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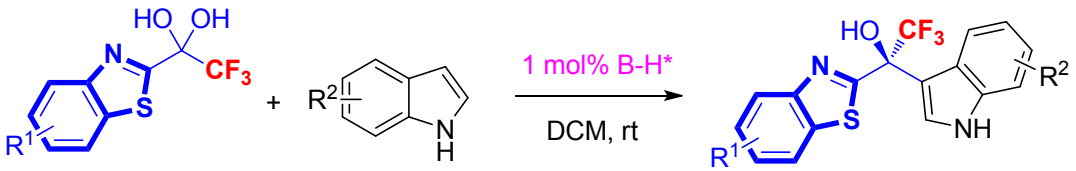
Brønsted Acid-Catalyzed Asymmetric Friedel–Crafts Alkylation of Indoles with Benzothiazole-Bearing Trifluoromethyl Ketone Hydrates

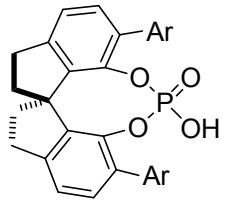
Wei Wang, Wenhui Xiong, Jinping Wang,* Qiu-An Wang,* and Wen Yang*

College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, People's Republic of China

E-mail: yangwen@hnu.edu.cn; wangqa@hnu.edu.cn; jinpingwang1985@126.com



up to 99% yield, >99% ee



Ar = 2,4,6-^{i}Pr$_3$C$_6$H$_2$

B-H*

- **Excellent efficiency and enantioselectivity**
- **Mild recation conditions and low catalyst loading**
- **Simple operation and easy gram-scale preparation**
- **Synthesis of enantioenriched α-trifluoromethyl tertiary alcohols with two important heterocycles (benzothiazoles and indoles)**

ABSTRACT

An efficient Brønsted acid-catalyzed asymmetric Friedel–Crafts alkylation of indoles with benzothiazole-bearing trifluoromethyl ketone hydrates as electrophiles has been developed. The mild organocatalytic reactions proceeded well with low catalyst loading to afford a range of enantioenriched α-trifluoromethyl tertiary alcohols containing both benzothiazole and indole rings with excellent yields and enantioselectivities.

INTRODUCTION

Trifluoromethylated compounds, due to their unique properties, including high electronegativity, lipophilicity, and metabolic stability, have attracted great attention in the past decades.[1,2] Particularly intriguing are chiral α-trifluoromethyl tertiary alcohols, which are important building blocks for the preparation of pharmaceuticals and agrochemicals (Figure 1).[3] The notable examples are efavirenz and indole-substituted trifluoromethyl alcohol **A**,[3a,e,f] which are HIV-1 reverse transcriptase inhibitors. Asymmetric Friedel−Crafts alkylation of indoles with trifluoromethyl ketones (trifluoroacetophenones and trifluoropyruvates) is an effective and straightforward access to chiral α-trifluoromethyl tertiary alcohols (Scheme 1a).[4,5] Although many examples have been reported, most of them suffer high catalyst loading, harsh conditions, and/or diarylated byproducts. Thus, addressing these shortcomings of this useful transformation is still in demand. To address these issues, previous reports mostly focus on the development of new catalytic systems, but rarely start with developing efficient substrates. Herein, we use benzothiazole-bearing trifluoromethyl ketone hydrates as electrophiles instead of trifluoroacetophenones and trifluoropyruvates (Scheme 1b).

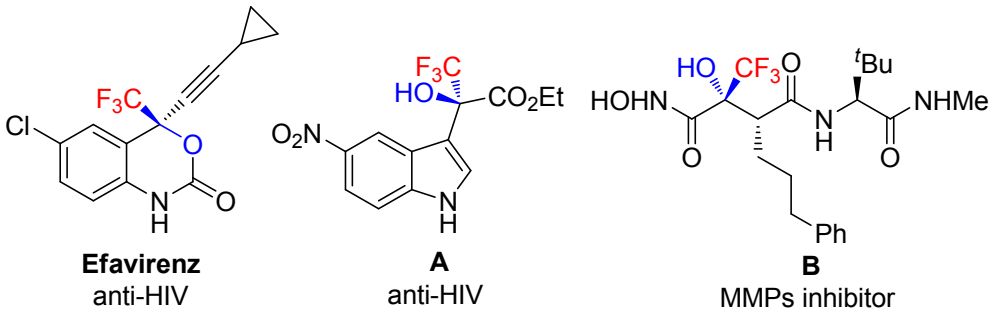
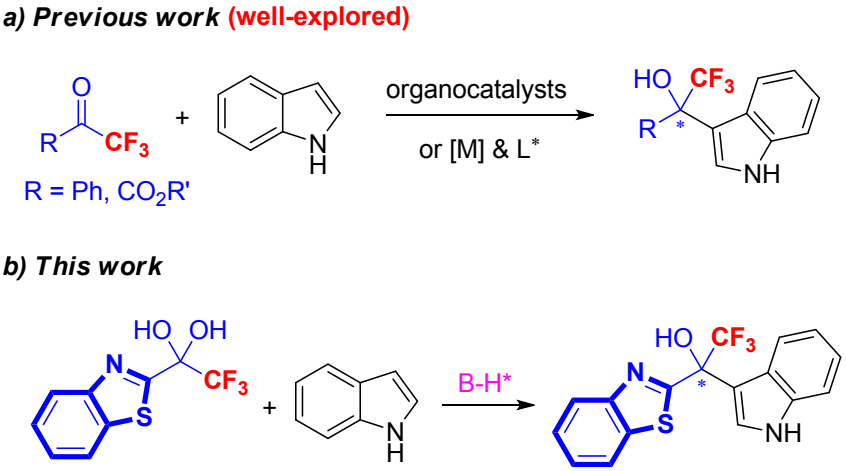


Figure 1. Examples of pharmaceuticals containing chiral α-trifluoromethyl tertiary alcohols.

Benzothiazole is an important heterocyclic skeleton frequently found in numerous natural products, pharmaceutical molecules, catalysts, fluorescent probes, and materials.[6] The combination of two privileged structures, a benzothiazole ring and a trifluoromethyl moiety, for the synthesis of chiral organic molecules could be of significant importance, especially for new drugs and materials. However, there are just a handful of reports on racemic or achiral synthesis.[7] In this paper, we realize the assembly of such chiral molecules via an efficient Brønsted acid-catalyzed asymmetric Friedel−Crafts alkylation

of indoles with benzothiazole-bearing trifluoromethyl ketone hydrates as electrophiles (Scheme 1b). Notably, the introduction of an electon-deficient benzothiazole ring could bring several benefits. First, it could significantly enhance the electrophilicity of substrates, solving the problem of low reactivity. Second, it could help to stabilize the monoarylated adducts, thereby suppressing the formation of diarylated byproducts. Third, it also gives us a good chance to introduce important benzothiazole heterocycles into chiral α-trifluoromethyl tertiary alcohols.

Scheme 1. Asymmetric Friedel–Crafts Alkylation of Indole for α-Trifluoromethyl Tertiary Alcohols

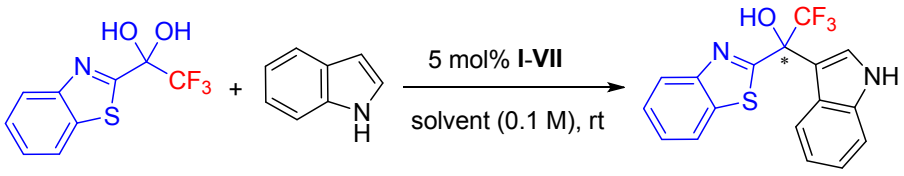


RESULTS AND DISCUSSION

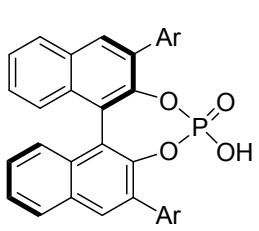
Initially, we readily prepared benzothiazole-bearing trifluoromethyl ketone hydrate **1a** in one step by a slightly modified procedure,[8] and directly used it as an electrophile for the catalytic asymmetric Friedel−Crafts alkylation of indole **2a**. In the presence of 5 mol% of chiral phosphoric acid **I**, we were pleased to find that the reaction proceeded smoothly in toluene at room temperature to provide the desired product **3aa** with full conversion, albeit with low enantioselectivity (16% ee, Table 1, entry 1). The initial success avoided the further synthesis of the corresponding unstable ketone **1a'** as an electrophile. Subsequently, a series of BINOL-derived chiral phosphoric acids **II**−**VI** with different substituents at the 3- and 3'-positions were screened, and the catalyst **V** was found to be superior, providing excellent efficiency and moderate enantioselectivity (Table 1, entries 2−6). The screening results showed that more acidic catalysts **III** and **IV** resulted in a handful of diarylated byproduct, while

less acidic catalyst **VI** just gave trace conversion. The solvent variation has a dramatic impact on the reaction outcome (Table 1, entries 7−13). Dichloromethane was identified as the best solvent providing higher enantioselectivity (78% ee), while other common solvents, such as THF, Et_2O, EtOAc, and MeCN, all resulted in very low conversion. To our delight, we tried SPINOL-derived chiral phosphoric acid **VII** (STRIP), and full conversion and high enantioselectivity (92% ee) were obtained (Table 1, entry 14). The use of 5 Å molecular sieves (MS) further increased the enantioselectivity to 98% ee, and also fulfilled full conversion in a much shorter time (Table 1, entry 15). The enhanced reactivity should be due to MS-accelerated dehydration of trifluoromethyl ketone hydrate **1a**. The reduced catalyst loading (1 or 2 mol %) resulted in essentially no erosion in efficiency and enantioselectivity, but further reducing the loading (0.5 mol %) decreased slightly the enantioselectivity (Table 1, entries 16−18).

