JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

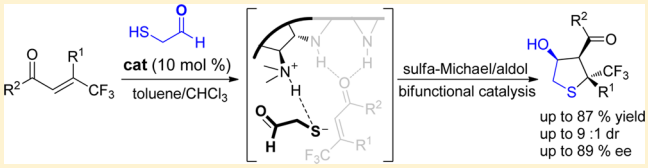
Organocatalytic Cascade Sulfa-Michael/Aldol Reaction of β,β-Disubstituted Enones: Enantioselective Synthesis of Tetrahydrothiophenes with a Trifluoromethylated Quaternary Center

Yu Su, Jun-Bing Ling, Shuang Zhang, and Peng-Fei Xu*

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P.R. China

Supporting Information

ABSTRACT: A bifunctional squaramide-catalyzed sulfa-Michael/aldol cascade reaction initiated by sulfa-Michael addition of mercaptoacetaldehyde to β-aryl-β-trifluoromethylated enones is successfully developed. The functionalized tetrahydrothiophenes with three continuous stereocenters including a trifluoromethylated quaternary carbon are readily obtained with moderate to good yields and high enantioselectivities.



The incorporation of a trifluoromethylated group into organic molecules will remarkably alter their physicochemical and biological properties due to the unique properties of fluorine.[1] Thus, tremendous efforts have been devoted toward the development of reliable and flexible approaches for the construction of trifluoromethylated compounds.[2] In this context, increasing attention has been focused on the catalytic asymmetric synthesis of functionalized molecules with a CF_3-containing stereocenter due to their potential application in agricultural and medicinal chemistry (Figure 1).[3] Recently, organocatalytic asymmetric transformations of prochiral trifluoromethylated substrates such as CF_3-ketone and CF_3-ketoimine emerged as a powerful strategy to achieve this goal.[4] However, the utility of trifluoromethylated α,β-unsaturated systems for the construction of stereocenters containing a trifluoromethyl group has not been well explored.[5] On the other hand, although organocatalytic cascade reaction has become a reliable tool for the direct synthesis of functionalized molecules with structural complexity and diversity,[6] the assembly of trifluoromethylated compounds (especially trifluoromethylated heterocycles with multiple stereocenters) by means of organocatalytic cascade reactions was scarcely studied.[7] Herein, we present an organocatalytic cascade reaction with the CF_3-activated enone as the CF_3 source, which enables the rapid synthesis of trifluoromethylated tetrahydrothiophenes with three continuous stereocenters in a practical and atom-economic manner.

The stereoselective formation of quaternary stereocenter is a long-standing pursuit in chemical synthesis.[8] Among various strategies, the organocatalytic Michael addition of reactive nucleophiles to β,β-disubstituted α,β-unsaturated systems represents an extremely challenging problem.[9] To implement such a transformation, issues associated with steric constraint and lower reactivity as well as difficulty in chiral discrimination between β substituents must be solved. Recently, Shibata and co-workers reported an organocatalytic asymmetric Michael addition to β-aryl-β-trifluoromethylated enones to create a trifluoromethyl-containing quaternary carbon.[5] Notably, the strong base-involved phase-transfer catalytic system was crucial to realize the competent conversion. Our group are interested in the development of novel asymmetric transformations[10] and recently reported a bifunctional squaramide-[11]catalyzed cascade sulfa-Michael/aldol[12] reaction of simple chalcones for the enantioselective synthesis of tetrahydrothiophene derivatives,[13] in which the reactive mercaptoaldehyde (in situ generated from its dimer 1,4-dithiane-2,5-diol) was exploited as a dual reactive substrate to initiate the cascade reaction.[10c] We speculated that using the β-aryl-β-trifluoromethylated enone, a quaternary carbon-forming sulfa-Michael addition would be feasible to trigger the sulfa-Michael/aldol cascade reaction to give rise to tetrahydrothiophene derivatives with a trifluoromethylated quaternary carbon (Scheme 1).

1,4-Dithiane-2,5-diol **2** and β-aryl-β-trifluoromethylated enone **3a** was chosen for initial optimization of the reaction parameters. Indeed, the desired reaction was found to take place in the presence of a variety of chiral bifunctional thiourea derivatives, although the trifluoromethylated product **4a** was formed with poor stereoinduction. On the basis of our previous study, the catalytic performance of bifunctional squaramides **1a**−**1g** was investigated (Table 1). Unfortunately, phenylalanine-derived catalyst **1a** in 1,2-dichloroethane at 40 °C for 48 h only gave the product **4a** in 11% yield with 25% ee (Table 1, entry 1), and cyclodiamine-derived catalysts **1b**−**1c** also led to poor stereochemical outcome (Table 1, entries 2−3). Comparatively, cinchona alkaloid-derived bifunctional squaramides **1d**−**1g** gave better selectivity with quinine-derived catalyst **1e** producing the best results (Table 1, entries 4−7). Subsequently, a brief survey of solvents revealed that nonpolar toluene led to the best enantioinduction albeit in low yield,

Received: July 23, 2013
Published: September 30, 2013

dx.doi.org/10.1021/jo4016024 | J. Org. Chem. 2013, 78, 11053−11058

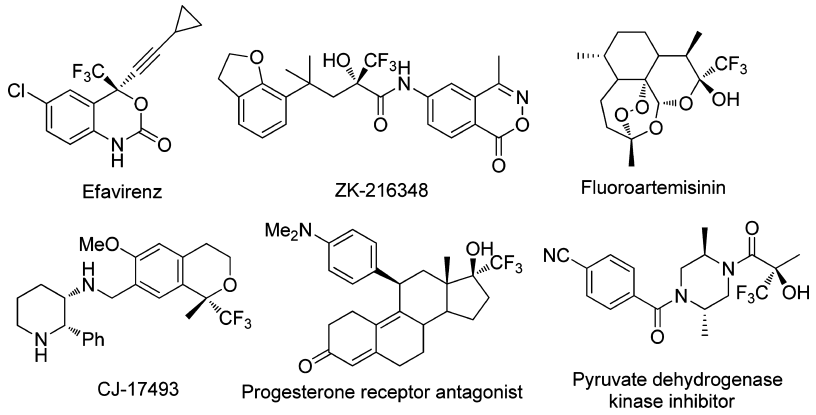


Figure 1. Some biologically important molecules with a CF_3-containing stereocenter.

