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Asymmetric Difluoromethylthiolation of Carbon Nucleophiles with Optically Pure Difluoromethylthiolating Reagents Derived from Camphorsultam

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Summary of main observation and conclusion The invention of a family of optically pure electrophilic difluoromethylthiolating reagents **9a**-**c** based on the camphorsultam skeleton was described. These reagents reacted with a variety of soft carbon nucleophiles such as oxazolone, oxindole, benzolactone and β-ketoester in good to excellent enantioselectivities.

Background and Originality Content

Over the past several decades, the magic "fluorine effect" of the fluorine atom and fluoroalkyl groups in new drug discovery have been well recognized,[1] as evidenced by the fact that 18 out of 42 small-molecule drugs approved by US Food and Drug Administration (FDA) in 2018 were fluorinated.[2] Not surprisingly, rational "fluorine scan" has become a routine practice in the fine tuning of the physico-chemical properties of the lead compounds.[3] The high-demand for fluorinated molecules in these fields has thus urged the organochemists to develop efficient methods that are able to site-specifically incorporate the fluorine or fluoroalkyl group into the target molecules under mild conditions. Consequently, a large number of such elegant fluorinating/fluoroalkylating methods have been reported in the last decades.[4]

It is also well-known that the development of efficient fluorinating/fluoroalkylating methods relied heavily on the inventions of new nucleophilic or electrophilic fluorinating/fluoroalkylating reagents.[5] For instance, the invention of nucleophilic trifluoromethylating reagent $TMSCF_3$ and several electrophilic trifluoromethylation reagents such as Umemoto's[6] and Togni's reagent[7] have revolutionized the way for the preparation of trifluoromethylated compounds. In this respect, the development of new broadly applicable fluoroalkylating reagents remains an urgent and unmet task.

More specifically, because the weakly acidic hydrogen of the difluoromethylthio group ($-SCF_2H$) is generally considered as a lipophilic hydrogen-bonding donor that could provide additional binding site when interacting with enzymes, the difluoromethylthio group represents a valuable yet underdeveloped fluoroalkyl group in the medicinal chemistry.[8]

Over the past few years, several difluoromethylthiolating reagents **1**-**8**[9] have been developed (Fig. 1), thus allowing efficient construction of $C(sp^2)$-SCF_2H and $C(sp^3)$-SCF_2H bonds under mild conditions. Nevertheless, few methods that can stereoselectively build chiral carbon center bearing a SCF_2H group have been reported.[10] To the best of our knowledge, only two such transformations have been described previously, both by Shibata and coworkers. The first method was based on the Pd-catalyzed decarboxylative asymmetric allylic alkylation of α-

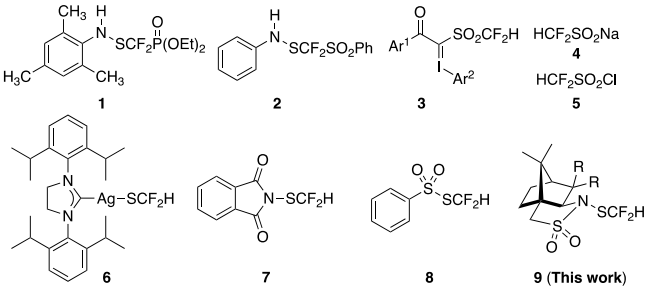


Figure 1 Difluoromethylthiolating reagents.

difluoromethylthiolated β-ketoesters[11a] and the second method utilized a chiral amine auxiliary for asymmetric difluoromethylthiolation of β-ketoesters with reagent **3**.[11b] Even though excellent enantioselectivities were achieved, the substrate scopes in both cases were limited to β-ketoesters. Thus, new strategies for asymmetric difluoromethylthiolation with broad substrates are urgently needed.

Herein, we reported an alternative strategy for the construction of chiral carbon center bearing a SCF_2H group with broad substrate scopes. The key of our strategy is the design and preparation of a family of optically pure electrophilic difluoromethylthiolating reagents **9a**-**c** based on the camphorsultam skeleton, a commercially available, optically pure crystalline solid which is typically used as chiral auxiliary.[12] Reactions of reagents **9a**-**c** with soft carbon nucleophiles such as oxazolone, oxindole, benzolactone and β-ketoester occurred with good to excellent enantioselectivities.

Results and Discussion

The invention of reagents **9a**-**c** was inspired by our recent success in the development of optically pure trifluoromethylthiolating reagent (1*S*)-(-)-*N*-trifluoromethylthio-2,10-camphorsultam,[13] we envisaged that if a difluoromethylthio group could be attached to the camphorsultam skeleton, an analogous optically pure difluoromethylthiolating reagent might be developed. Yet, the preparation of the target compounds is quite challenging. Our initial efforts to synthesize (1*S*)-(-)-*N*-difluoromethylthio-2,10-camphorsultam by reaction of (1*S*)-(-)-*N*-chloro-2,10-camphorsultam with a combination of $TMSCF_2H$ and sulfur in the presence of various activators such as cesium fluoride or potassium *tert*-butoxide were unsuccessful. Alternatively, reaction of (1*S*)-(-)-*N*-chloro-2,10-camphorsultam with nucleophilic difluoromethylthiolating reagent [(SIPr)Ag(SCF_2H)] (SIPr = 1,3-bis(2,6-di*iso*propyl phenyl) imidazolin-2-ylidene)[14] did not generate the desired product. Finally, it was found that treatment of difluoromethanesulfenyl chloride, which was *in situ* generated from difluoromethyl-benzylthioether with a solution of chlorine in chloroform, with the Oppolzer's sultam sodium salt at room temperature afforded reagent **9a** after 5 h in 74% yield (Figure 2). Likewise, reagents **9b**-**c** were prepared in 55% and 68% yields, respectively. White crystalline compounds **9a**-**c** were fully characterized by ^1H, ^{19}F and ^{13}C NMR spectroscopies[15] and the structures were further unambiguously confirmed by X-ray diffraction of their single crystals (Figure 3).

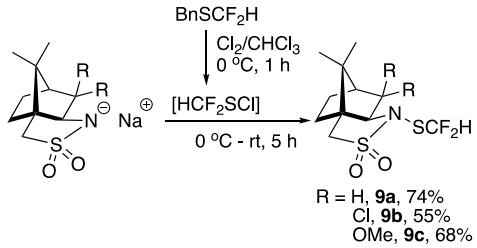
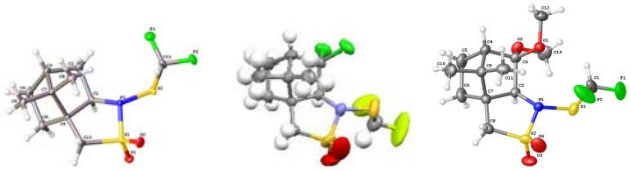


Figure 2. Preparation of (1*S*)-(-)-*N*-difluoromethylthio-2,10-camphorsultam and its derivatives.

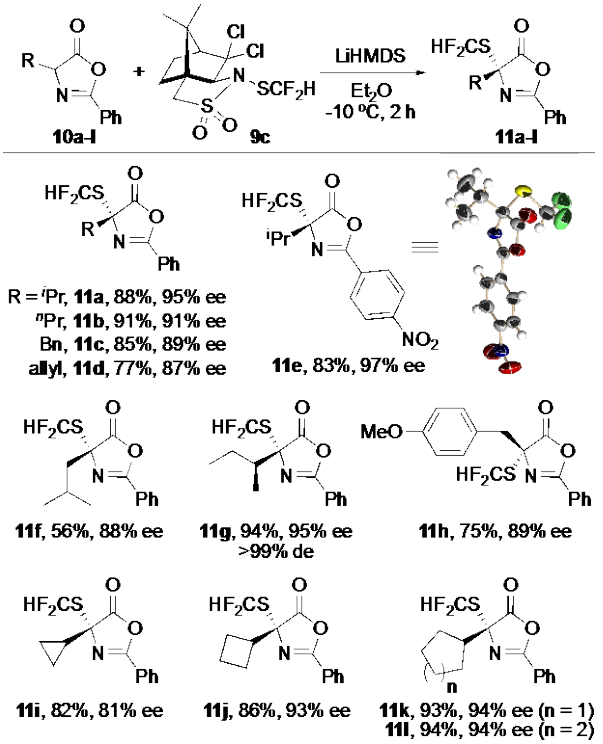


9a **9b** **9c**

Figure 3. X-ray structure of (1*S*)-(-)-*N*-difluoromethylthio-2,10-camphorsultam.

With a reliable method for the preparation of compounds **9a**-**c** in hand, the stage is now set for evaluation of their reactivities for stereo-selectively delivering the difluoromethylthio group into the target molecules. The reaction of enolate derived from oxazolone was initially chosen as a model reaction since oxazolones are a type of protected amino acids[16] and fluoroalkylated amino acids are potentially useful for the study of unnatural peptides and proteins.[17] Treatment of the lithium enolate derived from oxazolone **10a** with reagent **9b** in diethyl ether at -10 °C for 2 h afforded the desired difluoromethylthiolated product **11a** in 88% yield with 95% ee. As shown in Scheme 1, the reaction conditions were general since a variety of enolates derived from oxazolones with different substituents such as *n*-propyl, *iso*-propyl, benzyl and allyl group all reacted with reagent **9b** to give the corresponding difluoromethylthiolated products in good to excellent enantioselectivities (Scheme 1, **11a**-**d**). Cyclic alkyl groups are important structural motif present in many natural products and drug scaffolds.[18] We therefore studied reactions of enolates derived from oxazolones with cyclic alkyl groups. While reaction of enolate with a cyclopropyl group occurred in moderate enantioselectivity (Scheme 1, **11i**), reactions of enolates with a cyclobutyl, cyclopentyl or cyclohexyl group occurred in excellent

Scheme 1. Scope of asymmetric difluoromethylthiolation of oxazolone derivatives with reagent **9b**.[a]



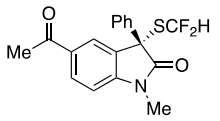
[a]Reaction conditions: oxazolone (0.30 mmol), reagent **9b** (0.36 mmol), LiHMDS (0.29 mmol) in 3.0 mL of diethyl ether at -10 °C for 2.0 h under an argon atmosphere. Isolated yields.

enantioselectivity (Scheme 1, **11j**-**l**).

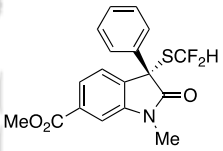
To determine the absolute configuration of difluoromethylthiolated compounds **11**, we investigated the reaction of 4-nitrophenyl substituted 10e with reagent **9b**, which afforded the desired product **11e** as a white solid in 97% ee. Single crystals were grown by evaporating a dichloromethane solution of compound **11e** and the absolute configuration of compound **11e** was determined to be *R* by X-ray diffraction of the single crystals (Scheme 1, **11e**). The configurations of the rest of compounds **11** were assigned based on the same mechanism assumption.