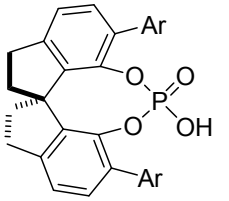
Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3aa**



I: Ar = 9-anthryl
II: Ar = 9-phenanthryl
III: Ar = 1-pyrenyl
IV: Ar = 3,5-$(CF_3)_2C_6H_3$
V: Ar = 2,4,6-$^i Pr_3C_6H_2$
VI: Ar = $SiPh_3$



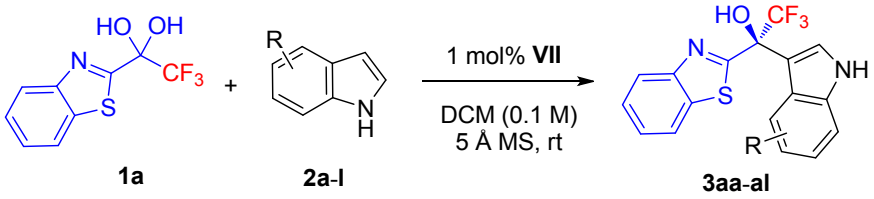
VII: Ar = 2,4,6-$^i Pr_3C_6H_2$

entry	catalyst	solvent	time (h)	conv. (%)[b]	ee (%)[c]
1	**I**	toluene	24	100	16
2	**II**	toluene	24	100	25
3	**III**	toluene	24	80	23
4	**IV**	toluene	24	70	2
5	**V**	toluene	24	95	61
6	**VI**	toluene	24	<10	–[d]
7	**V**	THF	24	<10	–[d]
8	**V**	Et_2O	24	<10	–[d]
9	**V**	EtOAc	24	<10	–[d]
10	**V**	MeCN	24	<10	–[d]
11	**V**	DCM	24	100	78
12	**V**	$CHCl_3$	24	100	48

13	**V**	DCE	24	95	62
14	**VII**	DCM	24	100	-92
15[e]	**VII**	DCM	2	100	-98
16[e,f]	**VII**	DCM	4	100	-98
17[e,g]	**VII**	DCM	6	100	-97
18[e,h]	**VII**	DCM	12	100	-93

[a]Reactions were performed with **1a** (0.10 mmol), **2a** (0.15 mmol), and catalyst (5 mol%) in solvent (1.0 mL). [b]Determined by ^{1}H NMR analysis. [c]Determined by HPLC analysis. [d]Not determined. [e]Run with 5 Å MS (60 mg). [f]Run with 2 mol% **VII**. [g]Run with 1 mol% **VII**. [h]Run with 0.5 mol% **VII**.

Table 2. Substrate Scope with Different Indoles[a]

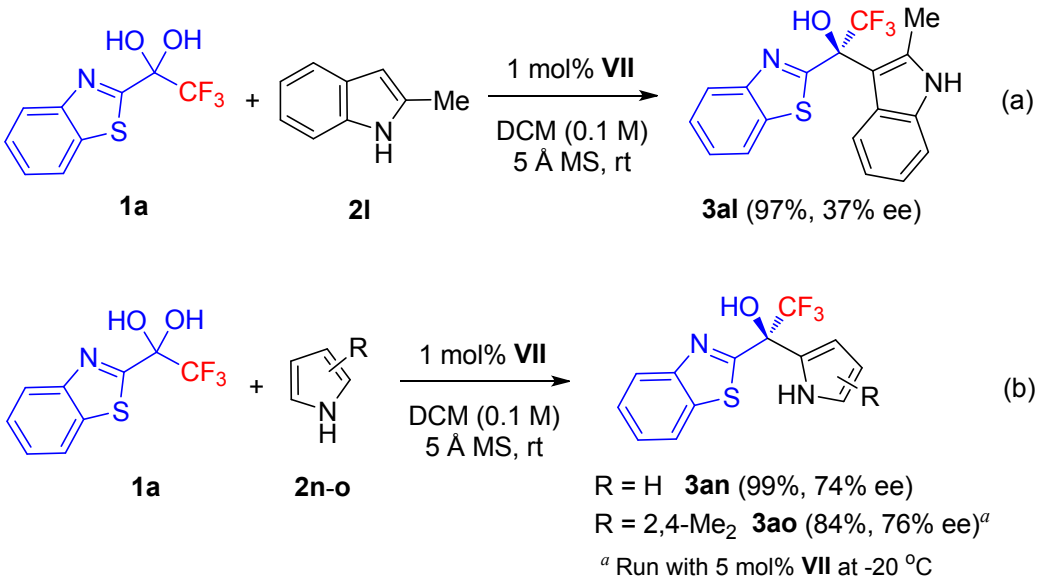


1a **2a-l** **3aa-al**

entry	R	time (h)	product	yield (%)[b]	ee (%)[c]
1	H	10	**3aa**	99	97
2	5-Me	7	**3ab**	99	92
3	6-Me	8	**3ac**	95	97
4	7-Me	7	**3ad**	99	97
5	4-Me	36	**3ae**	75	>99
6	5-OMe	6	**3af**	99	97
7	4-OMe	7	**3ag**	99	99
8	6-F	12	**3ah**	99	>99
9	5-Cl	16	**3ai**	99	97
10	5-Br	16	**3aj**	96	98
11	6-Br	16	**3ak**	99	95

[a]Reactions were performed with **1a** (0.20 mmol), **2** (0.30 mmol), catalyst **VII** (1 mol%), and 5 Å MS (120 mg) in DCM (2.0 mL). [b]Isolated yield. [c]Determined by chiral HPLC analysis.

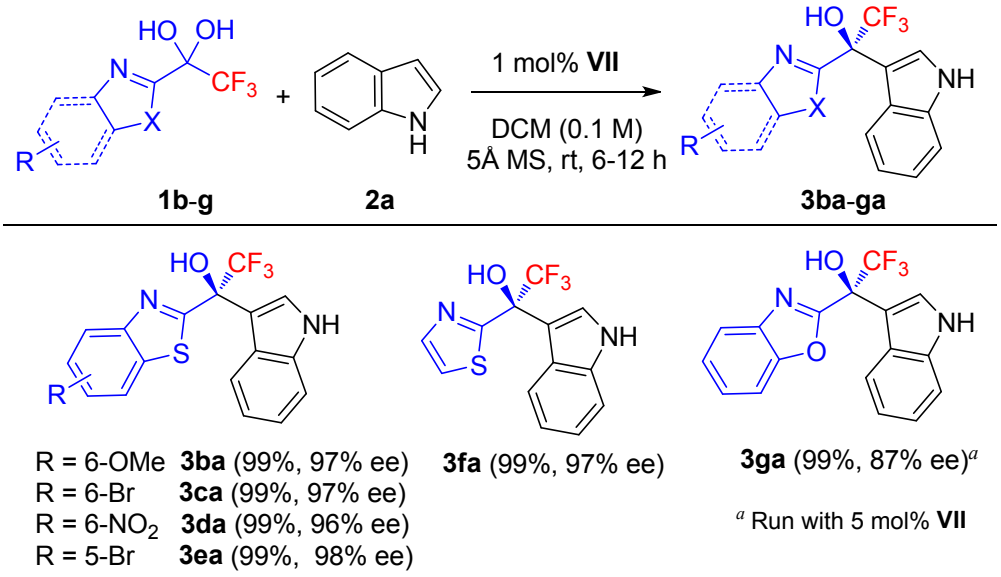
Scheme 2. Asymmetric Friedel–Crafts Alkylation with 2-Methylindole and Pyrroles