Scheme 1. Reaction Design

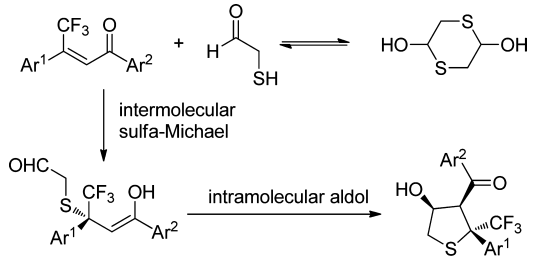
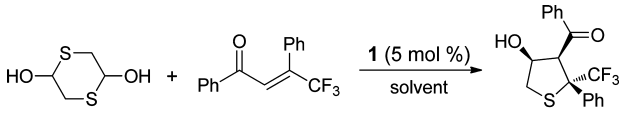


Table 1. Optimization of the Reaction Conditions

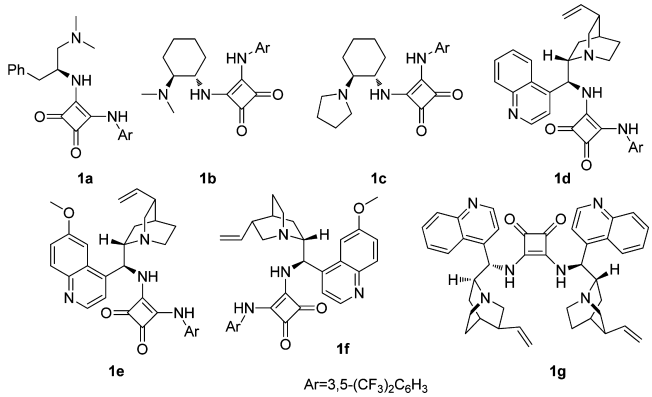


2 3a 4a

entry[a]	cat.	solvent	T (°C)	t (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	DCE	40	48	11	19:1	25
2	**1b**	DCE	40	48	61	7:1	−55
3	**1c**	DCE	40	48	82	3:1	−20
4	**1d**	DCE	40	48	38	19:1	75
5	**1e**	DCE	40	48	72	8:1	82
6	**1f**	DCE	40	48	61	14:1	−79
7	**1g**	DCE	40	48	76	6:1	60
8	**1e**	EA	40	48	61	3:1	29
9	**1e**	CH_3CN	40	48	65	13:1	39
10	**1e**	$CHCl_3$	40	48	55	13:1	88
11	**1e**	toluene	40	48	14	19:1	89
12	**1e**	xylene	40	48	<10	–	–
13	**1e**	toluene/DCE	40	48	47	8:1	77
14	**1e**	toluene/$CHCl_3$	40	48	40	19:1	84
15	**1e**	$CHCl_3$	50	48	69	6:1	80
16	**1e**	DCE	50	48	86	3:1	75
17	**1e**	toluene/$CHCl_3$	50	48	59	9:1	84
18[e]	**1e**	toluene/$CHCl_3$	50	60	85	4:1	84

[a]Unless otherwise noted, the reaction was carried out with **2** (0.3 mmol), **3a** (0.2 mmol), and **1** (0.01 mmol) in solvent (2 mL). [b]Isolated yield. [c]Determined by ^1H NMR analysis of crude product. [d]Determined by HPLC analysis. [e]10 mol % catalyst was used.

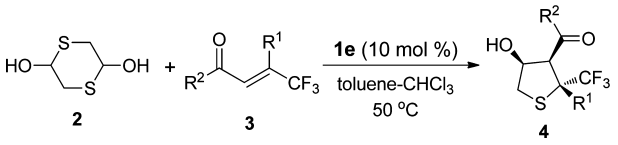
while $CHCl_3$ and DCE gave improved yields but slightly lower enantioselectivities (Table 1, entries 8−12). Further investigation showed that the reaction in a 1:1 mixture of toluene/$CHCl_3$ afforded better results in terms of both reactivity and selectivity (Table 1, entries 13−14). Furthermore, elevating the temperature to 50 °C in mixed solvents had a positive effect on the reactivity, while in DCE and $CHCl_3$ a pronounced erosion of stereoselectivities was observed presumably due to the reversibility associated with sulfa-Michael addition (Table 1, entries 15−17). The best result with regard to the balance between reactivity and selectivity was obtained with the reaction performed at 50 °C for 60 h and the catalyst loading increased to 10 mol % (Table 1, entry 18).



Under the optimized reaction conditions, the cascade sulfa-Michael/aldol reaction of a variety of β-aryl-β-trifluoromethylated enones with different electronic and steric properties were investigated and these results are outlined in Table 2. Trifluoromethylated enone derivatives with a series of substitutents such as bromo, chloro, methyl, methoxy, and trifluoromethyl on the aromatic ring gave the trifluoromethylated quaternary center-containing tetrahydrothiophenes **4a**−**4o** in moderate to good yields and with good enantioselectivities (up to 89% ee). The nature and the position of the substituents of the aromatic ring have no obvious influence on the enantioinduction, yet a little effect on the yield (Table 2, entries 1−15). Notably, satisfactory results with respect to yield and enantioselectivity were also achieved with the β-aryl-β-trifluoromethylated enones bearing heteroaromatic rings (Table 2, entries 8−9). Sterically demanding naphthyl-enone **3j** was also compatible with the reaction conditions, affording the corresponding products in high yield and enantioselectivity (Table 2, entry 10). It is worth noting that multiply substituted

dx.doi.org/10.1021/jo4016024 | J. Org. Chem. 2013, 78, 11053−11058

Table 2. Scope of Sulfa-Michael/Aldol Cascade Reaction



entry[a]	R^1, R^2	4	t (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	Ph, Ph	**4a**	60	85	4:1	84
2	Ph, 4-BrC_6H_4	**4b**	96	76	4:1	80
3	Ph, 4-ClC_6H_4	**4c**	96	74	4:1	80
4[e]	Ph, 4-$MeOC_6H_4$	**4d**	96	36	9:1	86
5	Ph, 4-MeC_6H_4	**4e**	72	70	4:1	82
6	Ph, 3-$MeOC_6H_4$	**4f**	60	69	4:1	82
7	Ph, 3-BrC_6H_4	**4g**	72	87	3:1	81
8	Ph, 2-furyl	**4h**	72	87	2:1	85
9	Ph, 2-thienyl	**4i**	72	81	1:1	89
10[e]	2-naphthyl, Ph	**4j**	72	83	4:1	80
11[e]	4-$MeOC_6H_4$, Ph	**4k**	96	49	8:1	82
12[e]	4-MeC_6H_4, Ph	**4l**	96	72	9:1	84
13[e]	3-$MeOC_6H_4$, Ph	**4m**	96	61	9:1	81
14	3,5-diMeC_6H_3, Ph	**4n**	96	73	8:1	84
15	3-$CF_3C_6H_4$, Ph	**4o**	48	56	4:1	83
16	Me, Ph	**4p**	72	37	4:1	66
17	Ph, Me	**4q**	72	trace	–	–