Encouraged by the excellent enantioselectivity for the reactions of enolates derived from oxazolone, we next tried to extend this high stereoselective reaction to other soft carbon nucleophiles such as oxindoles, benzolactones and β-ketoesters. Interestingly, it was found that reactions of oxindoles with reagent **9c** with two methoxy groups occurred in higher enantioselectivities than those with reagent **9b** when Cs_2CO_3 was used as the base and toluene as the solvent, as summarized in Scheme 2. It turned out that the reaction conditions were general toward a variety of oxindoles. For example, substrates with an electron-withdrawing group such as chloride (**13b**), cyano (**13c**) and ester group (**13e**) at the *para*-position of the phenyl substituent of the oxindoles reacted with reagent **9c** to give the corresponding difluoromethylthiolated products in 81-93% ee, while substrate with an electron-donating methoxy group (**13d**) occurred in 88% ee. Notably, enolizable ketone or nitrile were intact under these conditions and substrates with these two functional groups also reacted with reagent **9c** to afford the desired products in 91% ee and 94% ee, respectively (Scheme 2, **13f**-**g**). Likewise, oxindoles with both electron-donating and electron-withdrawing substituents at the oxindole skeleton also reacted to give the desired difluoromethylthiolated products in good to excellent enantioselectivities (81-93% ee) (Scheme 2, **13j**-**m**). Again, the

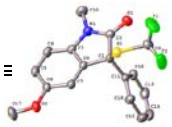
Scheme 2. Scope of asymmetric difluoromethylthiolation of oxindole, benzolactone and β-ketoester derivatives with reagent **9c**.[a]



13j, 94%, 81% ee



13l, 89%, 85% ee



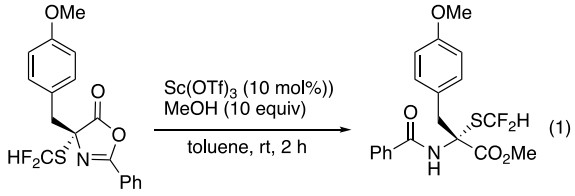
°C, 6 h

[a]Reaction conditions: oxindole, benzolactone or β-ketoester (0.30 mmol), reagent **9c** (0.36 mmol), Cs_2CO_3 (0.45 mmol or 0.33 mmol) in 3.0 mL of toluene at -40 °C for 12.0 h or 6.0 h under an argon atmosphere. Isolated yields.

absolute configuration of compound **13m** was determined by X-ray diffraction of its single crystals.

On the other hand, reactions of benzolactones and β-ketoesters with reagent **9c** occurred in slightly inferior but acceptable enantioselectivities 79-87% ee (Scheme 2, **14a**-**c**, **15a**-**c**). Efforts to improve the enantioselectivity of these two types of substrates by employing reagents **9a** or **9b** as the difluoromethylthio source were fruitless.

To probe the convertibility of difluoromethylthiolated oxazolone derivatives, we studied the reaction of compound **11h** under various conditions. While compound **11h** underwent defluorinative decomposition under both strong acidic or basic conditions, ring-opening esterification of the oxazolone in compound **11h** was successfully achieved when compound 11h was treated with a combination of 10 mol% $Sc(OTf)_3$ and 10.0 equivalent of methanol in toluene at room temperature for 2.0 h. The corresponding protected difluoromethylthiolated amino acid **16** was isolated in 55% yield without erosion of enantioselectivity (Eq.1). These results indicate the potential application of the current protocol in the preparation of optically pure difluoromethylthiolated or trifluoromethylthiolated amino acids and peptides.



11h (89% ee) **16**, 55%, 88% ee

Conclusions

In summary, we have successfully invented a family of easily available, optically pure, electrophilic difluoromethylthiolating reagents **9a**-**c** based on the camphorsultam skeleton. Reactions of a variety of soft carbon nucleophiles such as oxazolones, oxindoles, benzolactones and β-ketoesters with these reagents occurred with good to excellent enantioselectivities. Efforts to study the enantioselective difluoromethylthiolating reaction of reagents **9a**-**c** with other nucleophiles such as alkenes are undergoing currently in our lab.

Experimental

General information. All solvents were purified by standard method. ^1H , ^{13}C and ^{19}F NMR spectra were acquired on 400 MHz, 125 MHz, 100 MHz, 375 MHz spectrometer (400 MHz for ^1H ; 100 MHz or 125 MHz for ^{13}C; 375 MHz for ^{19}F). ^1H NMR and ^{13}C NMR chemical shifts were determined relative to internal standard TMS at δ 0.0 ppm and ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as inter standard. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All reactions were monitored by TLC or ^{19}F NMR. Flash column chromatograph was carried out using 300-400 mesh silica gel at medium pressure.

Materials. All reagents were received from commercial sources. Solvents were freshly dried and degassed according to the

purification handbook Purification of Laboratory Chemicals before using.

General Procedure for the Synthesis of (1*S*)-(-)-*N*-difluoromethylthio-2,10-camphorsultam. Potassium hydroxide (224 g, 4.00 mol, 20.0 equiv.), acetonitrile/H_2O (1.5 L, 1:1), and benzyl mercaptan (24.8 g, 200 mmol, 1.00 equiv.) were placed into three round-bottom flask equipped with a stirring bar. The mixture was cooled to −78 °C, and diethyl bromodifluoromethane phosphonate (107 g, 400 mmol, 2.0 equiv.) was added. The reaction was stirred at room temperature for 12 h. Et_2O (2.0 L) was added, and the organic phase was separated. The aqueous phase was extracted with Et_2O (400 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give difluoromethyl benzyl thioether as a colorless oil (29.0 g, 83%).

To a solution of (1*S*)-(-)-2,10-camphorsultam (1.29 g, 6.00 mmol, 1.20 equiv.) in toluene (50.0 mL) was added NaH (240 mg, 6.00 mmol, 1.20 equiv., 60%) under an argon atmosphere at 0 °C. The solution was then stirred at room temperature for 1 h to give a suspension of sodium (1*S*)-(-)-2,10-camphorsultam. The mixture can be used for the next step directly.

Into a 2.0 L Schlenk tube was added dry $CHCl_3$ (1.5 L) and get weighed. Chlorine gas was bubbled slowly for 15 min. The Schlenk tube was weighed again to get the amount of chlorine gas in $CHCl_3$. The concentration of Cl_2 in $CHCl_3$ was then calculated. An aliquot of Cl_2 in $CHCl_3$ (5.0 mL, 1.0 M) was added with 15.0 mL of $CHCl_3$ in a 100 mL three-neck round-bottom flask. The mixture was cooled to −40 °C in the dark, and $BnSCF_2H$ (871 mg, 5.00 mmol, 1.00 equiv.) was added slowly. The mixture was warmed to 23 °C, and the mixture was further stirred for 1 h. The mixture was then cooled to −40 °C, and was added via a syringe to a suspension of sodium (1*S*)-(-)-2,10-camphorsultam at -40 °C. The temperature was then warmed to 23 °C, and the reaction was further stirred at room temperature for 3 h. The mixture was extracted with Et_2O (25 mL × 3). The combined organic phase was separated and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum. The residue was purified by flash chromatography to give (1*S*)-(-)-*N*-difluoromethylthio-2,10-camphorsultam **9a** as a white solid (1.10 g, 74% yield).

(3a*R*,6*R*,7a*R*)-1-((Difluoromethyl)thio)-8,8-dimethylhexahydro-3*H*-3a,6-methanobenzo[c]isothiazole 2,2-dioxide 9a. Yield 74%, white solid. Mp: 64.0 – 65.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 223 K) δ 7.26 (dd, *J* = 63.4, 51.3 Hz, 0.5 H), 6.80 (dd, *J* = 60.4, 51.7 Hz, 0.5 H), 3.56 – 3.15 (m, 3 H), 2.11 (dd, *J* = 27.5, 13.1 Hz, 1 H), 1.96 (s, 1 H), 1.94 – 1.82 (m, 2 H), 1.76 (dt, *J* = 13.5, 8.2 Hz, 1 H), 1.41 – 1.38 (m, 1 H), 1.34 – 1.22 (m, 1 H), 1.01 – 0.88 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$, 223 K) δ 120.08 (dd, *J* = 286.4, 272.0 Hz), 119.59 (dd, *J* = 287.6, 273.3 Hz), 68.49, 67.98, 51.69, 50.73, 49.22, 48.44, 47.97, 43.77, 43.69, 34.55, 34.16, 32.15, 31.66, 27.19, 27.12, 20.38, 20.15, 20.05; ^{19}F NMR (376 MHz, $CDCl_3$, 223 K) δ -89.82 (dd, *J* = 266.0, 63.5 Hz), -92.39 (dd, *J* = 244.1, 60.5 Hz), -101.73 (dd, *J* = 244.1, 51.7 Hz), -105.05 (dd, *J* = 266.0, 51.3 Hz) ppm.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.04 (t, *J* = 57.4 Hz, 1 H), 3.43 (br, 1 H), 3.25 (q, *J* = 13.8 Hz, 2 H), 2.15 (ddd, *J* = 13.2, 6.7, 3.9 Hz, 1 H), 1.95 (t, *J* = 3.8 Hz, 1 H), 1.93 – 1.82 (m, 2 H), 1.77 (dd, *J* = 13.4, 8.1 Hz, 1 H), 1.43 (dd, *J* = 18.7, 10.0 Hz, 1 H), 1.36 – 1.20 (m, 1 H), 0.99 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 120.06 (t, *J* = 279.9 Hz), 68.42, 51.09, 48.93, 47.68, 44.17, 34.37, 32.09, 27.00, 20.07, 19.88; ^{19}F NMR (376 MHz, $CDCl_3$, 298 K) δ -92.65 (br, 1 F), -104.93 (br, 1 F) ppm.

^{1}H NMR (400 MHz, $CDCl_3$, 323 K) δ 7.04 (t, *J* = 57.2 Hz, 1 H), 3.48 – 3.40 (m, 1 H), 3.33 – 3.13 (m, 2 H), 2.29 – 2.07 (m, 1 H), 1.99 – 1.87 (m, 3 H), 1.84 – 1.74 (m, 1 H), 1.44 (dd, *J* = 17.1, 10.0 Hz, 1 H), 1.33 (dd, *J* = 16.7, 7.8 Hz, 1 H), 1.01 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, 323 K) δ 120.19 (t, *J* = 279.8 Hz), 68.56, 51.13, 49.02, 47.68, 44.36, 34.44, 32.20, 27.01, 20.08, 19.87; ^{19}F NMR (376 MHz, $CDCl_3$, 323 K) δ -97.65 (br, 2 F) ppm.

IR (KBr): ν_{max} = 3015, 3001, 2954, 2887, 1483, 1456, 1412, 1392, 1372, 1334, 1281, 1256, 1223, 1164, 1145, 1120, 1092, 1077, 1046, 1031 cm^{-1}. MS (DART POS): 298.0 (M+H); HRMS (DART POS): $C_{11}H_{18}O_2NF_2S_2$ (M+H) Calcd: 298.0742, Found: 298.0741.