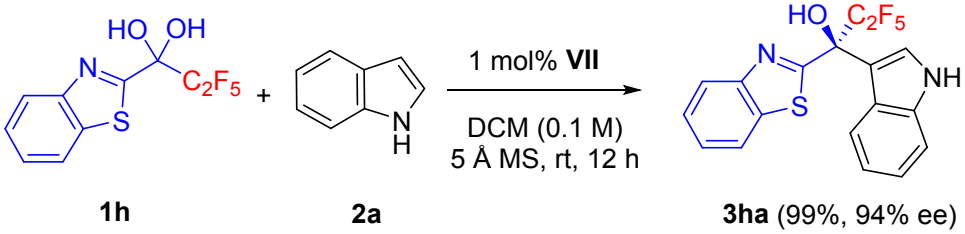
Having established the standard reaction conditions, we next examined the substrate scope of the catalytic asymmetric Friedel−Crafts reaction. A range of indoles with different substituents at the 4-, 5-, 6-, or 7- positions proceeded smoothly to afford the corresponding *α*-trifluoromethyl tertiary alcohols **3aa**−**ak** with excellent yields and enantioselectivities (Table 2, entries 1−11). Unfortunately, low enantioselectivity (37% ee) was observed for 2-methylindole **2l**, and no reaction occurred for 3-substituted indoles (Scheme 2a). Pyrroles **2n**−**o** were also viable substrates, but just good enantioselectivities (74−76% ee) were achieved (Scheme 2b). Subsequently, trifluoromethyl ketone hydrates **1b**−**g** were tested for this useful transformation (Scheme 3). Hydrates **1b**−**e** with different groups on the benzothiazole ring proceeded well, furnishing the desired products **3ba**−**ea** with excellent yields and enantioselectivities. The position and electronic property of substituents did not affect the process. Hydrate **1f** bearing a thiazole ring also gave a comparable result. Benzoxazole-based hydrate **1g** was also a suitable substrate, and the desired product **3ga** was obtained in excellent yield albeit with diminished enantioselectivity (87% ee). Unfortunately, trifluoromethyl ketone hydrates with other heterocycles, including imidazole, pyridine, and triazole, were infeasible substrates, presumably because their basicity affected the acid-catalyzed process. Notably, perfluoroethyl ketone hydrate **1h** as a viable substrate provided the corresponding product **3ha** with 99% yield and 94% ee (Scheme 4). In addition, under the standard conditions, we also used trifluoroacetophenone **1i** and ethyl trifluoropyruvate **1j** as electrophiles for Friedel−Crafts alkylation of indole. No reaction was observed

for the former, and the later provided the desired product **1ja** with 82% yield but just 6% ee (Scheme 5). The results show that the introduction of a benzothiazole ring makes a big difference in the reactivity and stereoselectivity. The benzothiazole ring as an electon-deficient group improves the eletrophilicity of trifluoromethyl ketone hydrates, and it also results in excellent enantioselectivity presumably because of the effect of steric hindrance and π–π interaction with indole.

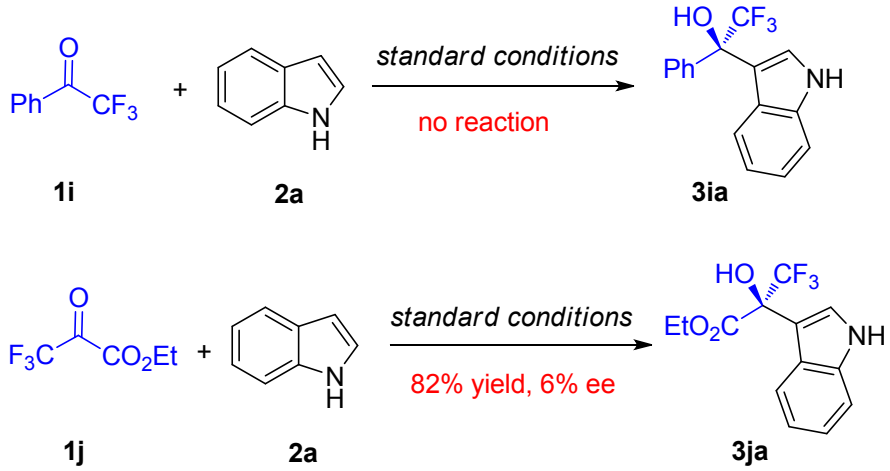
Scheme 3. Substrate Scope with Different Trifluoromethyl Ketone Hydrates



Scheme 4. Asymmetric Friedel–Crafts Alkylation of Indole with Perfluoroethyl Ketone Hydrate

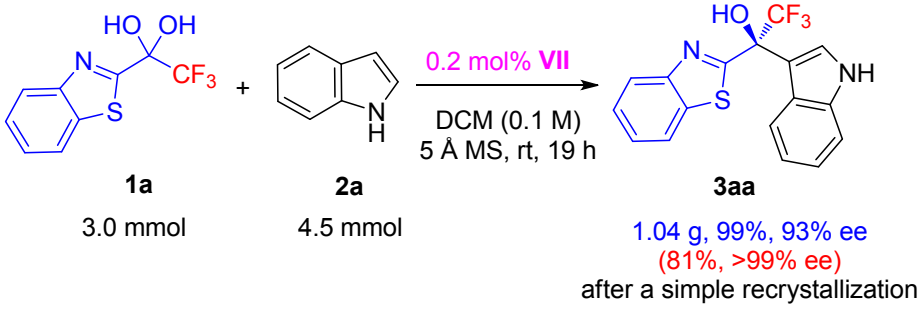


Scheme 5. Asymmetric Friedel–Crafts Alkylation of Indole with Trifluoroacetophenone and Ethyl Trifluoropyruvate

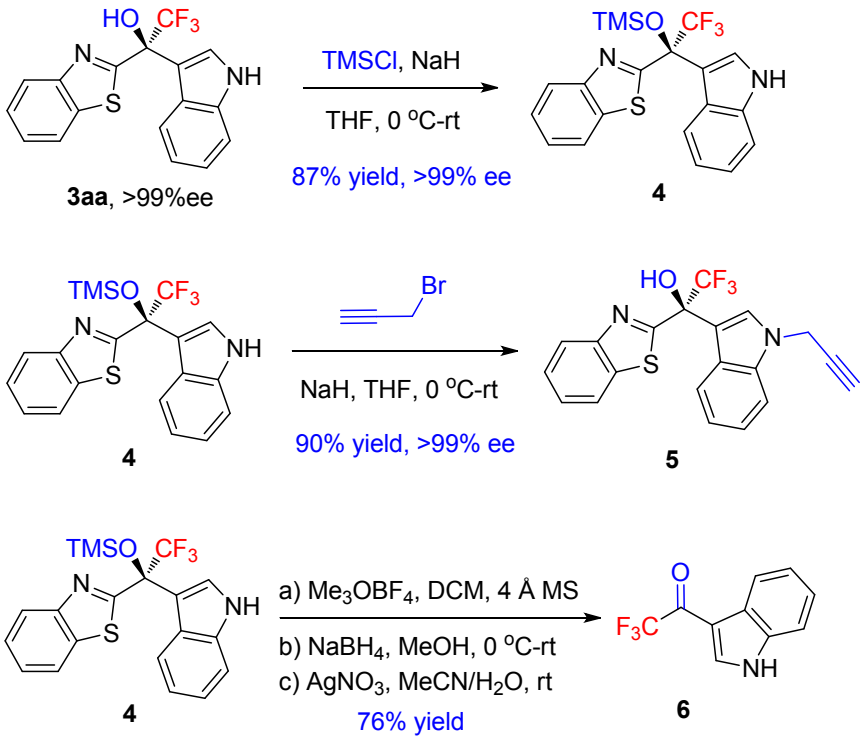


To show the synthetic potential of this protocol, we carried out the gram-scale synthesis and product transformations (Scheme 6 and 7). Notably, in the presence of 0.2 mol% of **VII**, a gram-scale catalytic reaction was performed well in quantitative yield with 93% ee, and optically pure product **3aa** was easily obtained by a simple recrystallization from petroleum ether/ethyl acetate. The absolute configuration of enantiopure (*R*)-**3aa** was unambiguously confirmed by single crystal X-ray analysis. Alcohol **3aa** was readily transformed into **4** by protection with chlorotrimethylsilane. Alkylation of **4** with 3-bromoprop-1-yne at the *N*-position, followed by deprotection in the workup step, provided the desired product **5** in high yield and with excellent enantioselectivity maintained. The alkyne moiety of **5** can be used to link other functional molecules via a click reaction. Moreover, we tried to convert the benzothiazole ring into a formyl group by a known procedure.[9] When alcohol **3aa** and its derivatives with different protecting groups (TMS, TBS, and Me) were used for this transformation, we all failed to get the corresponding chiral aldehyde. Instead, the simple ketone **6** was formed with good efficiency.