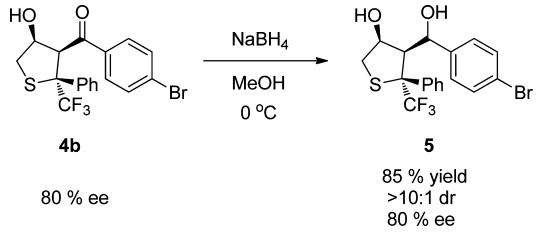
[a]Unless otherwise noted, the reaction was carried out at 50 °C for indicated time with **2** (0.3 mmol), **3** (0.2 mmol), and **1e** (0.02 mmol) in dry toluene and $CHCl_3$ (2.0 mL, V:V = 1:1). [b]Isolated yield. [c]Determined by ^1H NMR analysis of crude product. [d]Determined by chiral HPLC analysis. [e]Toluene (1 mL) was used as the solvent.

substrate **3n** was smoothly converted into the trifluoromethylated product with 84% enantioselectivity (Table 2, entry 14). In addition to *β*-aryl substituted substrates, the *β*-alkyl-*β*-trifluoromethylated enone **3p** also could provide the desired product with moderate enantioselectivity (Table 2, entry 16). However, aliphatic enone **3q** showed very low reactivity, and only a trace of product was obtained (Table 2, entry 17).

On the basis of our experimental results, a proposed catalytic cycle of the current cascade reaction is outlined in Scheme 2. First, both reaction partners are synergistically activated by the bifunctional catalyst via the formation of intermediate **A**, which undergoes the intramolecular sulfa-Michael addition to generate the enolate intermediate **B**. Subsequently aldol reaction of the enolate from its *Re* face to *Si* face of the tethered aldehyde delivers the final product and regenerates the catalyst. The absolute configuration of the product **4a** was determined as (2*S*,3*S*,4*S*) by X-ray crystallographic analysis, and all the other products were assigned by analogy (Scheme 2).[14]

Chiral 1,3-diol and its derivatives are frequently found in many natural products and biologically important molecules and therefore widely used as intermediates for synthetically useful transformations. To further demonstrate the synthetic utility of our cascade reaction, the product **4b** was subjected to diastereoselective reduction toward **5** containing a 1,3-diol motif (Scheme 3). Indeed, upon treatment with $NaBH_4$ in alcoholic solvent, the corresponding trifluoromethylated product **5** with four continugous stereocenters was readily produced with excellent diastereoselectivity and without erosion of ee.

Scheme 3. Diastereoselective Reduction of Product 4b

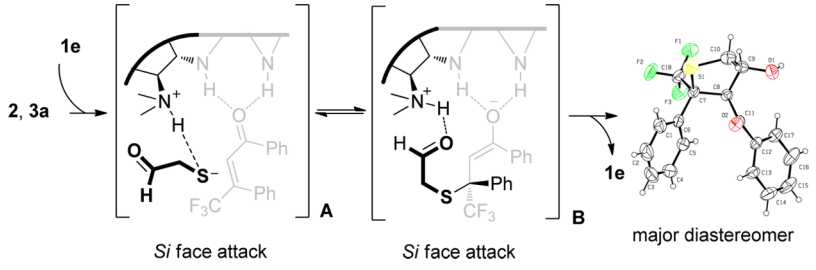


In summary, we have presented a *β*-aryl-*β*-trifluoromethylated enone-involved sulfa-Michael/aldol cascade reaction which furnished tetrahydrothiophene derivatives with a trifluoromethylated quaternary stereocenter in generally good yields with high enantioselectivities. The described methods demonstrated the reactivity and selectivity of *β*,*β*-disubstituted enones in the challenging quaternary carbon-forming sulfa-Michael addition and subsequent multistereocenter formation event. From a synthetic standpoint, this study provided a general method for rapid asymmetric construction of trifluoromethylated tetrahydrothiophenes and related heterocycles.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in glassware with magnetic stirring. Purification of reaction products was carried out by flash chromatography using silica gel at increased pressure. ^1H NMR, ^{13}C NMR, ^{19}F NMR spectra were recorded using $CDCl_3$ as solvents and TMS as an internal standard. The peak patterns of ^1H NMR are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet. The coupling constants, *J*, are reported in hertz (Hz). Data for ^{19}F NMR and ^{13}C NMR are reported in terms of chemical shift and multiplicity. HRMS were performed on FT-ICRMS mass instrument (ESI). IR spectra were recorded by FT-IR instrument and are reported in wavenumbers (cm^{-1}). HPLC analyses were conducted on the Daicel Chiralpak AS-H and eluting with *i*-PrOH and *n*-hexane. Optical rotations were recorded on polarimeter with $[\alpha]_D$ values reported in degrees; concentration (*c*) is in g/100 mL. Squaramide catalysts **1a**–**1g**[11c,e] and *β*, *β*-disubstituted enones **3**[15] were synthesized according to the previously reported methods.

Scheme 2. Proposed Catalytic Cycle of the Cascade Sulfa-Michael/Aldol Reaction



dx.doi.org/10.1021/jo4016024 | J. Org. Chem. 2013, 78, 11053–11058

General Procedure for the Synthesis of 4a–4c, 4e–4i, 4n–4p. To a suspension of compound **2** (0.3 mmol) in toluene (1 mL), were sequentially added catalyst **1e** (12.6 mg, 0.02 mmol), compound **3** (0.2 mmol), and $CHCl_3$ (1 mL), and the mixture was stirred and heated with an oil bath at 50 °C. The reaction was monitored by TLC analysis; when the reaction was completed, the mixture was subjected directly to flash column chromatography to yield the corresponding products.