(3a*R*,6*S*,7a*S*)-7,7-Dichloro-1-((difluoromethyl)thio)-8,8-dimethylhexahydro-3*H*-3a,6-methanobenzo[c]isothiazole 2,2-dioxide 9b. Yield 55%, white solid. Mp：104.5 – 105.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 223 K) δ 7.57 (dd, *J* = 65.0, 52.2 Hz, 0.76 H), 7.18 (dd, *J* = 61.3, 51.6 Hz, 0.24 H), 4.05 – 3..75 (m, 1 H), 3.51 – 3.33 (m, 2 H), 2.63 – 2.57 (m, 1 H), 2.34 – 2.21 (m, 1 H), 2.06 (t, *J* = 10.8 Hz, 1 H), 1.95 (t, *J* = 11.9 Hz, 1 H), 1.61 (t, *J* = 9.1 Hz, 1 H), 1.39 – 1.34 (m, 3 H), 1.03 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, 223 K) δ 123.92 (dd, *J* = 283.4, 271.5 Hz), 119.51 (dd, *J* = 289.0, 272.4 Hz), 93.07, 82.75, 81.29, 61.53, 52.67, 52.22, 49.94, 49.73, 48.89, 47.79, 32.06, 31.26, 25.68, 25.54, 23.46, 23.18; ^{19}F NMR (376 MHz, $CDCl_3$, 223 K) δ -89.69 (dd, *J* = 250.4, 61.3 Hz), -90.04 (dd, *J* = 276.9, 65.0 Hz), -100.94 (dd, *J* = 250.2, 51.7 Hz), -105.04 (dd, *J* = 276.7, 52.4 Hz) ppm.

^{1}H NMR (400 MHz, $CDCl_3$, 263 K) δ 7.46 (t, *J* = 58.2 Hz, 1 H), 3.96 (s, 1 H), 3.39 (s, 2 H), 2.57 (s, 1 H), 2.29 (t, *J* = 11.4 Hz, 1 H), 2.06 (d, *J* = 12.0 Hz, 1 H), 1.93 (t, *J* = 11.8 Hz, 1 H), 1.59 (t, *J* = 10.4 Hz, 1 H), 1.37 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, 263 K) δ 92.96, 81.99, 61.83, 52.50, 49.72, 48.58, 31.42, 25.48, 23.45, 23.04; ^{19}F NMR (376 MHz, $CDCl_3$, 263 K) δ -90.55 (dd, *J* = 267.9, 63.2 Hz, 1 F), -103.47 (br, 1 F) ppm.

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.43 (dd, *J* = 62.6, 53.1 Hz, 1 H), 3.95 (s, 1 H), 3.36 (s, 2 H), 2.57 (d, *J* = 4.8 Hz, 1 H), 2.36 – 2.28 (m, 1 H), 2.10 – 1.99 (m, 1 H), 1.93 (td, *J* = 12.2, 4.2 Hz, 1 H), 1.59 (ddd, *J* = 13.0, 9.0, 4.2 Hz, 1 H), 1.40 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$, 298 K) δ 120.88 (t, *J* = 277.6 Hz), 92.91, 82.22, 62.06, 52.47, 49.67, 48.58, 31.54, 25.39, 23.41, 22.92; ^{19}F NMR (376 MHz, $CDCl_3$, 298 K) δ -91.09 (dd, *J* = 266.7, 62.7 Hz, 1 F), -103.29 (br, 1 F) ppm.

^{1}H NMR (400 MHz, $CDCl_3$, 323 K) δ 7.42 (dd, *J* = 62.2, 53.4 Hz, 1 H), 3.96 (s, 1 H), 3.35 (s, 2 H), 2.58 – 2.55 (d, 1H), 2.34 (ddd, *J* = 13.3, 9.0, 4.1 Hz, 1 H), 2.11 – 2.00 (m, 1 H), 2.00 – 1.89 (m, 1 H), 1.63 – 1.55 (m, 1 H), 1.41 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, 323 K) δ 120.98 (dd, *J* = 286.1, 273.5 Hz), 92.95, 82.43, 62.25, 52.52, 49.71, 48.64, 31.62, 25.38, 23.42, 22.88; ^{19}F NMR (376 MHz, $CDCl_3$, 323 K) δ -91.33 (dd, *J* = 266.0, 62.4 Hz, 1 F), -103.04 (dd, *J* = 267.2, 49.6 Hz, 1 F) ppm.

IR (KBr): ν_{max} = 3043, 3000, 2953, 2906, 1485, 1464, 1413, 1396, 1376, 1340, 1285, 1256, 1225, 1156, 1124, 1091, 1072, 1051 cm^{-1}. MS (DART POS): 366.0 (M+H); HRMS (DART POS): $C_{11}H_{16}O_2NCl_2F_2S_2$ (M+H) Calcd: 365.9962, Found: 365.9962.

(3a*R*,6*S*,7a*S*)-1-((Difluoromethyl)thio)-7,7-dimethoxy-8,8-dimethylhexahydro-3*H*-3a,6-methanobenzo[c]isothiazole 2,2-dioxide 9c. Yield 68%, white solid. Mp：132.5 – 133.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 223 K) δ 7.48 (dd, *J* = 65.3, 53.9 Hz, 0.09 H), 7.06 (dd, *J* = 62.1, 52.2 Hz, 0.85 H), 3.61 – 3.04 (m, 9 H), 3.30 – 3.20 (m, 1 H), 1.99 – 1.65 (m, 3 H), 1.47 (dd, *J* = 16.5, 8.2 Hz, 1 H), 1.28 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, 223 K) δ 123.95 (dd, *J* = 284.0, 269.3 Hz), 108.97, 74.50, 51.17, 50.90, 49.86, 48.46, 47.98, 47.71, 31.99, 21.67, 20.78, 20.36; ^{19}F NMR (376 MHz, $CDCl_3$, 223 K) δ -93.10 (dd, *J* = 249.5, 62.1 Hz), -94.72 (dd, *J* = 272.3, 65.5 Hz), -103.85 (dd, *J* = 249.5, 52.3 Hz), -106.19 (dd, *J* = 272.3, 53.9 Hz) ppm.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.13 (dd, *J* = 61.1, 53.6 Hz, 1 H), 3.44 – 3.20 (m, 9 H), 2.24 (d, *J* = 4.7 Hz, 1 H), 1.97 (ddd, *J* = 13.2, 9.3, 4.0 Hz, 1 H), 1.83 (td, *J* = 11.8, 4.0 Hz, 1 H), 1.77 – 1.65 (m, 1 H), 1.55 – 1.43 (m, 1 H), 1.31 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 123.27 (t, *J* = 278.8 Hz), 109.10, 74.66 (t, *J* = 2.2 Hz), 51.02, 50.75, 49.40, 49.03, 47.99, 47.67, 32.22, 21.45, 20.63, 20.35; ^{19}F NMR (376 MHz, $CDCl_3$, 298 K) δ -94.02 (dd, *J* = 252.7, 61.2 Hz), -103.20 (d, *J* = 243.1 Hz) ppm.

^{1}H NMR (400 MHz, $CDCl_3$, 323 K) δ 7.14 (dd, *J* = 60.9, 53.9 Hz, 1 H), 3.56 – 3.16 (m, 9 H), 2.43 – 2.16 (m, 1 H), 2.05 – 1.94 (m , 1 H), 1.93 – 1.66 (m, 2 H), 1.63 – 1.41 (m, 1 H), 1.33 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, 323 K) δ 123.27 (dd, *J* = 285.1, 273.4 Hz), 109.23, 74.80, 51.10, 50.74, 49.38, 49.25, 48.10, 47.69, 32.22, 21.46, 20.66, 20.38; ^{19}F NMR (376 MHz, $CDCl_3$, 323 K) δ -94.21 (dd, *J* = 253.2, 60.9 Hz), -102.99 (dd, *J* = 253.4, 53.5 Hz) ppm.

IR (KBr): ν_{max} = 2994, 2960, 2839, 1478, 1461, 1419, 1397, 1378, 1327, 1273, 1263, 1230, 1195, 1161, 1136, 1114, 1065, 1039, 1023 cm^{-1}. HRMS (DART POS): $C_{13}H_{22}O_4NF_2S_2$ (M+H) Calcd: 358.0953, Found: 358.0952.

General procedure for asymmetric difluoromethylthiolation of oxazolones. To a 25 mL flame-dried Schlenk tube was added oxazolone **10a** (61 mg, 0.30 mmol, 1.00 equiv). Dry Et_2O (3.0 mL) was added under argon atmosphere. The solution was cooled to -10 °C, then LiHMDS (291 μL, 0.290 mmol, 0.970 equiv.; 1.00 M in THF) was add at -10 °C. The solution was stirred at -10 °C for 20 min, and the reagent **9b** (132 mg, 0.360 mmol, 1.20 equiv.) was added. The resulting solution was stirred at -10 °C for 2 h. After the reaction was completed as monitored by ^{19}F NMR spectroscopy, addition of an aqueous solution of HCl (2.0 N) or water. The mixture was extracted with Et_2O (10 mL × 3). The combined organic phase was separated and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum. The residue was purified by flash chromatography to give the difluoromethylthiolated product **11a** (*R*)-4-((Difluoromethyl)thio)-4-isopropyl-2-phenyloxazol-5-(4*H*)-one as a yellow oil (75 mg, 88% yield).

(*R*)-4-((Difluoromethyl)thio)-4-isopropyl-2-phenyloxazol-5-(4*H*)-one 11a. Yield 88%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.4 Hz, 2 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 7.52 (t, *J* = 7.7 Hz, 2 H), 6.92 (dd, *J* = 60.4, 54.0 Hz, 1 H), 2.53 – 2.26 (m, 1 H), 1.22 (d, *J* = 6.8 Hz, 3 H), 1.04 (d, *J* = 6.7 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.48 (dd, *J* = 258.5, 60.4 Hz, 1 F), -99.52 (dd, *J* = 258.4, 54.0 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.09, 162.47, 133.72, 129.00, 128.45, 124.75, 119.13 (dd, *J* = 278.6, 270.2 Hz), 78.42 (d, *J* = 4.2 Hz), 35.76, 16.97, 16.82 ppm. IR (KBr): ν_{max} = 2975, 1836, 1643, 1581, 1495, 1469, 1452, 1323, 1161, 1062, 1045, 1026 cm^{-1}. MS (DART POS): 286.1 (M+H); HRMS (DART POS): $C_{13}H_{14}NO_2F_2S$ (M+H) Calcd: 286.0708, Found: 286.0708. HPLC: (OJH, Hexane/^{i}PrOH = 98/2, 0.7 mL/min, 214 nm), t_R (major) = 9.82 min, t_R (minor) = 10.71 min (95% ee); $[\alpha]_D^{20}$ = +53.20 (c = 0.200, $CHCl_3$, 95% ee).