Scheme 6. The Gram-Scale Catalytic Reaction



Scheme 7. Product Transformations



To understand the mechanism, we carried out some control experiments (Scheme 8). When trifluoromethyl ketone **1a'** instead of hydrate **1a** was subjected to the standard conditions, almost the same reaction outcome was achieved (99% yield, 97.5% ee). The result showed that the process firstly underwent the acid-promoted dehydration of hydrate **1a** to form ketone **1a'**. *N*-Methyl indole **2m** was also subjected to the standard conditions, but just trace conversion was observed. Under otherwise identical conditions, 5 mol% of BINOL-derived phosphoric acid **V** was employed to evaluate the performance of both indole **2a** and *N*-methyl indole **2m**, and **2a** provided much higher efficiency and enantioselectivity than **2m**. The results show that the N−H group of indole is the active site of catalyst through the hydrogen bonding, and plays an important role in both reactivity and stereocontrol.

Scheme 8. Control Experiments

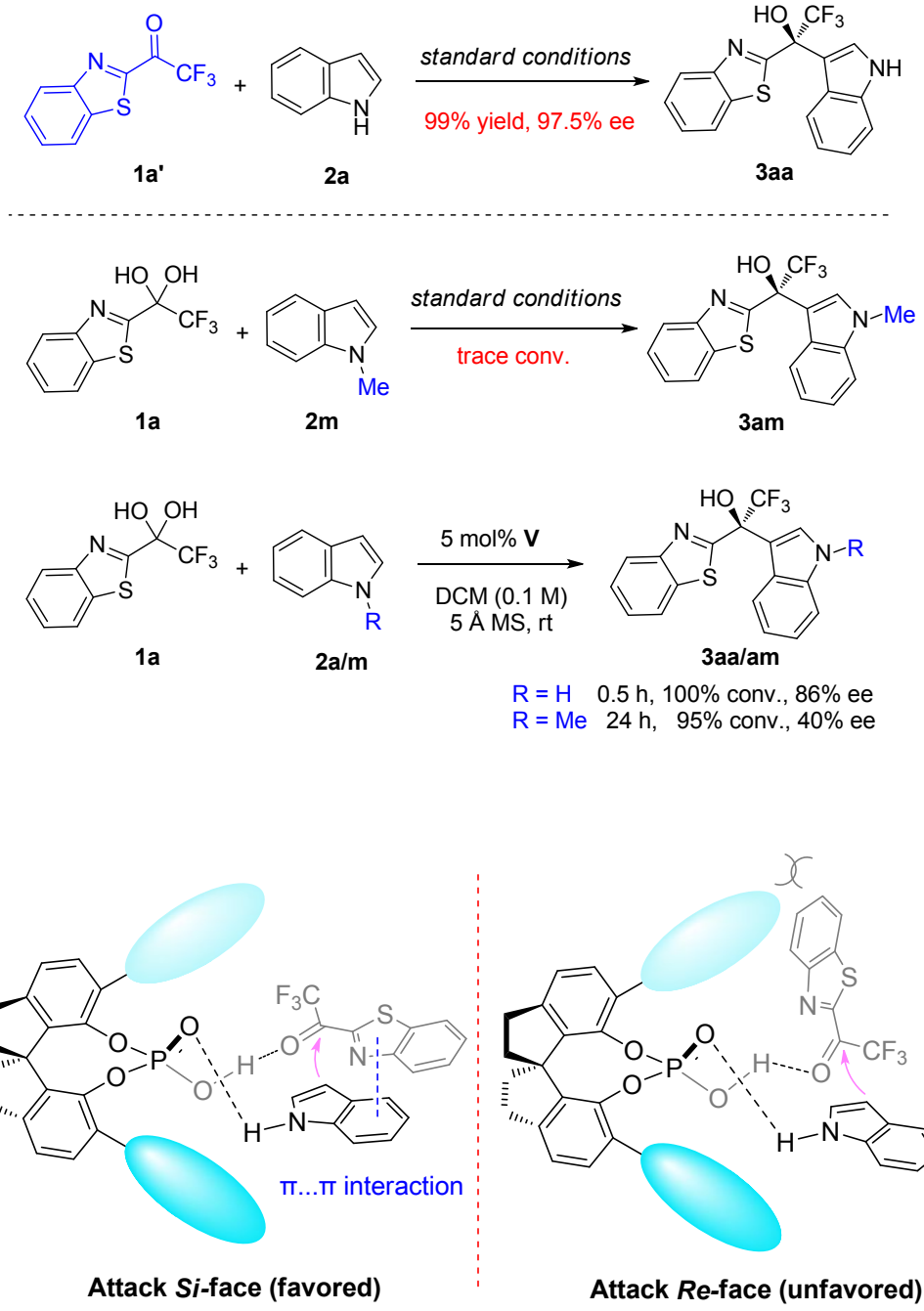


Figure 2. Possible transition state model.

Based on the observed results of control experiments and the absolute configuration of **3aa**, we proposed a possible transition state model (Figure 2). First, trifluoromethyl ketone hydrate **1a** undergoes the acid-promoted dehydration to form trifluoromethyl ketone **1a'**. Then, the chiral phosphoric acid catalyst **VII** acts in a bifunctional fashion. The ketone **1a'** is activated by the acid proton moiety through the hydrogen bonding. Meanwhile, the phosphoryl oxygen atom as a basic site interacts with indole through the hydrogen bonding. Considering the steric effect between the catalyst substituent and the

benzothiazole moiety of ketone, and possible π–π interaction, indole **2a** favors the *Si*-face attack of ketone to provide the (*R*)-configured product **3aa**.

CONCLUSIONS

In summary, we have developed an efficient Brønsted acid-catalyzed asymmetric Friedel−Crafts alkylation of indoles with trifluoromethyl ketone hydrates. With a suitable employment of benzothiazole-bearing trifluoromethyl ketone hydrates as electrophiles, chiral phosphoric acid catalyst (STRIP), and 5 Å molecular sieve, the present reaction provided a range of enantioenriched *α*-trifluoromethyl tertiary alcohols bearing both benzothiazole and indole rings with excellent yields and enantioselectivities. This protocol features excellent efficiency and enantioselectivity, mild reaction conditions, low catalyst loading, simple operation, and easy gram-scale preparation. This work represents a new and rare example of catalytic asymmetric method for chiral molecules bearing a benzothiazole ring and a trifluoromethyl moiety located at a stereogenic carbon atom, which should be attractive and potential for drug discovery. Further investigation on catalytic asymmetric reactions with trifluoromethyl ketone hydrates is underway.

EXPERIMENTAL SECTION

General Information. Column chromatography was performed over silica gel (200-300 mesh) purchased from Qindao Puke Co., China. All air or moisture sensitive reactions were conducted in oven-dried glassware under nitrogen atmosphere using anhydrous solvents. Anhydrous dichloromethane, tetrahydrofuran, and acetonitrile were purchased from Energy Chemical and used as received. ACS grade 2,2,2-trifluoroacetic anhydride (TFA), Et_3N, toluene, and 1,2-dichloroethane were purchased from Sinopharm Chemical Reagent Co.,Ltd and used as received. ^1H, ^{13}C, and ^{19}F NMR spectra were collected on a Varian INOVA-400 or a Bruker AV-400 NMR spectrometer using peaks of deuterated solvents as an internal standard (^1H NMR: $CDCl_3$ at 7.26 ppm, d6-acetone at 2.05 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm, d6-acetone at 206.26 ppm). High resolution mass spectra were collected on a

MALDI Micro MX mass spectrometer. Optical rotations were measured on JASCO P-2000 polarimeter with $[\alpha]_D$ values reported in degrees; concentration (c) is in 10 mg/mL. The enantiomeric excesses were determined by chiral HPLC using a Shimadzu Prominence LC-20A instrument with a Daicel Chiralcel OD-H column or a Daicel Chiralpak AD-H or AS-H column.

The Synthesis of Ketone Hydrates 1a-h.[8] *1-(Benzo[d]thiazol-2-yl)-2,2,2-trifluoroethane-1,1-diol* **(1a)**. To a solution of benzothiazole (1.35 g, 10.0 mmol) in toluene (20 mL) at -20 °C was added dropwise trifluoroacetic anhydride (2.52 g, 12.0 mmol) over 10 min. The mixture was stirred for 0.5 h, and triethylamine (1.21 g, 12.0 mmol) was slowly added. After stirring at -20 °C for overnight, the resulting reaction mixture was spontaneously warmed to room temperature and stirred 12 h. The solvent was removed in *vacuo*, and water (5 mL) was added to form white precipitation, which was dissolved in ethyl acetate (80 mL). The organic phase was successively washed with 1 M HCl (30 mL), water (30 mL), and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo* to afford the crude product. The pure ketone hydrate **1a** was obtained by recrystallization from petroleum ether/ethyl acetate (5:1) as a white solid (2.30 g, 92% yield), m.p. 144-146 °C. ^{1}H NMR (400 MHz, d6-acetone) δ 8.11-8.08 (m, 2H), 7.60 (s, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 168.8, 153.5, 136.6, 127.1, 126.8, 124.3, 123.4 (q, J = 286.3 Hz), 122.8, 93.2 (q, J = 33.0 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -83.5 ppm. HRMS (ESI) m/z: $[M - H_2O]^+$ Calcd for $C_9H_4F_3NOS$ 230.9966; Found 230.9961.