((2*S*,3*S*,4*S*)-4-Hydroxy-2-phenyl-2-(trifluoromethyl)tetrahydrothiophen-3-yl)(phenyl)methanone (**4a**): white solid; 85% yield (48 mg); dr = 4:1 ; 84% ee; $[\alpha]_D^{20}$ = 124.567, (*c* 0.58, CH_2Cl_2); mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66–2.68 (d, *J* = 5.2 Hz, 1H), 3.27–3.31 (m, 1H), 3.34–3.39 (m, 1H), 5.06–5.07 (d, *J* = 6 Hz, 1H), 5.10–5.15 (m, 1H), 7.12–7.22 (m, 3H), 7.37–7.45 (m, 4H), 7.54–7.58 (m, 1H), 7.76–7.78 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.1 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.7, 53.9, 66.9 (q, *J* = 26 Hz), 77.2, 127.1 (q, *J* = 279 Hz), 127.7, 128.2, 128.3, 128.7, 129.2, 133.4, 134.7, 139.0, 198.3 ppm; IR (KBr): ν 3459, 2926, 1678, 1596, 1446, 1364, 1239, 1170, 1144, 1058, 694, 630 cm^{-1}, ESI-HRMS: calcd for $C_{18}H_{15}F_3O_2S$ [M+H]$^+$: 353.0818, found 353.0814. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 11.2 min, t_{major} = 36.4 min

(4-Bromophenyl)((2*S*,3*S*,4*S*)-4-hydroxy-2-phenyl-2-(trifluoromethyl)tetrahydrothiophen-3-yl)methanone (**4b**): white solid; 76% yield (52 mg); dr = 4:1; 80% ee; $[\alpha]_D^{20}$ = 141.914, (*c* 0.61, CH_2Cl_2); mp 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.68 (s, 1H), 3.26–3.38 (m, 2H), 5.00–5.02 (d, *J* = 6.4 Hz, 1H), 5.15 (s, 1H), 7.14–7.23 (m, 3H), 7.34–7.36 (d, *J* = 7.2 Hz, 2H), 7.55–7.64 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.2 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.5, 54.1, 66.6 (q, *J* = 27 Hz), 76.8, 127.0 (q, *J* = 280 Hz), 127.8, 128.7, 129.1, 129.6, 130.0, 132.0, 134.7, 137.8, 197.3 ppm; IR (KBr): ν 3398, 2926, 1678, 1583, 1398, 1363, 1240, 1174, 1145, 738, 706, 636 cm^{-1}; ESI-HRMS: calcd for $C_{18}H_{14}BrF_3O_2S$ [M+H]$^+$: 430.9923, found 430.9919. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 23.5 min, t_{major} = 52.8 min.

(4-Chlorophenyl)((2*S*,3*S*,4*S*)-4-hydroxy-2-phenyl-2-(trifluoromethyl)tetrahydrothiophen-3-yl)methanone (**4c**): white solid; 74% yield (46 mg); dr =4:1; 80% ee; $[\alpha]_D^{20}$ = 69.672, (*c* 0.24, CH_2Cl_2); mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 1H), 3.27–3.38 (m, 2H), 5.01–5.02 (d, *J* = 6 Hz, 1H), 5.13–5.16 (m, 1H), 7.14–7.25 (m, 3H), 7.34–7.36 (d, *J* = 7.2 Hz, 2H), 7.39–7.41 (m, 2H), 7.69–7.71 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.2 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.5, 54.1, 66.7 (q, *J* = 28 Hz), 76.8, 127.0 (q, *J* = 279 Hz), 127.8, 128.7, 129.0, 129.1, 129.6, 134.7, 137.3, 140.0, 197.0 ppm; IR (KBr): ν 3369, 2925, 1677, 1588, 1402, 1216, 1175, 1146, 1091, 1046, 707, 638 cm^{-1}; ESI-HRMS: calcd for $C_{18}H_{14}ClF_3O_2S$ [M + H]$^+$: 387.0428, found: 387.0432. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 10.6 min, t_{major} = 24.8 min.

((2*S*,3*S*,4*S*)-4-Hydroxy-2-phenyl-2-(trifluoromethyl)tetrahydrothiophen-3-yl)(p-tolyl)methanone (**4e**): white solid; 70% yield (41 mg); dr =4:1; 82% ee; $[\alpha]_D^{20}$ = 142.857, (*c* 0.24, CH_2Cl_2); mp 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.58–2.59 (d, *J* = 5.6 Hz, 1H), 3.29–3.34 (m, 1H), 3.36–3.41 (m, 1H), 5.00–5.02 (d, *J* = 6 Hz, 1H), 5.11–5.14 (m, 1H), 7.13–7.20 (m, 3H), 7.24–7.25 (d, *J* = 6.4 Hz, 2H), 7.40–7.42 (d, *J* = 7.6 Hz, 2H), 7.70–7.72 (d, *J* = 8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −69.8 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 37.1, 53.6, 67.1 (q, *J* = 26 Hz), 77.2, 125.8, 127.1 (q, *J* = 262 Hz), 127.7, 128.3, 129.3, 129.4, 134.7, 136.5, 144.5, 197.7 ppm; IR (KBr): ν 3370, 2925, 1673, 1605, 1444, 1363, 1243, 1173, 1144, 1047, 707, 606 cm^{-1}; ESI-HRMS: calcd for $C_{19}H_{17}F_3O_2S$ [M + H]$^+$: 367.0974, found 367.0970. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 11.8 min, t_{major} = 47.7 min.

((2*S*,3*S*,4*S*)-4-Hydroxy-2-phenyl-2-(trifluoromethyl)tetrahydrothiophen-3-yl)(3-methoxyphenyl)methanone (**4f**): white solid; 69% yield (42 mg); dr = 4:1; 82% ee; $[\alpha]_D^{20}$ = 93.220, (*c* 0.23, CH_2Cl_2); mp 50–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60–2.61 (d, *J* = 6 Hz, 1H), 3.28–3.32 (m, 1H), 3.35–3.40 (m, 1H), 3.79 (s, 3H), 5.04–5.05 (d, *J* = 6.4 Hz, 1H), 5.10–5.17 (m, 1H), 7.10–7.23 (m, 5H), 7.35–7.45 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.1 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.7, 54.1, 55.4, 66.9 (q, *J* = 27 Hz), 77.2, 112.5, 119.9, 120.8, 127.1 (q, *J* = 280 Hz), 127.8, 128.3, 129.2, 129.7, 134.7, 140.3 159.8, 198.0 ppm; IR (KBr): ν 3436, 2929, 1678, 1597, 1488, 1429, 1267, 1169, 1139, 1052, 777, 695 cm^{-1}; ESI-HRMS: calcd for $C_{19}H_{17}F_3O_3S$ [M + H]$^+$: 383.0923, found 383.0928. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 7.3 min, t_{major} = 36.0 min.