(*R*)-4-((Difluoromethyl)thio)-2-phenyl-4-propyloxazol-5-(4*H*)-one 11b. Yield 91%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.1, 0.9 Hz, 2 H), 7.64 (t, *J* = 7.5 Hz, 1 H), 7.52 (t, *J* = 7.7 Hz, 2 H), 6.93 (dd, *J* = 59.7, 54.2 Hz, 1 H), 2.26 – 2.13 (m, 1 H), 2.12 – 2.02 (m, 1 H), 1.54 – 1.38 (m, 1 H), 1.38 – 1.22 (m, 1 H), 0.95 (t, *J* = 7.3 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.92 (dd, *J* = 258.0, 59.7 Hz, 1 F), -98.56 (dd, *J* = 258.1, 54.3 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.13, 162.43, 133.77, 129.02, 128.44, 124.74, 119.00 (dd, *J* = 278.2, 271.3 Hz), 74.44 (d, *J* = 4.1 Hz), 39.49, 17.39, 13.56 ppm. IR (KBr): ν_{max} = 2965, 2933, 2877, 1829, 1643, 1581, 1495, 1453, 1323, 1293, 1074, 1046, 1024 cm^{-1}. MS (DART POS): 286.1 (M+H); HRMS (DART POS): $C_{13}H_{14}NO_2F_2S$ (M+H) Calcd: 286.0708, Found: 286.0707. HPLC: (ODH, Hexane/^{i}PrOH = 98/2, 0.7 mL/min, 214 nm), t_R (major) = 7.45 min, t_R (minor) = 6.97 min (91% ee); $[\alpha]_D^{20}$ = +6.20 (c = 0.200, $CHCl_3$, 91% ee).

(*R*)-4-Benzyl-4-((difluoromethyl)thio)-2-phenyloxazol-5-(4*H*)-one 11c. yield 85%, colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.7 Hz, 2 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.46 (t, *J* = 7.8 Hz, 2 H), 7.21 (s, 5 H), 7.00 (dd, *J* = 59.6, 54.4 Hz, 1 H), 3.55 (d, *J* = 13.4 Hz, 1 H), 3.40 (d, *J* = 13.5 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.79 (dd, *J* = 257.9, 59.6 Hz, 1 F), -98.05 (dd, *J* = 258.0, 54.4 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.37, 162.36, 133.68, 132.04, 130.50, 128.93, 128.46, 128.31, 128.06, 124.58, 119.04 (dd, *J* = 278.4, 271.8 Hz), 75.02 (d, *J* = 3.8 Hz), 43.56 ppm. IR (KBr): ν_{max} = 2927, 1824, 1644, 1580, 1496, 1452, 1323, 1292, 1093, 1061 cm^{-1}. MS (DART POS): 334.1 (M+H); HRMS (DART POS): $C_{17}H_{14}NO_2F_2S$ (M+H) Calcd: 334.0708, Found: 334.0706. HPLC: (ADH, Hexane/^{i}PrOH = 97/3, 0.7 mL/min, 214 nm), t_R (major) = 8.65 min, t_R (minor) = 9.67 min (89% ee); $[\alpha]_D^{20}$ = +90.67 (c = 0.060, $CHCl_3$, 89% ee).

(*R*)-4-Allyl-4-((difluoromethyl)thio)-2-phenyloxazol-5-(4*H*)-one 11d. Yield 77%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.5 Hz, 2 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 7.52 (t, *J* = 7.7 Hz, 2 H), 6.96 (dd, *J* = 59.6, 54.4 Hz, 1 H), 5.88 – 5.55 (m, 1 H), 5.38 – 5.16 (m, 2 H), 2.96 (dd, *J* = 13.7, 6.6 Hz, 1 H), 2.82 (dd, *J* = 13.7, 7.9 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.98 (dd, *J* = 258.2, 59.6 Hz, 1 F), -98.22 (dd, *J* = 258.2, 54.4 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.41, 162.44, 133.78, 128.98, 128.43 (br, 2 C), 124.64, 122.57, 118.90 (dd, *J* = 278.3, 271.8 Hz), 74.13 (d, *J* = 4.1 Hz), 41.53 ppm. IR (KBr): ν_{max} = 2958, 1825, 1642, 1452, 1323, 1294, 1258, 1075, 1012 cm^{-1}. MS (DART POS): 284.1 (M+H); HRMS (DART POS): $C_{13}H_{12}NO_2F_2S$ (M+H) Calcd: 284.0551, Found: 284.0551. HPLC: (ODH, Hexane/^{i}PrOH = 99/1, 0.7 mL/min, 214 nm), t_R (major) = 8.93 min, t_R (minor) = 8.38 min (87% ee); $[\alpha]_D^{20}$ = +76.85 (c = 0.400, $CHCl_3$, 87% ee).

(*R*)-4-((Difluoromethyl)thio)-4-isopropyl-2-(4-nitrophenyl) oxazol-5-(4*H*)-one 11e. Yield 83%, yellow soild. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.7 Hz, 2 H), 8.25 (d, *J* = 8.6 Hz, 2 H), 6.90 (dd, *J* = 59.4, 54.0 Hz, 1 H), 2.41 (dt, *J* = 13.3, 6.6 Hz, 1 H), 1.22 (d, *J* = 6.7 Hz, 3 H), 1.04 (d, *J* = 6.7 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -94.38 (dd, *J* = 256.1, 59.4 Hz, 1 F), -103.05 (dd, *J* = 256.1, 53.9 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.08, 160.76, 150.75, 130.26, 129.48, 124.10, 118.82 (dd, *J* = 279.0, 271.9 Hz), 78.51 (d, *J* = 4.1 Hz), 35.80, 16.93, 16.79 ppm. IR (KBr): ν_{max} = 2985, 1840, 1642, 1599, 1527, 1491, 1465, 1351, 1325, 1307, 1294, 1157, 1087, 1063, 1035, 1020, 1013 cm^{-1}. MS (DART POS): 331.0 (M+H); HRMS (DART POS): $C_{13}H_{13}N_2O_4F_2S$ (M+H) Calcd: 331.0559, Found: 331.0557. Mp: 122.0 – 123.0 ^{o}C. HPLC: (ADH, Hexane/^{i}PrOH = 92/8, 0.7 mL/min, 214 nm), t_R (major) = 13.43 min, t_R (minor) = 12.79 min (97% ee); $[\alpha]_D^{20}$ = +39.75 (c = 0.160, $CHCl_3$, 97% ee).

(*R*)-4-((Difluoromethyl)thio)-4-isobutyl-2-phenyloxazol-5-(4*H*) -one 11f. Yield 56%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dt, *J* = 8.5, 1.6 Hz, 2 H), 7.70 – 7.60 (m, 1 H), 7.60 – 7.48 (m, 2 H), 6.93 (dd, *J* = 59.6, 54.2 Hz, 1 H), 2.23 (dd, *J* = 14.2, 5.5 Hz, 1 H), 2.02 (dd, *J* = 14.2, 7.2 Hz, 1 H), 1.87 – 1.68 (m, 1 H), 0.95 (d, *J* = 6.7 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.01 (dd, *J* = 258.5, 59.6 Hz, 1 F), -98.46 (dd, *J* = 258.5, 54.2 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.54, 162.25, 133.77, 129.05, 128.74, 124.82, 119.03 (dd, *J* = 278.1, 271.3 Hz), 74.26 (d, *J* = 3.8 Hz), 45.92, 25.44, 23.83, 22.96 ppm. IR (KBr): ν_{max} = 2961, 2929, 2874, 1822, 1642, 1580, 1495, 1452, 1323, 1292, 1262, 1153, 1074, 1053, 1026 cm^{-1}. MS (DART POS): 300.1 (M+H); HRMS (DART POS): $C_{14}H_{16}NO_2F_2S$ (M+H) Calcd: 300.0864, Found: 300.0864. HPLC: (OJH, Hexane/^{i}PrOH = 98/2, 0.7 mL/min, 214 nm), t_R (major) = 7.89 min, t_R (minor) = 8.77 min (88% ee); $[\alpha]_D^{20}$ = +95.20 (c = 0.350, $CHCl_3$, 88% ee).

(*R*)-4-((*S*)-*sec*-Butyl)-4-((difluoromethyl)thio)-2-phenyloxazol-5-(4*H*)-one 11g. Yield 94%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.03 (m, 2 H), 7.67 – 7.60 (m, 1 H), 7.56 – 7.46 (m, 2 H), 6.93 (dd, *J* = 60.4, 53.9 Hz, 1 H), 2.16 – 2.03 (m, 1 H), 1.53 (dqd, *J* = 14.9, 7.4, 2.8 Hz, 1 H), 1.33 – 1.14 (m, 4 H), 0.94 (t, *J* = 7.4 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.37 (dd, *J* = 258.6, 60.3 Hz, 1 F), -99.48 (dd, *J* = 258.5, 53.9 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.32, 162.35, 133.70, 129.00, 128.44, 124.79, 119.14 (dd, *J* = 278.5, 270.0 Hz), 78.80 (d, *J* = 4.2 Hz), 42.20, 24.04, 13.18, 11.92 ppm. IR (KBr): ν_{max} = 2972, 2937, 2880, 1831, 1643, 1581, 1495, 1452, 1323, 1292, 1064, 1047 cm^{-1}. MS (DART POS): 300.1 (M+H); HRMS (DART POS): $C_{14}H_{16}NO_2F_2S$ (M+H) Calcd: 300.0864, Found: 300.0864. HPLC: (ADH, Hexane/^{i}PrOH = 97/3, 0.7 mL/min, 214 nm), t_R (major) = 7.03 min, t_R (minor) = 6.51 min (95% ee); $[\alpha]_D^{20}$ = +43.50 (c = 0.200, $CHCl_3$, 95% ee).

(*R*)-4-((Difluoromethyl)thio)-4-(4-methoxybenzyl)-2-phenyl oxazol-5-(4*H*)-one 11h. Yield 75%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.5 Hz, 2 H), 7.59 (t, *J* = 7.3 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.12 (d, *J* = 8.6 Hz, 2 H), 6.99 (dd, *J* = 58.6, 53.5 Hz, 1 H), 6.73 (d, *J* = 8.4 Hz, 2 H), 3.70 (s, 3 H), 3.48 (d, *J* = 13.6 Hz, 1 H), 3.34 (d, *J* = 13.6 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.75 (dd, *J* = 257.9, 59.6 Hz, 1 F), -97.99 (dd, *J* = 257.9, 54.4 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.40, 162.28, 160.76 (d, *J* = 305.4 Hz), 133.61, 131.57, 128.89, 128.28, 124.59, 123.93, 119.02 (dd, *J* = 278.4, 271.7 Hz), 113.79, 75.09 (d, *J* = 3.5 Hz), 55.08, 42.71 ppm. IR (KBr): ν_{max} = 3008, 2980, 2956, 2935, 2839, 1825, 1643, 1611, 1510, 1466, 1452, 1324, 1302, 1248, 1179, 1117, 1032 cm^{-1}. MS (DART POS): 364.1 (M+H); HRMS (DART POS): $C_{18}H_{16}NO_3F_2S$ (M+H) Calcd: 364.0813, Found: 364.0811. HPLC: (IG, Hexane/^{i}PrOH = 99/1, 0.7 mL/min, 214 nm), t_R (major) = 14.86 min, t_R (minor) = 15.67 min (89% ee); $[\alpha]_D^{20}$ = +126.00 (c = 0.260, $CHCl_3$, 89% ee).