2,2,2-Trifluoro-1-(6-methoxybenzo[d]thiazol-2-yl)ethane-1,1-diol **(1b)** was prepared from 6-methoxybenzothiazole (0.83 g, 5.0 mmol) according to the above procedure. White solid, m.p. 126-128 °C; 1.01 g, 72% yield. ^{1}H NMR (400 MHz, d6-acetone) δ 7.94 (d, J = 8.8 Hz, 1H), 7.61 (s, 1H), 7.51 (br s, 2H), 7.14 (d, J = 8.8 Hz, 1H), 3.88 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 165.4, 158.7, 147.3, 137.7, 124.3, 123.0 (q, J = 286.3 Hz), 116.5, 104.1, 92.6 (q, J = 33.0 Hz), 55.5 ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -83.6 ppm. HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{10}H_8F_3NO_3S$ 279.0177; Found 279.0169.

1-(6-Bromobenzo[d]thiazol-2-yl)-2,2,2-trifluoroethane-1,1-diol **(1c)** was prepared from 6-bromobenzothiazole (1.07 g, 5.0 mmol) according to the above procedure. White solid, m.p. 136-138 °C; 0.45 g, 28% yield. ^{1}H NMR (400 MHz, d6-acetone) δ 8.32 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.62 (s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 169.2, 151.9, 137.8, 129.9, 125.1, 124.8, 122.6 (q, J = 286.4 Hz), 119.3, 92.5 (q, J = 33.1 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -83.4 ppm. HRMS (ESI) Calcd for $C_9H_3BrF_3NOS$ [M - H_2O]$^+$: 308.9071, Found: 308.9063.

2,2,2-Trifluoro-1-(6-nitrobenzo[d]thiazol-2-yl)ethane-1,1-diol **(1d)** was prepared from 6-nitrobenzothiazole (1.80 g, 10.0 mmol) according to the above procedure. White solid, m.p. 102-103 °C; 1.24 g, 42% yield. ^{1}H NMR (400 MHz, d6-acetone) δ 9.17 (d, J = 2.4 Hz, 1H), 8.44 (dd, J = 2.4, 9.2 Hz, 1H), 8.28 (d, J = 8.8 Hz, 1H), 7.80 (s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 174.9, 156.7, 145.7, 136.4, 124.4, 122.6 (q, J = 286.5 Hz), 121.7, 119.2, 92.6 (q, J = 33.2 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -83.5 ppm. HRMS (ESI) m/z: [M - H_2O]$^+$ Calcd for $C_9H_3F_3N_2O_3S$ 275.9816; Found 275.9818.

1-(5-Bromobenzo[d]thiazol-2-yl)-2,2,2-trifluoroethane-1,1-diol **(1e)** was prepared from 5-bromobenzothiazole (1.61 g, 7.5 mmol) according to the above procedure. White solid, m.p. 120-121 °C; 1.84 g, 75% yield. ^{1}H NMR (400 MHz, d6-acetone) δ 8.24 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 12.0 Hz, 1H), 7.61 (s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 170.8, 154.5, 135.4, 129.5, 126.6, 124.2, 123.0 (q, J = 286.4 Hz), 119.9, 92.8 (q, J = 33.3 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -83.5 ppm. HRMS (ESI) Calcd for $C_9H_5BrF_3NO_2S$ [M]$^+$: 326.9176, Found: 326.9171.

2,2,2-Trifluoro-1-(thiazol-2-yl)ethane-1,1-diol **(1f)** was prepared from thiazole (0.85 g, 10.0 mmol) according to the above procedure. White solid, m.p. 93-95 °C; 0.30 g, 15% yield. ^{1}H NMR (400 MHz, d6-acetone) δ, 7.83 (s, 1H), 7.74 (s, 1H), 7.40 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 166.4, 142.0, 122.05 (q, J = 286.1 Hz), 122.02, 91.7 (q, J = 33.0 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -84.0 ppm. HRMS (ESI) m/z: [M - H_2O]$^+$ Calcd for $C_5H_2F_3NOS$ 180.9809; Found 180.9814.

1-(Benzo[d]oxazol-2-yl)-2,2,2-trifluoroethane-1,1-diol **(1g)** was prepared from benzooxazole (1.19 g, 10.0 mmol) according to the above procedure. White solid, m.p. 120-121 °C; 1.01 g, 43% yield. ^{1}H

NMR (400 MHz, d6-acetone) δ 7.81 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.63 (br s, 2H), 7.51-7.42 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, d6-acetone) δ 160.7, 150.8, 140.0, 126.4, 125.0, 122.3 (q, J = 285.9 Hz), 120.5, 111.1, 93.2 (q, J = 33.0 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -83.8 ppm. HRMS (ESI) m/z: $[M]^+$ Calcd for $C_9H_6F_3NO_3$ 233.0300; Found 233.0298.

1-(Benzo[d]thiazol-2-yl)-2,2,3,3,3-pentafluoropropane-1,1-diol **(1h)** was prepared from benzothiazole (1.35 g, 10.0 mmol) and 2,2,3,3,3-pentafluoropropanoic anhydride (3.72 g, 12.0 mmol) according to the above procedure. White solid, m.p. 81-82 ^oC; 1.01 g, 33% yield. ^1H NMR (400 MHz, d6-acetone) δ 8.13 (d, J = 8.0 Hz, 1H), 8.08 (q, J = 8.0 Hz, 1H), 7.59 (s, 2H), 7.57-7.51 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, d6-acetone) δ 169.0, 153.1, 136.9, 127.1, 126.8, 124.3, 122.8, 119.8 (qt, J_1 = 285.2 Hz, J_2 = 43.5 Hz), 112.6 (tq, J_1 = 262.1 Hz, J_2 = 34.9 Hz), 94.3 (t, J = 25.8 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -79.3, -81.9, -118.2, -124.9 ppm. HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{10}H_6F_5NO_2S$ 299.0039; Found 298.9996.

.**General Procedure for Catalytic Asymmetric Friedel−Crafts Alkylation.** To a solution of trifluoromethyl ketone hydrate **1** (0.20 mmol), and catalyst **VII** (1 mol%) in dichloromethane (2.0 mL) was added 5 Å MS (120 mg) and indole or pyrrole **2** (0.30 mmol). After stirring at room temperature for specified time, the mixture was directly purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5:1 to 3:1) to afford the desired product **3**.

(R)-1-(Benzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(1H-indol-3-yl)ethan-1-ol **(3aa)**. White solid, m.p. 133-134 ^oC, 69.1 mg, 99% yield. $[\alpha]_D^{10}$: −53.8 (c = 0.51, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 ^oC): t_1 = 8.7 min (minor), t_2 = 11.1 min (major), 97% ee. ^1H NMR (400 MHz, d6-acetone) δ 10.58 (br s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.09 (t, J = 7.2 Hz, 1H), 6.98 (s, 1H), 6.94 (t, J = 7.6 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, d6-acetone) δ 172.3, 154.0, 137.4, 136.1, 126.8, 126.2, 125.6 (q, J = 285.4 Hz), 125.5, 124.1, 124.0, 122.6, 122.4, 121.3, 120.2, 112.3, 111.8, 78.0 (q, J = 30.4 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.4 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{11}F_3N_2NaOS$ 371.0442; Found 371.0485.

(R)-1-(Benzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(5-methyl-1H-indol-3-yl)ethan-1-ol **(3ab)**. White solid, m.p. 182-183 ^oC, 71.7 mg, 99% yield. $[\alpha]_D^{10}$: −98.8 (c = 0.51, acetone). The enantioselectivity was

determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 7.1 min (minor), t_2 = 9.0 min (major), 92% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.45 (br s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.62 (s, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 1.6 Hz, 1H), 2.25 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 172.5, 154.2, 136.3, 136.0, 129.1, 127.0, 126.7, 126.4, 125.75, 125.74 (q, J = 285.3 Hz), 124.3, 124.2, 122.7, 121.2, 112.1, 111.4, 78.2 (q, J = 30.5 Hz), 21.6 ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.5 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{13}F_3N_2NaOS$ 385.0598; Found 385.0608.