(3-Bromophenyl)((2*S*,3*S*,4*S*)-4-hydroxy-2-phenyl-2-(trifluoromethyl)tetrahydrothiophen-3-yl)methanone (**4g**): colorless oil; 87% yield (56 mg); dr =3:1; 81% ee; $[\alpha]_D^{20}$ = 104.651, (*c* 0.34, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59–2.64 (dd, *J* = 5.6, 16.8 Hz, 1H), 3.26–3.36 (m, 2H), 5.01–5.02 (d, *J* = 6.4 Hz, 1H), 5.12–5.17 (m, 1H), 7.15–7.22 (m, 3H), 7.29–7.35 (m, 3H), 7.67–7.69 (d, *J* = 7.6 Hz, 2H), 7.86–7.87 (t, *J* = 1.6 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.3 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.3, 54.3, 66.5 (q, *J* = 27 Hz), 77.2, 122.7, 123.0, 126.7, 126.9 (q, *J* = 279 Hz), 127.9, 128.4, 129.1, 130.2, 134.7, 136.1, 140.7, 196.9 ppm; IR (KBr): ν 3492, 2925, 1687, 1565, 1420, 1364, 1238, 1213, 1148, 1059, 737, 632 cm^{-1}; ESI-HRMS: calcd for $C_{18}H_{14}BrF_3O_2S$ [M + H]$^+$: 430.9923, found 430.9927. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 10.8 min, t_{major} = 31.7 min.

Furan-2-yl((2*S*,3*S*,4*S*)-4-hydroxy-2-phenyl-2-(trifluoromethyl)-tetrahydrothiophen-3-yl)methanone (**4h**): white solid; 87% yield (40 mg); dr = 2:1; 85% ee; $[\alpha]_D^{20}$ = 177.215, (*c* 0.16, CH_2Cl_2); mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 1H), 3.29–3.33 (m, 1H), 3.37–3.41 (m, 1H), 4.93–4.95 (d, *J* = 5.6 Hz, 1H), 5.10–5.14 (m, 1H), 6.55–6.56 (q, *J* = 1.6 Hz, 1H), 7.14–7.15 (d, *J* = 3.6 Hz, 1H), 7.18–7.22 (m, 3H), 7.47–7.48 (d, *J* = 7.2 Hz, 2H), 7.63–7.64 (t, *J* = 0.4 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.1 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.8, 54.5, 66.5 (q, *J* = 26 Hz), 77.3, 113.1, 118.0, 127.0 (q, *J* = 273 Hz), 127.8, 128.5, 129.1, 134.5, 147.0, 153.8, 185.7 ppm; IR (KBr): ν 3411, 2925, 1668, 1566, 1465, 1265, 1233, 1169, 1148, 1058, 764, 711 cm^{-1}; ESI-HRMS: calcd for $C_{16}H_{13}F_3O_3S$ [M + H]$^+$: 343.0610, found 343.0607. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 17.4 min, t_{major} = 38.9 min.

((2*S*,3*S*,4*S*)-4-Hydroxy-2-phenyl-2-(trifluoromethyl)tetrahydrothiophen-3-yl)(thiophen-2-yl)methanone (**4i**): white solid; 81% yield (29 mg); dr = 1:1; 89% ee; $[\alpha]_D^{20}$ = 129.496, (*c* 0.28, CH_2Cl_2); mp 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73–2.75 (m, 1H), 3.28–3.32 (m, 1H), 3.35–3.40 (m, 1H), 4.76–4.78 (d, *J* = 6 Hz, 1H), 5.08–5.12 (m, 1H), 7.15–7.24 (m, 4H), 7.50–7.52 (d, *J* = 7.6 Hz, 2H), 7.67–7.69 (d, *J* = 4.8 Hz, 1H), 7.77–7.78 (d, *J* = 3.6 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −69.7 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.0, 56.1, 66.8 (q, *J* = 27 Hz), 77.2, 127.1 (q, *J* = 271 Hz), 127.8, 128.4, 129.1, 132.9, 134.4, 135.4, 146.1, 189.8 ppm; IR (KBr): ν 3376, 2925, 1652, 1518, 1416, 1245, 1219, 1142, 1047, 710, 637 cm^{-1}; ESI-HRMS: calcd for $C_{16}H_{13}F_3O_2S_2$ [M + H]$^+$: 359.0382, found 359.0378. HPLC analysis: Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 17.7 min, t_{major} = 47.1 min.

((2*S*,3*S*,4*S*)-2-(3,5-Dimethylphenyl)-4-hydroxy-2-(trifluoromethyl)-tetrahydrothiophen-3-yl)(phenyl)methanone (**4n**): white solid; 73% yield (49 mg); dr = 8:1; 84% ee; $[\alpha]_D^{20}$ = 96.847, (*c* 0.44, CH_2Cl_2); mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 6H), 2.59–2.60 (d, *J* = 6 Hz, 1H), 3.26–3.30 (m, 1H), 3.36–3.41 (t, *J* = 8.8 Hz, 1H), 5.06–5.08 (d, *J* = 6.4 Hz, 1H), 5.09–5.16 (m, 1H), 6.80 (s, 1H), 6.90 (s, 2H), 7.42–7.46 (t, *J* = 7.6 Hz, 2H), 7.53–7.57 (t, *J* = 7.2 Hz, 1H), 7.74–7.76 (d, *J* = 7.2 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.5 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 36.5, 54.0, 66.5 (q, *J* = 26 Hz), 76.7, 127.2, 127.5 (q, *J* = 279 Hz), 128.0, 128.5, 130.0, 133.0, 134.3, 137.2, 139.6, 198.5 ppm; IR (KBr): ν 3409, 2920, 1678, 1602, 1448, 1373, 1245, 1220, 1163, 1051, 738, 636 cm^{-1}; ESI-HRMS: calcd for $C_{20}H_{19}F_3O_2S$ [M + H]$^+$: 381.1131, found 381.1126. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 8.3 min, t_{major} = 32.1 min.