(*R*)-4-Cyclopropyl-4-((difluoromethyl)thio)-2-phenyloxazol-5-(4*H*)-one 11i. Yield 82%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dt, *J* = 8.5, 1.6 Hz, 2 H), 7.70 – 7.59 (m, 1 H), 7.56 – 7.47 (m, 2 H), 6.92 (dd, *J* = 59.4, 54.4 Hz, 1 H), 1.62 (tt, *J* = 8.2, 5.1 Hz, 1 H), 0.90 – 0.81 (m, 1 H), 0.81 – 0.72 (m, 1 H), 0.68 – 0.58 (m, 1 H), 0.53 (ddt, *J* = 10.0, 6.1, 5.0 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.07 (dd, *J* = 257.3, 59.3 Hz, 1 F), -97.65 (dd, *J* = 257.3, 54.4 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.37, 162.77, 133.84, 129.00, 128.49, 124.70, 119.03 (dd, *J* = 278.0, 271.9 Hz), 74.50 (d, *J* = 3.4 Hz), 17.21, 2.76, 2.41 ppm. IR (KBr): ν_{max} = 2960, 2926, 2855, 1824, 1643, 1580, 1494, 1452, 1322, 1293, 1155, 1063 cm^{-1}. MS (DART POS): 284.1 (M+H); HRMS (DART POS): $C_{13}H_{12}NO_2F_2S$ (M+H) Calcd: 284.0551, Found: 284.0551. HPLC: (ODH, Hexane/^{i}PrOH = 99/1, 0.7 mL/min, 214 nm), t_R (major) = 9.51 min, t_R (minor) = 12.05 min (81% ee); $[\alpha]_D^{20}$ = +17.84 (c = 0.250, $CHCl_3$, 81% ee).

(*R*)-4-Cyclobutyl-4-((difluoromethyl)thio)-2-phenyloxazol-5-(4*H*)-one 11j. Yield 86%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.5 Hz, 2 H), 7.65 (t, *J* = 7.4 Hz, 1 H), 7.53 (t, *J* = 7.7 Hz, 2 H), 6.89 (dd, *J* = 60.2, 54.1 Hz, 1 H), 3.18 – 2.93 (m, 1 H), 2.32 – 2.03 (m, 2 H), 2.02 – 1.75 (m, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.40 (dd, *J* = 257.3, 60.2 Hz, 1 F), -98.97 (dd, *J* = 257.3, 54.1 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.82, 157.75, 128.94, 124.21, 123.69, 120.03, 114.24 (dd, *J* = 278.9, 271.0 Hz), 71.41 (d, *J* = 4.2 Hz), 35.79, 18.84, 17.30, 12.34 ppm. IR (KBr): ν_{max} = 2960, 2856, 1833, 1641, 1580, 1495, 1452, 1322, 1292, 1260, 1149, 1080, 1045, 1025 cm^{-1}. MS (DART POS): 298.1 (M+H); HRMS (DART POS): $C_{14}H_{14}NO_2F_2S$ (M+H) Calcd: 298.0708, Found: 298.0708. HPLC: (OJH, Hexane/^{i}PrOH = 98/2, 0.7 mL/min, 214 nm), t_R (major) = 4.274 min, t_R (minor) = 4.082 min (93% ee); $[\alpha]_D^{20}$ = +10.80 (c = 0.100, $CHCl_3$, 93% ee).

(*R*)-4-Cyclopentyl-4-((difluoromethyl)thio)-2-phenyloxazol-5-(4*H*)-one 11k. Yield 93%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.4 Hz, 2 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.52 (t, *J* = 7.7 Hz, 2 H), 6.88 (dd, *J* = 60.4, 53.9 Hz, 1 H), 2.66 – 2.56 (m, 1 H), 2.06 – 1.89 (m, 1 H), 1.83 – 1.53 (m, 6 H), 1.40 – 1.21 (m, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.35 (dd, *J* = 258.2, 60.5 Hz, 1 F), -99.70 (dd, *J* = 258.2, 53.9 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.56, 159.78, 131.07, 126.38, 125.83, 122.21, 116.44 (dd, *J* = 279.1, 270.5 Hz), 74.51 (d, *J* = 4.5 Hz), 43.48, 25.31, 24.42, 23.10, 22.92 ppm. IR (KBr): ν_{max} = 2960, 2871, 1830, 1642, 1580, 1452, 1323, 1292, 1061 cm^{-1}. MS (DART POS): 312.1 (M+H); HRMS (DART POS): $C_{15}H_{16}NO_2F_2S$ (M+H) Calcd: 312.0864, Found: 312.0864. HPLC: (PC1, Hexane/^{i}PrOH = 98/2, 0.7 mL/min, 214 nm), t_R (major) = 4.139 min, t_R (minor) = 3.846 min (94% ee); $[\alpha]_D^{20}$ = +17.14 (c = 0.280, $CHCl_3$, 94% ee).

(*R*)-4-Cyclohexyl-4-((difluoromethyl)thio)-2-phenyloxazol-5-(4*H*)-one 11l. Yield 94%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.4 Hz, 2 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 6.91 (dd, *J* = 60.3, 54.1 Hz, 1 H), 2.19 – 1.98 (m, 2 H), 1.92 – 1.63 (m, 4 H), 1.35 – 1.02 (m, 5 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.38 (dd, *J* = 258.4, 60.4 Hz, 1 F), -99.49 (dd, *J* = 258.4, 54.1 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.31, 157.49, 128.88, 124.20, 123.63, 119.98, 114.39 (dd, *J* = 278.6, 270.3 Hz), 73.52 (d, *J* = 4.1 Hz), 40.02, 22.12, 22.00, 21.11, 20.97, 20.86 ppm. IR (KBr): ν_{max} = 2934, 2856, 1829, 1640, 1580, 1495, 1452, 1323, 1292, 1153, 1067, 1051 cm^{-1}. MS (DART POS): 326.1 (M+H); HRMS (DART POS): $C_{16}H_{18}NO_2F_2S$ (M+H) Calcd: 326.1021, Found: 326.1020. HPLC: (IG, Hexane/^{i}PrOH = 99/1, 0.7 mL/min, 214 nm), t_R (major) = 8.79 min, t_R (minor) = 8.05 min (94% ee); $[\alpha]_D^{20}$ = +31.43 (c = 0.140, $CHCl_3$, 94% ee).

General procedure for asymmetric difluoromethylthiolation of oxindoles. Oxindole **12a** (67 mg, 0.30 mmol, 1.00 equiv.), cesium carbonate (147 mg, 0.450 mmol, 1.50 equiv.) and compound 9c (118 mg, 0.330 mmol, 1.10 equiv.) were added into a flame-dried Schlenk tube. The tube was putted into liquid nitrogen. Dry toluene (3.0 mL) was added under argon atmosphere. The resulting solution was stirred at -40 °C for 12 h. After the reaction was completed as monitored by ^{19}F NMR spectroscopy, the reaction was quenched by addition of an aqueous solution of HCl (2.0 N). The mixture was extracted with Et_2O (10 mL × 3). The combined organic phase was separated and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum. The residue was purified by flash chromatography to give the difluoromethylthiolated product 13a (*S*)-3-((difluoromethyl)thio)-1-methyl-3- phenylindolin-2-one as a white solid (81 mg, 88% yield).

(*S*)-3-((Difluoromethyl)thio)-1-methyl-3-phenylindolin-2-one 13a. yield 88%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.60 (m, 2 H), 7.43 – 7.29 (m, 5 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 6.94 (dd, *J* = 58.2, 53.8 Hz, 1 H), 6.93 (d, *J* = 7.6 Hz, 1 H), 3.32 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.77 (dd, *J* = 253.7, 58.3 Hz, 1 F), -96.01 (dd, *J* = 253.7, 53.7 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.41, 142.35, 136.04, 130.02, 129.01, 128.67, 128.48, 127.65, 125.54, 123.49, 120.37 (dd, *J* = 274.5, 269.4 Hz), 109.03, 57.32, 26.97 ppm. IR (KBr): ν_{max} = 3063, 2941, 1710, 1608, 1489, 1470, 1446, 1421, 1368, 1349, 1302, 1257, 1227, 1156, 1129, 1091, 1063, 1038 cm^{-1}. MS (EI): 222 (100), 305 (5.22); HRMS (EI) for $C_{16}H_{13}NOF_2S$ Calcd: 305.0686, Found: 305.0676. Mp: 101.0 – 102.0 °C. HPLC: (IE-3, Hexane/^{i}PrOH = 95/5, 0.7 mL/min, 214 nm), t_R (major) = 9.12 min, t_R (minor) = 10.01 min (94% ee); $[\alpha]_D^{25}$ = -56.73 (c = 0.100, $CHCl_3$, 94% ee).

(*S*)-3-(4-Chlorophenyl)-3-((difluoromethyl)thio)-1-methyl indolin -2-one 13b. Yield 92%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.53 (m, 2 H), 7.43 – 7.31 (m, 4 H), 7.14 (td, *J* = 7.6, 0.9 Hz, 1 H), 6.93 (d, *J* = 8.0 Hz, 1 H), 6.92 (dd, *J* = 58.5, 53.6 Hz, 1 H), 3.32 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.78 (dd, *J* = 254.5, 58.4 Hz, 1 F), -96.49 (dd, *J* = 254.5, 53.6 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.98, 142.31, 134.82, 134.59, 130.20, 129.14, 129.13, 128.04, 125.45, 123.59, 119.99 (dd, *J* = 275.3, 269.9 Hz), 109.13, 56.74 (d, *J* = 3.7 Hz), 27.01 ppm. IR (KBr): ν_{max} = 3068, 2968, 2937, 1707, 1611, 1591, 1492, 1473, 1419, 1400, 1371, 1351, 1304, 1261, 1159, 1132, 1112, 1096, 1071, 1042, 1013 cm^{-1}. MS (EI): 256 (100), 339 (3.92); HRMS (EI) for $C_{16}H_{12}NOF_2SCl$ Calcd: 339.0296, Found: 339.0287. HPLC: (ADH, Hexane/^{i}PrOH = 95/5, 0.7 mL/min, 214 nm), t_R (major) = 15.21 min, t_R (minor) = 20.80 min (93% ee); $[\alpha]_D^{25}$ = -74.35 (c = 0.100, $CHCl_3$, 93% ee).