(R)-1-(Benzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(6-methyl-1H-indol-3-yl)ethan-1-ol **(3ac)**. White solid, m.p. 145-146 °C, 68.6 mg, 95% yield. $[\alpha]_D^{10}$: −51.8 (*c* = 0.50, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 12.6 min (minor), t_2 = 15.1 min (major), 97% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.43 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.61 (s, 2H), 7.52-7.45 (m, 3H), 7.23 (s, 1H), 6.91 (s, 1H), 6.80 (d, J = 8.4 Hz, 1H), 2.35 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 172.4, 154.0, 137.9, 136.2, 132.1, 126.8, 126.2, 125.6 (q, J = 285.6 Hz), 124.9, 124.2, 124.0, 122.6, 122.0, 121.1, 112.1, 111.7, 78.0 (q, J = 30.4 Hz), 21.4 ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.4 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{13}F_3N_2NaOS$ 385.0598; Found 385.0608.

(R)-1-(Benzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(7-methyl-1H-indol-3-yl)ethan-1-ol **(3ad)**. White solid, m.p. 163-164 °C, 72.0 mg, 99% yield. $[\alpha]_D^{10}$: −42.1 (*c* = 0.50, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 7.7 min (minor), t_2 = 14.0 min (major), 97% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.55 (br s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 2H), 6.96 (s, 1H), 6.89 (d, J = 7.2 Hz, 1H), 6.85 (t, J = 7.2 Hz, 1H), 2.43 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 172.3, 153.9, 136.9, 136.1, 126.8, 126.2, 125.9, 125.5 (q, J = 285.3 Hz), 125.0, 124.0, 123.0, 122.5, 121.5, 120.4, 119.0, 112.2, 78.0 (q, J = 30.3 Hz), 16.6 ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.3 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{13}F_3N_2NaOS$ 385.0598; Found 385.0595.

(R)-1-(Benzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(4-methyl-1H-indol-3-yl)ethan-1-ol **(3ae)**. White solid, m.p. 207-208 °C, 54.7 mg, 75% yield. $[\alpha]_D^{10}$: −10.3 (*c* = 0.52, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 7.7 min (minor), t_2 = 11.2 min (major), >99% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.65 (br s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.49-7.40 (m, 2H), 7.29 (d, J = 8.0 Hz, 1H), 6.96 (t, J = 8.0 Hz, 1H), 6.68-6.65 (m, 2H), 2.94 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 172.2, 153.4, 138.3, 137.3, 131.1, 126.9, 126.5,

126.0 (q, J = 3.8 Hz), 125.9 (q, J = 286.8 Hz), 125.7, 124.2, 122.90, 122.88, 122.7, 111.7, 110.2, 78.1 (q, J = 29.0 Hz), 22.2 ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -74.3 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{13}F_3N_2NaOS$ 385.0598; Found 385.0627.

(R)-1-(Benzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(5-methoxy-1H-indol-3-yl)ethan-1-ol **(3af)**. White solid, m.p. 183.5-184.3 °C, 75.4 mg, 99% yield. $[\alpha]_D^{10}$: −93.1 (c = 0.50, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H column, *n*-hexane/*i*-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 13.4 min (major), t_2 = 15.3 min (minor), 97% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.45 (br s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 9.2 Hz, 1H), 7.09 (s, 1H), 6.95 (s, 1H), 6.73 (d, J = 8.8 Hz, 1H), 3.59 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 172.5, 154.8, 154.2, 136.2, 132.7, 127.0, 126.9, 126.4, 126.2, 125.8 (q, J = 285.2 Hz), 124.2, 122.7, 113.0, 112.8, 111.6, 103.3, 78.1 (q, J = 30.7 Hz), 55.5 ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -74.5 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{13}F_3N_2NaO_2S$ 401.0548; Found 401.0546.

(R)-1-(Benzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(4-methoxy-1H-indol-3-yl)ethan-1-ol **(3ag)**. White solid, m.p. 214-215 °C, 74.9 mg, 99% yield. $[\alpha]_D^{10}$: −243.1 (c = 0.51, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 7.5 min (minor), t_2 = 9.8 min (major), 99% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.76 (br s, 1H), 8.12-8.09 (m, 2H), 7.77 (s, 1H), 7.69 (s, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.23-7.16 (m, 2H), 6.79 (d, J = 7.2 Hz, 1H), 4.11 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 172.6, 154.4, 151.6, 139.6, 136.1, 127.0, 126.9, 126.4, 125.6 (q, J = 285.4 Hz), 124.2, 123.9, 122.7, 116.1, 111.2, 107.4, 102.1, 77.4 (q, J = 30.0 Hz), 55.7 ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -72.6 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}F_3N_2O_2S$ 379.0728; Found 379.0735.

(R)-1-(Benzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(6-fluoro-1H-indol-3-yl)ethan-1-ol **(3ah)**. White solid, m.p. 110-112 °C, 72.6mg, 99% yield. $[\alpha]_D^{10}$: −42.3 (c = 0.50, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 12.3 min (minor), t_2 = 13.3 min (major), >99% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.66 (br s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.63 (dd, J = 8.4, 5.6 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 9.6 Hz, 1H), 7.09 (br s, 1H), 6.78 (t, J = 9.6 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 172.1, 160.4 (d, J = 234.8 Hz), 154.1, 137.7, 137.5, 136.2, 127.0, 126.4, 125.6 (q, J = 283.8 Hz), 124.2, 123.1, 122.7, 122.6, 112.2, 108.9 (d, J = 24.4 Hz), 98.3 (d, J = 25.8 Hz), 78.0 (q, J = 30.5 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.6, -122.5 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{10}F_4N_2NaOS$ 389.0348; Found 389.0359.

(R)-1-(Benzo[d]thiazol-2-yl)-1-(5-chloro-1H-indol-3-yl)-2,2,2-trifluoroethan-1-ol **(3ai)**. White solid, m.p. 104-105 °C, 76.0 mg, 99% yield. $[\alpha]_D^{10}$: −75.1 (*c* = 0.50, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 17.5 min (minor), t_2 = 19.7 min (major), 97% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.79 (br s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.10 (t, *J* = 8.8 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 171.7, 153.8, 135.8, 135.7, 127.2, 127.1, 126.7, 126.2, 125.4, 125.2 (q, *J* = 284.7 Hz), 123.8, 122.5, 122.4, 121.0, 120.6, 113.6, 77.7 (q, *J* = 30.8 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.7 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{11}ClF_3N_2OS$ 383.0233; Found 383.0227.

(R)-1-(Benzo[d]thiazol-2-yl)-1-(5-bromo-1H-indol-3-yl)-2,2,2-trifluoroethan-1-ol **(3aj)**. White solid, m.p. 172-173 °C, 75.8 mg, 96% yield. $[\alpha]_D^{10}$: −114.1 (*c* = 0.51, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 10.5 min (minor), t_2 = 11.6 min (major), 98% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.80 (br s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.91 (s, 1H), 7.77 (s, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.17 (s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 171.9, 154.0, 136.2, 136.0, 128.0, 127.3, 127.0, 125.4 (q, *J* = 285.0 Hz), 125.3, 124.1, 124.0, 123.9, 122.7, 114.2, 113.2, 111.6, 77.9 (q, *J* = 30.6 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.7 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{11}BrF_3N_2OS$ 428.9707; Found 428.9710.

(R)-1-(Benzo[d]thiazol-2-yl)-1-(6-bromo-1H-indol-3-yl)-2,2,2-trifluoroethan-1-ol **(3ak)**. White solid, m.p. 118-119 °C, 84.7 mg, 99% yield. $[\alpha]_D^{10}$: −63.7 (*c* = 0.52, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AS-H column, *n*-hexane/*i*-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 16.6 min (minor), t_2 = 21.8 min (major), 95% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.73 (br s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.73 (s, 1H), 7.63 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.13 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 171.9, 154.0, 138.4, 136.1, 126.9, 126.7, 126.4, 125.5 (q, *J* = 285.5 Hz), 125.3, 124.1, 123.4, 123.0, 122.6, 115.7, 115.2, 112.2, 77.9 (q, *J* = 30.6 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.6 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{11}BrF_3N_2OS$ 428.9707; Found 428.9708.

(R)-1-(Benzo[d]thiazol-2-yl)-1-(2,6-dimethyl-1H-indol-3-yl)-2,2,2-trifluoroethan-1-ol **(3al)**. White solid, m.p. 140-142 °C, 70.6 mg, 97% yield. $[\alpha]_D^{10}$: −28.5 (*c* = 0.52, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 7.9 min (minor), t_2 = 10.3 min (major), 37% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.34 (br s, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.55

(t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 6.89 (s, 1H), 6.83 (t, J = 7.6 Hz, 1H), 2.38 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, d6-acetone) δ 172.5, 152.6, 136.4, 136.3, 135.7, 128.0, 126.8, 126.5, 126.2 (q, J = 285.3 Hz), 124.3, 122.5, 121.2, 120.7, 119.8, 111.0, 107.2, 78.8 (q, J = 30.4 Hz), 13.6 ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -75.9 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{13}F_3N_2NaOS$ 385.0598; Found 385.0656.