((2*S*,3*S*,4*S*)-4-hydroxy-2-(trifluoromethyl)-2-(3-(trifluoromethyl)-phenyl)tetrahydrothiophen-3-yl)(phenyl)methanone (**4o**): white

dx.doi.org/10.1021/jo4016024 | J. Org. Chem. 2013, 78, 11053–11058

solid; 56% yield (37.6 mg); dr =4:1; 83% ee; $[\alpha]_D^{20}$ = 94.444, (*c* 0.36, CH_2Cl_2); mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72−2.74 (d, *J* = 5.6 Hz, 1H), 3.31−3.35 (m, 1H), 3.40−3.44 (t, *J* = 9.2 Hz, 1H), 5.04−5.06 (d, *J* = 6 Hz, 1H), 5.13−5.16 (m, 1H), 7.29−7.33 (t, *J* = 8 Hz, 1H), 7.43−7.48 (m, 3H), 7.57−7.61 (m, 2H), 7.66−7.68 (d, *J* = 8 Hz, 1H), 7.75−7.77 (d, *J* = 7.2 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.9 (s, 3F), −69.8 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.0, 53.9, 66.7 (q, *J* = 27 Hz), 77.1, 125.3 (q, *J* = 3.7 Hz), 125.4, 126.1, 126.2 (q, *J* = 270 Hz), 128.2, 128.4, 128.8, 130.0 (q, *J* = 32 Hz), 131.0, 132.8, 133.8, 135.9, 138.6, 198.3 ppm; IR (KBr): ν 3411, 2924, 1675, 1595, 1446, 1373, 1328, 1245, 1169, 1131, 1052, 699 cm^{-1}; ESI-HRMS: calcd for $C_{19}H_{14}F_6O_2S$ [M + H]$^+$: 421.0691, found 421.0696. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.8 min, t_{major} = 18.4 min.

((2**R**,3**S**,4**S**)-4-hydroxy-2-methyl-2-(trifluoromethyl)tetrahydrothiophen-3-yl)(phenyl)methanone (**4p**). white solid; 37% yield (17 mg); dr =4:1; 66% ee; $[\alpha]_D^{20}$ = 18.868, (c 0.32, CH_2Cl_2); mp 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 3H), 3.21−3.29 (m, 2H), 4.12 (s, 1H), 4.27−4.28 (d, *J* = 3.6 Hz, 1H), 4.88 (s, 1H), 7.50−7.54 (t, *J* = 7.6 Hz, 2H), 7.64−7.68 (t, *J* = 7.6 Hz, 1H), 7.95−7.97 (d, *J* = 7.6 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.2 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 39.2, 51.4, 59.7 (q, *J* = 27 Hz), 78.3, 127.6 (q, *J* = 279 Hz), 128.7, 128.9, 134.5, 136.9, 200.4 ppm; IR (KBr): ν 3450, 2943, 1678, 1596, 1449, 1271, 1221, 1191, 1147, 1083, 724, 688 cm^{-1}; ESI-HRMS: calcd for $C_{13}H_{13}F_3O_2S$ [M+H]$^+$: 291.0661, found 291.0658. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 4.8 min, t_{major} = 7.4 min.

General procedure for the synthesis of 4d, 4j-4m. To a suspension of compound **2** (0.3 mmol) in toluene (1 mL), catalyst **1e** (12.6 mg, 0.02 mmol) and compound **3** (0.2 mmol) were added sequentially and the mixture was stirred and heated with an oil bath at 50 °C. The reaction was monitored by TLC analysis and when the reaction was completed, the mixture was subjected directly to flash column chromatography to yield the corresponding products.

((2**S**,3**S**,4**S**)-4-Hydroxy-2-phenyl-2-(trifluoromethyl)tetrahydrothiophen-3-yl)(4-methoxyphenyl)methanone (**4d**): white solid; 36% yield (25 mg); dr = 9:1; 86% ee; $[\alpha]_D^{20}$ = 135.593, (*c* 0.29, CH_2Cl_2); mp 114−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92−2.99 (m, 1H), 3.25−3.29 (m, 1H), 3.33−3.37 (m, 1H), 3.86 (s, 3H), 4.95−4.96 (d, *J* = 6 Hz, 1H), 5.06−5.09 (m, 1H), 6.87−6.92 (m, 2H), 7.13−7.25 (m, 3H), 7.40−7.42 (d, *J* = 7.6 Hz, 2H), 7.76−7.81 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −69.7 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.0, 53.4, 55.5, 67.1 (q, *J* = 26 Hz), 77.1, 113.9, 127.2 (q, *J* = 279 Hz), 127.6, 128.2, 129.2, 130.7, 131.9, 134.8, 163.9, 196.5 ppm; IR (KBr): ν 3447, 2927, 1667, 1599, 1511, 1244, 1172, 1145, 1058, 709, 606 cm^{-1}; ESI-HRMS: calcd for $C_{19}H_{17}F_3O_3S$ [M + H]$^+$: 383.0923, found 383.0920. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 7.8 min, t_{major} = 32.3 min.

((2**S**,3**S**,4**S**)-4-Hydroxy-2-(naphthalen-2-yl)-2-(trifluoromethyl)-tetrahydrothiophen-3-yl)(phenyl)methanone (**4j**): white solid; 83% yield (53 mg); dr = 4:1; 80% ee; $[\alpha]_D^{20}$ = 193.878, (*c* 0.69, CH_2Cl_2); mp 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53−2.55 (d, *J* = 5.6 Hz, 1H), 3.35−3.39 (m, 1H), 3.42−3.47 (m, 1H), 5.16−5.23 (m, 2H), 7.36−7.45 (m, 5H), 7.56−7.58 (m, 2H), 7.63−7.65 (d, *J* = 7.2 Hz, 1H), 7.71−7.73 (d, *J* = 7.2 Hz, 1H), 7.76−7.78 (d, *J* = 7.6 Hz, 2H), 7.98 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −69.8 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.7, 54.0, 67.0 (q, *J* = 26 Hz), 77.2, 126.3, 126.6, 127.2, 127.2 (q, *J* = 280 Hz), 128.2, 128.3, 128.6, 129.3, 132.1, 132.4, 132.7, 133.3, 139,1, 198.3 ppm; IR (KBr): ν 3423, 2928, 1679, 1596, 1447, 1357, 1232, 1188, 1140, 1055, 734, 689 cm^{-1}; ESI-HRMS: calcd for $C_{22}H_{17}F_3O_2S$ [M + H]$^+$: 403.0974, found 403.0969. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 16.2 min, t_{major} = 50.8 min.