(*S*)-4-(3-((Difluoromethyl)thio)-1-methyl-2-oxoindolin-3-yl) benzonitrile 13c. Yield 81%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 2 H), 7.70 – 7.63 (m, 2 H), 7.41 (td, *J* = 7.8, 1.2 Hz, 1 H), 7.31 (dd, *J* = 7.5, 0.7 Hz, 1 H), 7.15 (td, *J* = 7.6, 0.9 Hz, 1 H), 6.97 (dd, *J* = 58.7, 53.4 Hz, 1 H), 6.96 (d, *J* = 7.9 Hz, 1 H), 3.34 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.61 (dd, *J* = 255.4, 58.7 Hz, 1 F), -97.02 (dd, *J* = 255.2, 53.4 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.35, 142.33, 141.37, 132.65, 130.57, 128.61, 127.30, 125.40, 123.82, 119.50 (dd, *J* = 276.8, 270.0 Hz), 118.18, 112.62, 109.39, 56.96, 27.12 ppm. IR (KBr): ν_{max} = 3061, 2925, 2853, 2230, 1716, 1611, 1492, 1472, 1422, 1408, 1370, 1348, 1300, 1261, 1158, 1130, 1069 cm^{-1}. MS (DART POS): 331.1 (M+H); HRMS (DART POS): $C_{17}H_{13}ON_2F_2S$ (M+H) Calcd: 331.0711, Found: 331.0709. HPLC: (ODH, Hexane/^{i}PrOH = 95/5, 0.7 mL/min, 214 nm), t_R (major) = 32.39 min, t_R (minor) = 36.61 min (81% ee); $[\alpha]_D^{25}$ = -67.16 (c = 0.090, $CHCl_3$, 81% ee).

(*S*)-3-((Difluoromethyl)thio)-3-(4-methoxyphenyl)-1-methyl indolin-2-one 13d. Yield 63%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 2 H), 7.37 (ddd, *J* = 9.0, 7.9, 0.9 Hz, 2 H), 7.13 (td, *J* = 7.6, 0.9 Hz, 1 H), 6.94 – 6.88 (m, 3 H), 6.87 (dd, *J* = 58.3, 53.8 Hz, 1 H), 3.78 (s, 3 H), 3.30 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.90 (dd, *J* = 254.0, 58.3 Hz, 1 F), -96.18 (dd, *J* = 254.0, 53.8 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.53, 159.76, 142.31, 129.88, 129.01, 128.70, 127.67, 125.53, 123.41, 120.44 (dd, *J* = 274.4, 269.5 Hz), 114.32, 108.94, 56.90, 55.34, 26.92 ppm. IR (KBr): ν_{max} = 3051, 3004, 2936, 2838, 1717, 1608, 1579, 1510, 1492, 1471, 1418, 1370, 1348, 1297, 1255, 1185, 1169, 1130, 1062, 1035 cm^{-1}. MS (EI): 252 (100), 335 (0.79); HRMS (EI) for $C_{17}H_{15}NO_2F_2S$ Calcd: 335.0792, Found: 335.0790. HPLC: (ODH, Hexane/^{i}PrOH = 8/2, 0.7 mL/min, 214 nm), t_R (major) = 9.09 min, t_R (minor) = 12.04 min (88% ee); $[\alpha]_D^{25}$ = -78.03 (c = 0.050, $CHCl_3$, 88% ee).

Methyl-(*S*)-4-(3-((difluoromethyl)thio)-1-methyl-2-oxoindolin-3-yl)benzoate 13e. Yield 99%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.92 (m, 2 H), 7.77 – 7.62 (m, 2 H), 7.38 (td, *J* = 7.8, 1.1 Hz, 1 H), 7.33 (d, *J* = 7.6 Hz, 1 H), 7.16 – 7.10 (m, 1 H), 6.97 (dd, *J* = 58.5, 53.5 Hz, 1 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 3.91 (s, 3 H), 3.34 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.72 (dd, *J* = 254.3, 58.5 Hz, 1 F), -96.53 (dd, *J* = 254.2, 53.4 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.86, 166.39, 142.33, 140.99, 130.34, 130.26, 130.15, 127.90, 127.78, 125.44, 123.64, 119.90 (dd, *J* = 275.7, 269.6 Hz), 109.16, 57.10, 52.29, 27.05 ppm. IR (KBr): ν_{max} = 3059, 2952, 2925, 2851, 1717, 1611, 1574, 1492, 1472, 1436, 1407, 1370, 1347, 1281, 1191, 1158, 1113, 1066, 1020 cm^{-1}. MS (EI): 280 (100), 363 (6.12); HRMS (EI) for $C_{18}H_{15}NO_3F_2S$ Calcd: 363.0741, Found: 363.0745. HPLC: (ODH, Hexane/^{i}PrOH = 95/5, 0.7 mL/min, 214 nm), t_R (major) = 18.99 min, t_R (minor) = 22.42 min (90% ee); $[\alpha]_D^{25}$ = -31.81 (c = 0.050, $CHCl_3$, 90% ee).

(*S*)-3-(4-Acetylphenyl)-3-((difluoromethyl)thio)-1-methylindolin-2-one 13f. Yield 90%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 2 H), 7.75 – 7.69 (m, 2 H), 7.38 (t, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 7.5 Hz, 1 H), 7.15 – 7.10 (t, *J* = 8.0 Hz 1 H), 6.97 (dd, *J* = 58.5, 53.4 Hz, 1 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 3.33 (s, 3 H), 2.57 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.63 (dd, *J* = 254.3, 58.5 Hz, 1 F), -96.52 (dd, *J* = 254.5, 53.5 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.36, 174.81, 142.33, 141.15, 137.00, 130.32, 128.87, 127.99, 127.82, 125.42, 123.67, 119.88 (dd, *J* = 275.8, 269.6 Hz), 109.22, 57.13 (d, *J* = 3.7 Hz), 27.04, 26.68 ppm. IR (KBr): ν_{max} = 3059, 2937, 1716, 1685, 1610, 1568, 1491, 1472, 1423, 1405, 1366, 1347, 1291, 1268, 1191, 1158, 1129, 1064 cm^{-1}. MS (EI): 264 (100), 347 (5.4); HRMS (EI) for $C_{18}H_{15}NO_2F_2S$ Calcd: 347.0792, Found: 347.0788. HPLC: (ADH, Hexane/^{i}PrOH = 9/1, 0.7 mL/min, 214 nm), t_R (major) = 25.20 min, t_R (minor) = 30.15 min (91% ee); $[\alpha]_D^{25}$ = -120.86 (c = 0.125, $CHCl_3$, 91% ee).

(*S*)-2-(4-(3-((Difluoromethyl)thio)-1-methyl-2-oxoindolin-3-yl)phenyl)acetonitrile 13g. Yield 92%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 1 H), 7.64 – 7.60 (m, 1 H), 7.37 (m, 4 H), 7.13 (td, *J* = 7.6, 0.9 Hz, 1 H), 6.94 (d, *J* = 7.6 Hz, 1 H), 6.92 (dd, *J* = 58.4, 53.6 Hz, 1 H), 3.74 (s, 2 H), 3.33 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.76 (dd, *J* = 254.5, 58.5 Hz, 1 F), -96.49 (dd, *J* = 254.4, 53.6 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.06, 142.32, 131.14, 130.47, 130.19, 128.55, 128.52, 128.11, 125.44, 123.60, 120.01 (dd, *J* = 275.4, 269.5 Hz), 117.39, 109.13, 56.91 (d, *J* = 4.0 Hz), 27.02, 23.25 ppm. IR (KBr): ν_{max} = 3059, 2924, 2852, 2252, 1709, 1609, 1511, 1492, 1471, 1417, 1370, 1348, 1301, 1259, 1198, 1158, 1129, 1062 cm^{-1}. MS (EI): 261 (100), 344 (3.67); HRMS (EI) for $C_{18}H_{14}N_2OF_2S$ Calcd: 344.0795, Found: 344.0790. HPLC: (ADH, Hexane/^{i}PrOH = 9/1, 0.7 mL/min, 214 nm), t_R (major) = 37.23 min, t_R (minor) = 45.93 min (94% ee); $[\alpha]_D^{25}$ = -73.29 (c = 0.150, $CHCl_3$, 94% ee).

(*S*)-3-(3-((Difluoromethyl)thio)-1-methyl-2-oxoindolin-3-yl)benzonitrile 13h. Yield 86%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (ddd, *J* = 8.1, 2.0, 1.2 Hz, 1 H), 7.86 (t, *J* = 1.6 Hz, 1 H), 7.61 (dt, *J* = 7.7, 1.3 Hz, 1 H), 7.54 – 7.48 (m, 1 H), 7.41 (td, *J* = 7.8, 1.2 Hz, 1 H), 7.34 (dd, *J* = 7.6, 0.7 Hz, 1 H), 7.16 (td, *J* = 7.6, 0.9 Hz, 1 H), 6.97 (d, *J* = 7.9 Hz, 1 H), 6.94 (dd, *J* = 58.8, 53.5 Hz, 1 H), 3.33 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.66 (dd, *J* = 255.7, 58.8 Hz, 1 F), -97.13 (dd, *J* = 255.7, 53.5 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.33, 142.34, 137.92, 132.37, 132.23, 131.32, 130.63, 129.90, 127.22, 125.42, 123.87, 119.52 (dd, *J* = 276.7, 270.2 Hz), 118.24, 113.14, 109.48, 56.52, 27.13 ppm. IR (KBr): ν_{max} = 3066, 2937, 2232, 1716, 1611, 1579, 1491, 1472, 1419, 1370, 1349, 1302, 1260, 1180, 1159, 1130, 1066 cm^{-1}. MS (DART POS): 331.1 (M+H); HRMS (DART POS): $C_{17}H_{13}ON_2F_2S$ (M+H) Calcd: 331.0711, Found: 331.0708. HPLC: (ID-3, Hexane/^{i}PrOH = 95/5, 0.7 mL/min, 214 nm), t_R (major) = 23.88 min, t_R (minor) = 28.17 min (92% ee); $[\alpha]_D^{25}$ = -45.30 (c = 0.100, $CHCl_3$, 92% ee).