(R)-1-(Benzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(1H-pyrrol-2-yl)ethan-1-ol **(3an)**. White solid, m.p. 84-85 °C, 59.2 mg, 99% yield. $[\alpha]_D^{10}$: -54.2 (c = 0.51, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 8.6 min (minor), t_2 = 27.1 min (major), 74% ee. ^1H NMR (400 MHz, d6-acetone) δ 10.50 (br s, 1H), 8.11-8.06 (m, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.30 (s, 1H), 6.89 (s, 1H), 6.51 (s, 1H), 6.14 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, d6-acetone) δ 171.1, 154.0, 135.8, 127.0, 126.4, 126.0, 124.7 (q, J = 284.6 Hz), 124.1, 122.6, 120.3, 109.3, 108.6, 76.5 (q, J = 31.2 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -78.2 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_9F_3N_2NaOS$ 321.0285; Found 321.0295.

(R)-1-(Benzo[d]thiazol-2-yl)-1-(3,5-dimethyl-1H-pyrrol-2-yl)-2,2,2-trifluoroethan-1-ol **(3ao)**. The product was prepared according to the general procedure with minor modification (5 mol% VII & -20 °C). White solid, m.p. 123-125 °C, 58.6 mg, 84% yield. $[\alpha]_D^{10}$: -81.2 (c = 0.51, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 6.1 min (major), t_2 = 6.7 min (minor), 76% ee. ^1H NMR (400 MHz, d6-acetone) δ 9.88 (br s, 1H), 8.10 (d, J = 8.0 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.06 (s, 1H), 5.65 (s, 1H), 2.19 (s, 3H) 1.97 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, d6-acetone) δ 172.5, 153.8, 135.9, 128.2, 127.0, 126.5, 125.2 (q, J = 286.6 Hz), 124.2, 122.6, 120.0, 119.0, 110.8, 76.9 (q, J = 31.9 Hz), 12.6, 12.2 ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -77.2 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{13}F_3N_2NaOS$ 349.0598; Found 349.0656.

(R)-2,2,2-Trifluoro-1-(1H-indol-3-yl)-1-(6-methoxybenzo[d]thiazol-2-yl)ethan-1-ol **(3ba)**. White solid, m.p. 155-156 °C, 75.1 mg, 99% yield. $[\alpha]_D^{10}$: -7.0 (c = 0.51, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 10.5 min (minor), t_2 = 13.1 min (major), 97% ee. ^1H NMR (400 MHz, d6-acetone) δ 10.56 (br s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.62 (d, J = 8.0 Hz,

1H), 7.57 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 2H), 6.89 (s, 1H), 3.83 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, d6-acetone) δ 169.2, 158.7, 148.2, 137.6, 137.4, 126.2, 125.5 (q, *J* = 285.2 Hz), 125.4, 124.5, 122.4, 121.3, 120.1, 116.4, 112.2, 111.9, 104.5, 77.4 (q, *J* = 30.4 Hz), 55.8 ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.7 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}F_3N_2O_2S$ 379.0728; Found 379.0730.

(R)-1-(6-Bromobenzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(1H-indol-3-yl)ethan-1-ol **(3ca)**. White solid, m.p. 203-204 °C, 84.8 mg, 99% yield. $[\alpha]_D^{10}$: -13.5 (*c* = 0.50, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 8.8 min (minor), t_2 = 10.8 min (major), 97% ee. ^1H NMR (400 MHz, d6-acetone) δ 10.61 (br s, 1H), 8.32 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.73 (s, 1H), 7.66 (t, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 6.98 (t, *J* = 7.6 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, d6-acetone) δ 173.4, 153.0, 138.0, 137.5, 130.2, 126.2, 125.6, 125.5 (q, *J* = 285.4 Hz), 125.5, 125.2, 122.6, 121.3, 120.3, 119.4, 112.3, 111.5, 78.0 (q, *J* = 30.4 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.4 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{10}BrF_3N_2NaO_2S$ 450.9527; Found 450.9526.

(R)-2,2,2-Trifluoro-1-(1H-indol-3-yl)-1-(6-nitrobenzo[d]thiazol-2-yl)ethan-1-ol **(3da)**. Yellow solid, m.p. 158-160 °C, 78.0 mg, 99% yield. $[\alpha]_D^{10}$: -2.9 (*c* = 0.51, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 11.6 min (minor), t_2 = 14.6 min (major), 96% ee. ^1H NMR (400 MHz, d6-acetone) δ 10.62 (br s, 1H), 9.09 (s, 1H), 8.34 (d, *J* = 9.2 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.72 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.25 (s, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, d6-acetone) δ 178.9, 157.6, 145.9, 137.4, 136.5, 126.0, 125.6, 125.3 (q, *J* = 285.3 Hz), 124.5, 122.6, 122.0, 121.1, 120.3, 119.5, 112.3, 111.0, 78.3 (q, *J* = 30.8 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.3 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{10}F_3N_3NaO_3S$ 416.0293; Found 416.0287.

(R)-1-(5-Bromobenzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(1H-indol-3-yl)ethan-1-ol **(3ea)**. White solid, m.p. 166-167 °C, 85.0 mg, 99% yield. $[\alpha]_D^{10}$: -101.1 (*c* = 0.50, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 9.3 min (minor), t_2 = 11.9 min (major), 98% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.66 (br s, 1H), 8.24 (s, 1H), 8.09 (d, J = 6.8 Hz, 1H), 7.77 (s, 1H), 7.66 (dd, J_1 = 8.0 Hz, J_2 = 14.4 Hz, 2H), 7.50 (d, J = 8.0 Hz, 1H), 7.17-7.14 (m, 2H), 7.02 (t, J = 7.6 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 174.6, 155.2, 137.4, 135.2, 129.2, 126.6, 126.1, 125.6, 125.4 (q, J = 285.4 Hz), 124.2, 122.6, 121.2, 120.3, 119.9, 112.3, 111.5, 78.0 (q, J = 30.6 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.4 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{10}BrF_3N_2NaO_2S$ 450.9527; Found 450.9526.

(R)-2,2,2-Trifluoro-1-(1H-indol-3-yl)-1-(thiazol-2-yl)ethan-1-ol **(3fa)**. White solid, m.p. 108-110 °C, 59.2 mg, 99% yield. $[\alpha]_D^{10}$: -6.0 (*c* = 0.51, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 16.2 min (minor), t_2 = 17.3 min (major), 97% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.51 (br s, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.61 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.73 (s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, d6-acetone) δ 171.1, 143.3, 137.4, 126.2, 125.5 (q, J = 285.1 Hz), 125.4, 121.8, 121.4, 121.2, 120.0, 112.2, 112.1, 77.56 (q, J = 30.5 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -76.9 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_9F_3N_2NaOS$ 321.0285; Found 321.0326.

(S)-1-(Benzo[d]oxazol-2-yl)-2,2,2-trifluoro-1-(1H-indol-3-yl)ethan-1-ol **(3ga)**. The product was prepared according to the general procedure with minor modification (5 mol% **VII**). White solid, m.p. 215-216 °C, 65.9 mg, 99% yield. $[\alpha]_D^{10}$: -43.8 (*c* = 0.51, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 11.6 min (major), t_2 = 14.9 min (minor), 87% ee. ^{1}H NMR (400 MHz, d6-acetone) δ 10.62 (br s, 1H), 7.82-7.81 (m, 1H), 7.65 (s, 1H), 7.61-7.58 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.42-7.40 (m, 2H), 7.10 (t, J = 7.6 Hz, 1H), 6.96 (t, J = 8.0 Hz, 1H), 6.86 (s, 1H) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, d6-acetone) δ 163.1, 151.3, 141.0, 137.4, 126.7, 126.1, 125.7, 125.5, 125.3 (q, J = 284.3 Hz), 122.5, 121.1, 120.8, 120.3, 112.3, 111.5, 110.5, 75.6 (q, J = 31.7 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -77.3 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{11}F_3N_2NaO_2$ 355.0670; Found 355.0725.

