0.55 mmol of **1**, 0.5 mmol of **2a** in 0.2 mL of toulene. [b] Isolated yield. [c] Determined by HPLC analysis.

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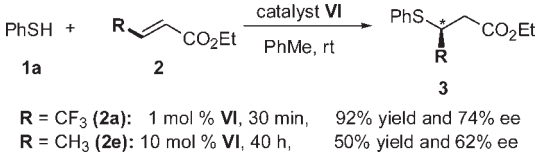
With the optimized reaction conditions in hand, we turned our attention to the scope of this sulfa-Michael addition of various thiols to (*Z*)-ethyl 4,4,4-trifluorocrotonate **2c**. As summarized in Table 2, a wide array of aryl thiols reacted smoothly with (*Z*)-**2c** to afford the expected adducts in high yields and excellent enantioselectivities in the presence of 1 mol % of catalyst **VI**. Aryl thiols bearing electron-rich (Table 2, entries 2−8), electron-neutral (Table 2, entries 1 and 11), and electron-deficient substituents (Table 2, entries 9 and 10) all worked well, providing the corresponding products in high yields (88−96%) and excellent enantioselectivities (90−96% ee). Noticeably, the substitution pattern of the arene had little effect on the selectivity of the reaction, and *ortho*-substituted thiols **1b** and **1e** underwent this transformation leading to desired adduct **3bc** and **3ec** with 91% ee and 96% ee, respectively (Table 2, entries 2 and 5). Less reactive alkyl thiol benzyl mercaptan **1l** also worked in this reaction affording a good yield and moderate enantioselectivity (Table 2, entry 12).

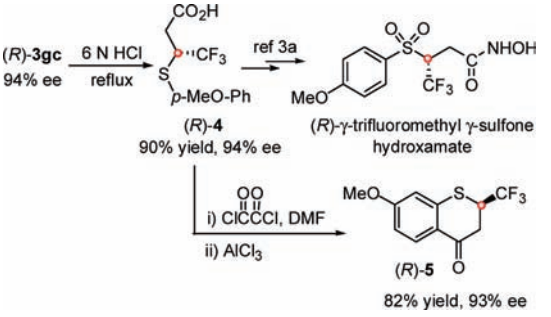
In order to evaluate the significant role of the electron-withdrawing CF_3 group played in this sulfa-Michael addition reaction, a control experiment was carried out with thiophenol as the Michael donor and ethyl crotonate as the Michael acceptor in the presence of 10 mol % **VI** (Scheme 1). The reaction became very sluggish, and the corresponding product was formed in 50% yield with only 62% ee even after 40 h. This indicated that the carbon−carbon double bond in ethyl 4,4,4-trifluorocrotonate was greatly activated by the σ-electron-withdrawing character of the CF_3 group and hence facilitated undergoing this asymmetric sulfa-Michael addition.[17]

Scheme 1. Control Experiments To Evaluate the Role of the Electron-Withdrawing CF_3 Group Played in the Sulfa-Michael Addition Reaction



To demonstrate the utility of this catalytic asymmetric sulfa-Michael addition, we studied the synthesis of (*R*)-**4**, a key intermediate in the preparation of the potent inhibitor of MMP-3 (stromelysin-1), (*R*)-γ-trifluoromethyl γ-sulfone hydroxamate[3a] (Scheme 2). The ester group of (*R*)-**3gc** was efficiently hydrolyzed to give the key intermediate (*R*)-carboxylic acid **4** in high yield under mild conditions.[18] On the other hand, synthetically useful thiochroman-4-one[19] (*R*)-**5** was easily attained by a one-pot intramolecular Friedel−Crafts reaction without loss of enantiomeric excess. An optical rotation comparison of the obtained acid **4** with the data reported in the literature[3a] revealed an *R* configuration for the generated tertiary stereogenic center bearing a unique trifluoromethyl group and a sulfur atom also for the corresponding moiety in **3gc** and thiochroman-4-one **5**. Those of other adducts were tentatively proposed on the basis of these results.

Scheme 2. Synthetic Transformation of the SMA Product (*R*)-**3gc**



In conclusion, we successfully developed the highly efficient asymmetric sulfa-Michael addition of thiols to (*Z*)-ethyl 4,4,4-trifluorocrotonate catalyzed by bifunctional amine-thiourea for the first time. This reaction can serve as a general method for the direct construction of chiral building blocks bearing a unique trifluoromethyl group and a sulfur atom at the stereogenic carbon center, including the key intermediate of the potent inhibitor of MMP-3, (*R*)-γ-trifluoromethyl γ-sulfone hydroxamate. Further investigations of the scope and synthetic application of this methodology are ongoing, and the results will be reported in due course.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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