((2**S**,3**S**,4**S**)-4-Hydroxy-2-(4-methoxyphenyl)-2-(trifluoromethyl)-tetrahydrothiophen-3-yl)(phenyl)methanone (**4k**): white solid; 49% yield (33 mg); dr = 8:1; 82% ee; $[\alpha]_D^{20}$ = 135.714, (*c* 0.42, CH_2Cl_2); mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.80 (s, 1H), 3.26−3.30 (m, 1H), 3.35−3.39 (m, 1H), 3.72 (s, 3H), 4.99−5.01 (d, *J* = 6 Hz, 1H), 5.08−5.14 (m, 1H), 6.65−6.67 (d, *J* = 8.8 Hz, 2H), 7.29−7.31 (d, *J* = 8.8 Hz, 2H), 7.41−7.45 (m, 2H), 7.55−7.58 (m, 1H), 7.77−7.78 (d, *J* = 7.2 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.2 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.0, 53.9, 55.1, 66.4 (q, *J* = 26 Hz), 77.1, 113.1, 126.5, 127.2 (q, *J* = 279 Hz), 128.2, 128.6, 130.4, 133.4, 138.9, 159.2, 198.5 ppm; IR (KBr): ν 3482, 2937, 1679, 1611, 1513, 1445, 1246, 1170, 1146, 1059, 735, 630 cm^{-1}; ESI-HRMS: calcd for $C_{19}H_{17}F_3O_3S$ [M + H]$^+$: 383.0923, found 383.0918. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 20.8 min, t_{major} = 71.9 min.

((2**S**,3**S**,4**S**)-4-Hydroxy-2-(*p*-tolyl)-2-(trifluoromethyl)tetrahydrothiophen-3-yl)(phenyl)methanone (**4l**): white solid; 72% yield (47 mg); dr = 9:1; 84% ee; $[\alpha]_D^{20}$ = 128.931, (*c* 0.32, CH_2Cl_2); mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.68−2.73 (m, 1H), 3.25−3.29 (m, 1H), 3.33−3.37 (m, 1H), 5.03−5.05 (d, *J* = 6 Hz, 1H), 5.10−5.13 (m, 1H), 6.94−6.96 (d, *J* = 8 Hz, 2H), 7.24−7.26 (m, 2H), 7.42−7.46 (m, 2H), 7.55−7.59 (m, 1H), 7.78−7.80 (d, *J* = 7.6 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.2 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 36.7, 53.8, 66.6 (q, *J* = 26 Hz), 77.3, 127.1 (q, *J* = 279 Hz), 128.2, 128.5, 128.6, 129.0, 131.7, 133.4, 138.1, 138.9, 198.4 ppm; IR (KBr): ν 3378, 2926, 1676, 1593, 1443, 1366, 1241, 1169, 1144, 1050, 734, 692, 631 cm^{-1}; ESI-HRMS: calcd for $C_{19}H_{17}F_3O_2S$ [M + H]$^+$: 367.0974, found 367.0978. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 12.3 min, t_{major} = 37.5 min.

((2**S**,3**S**,4**S**)-4-Hydroxy-2-(3-methoxyphenyl)-2-(trifluoromethyl)-tetrahydrothiophen-3-yl)(phenyl)methanone (**4m**): white solid; 61% yield (42 mg); dr = 9:1; 81% ee; $[\alpha]_D^{20}$ = 96.983, (*c* 0.46, CH_2Cl_2); mp 72−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66−2.68 (d, *J* = 5.6 Hz, 1H), 3.26−3.30 (m, 1H), 3.36−3.41 (t, *J* = 8.8 Hz, 1H), 3.51 (s, 3H), 5.05−5.07 (d, *J* = 6.4 Hz, 1H), 5.10−5.17 (m, 1H), 6.72−6.74 (dd, *J* = 2, 8 Hz, 1H), 6.92−6.97 (m, 2H), 7.03−7.07 (q, *J* = 8 Hz, 1H), 7.42−7.46 (t, *J* = 8 Hz, 2H), 7.54−7.58 (t, *J* = 7.6 Hz, 1H), 7.78−7.80 (d, *J* = 7.6 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.1 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.8, 53.9, 54.9, 66.9 (q, *J* = 27 Hz), 77.3, 114.4, 115.2, 121.7, 127.1 (q, *J* = 279 Hz), 128.3, 128.8, 128.8, 133.4, 136.2, 139.2, 158.9, 198.2 ppm; IR (KBr): ν 3445, 2931, 1680, 1600, 1492, 1448, 1251, 1182, 1136, 1052, 781, 692 cm^{-1}; ESI-HRMS: calcd for $C_{19}H_{17}F_3O_3S$ [M + H]$^+$: 383.0923, found 383.0929. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 15.4 min, t_{major} = 56.2 min.

Synthesis of Compound 5. Mixture of the compound **4b** (0.1 mmol) and sodium borohydride (5.7 mg, 0.15 mmol) in anhydrous methanol (1 mL) was stirred at 0 °C. The reaction was monitored by TLC analysis and when the reaction was completed, saturated $NaHCO_3$ and CH_2Cl_2 were added, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated. The mixture was purified by flash chromatography to yield the product as a white solid.