(R)-1-(Benzo[d]thiazol-2-yl)-2,2,3,3,3-pentafluoro-1-(1H-indol-3-yl)propan-1-ol **(3ha)**. White solid, m.p. 147-148 °C, 85.0 mg, 99% yield. $[\alpha]_D^{10}$: -45.1 (c = 0.50, acetone). The enantioselectivity was determined by HPLCanalysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 10.9 min (minor), t_2 = 11.8 min (major), 94% ee. ^1H NMR (400 MHz, d6-acetone) δ 10.63 (s, 1H), 8.05 (t, J = 7.6 Hz, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.84 (d, J =1.0 Hz, 1H), 7.52-7.40 (m, 3H), 7.20 (s, 1H), 7.13 (t, J = 9.6 Hz, 1H), 7.03 (t, J = 9.6 Hz, 1H) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, d6-acetone) δ 172.3, 153.6, 137.1, 135.6, 126.4, 126.0, 125.8, 125.7, 123.6, 122.1, 121.49, 121.46, 119.82, 119.80 (qt, J_1 = 286.8 Hz, J_2 = 36.1 Hz), 114.5 (tq, J_1 = 263.6 Hz, J_2 = 34.2 Hz), 111.9, 111.2, 78.1 (t, J = 25.1 Hz) ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -78.0 (s, 3F), -117.5 (d, J = 274.5 Hz, 1F), -119.1 (d, J = 274.8 Hz, 1F) ppm. HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{18}H_{11}F_5N_2OS$ 398.0512; Found 398.0498.

The Gram-Scale Preparation of 3aa. To a solution of trifluoromethyl ketone hydrate **1** (748 mg, 3.0 mmol), and catalyst **VII** (4.3 mg, 0.006 mmol, 0.2 mol%) in dichloromethane (30.0 mL) was added 5 Å MS (1.80 g) and indole (527 mg, 0.30 mmol), and the reaction mixture was stirred at room temperature for 19 h. Upon completion (monitored by TLC), the mixture was filtered through celite, and washed with dichloromethane (3 × 10 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to afford the desired product **3aa** as a white solid (1.04 g, 99% yield, 93% ee). The pure enantiomer was obtained by a simple recrystallization from petroleum ether/ethyl acetate (5:1) as a white solid (846 mg, 81% yield, >99% ee). m.p. 134-135 °C. $[\alpha]_D^{10}$: −56.8 (c = 0.50, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t = 11.6 min (major), >99% ee.

(R)-2-(2,2,2-Trifluoro-1-(1H-indol-3-yl)-1-((trimethylsilyl)oxy)ethyl)benzo[d]thiazole ***(4)***. Under N_2, to a stirring suspension of NaH (24.0 mg, 0.60 mmol, 60% wt) in dry THF (4 mL) at 0 °C was added dropwise **3aa** (104.5 mg, 0.30 mmol, >99% ee) in dry THF (2.0 mL), and the mixture was stirred at room temperature for 1 h. Then TMSCl (0.15 mL, 1.20 mmol) was added dropwise, and the mixture was stirred for another 3 h. Upon completion, the reaction was quenched with water (1 mL) and saturated NH_4Cl aqueous solution (5 mL) at 0 °C. The mixture was extracted with EtOAc (15 mL × 2), and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1 to 5:1) to afford the desired product **4** as a white solid, m.p. 195-197 °C, 109.5 mg, 87% yield. $[\alpha]_D^{10}$: +20.2 (*c* = 0.50, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane/*i*-propanol = 98:2, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 18.3 min (minor), t_2 = 19.9 min (major), >99% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.46-7.38 (m, 2H), 6.96 (d, *J* = 7.6 Hz, 2H), 6.88 (t, *J* = 7.2 Hz, 1H), 6.83-6.76 (m, 2H), 0.02 (s, 9H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.6, 153.4, 136.4, 135.7, 126.1, 125.5, 125.2, 125.0, 124.1 (q, *J* = 286.4 Hz), 123.2, 122.1, 121.8, 119.7, 119.5, 111.7, 109.9, 79.4 (q, *J* = 30.4 Hz), 0.9 ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -74.2 ppm. HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{20}H_{19}F_3N_2OSSi$ 420.0939; Found 420.0938.

(R)-1-(Benzo[d]thiazol-2-yl)-2,2,2-trifluoro-1-(1-(prop-2-yn-1-yl)-1H-indol-3-yl)ethanol ***(5)***. Under N_2, to a stirring suspension of NaH (18.0 mg, 0.45 mmol, 60% wt) in dry THF (4 mL) at 0 °C was added dropwise **4** (63.0 mg, 0.15 mmol) in dry THF (2 mL), and the mixture was stirred at room temperature for 1 h. Then 3-bromo-1-propyne (53.5 mg, 0.45 mmol) was added dropwise, and the resulting reaction mixture was spontaneously warmed to room temperature and stirred for another 3 h. Upon completion, the reaction was quenched with water (5 mL) at 0 °C, and stirred for 2 h at room temperature. The mixture was extracted with EtOAc (10 mL × 2), and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1 to 5:1) to afford the desired product **5** as colorless oil, 52.0 mg, 90% yield. $[\alpha]_D^{10}$: -8.7 (*c* = 0.50, acetone). The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak OD-H column, *n*-hexane/*i*-propanol = 95:5, flow rate 1.0 mL/min, detection at 254 nm, 35 °C): t_1 = 19.6 min (minor), t_2 = 24.0 min (major), >99% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.61 (s, 1H), 7.59-7.52 (m, 2H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 3.6 Hz, 1H), 5.19 (s, 1H), 4.89 (d, *J* = 2.4 Hz, 2H), 2.47 (t, *J* = 2.4 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.2, 151.6, 136.5, 136.2, 126.7 (q, *J* = 2.7 Hz), 126.4, 126.2, 125.9, 124.1 (q, *J* = 285.1 Hz), 123.7, 122.8, 121.8, 120.9, 120.8, 110.5, 109.8, 77.0 (q, *J* = 31.1 Hz), 76.9, 74.3, 36.1 ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -76.3 ppm. HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{20}H_{13}F_3N_2OS$ 386.0701; Found 386.0697.

*2,2,2-Trifluoro-1-(1H-indol-3-yl)ethanone (**6**)*. The mixture of **4** (168.2 mg, 0.40 mmol), 4 Å MS (750 mg), and anhydrous dichloromethane (5.0 mL) was stirred at room temperature for 10 min, and then Me_3OBF_4 (184.9 mg, 1.25 mmol) was added. After stirred for 2 h, another batch of Me_3OBF_4 (184.9 mg, 1.25 mmol) was added. Upon completion (monitored by TLC), the reaction was concentrated without filtering off the molecular sieves to give the crude benzothiazolium salt. It was redissolved in MeOH (5.0 mL), and cooled to 0 °C. Then $NaBH_4$ (1.25 mmol) was added in portions. Upon completion (monitored by TLC), the mixture was diluted with acetone (5 mL), filtered through a pad of Celite, and concentrated to give the crude benzothiazoline. To a vigorously stirred solution of the crude benzothiazoline in CH_2Cl_2 (1.5 mL) and CH_3CN (7.5 mL) were added H_2O (0.90 mL) and $AgNO_3$ (254.8 mg, 1.5 mmol). Upon completion (monitored by TLC), and the reaction was quenched with 1 M phosphate buffer (0.5 mL, pH = 7). After stirred for 15 min, the reaction mixture was diluted with 1 M phosphate buffer (12.5 mL, pH 7) and partially concentrated to remove CH_3CN. The suspension was extracted with EtOAc (15 mL × 2), and the combined organic layers were dried over Na_2SO_4, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1 to 5:1) to afford the desired

product **6** as a yellow solid, m.p. 210-211 °C, 70.0 mg, 76% yield. ^{1}H NMR (400 MHz, d6-acetone) δ 11.68 (s, 1H), 8.42 (s, 1H), 8.32 (d, J = 7.2 Hz, 1H), 7.63 (t, J = 5.6 Hz, 1H), 7.36 (t, J = 2.8 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, Acetone) δ 175.3 (q, J = 34.1 Hz), 137.6, 137.2 (q, J = 5.0 Hz), 127.0, 125.2, 124.2, 122.4, 118.0 (q, J = 289.2 Hz), 113.4, 110.6 ppm. ^{19}F NMR (376.5 MHz, d6-acetone) δ -72.9 ppm.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxxxx.

Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra, X-ray crystallographic data of **3aa** (PDF)

X-ray crystallographic data of **3aa** (CIF).

AUTHOR INFORMATION

Corresponding Author

*E-mail: yangwen@hnu.edu.cn

*E-mail: wangqa@hnu.edu.cn

*E-mail: jinpingwang1985@126.com

Notes

The authors declare no competing financial interests.

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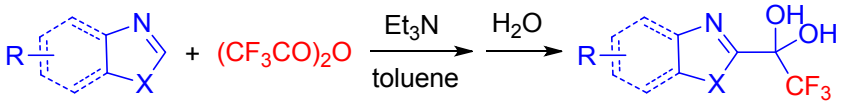

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