(*S*)-3-((Difluoromethyl)thio)-1-methyl-3-(naphthalen-2-yl)indolin-2-one 13i. Yield 96%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1 H), 7.89 (d, *J* = 8.7 Hz, 1 H), 7.82 (m, 3 H), 7.55 – 7.47 (m, 2 H), 7.44 (d, *J* = 7.5 Hz, 1 H), 7.38 (t, *J* = 7.8 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.04 (dd, *J* = 58.1, 53.6 Hz, 1 H), 6.95 (d, *J* = 7.8 Hz, 1 H), 3.38 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.58 (dd, *J* = 253.2, 58.1 Hz, 1 F), -95.74 (dd, *J* = 253.2, 53.7 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.40, 142.37, 133.25, 133.00, 132.98, 130.06, 129.10, 128.48, 128.40, 127.60, 127.07, 126.95, 126.68, 125.55, 124.95, 123.53, 120.43 (dd, *J* = 274.4, 269.4 Hz), 109.07, 57.48 (d, *J* = 3.7 Hz), 27.04 ppm. IR (KBr): ν = 3056, 3025, 2937, 1708, 1608, 1491, 1470, 1420, 1372, 1348, 1324, 1299, 1263, 1228, 1164, 1156, 1125, 1090, 1059, 1036 cm^{-1}. MS (EI): 272 (100), 355 (4.27); HRMS (EI) for $C_{20}H_{15}NOF_2S$ Calcd: 355.0842, Found: 355.0837. Mp: 129.5 – 130.5 ^{o}C. HPLC: (ODH, Hexane/^{i}PrOH = 95/5, 0.7 mL/min, 214 nm), t_R (major) = 14.19 min, t_R (minor) = 16.14 min (89% ee); $[\alpha]_D^{25}$ = -54.53 (c = 0.100, $CHCl_3$, 89% ee).

(*S*)-5-Acetyl-3-((difluoromethyl)thio)-1-methyl-3-phenylindolin-2-one 13j. Yield 94%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 1 H), 7.98 (s, 1H), 7.61 (d, *J* = 7.2 Hz, 2 H), 7.47 – 7.30 (m, 3 H), 6.98 (d, *J* = 8.2 Hz, 1 H), 6.93 (dd, *J* = 57.7, 53.8 Hz, 1 H), 3.37 (s, 3 H), 2.57 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.97 (dd, *J* = 252.8, 57.6 Hz, 1 F), -95.54 (dd, *J* = 252.8, 53.8 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.19, 175.69, 146.37, 135.24, 132.92, 131.47, 129.20, 129.09, 128.95, 127.56, 125.59, 120.03 (dd, *J* = 274.9, 270.7 Hz), 108.53, 56.94 (d, *J* = 4.2 Hz), 27.23, 26.43 ppm. IR (KBr): ν_{max} = 2960, 2923, 2853, 1722, 1678, 1608, 1497, 1443, 1340, 1274, 1100, 1056 cm^{-1}. MS (DART POS): 347.9 (M+H); HRMS (DART POS): $C_{18}H_{16}O_2NF_2S$ (M+H) Calcd: 348.0864, Found: 348.0864. Mp: 130.5 – 131.5 ^{o}C. HPLC: (ODH, Hexane/^{i}PrOH = 8/2, 0.7 mL/min, 214 nm), t_R (major) = 13.22 min, t_R (minor) = 16.93 min (81% ee); $[\alpha]_D^{20}$ = -7.00 (c = 0.200, $CHCl_3$, 81% ee).

(*S*)-3-((Difluoromethyl)thio)-1,5-dimethyl-3-phenylindolin-2-one 13k. Yield 95%, white solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.62 (d, *J* = 7.3 Hz, 2 H), 7.36 (dt, *J* = 15.2, 7.2 Hz, 3 H), 7.15 (d, *J* = 5.2 Hz, 2 H), 6.96 (dd, *J* = 57.5, 52.8 Hz, 1 H), 6.81 (d, *J* = 8.2 Hz, 1 H), 3.31 (s, 3 H), 2.33 (s, 3 H); ^{19}F NMR (376 MHz, cdcl$_3$) δ -90.85 (dd, *J* = 253.6, 58.3 Hz, 1 F), -96.11 (dd, *J* = 253.7, 53.6 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.38, 139.93, 136.26, 133.22, 130.31, 128.96, 128.55, 127.64, 126.08, 120.40 (dd, *J* = 274.2, 269.1 Hz), 108.71, 57.45 (d, *J* = 4.1 Hz), 26.97, 21.14 ppm. IR (KBr): ν_{max} = 2952, 2923, 2855, 1698, 1618, 1602, 1500, 1352, 1322, 1272, 1147, 1059, 1039 cm^{-1}. MS (EI): 236 (100), 319 (7.33); HRMS (EI) for $C_{17}H_{15}NOF_2S$ Calcd: 319.0842, Found: 319.0847. Mp: 129.5 –

130.5 °C. nHPLC: (ADH, Hexane/^{i}PrOH = 97/3, 0.7 mL/min, 214 nm), t_R (major) = 14.61 min, t_R (minor) = 13.39 min (85% ee); $[\alpha]_D^{20}$ = -32.60 (c = 0.100, $CHCl_3$, 85% ee).

Methyl-(*S*)-3-((difluoromethyl)thio)-1-methyl-2-oxo-3-phenyl indoline-6-carboxylate 13l. Yield 89%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.9 Hz, 1 H), 7.59 (d, *J* = 6.9 Hz, 3 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 7.42 – 7.31 (m, 3 H), 6.91 (dd, *J* = 57.8, 53.9 Hz, 1 H), 3.94 (s, 3 H), 3.36 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.90 (dd, *J* = 253.1, 57.8 Hz, 1 F), -95.57 (dd, *J* = 253.2, 53.9 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.02, 166.20, 142.65, 135.20, 133.47, 131.88, 129.13, 128.93, 127.58, 125.52, 125.05, 119.98 (dd, *J* = 275.1, 271.1 Hz), 109.68, 57.17 (d, *J* = 3.5 Hz), 52.53, 27.18 ppm. IR (KBr): ν_{max} = 2998, 2953, 2925, 2853, 1720, 1621, 1452, 1333, 1300, 1273, 1249, 1158, 1111, 1062, 1040 cm^{-1}. MS (EI): 280 (100), 363 (4.63); HRMS (EI) for $C_{18}H_{15}NO_3F_2S$ Calcd: 363.0741, Found: 363.0732. HPLC: (IG, Hexane/^{i}PrOH = 9/1, 0.7 mL/min, 214 nm), t_R (major) = 14.29 min, t_R (minor) = 16.35 min (85% ee); $[\alpha]_D^{20}$ = -37.00 (c = 0.140, $CHCl_3$, 85% ee).

(*S*)-3-((Difluoromethyl)thio)-5-methoxy-1-methyl-3-phenyl indolin-2-one 13m. Yield 95%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.4 Hz, 2 H), 7.40 – 7.31 (dt, *J* = 21.3, 7.1 Hz, 3 H), 6.95 (d, *J* = 2.5 Hz, 1 H), 6.93 (dd, *J* = 58.2, 53.7 Hz,1 H), 6.89 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.83 (d, *J* = 8.5 Hz, 1 H), 3.78 (s, 3 H), 3.30 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -95.63 (dd, *J* = 253.8, 58.2 Hz, 1 F), -100.85 (dd, *J* = 253.7, 53.7 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.08, 156.50, 136.04, 135.76, 129.74, 128.99, 128.63, 127.60, 120.32 (dd, *J* = 274.6, 269.6 Hz), 114.46, 112.62, 109.40, 57.70 (d, *J* = 3.7 Hz), 55.88, 27.03 ppm. IR (KBr): ν_{max} = 2960, 2925, 1710, 1603, 1591, 1497, 1460, 1306, 1261, 1190, 1128, 1106, 1059, 1037 cm^{-1}. MS (EI): 253 (100), 335 (14.16); HRMS (EI) for $C_{17}H_{15}NO_2F_2S$ Calcd: 335.0792, Found: 335.0790. Mp: 94.5 – 95.5 °C. HPLC: (ADH, Hexane/^{i}PrOH = 8/2, 0.7 mL/min, 214 nm), t_R (major) = 9.72 min, t_R (minor) = 8.96 min (93% ee); $[\alpha]_D^{20}$ = -55.46 (c = 0.150, $CHCl_3$, 93% ee). The ee of the product after recrystallization was more than 99%.

General procedure for asymmetric difluoromethylthiolation of benzofuran-2(3*H*)-one. Benzofuran-2(3*H*)-one (63 mg, 0.30 mmol, 1.0 equiv.), cesium carbonate (147 mg, 0.450 mmol, 1.50 equiv.) and compound **9c** (129 mg, 0.360 mmol, 1.20 equiv.) were added into a flame-dried Schlenk tube. The tube was putted into liquid nitrogen. Dry toluene (3.0 mL) was added under argon atmosphere. The resulting solution was stirred at -40 °C for 12 h. After the reaction was completed as monitored by ^{19}F NMR spectroscopy, the reaction was quenched by addition of an aqueous solution of HCl (2.0 N). The mixture was extracted with Et_2O (10 mL × 3). The combined organic phase was separated and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum. The residue was purified by flash chromatography to give the difluoromethylthiolated product **14a** (*S*)-3-((difluoromethyl)thio)-3-phenyl benzofuran-2(3*H*)-one as a yellow solid (81 mg, 84% yield).

(*S*)-3-((Difluoromethyl)thio)-3-phenylbenzofuran-2(3*H*)-one 14a. Yield 84%, Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.2, 1.4 Hz, 2 H), 7.50 – 7.37 (m, 5 H), 7.27 (td, *J* = 7.6, 0.9 Hz, 1 H), 7.21 (d, *J* = 8.1 Hz, 1 H), 6.70 (dd, *J* = 58.3, 53.6 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.74 (dd, *J* = 255.5, 58.2 Hz, 1 F), -97.18 (dd, *J* = 255.6, 53.5 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.55, 152.06, 134.46, 130.96, 129.35, 129.32, 127.33, 126.84, 125.93, 125.21, 119.73 (dd, *J* = 277.2, 271.7 Hz), 111.63, 56.02 (d, *J* = 4.0 Hz) ppm. IR (KBr): ν_{max} = 3063, 1807, 1617, 1598, 1495, 1477, 1464, 1448, 1318, 1298, 1230, 1126, 1061 cm^{-1}. MS (EI): 209 (100), 292 (0.32); HRMS (EI) for $C_{15}H_{10}O_2F_2S$ Calcd: 292.0370, Found: 292.0361. Mp: 72.0 – 73.0 °C. HPLC: (ADH, Hexane/^{i}PrOH = 95/5, 0.7 mL/min, 214 nm), t_R (major) = 8.52 min, t_R (minor) = 9.22 min (87% ee); $[\alpha]_D^{25}$ = -4.96 (c = 0.120, $CHCl_3$, 87% ee).

(*S*)-3-(4-Chlorophenyl)-3-((difluoromethyl)thio)benzofuran-2 (3*H*)-one 14b. Yield 90%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.54 (m, 2 H), 7.47 – 7.43 (m, 2 H), 7.41 – 7.36 (m, 2 H), 7.29 (td, *J* = 7.7, 0.8 Hz, 1 H), 7.24 – 7.20 (m, 1 H), 6.69 (dd, *J* = 58.4, 53.4 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.63 (dd, *J* = 255.7, 58.4 Hz, 1 F), -97.42 (dd, *J* = 255.9, 53.4 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.17, 152.05, 135.65, 132.96, 131.21, 129.50, 128.82, 126.36, 125.83, 125.36, 119.45 (dd, *J* = 278.0, 272.2 Hz), 111.79, 55.45 (d, *J* = 4.4 Hz) ppm. IR (KBr): ν_{max} = 3071, 2965, 1809, 1618, 1597, 1491, 1476, 1464, 1402, 1320, 1298, 1288, 1127, 1063, 1015 cm^{-1}. MS (EI): 243 (100), 326.0; HRMS (EI) for $C_{15}H_9O_2F_2SCl$ Calcd: 325.9980, Found: 325.9978. HPLC: (ADH, Hexane/^{i}PrOH = 95/5, 0.7 mL/min, 214 nm), t_R (major) = 10.09 min, t_R (minor) = 11.13 min (82% ee); $[\alpha]_D^{25}$ = -1.87 (c = 0.225, $CHCl_3$, 82% ee).