(3***S***,4***R***,5***S***)-4-((***S***)-(4-bromophenyl)(hydroxy)methyl)-5-phenyl-5-(trifluoromethyl)tetrahydrothiophen-3-ol (**5**) white solid; 85% yield (37 mg); 80% ee; $[\alpha]_D^{20}$ = −50.000, (c 0.30, CH_2Cl_2); mp 164−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43−1.44 (d, *J* = 3.2 Hz, 1H), 1.90−1.91 (d, *J* = 5.6 Hz, 1H,), 2.80−2.85 (m, 2H), 3.21−3.25 (dd, *J* = 2.8, 12.4 Hz, 1H), 4.05 (s, 1H), 4.48−4.51 (dd, *J* = 2.4, 10 Hz, 1H), 7.25−7.29 (m, 2H), 7.33−7.40 (m, 1H), 7.42−7.45(m, 4H), 8.00−8.02 (d, *J* = 8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.77 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.1, 60.4, 67.8 (q, *J* = 26 Hz), 71.2, 77.9, 122.0, 128.1, 128.3 (q, *J* = 280 Hz), 128.8, 130.0, 130.8, 131.5, 134.1, 142.0 ppm; IR (KBr): ν 3460, 2936, 1487, 1244, 1192, 1130, 1072, 1011, 829, 719 cm^{-1}; ESI-HRMS: calcd for $C_{19}H_{18}O_4S$ [M − H]$^+$: 430.9923, found 430.9916. HPLC analysis: Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 12.2 min, t_{minor} = 17.5 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

HPLC chromatograms of **4** and **5**, X-ray crystallographic data for **4a** (CIF), and ^{1}H, ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/jo4016024 | J. Org. Chem. 2013, 78, 11053−11058

AUTHOR INFORMATION

Corresponding Author

*E-mail: xupf@lzu.edu.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful for the NSFC (21032005, 21172097, 21202070), PCSIRT (IRT1138), the International S&T Cooperation Pragram of China (2013DFR70580), the National Basic Research Program of China (No. 2010CB833203), and the"111" program from MOE of P.R. China.

REFERENCES

(1) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (d) Uneyama, K. *Organofluorine Chemistry*; Blackwell Publishing Ltd.: Oxford, 2006.

(2) (a) Ma, J. A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (c) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, 1804. (d) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708. (e) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J. F. *Chem. Soc. Rev.* **2011**, *40*, 2867.

(3) Nie, J.; Guo, H. C.; Cahard, D.; Ma, J. A. *Chem. Rev.* **2011**, *111*, 455.

(4) For selected examples, see: (a) Xie, H.; Zhang, Y.; Zhang, S.; Chen, X.; Wang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 11773. (b) Liu, Y. L.; Shi, T. D.; Zhou, F.; Zhao, X. L.; Wang, X.; Zhou, J. *Org. Lett.* **2011**, *13*, 3826. (c) Palacio, C.; Connon, S. J. *Org. Lett.* **2011**, *13*, 1298.

(5) For examples, see: (a) Matoba, K.; Kawai, H.; Furukawa, T.; Kusuda, A.; Tokunaga, E.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 5762. (b) Kawai, H.; Okusu, S.; Tokunaga, E.; Sato, H.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4959. (c) Kawai, H.; Okusu, S.; Yuan, Z.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 2221. (d) Kawai, H.; Yuan, Z.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5575.

(6) (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (c) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (d) Mayano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703.

(7) Mo, J.; Chen, X.; Chi, Y .R. *J. Am. Chem. Soc.* **2012**, *134*, 8810.

(8) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (d) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

(9) For organocatalytic Michael addition to β,β-disubstituted enones, see: (a) Lu, H. H.; Zhang, F. G.; Meng, X. G.; Duan, S. W.; Xiao, W. J. *Org. Lett.* **2009**, *11*, 3946. (b) Wen, S.; Li, P.; Wu, H.; Yu, F.; Liang, X.; Ye, J. *Chem. Commun.* **2010**, *46*, 4806. (c) Kwiatkowski, P.; Dudziński, K.; Łyżwa, D. *Org. Lett.* **2011**, *13*, 3624.

(10) (a) Jia, Z. X.; Luo, Y. C.; Wang, Y.; Chen, L.; Xu, P. F. *Chem.—Eur. J.* **2012**, *18*, 12958. (b) Ling, J. B.; Wang, W. P.; Xu, P. F. *CatChemCat* **2011**, *3*, 302. (c) Ling, J. B.; Su, Y.; Zhu, H. L.; Wang, G. Y.; Xu, P. F. *Org. Lett.* **2012**, *14*, 1090. (d) Duan, G. J.; Ling, J. B.; Wang, W. P.; Luo, Y. C.; Xu, P. F. *Chem. Commun.* **2013**, *49*, 4625. (e) Tian, L.; Hu, X. Q.; Li, Y. H.; Xu, P. F. *Chem. Commun.* **2013**, *49*, 7213.

(11) (a) Storer, R. L.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330. (b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, *17*, 6890. (c) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416. (d) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 153. (e) Dai, L.; Wang, S. X.; Chem, F. E. *Adv. Synth. Catal.* **2010**, *352*, 2137. (f) Yang, W.; Du, D. M. *Chem. Commun.* **2011**, *47*, 12706.

(12) For selected examples of organocatalytic sulfa-Michael/aldol cascade reactions, see: (a) O'Connor, C. J.; Roydhouse, M. D.; Przybył, A. M.; Wall, M. D.; Southern, J. M. *J. Org. Chem.* **2010**, *75*, 2534. (b) Tang, J.; Xu, D. Q.; Xia, A. B.; Wang, Y. F.; Jiang, J. R.; Luo, S. P.; Xu, Z. Y. *Adv. Synth. Catal.* **2010**, *352*, 2121. (c) Duan, S. W.; Li, Y.; Liu, Y. Y.; Zou, Y. Q.; Shi, D. Q.; Xiao, W. J. *Chem. Commun.* **2012**, *48*, 5160.

(13) (a) Williams, D. R.; Jass, P. A.; Tse, H. L. A.; Gaston, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4552. (b) Li, A. H.; Dai, L. X.; Hou, X.-L.; Huang, Y. Z.; Li, F. W. *J. Org. Chem.* **1996**, *61*, 489. (c) Julienne, K.; Metzner, P. *J. Org. Chem.* **1998**, *63*, 4532. (d) Zanardi, J.; Lamazure, D.; Miniere, S.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2002**, *67*, 9083. (e) Piccinini, A.; Kavanagh, S. A.; Connon, P. B.; Connon, S. J. *Org. Lett.* **2010**, *12*, 608.

(14) CCDC 933238 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) Konno, T.; Takehana, T.; Mishima, M.; Ishihara, T. *J. Org. Chem.* **2006**, *71*, 3545.