(*S*)-3-(Benzo[d][1,3]dioxol-5-yl)-3-((difluoromethyl)thio) benzofuran-2(3*H*)-one 14c. Yield 99%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2 H), 7.27 (td, *J* = 7.6, 0.8 Hz, 1 H), 7.20 (d, *J* = 8.2 Hz, 1 H), 7.16 (d, *J* = 2.0 Hz, 1 H), 7.02 (dd, *J* = 8.3, 2.0 Hz, 1 H), 6.79 (d, *J* = 8.1 Hz, 1 H), 6.66 (dd, *J* = 58.4, 53.7 Hz, 1 H), 5.99 (s, 2 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.84 (dd, *J* = 255.7, 58.3 Hz, 1 F), -97.31 (dd, *J* = 255.8, 53.6 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.46, 152.01, 148.58, 148.56, 130.95, 127.74, 126.85, 125.91, 125.18, 121.39, 119.68 (dd, *J* = 277.3, 272.0 Hz), 111.64, 108.55, 107.94, 101.78, 55.79 (d, *J* = 4.3 Hz) ppm. IR (KBr): ν_{max} = 2904, 2782, 1808, 1617, 1598, 1505, 1489, 1464, 1440, 1350, 1320, 1290, 1252, 1232, 1132, 1063 cm^{-1}. MS (EI): 253 (100), 336 (2.02); HRMS (EI) for $C_{16}H_{10}O_4F_2S$ Calcd: 336.0268, Found: 336.0258. HPLC: (ADH, Hexane/^{i}PrOH = 95/5, 0.7 mL/min, 214 nm), t_R (major) = 14.31 min, t_R (minor) = 16.14 min (86% ee); $[\alpha]_D^{25}$ = -4.24 (c = 0.150, $CHCl_3$, 86% ee).

General procedure for enantioselective difluoromethylthiolation of β-ketoester. β-ketoester (57 mg, 0.30 mmol, 1.0 equiv.), cesium carbonate (108 mg, 0.330 mmol, 1.10 equiv.) and the reagent **9c** (129 mg, 0.360 mmol, 1.20 equiv.) were added into a flame-dried Schlenk tube. The tube was putted into liquid nitrogen. Anhydrous toluene (3.0 mL) was added under argon atmosphere. The resulting solution was stirred at -40 °C for 6 h. After the reaction was completed as monitored by ^{19}F NMR spectroscopy, the reaction was quenched by addition of an aqueous solution of HCl (2.0 N). The mixture was extracted with Et_2O (10 mL × 3). The combined organic phase was separated and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum. The residue was purified by flash

chromatography to give the difluoromethylthiolated product **15a** (*R*)-Methyl-1-oxo-2-((difluoromethyl)thio) -2,3-dihydro-1*H*-indene-2-carboxylate as a white solid (79 mg, 96.7% yield).

Methyl-(*R*)-2-((difluoromethyl)thio)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate 15a. Yield 97%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.7 Hz, 1 H), 7.68 (t, *J* = 7.5 Hz, 1 H), 7.50 (t, *J* = 55.6 Hz, 1 H), 7.48 – 7.43 (m, 2 H), 4.03 (d, *J* = 17.9 Hz, 1 H), 3.80 (s, 3 H), 3.26 (d, *J* = 17.9 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -91.58 (dd, *J* = 250.7, 55.6 Hz, 1 F), -92.90 (dd, *J* = 250.7, 55.6 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.67, 168.74, 150.52, 136.31, 132.94, 128.60, 126.26, 125.75, 120.24 (t, *J* = 271.1 Hz), 58.50, 53.95, 39.48 ppm. IR (KBr): ν_{max} = 3032, 2963, 1757, 1720, 1602, 1588, 1465, 1434, 1334, 1309, 1277, 1247, 1218, 1190, 1154, 1074, 1032 cm^{-1}. MS (EI): 189 (100), 272 (1.54); HRMS (EI) for $C_{12}H_{10}O_3F_2S$ Calcd: 272.0319, Found: 272.0322. Mp: 98.5 – 99.5 °C. HPLC: (ODH, Hexane/^{i}PrOH = 95/5, 0.7 mL/min, 214 nm), t_R (major) = 12.65 min, t_R (minor) = 14.21 min (83% ee); $[\alpha]_D^{25}$ = -1.96 (c = 0.100, $CHCl_3$, 83% ee).

Methyl-(*R*)-2-((difluoromethyl)thio)-6-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate 15b. Yield 99%, white oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1 H), 7.50 (d, *J* = 7.3 Hz, 1 H), 7.49 (t, *J* = 55.7 Hz, 1 H), 7.35 (d, *J* = 7.9 Hz, 1 H), 3.97 (d, *J* = 17.8 Hz, 1 H), 3.80 (s, 3 H), 3.21 (d, *J* = 17.8 Hz, 1 H), 2.42 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -91.62 (dd, *J* = 251.0, 55.7 Hz, 1 F), -92.90 (dd, *J* = 251.0, 55.7 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.80, 168.92, 147.98, 138.86, 137.65, 133.18, 125.95, 125.66, 120.29 (t, *J* = 271.1 Hz), 58.89, 53.96, 39.24, 21.09 ppm. IR (KBr): ν_{max} = 2957, 1748, 1716, 1618, 1585, 1495, 1434, 1281, 1252, 1222, 1064, 1039 cm^{-1}. MS (DART POS): 287.1 (M+H); HRMS (DART POS): $C_{13}H_{13}O_3F_2S$ (M+H) Calcd: 287.0548, Found: 287.0546. HPLC: (ADH, Hexane/^{i}PrOH = 9/1, 0.7 mL/min, 214 nm), t_R (major) = 8.83 min, t_R (minor) = 9.44 min (80% ee); $[\alpha]_D^{25}$ = +4.01 (c = 0.120, $CHCl_3$, 80% ee).

Methyl-(R)-5-chloro-2-((difluoromethyl)thio)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate 15c. Yield 87%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 1 H), 7.46 (t, *J* = 55.6 Hz, 1 H), 7.47 – 7.43 (m, 2 H), 4.02 (d, *J* = 18.0 Hz, 1 H), 3.81 (s, 3 H), 3.26 (d, *J* = 18.1 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -91.45 (dd, *J* = 250.5, 55.7 Hz, 1 F), -92.91 (dd, *J* = 250.5, 55.6 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.26, 168.40, 152.00, 143.11, 131.46, 129.53, 126.88, 126.56, 120.12 (t, *J* = 271.7 Hz), 58.72, 54.14, 39.20 ppm. IR (KBr): ν_{max} = 3068, 2958, 1751, 1717, 1600, 1581, 1435, 1321, 1265, 1209, 1181, 1071, 1041 cm^{-1}. MS (DART POS): 307.0 (M+H); HRMS (DART POS): $C_{12}H_{10}O_3F_2SCl$ (M+H) Calcd: 307.0002, Found: 306.9998. Mp: 101.5 – 102.5 °C. HPLC: (ADH, Hexane/^{i}PrOH = 95/5, 0.7 mL/min, 214 nm), t_R (major) = 15.35 min, t_R (minor) = 14.62 min (79% ee); $[\alpha]_D^{25}$ = +1.82 (c = 0.150, $CHCl_3$, 79% ee).

General procedure for alcoholysis of difluoromethylthiolated oxazolone. To a 25 mL flame-dried Schlenk tube was added difluoromethylthiolated oxazolone **11h** (36 mg, 0.10 mmol, 1.0 equiv.). Anhydrous toluene (0.5 mL) and MeOH (32 mg, 1.0 mmol, 10 equiv.) was added under argon atmosphere. Then $Sc(OTf)_3$ (5.0 mg, 0.010 mmol, 0.10 equiv.) was added under argon atmosphere. The resulting solution was stirred for 2 h at room temperature. After the reaction was completed as monitored by ^{19}F NMR spectroscopy, the reaction mixture was extracted with Et_2O (10 mL × 3). The combined organic phase was separated and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum. The residue was purified by flash chromatography to give the difluoromethylthiolated product **16** methyl-(*R*)-2-benzamido-2-((difluoromethyl)thio)-3-(4-methoxyphenyl)propanoate as a yellow oil (22 mg, 55% yield).

Methyl-(*R*)-2-benzamido-2-((difluoromethyl)thio)-3-(4-methoxyphenyl)propanoate 16. Yield 55%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.1 Hz, 2 H), 7.54 (t, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.29 (s, 1 H), 7.02 (d, *J* = 8.7 Hz, 2 H), 6.96 (t, *J* = 56.0 Hz, 1 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 4.16 (d, *J* = 13.8 Hz, 1 H), 3.93 (s, 3 H), 3.74 (s, 3 H), 3.46 (d, *J* = 13.8 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.21 (dd, *J* = 254.2, 56.5 Hz, 1 F), -94.42 (dd, *J* = 254.3, 55.6 Hz, 1 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.46, 166.52, 159.10, 134.00, 132.19, 131.13, 128.81, 126.99, 125.68, 120.25 (t, *J* = 273.1 Hz), 113.93, 68.13, 55.17, 53.87, 38.88 ppm. IR (KBr): ν_{max} = 2956, 2923, 2853, 1733, 1672, 1611, 1581, 1511, 1483, 1440, 1291, 1250, 1215, 1178, 1025 cm^{-1}. MS (DART POS): 417.9 (M+Na); HRMS (DART POS): $C_{18}H_{16}NO_3F_2S$ (M+H) Calcd: 396.1076, Found: 396.1074. HPLC: (IG, Hexane/^{i}PrOH = 92/8, 0.7 mL/min, 214 nm), t_R (major) = 51.96 min, t_R (minor) = 42.71 min (88% ee); $[\alpha]_D^{20}$ = -51.29 (c = 0.700, $CHCl_3$, 88% ee).

Supporting Information

NMR data of compounds **9a**-**c**, **11a**-**l**, **13a**-**m**, **14a**-**c** and **15a**-**c**, x-ray crystallograghy data of **9a**-**c**, **11e** and **13m**. The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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[19] CCDC 1913046-1913050 contain the supplementary crystallographic data for the compound **9a**-**c**, **11e** and **13m** reported in this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or pm application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [fax: +44-1223/336-033; email: deposit@ccdc.cam.ac.uk].

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Entry for the Table of Contents

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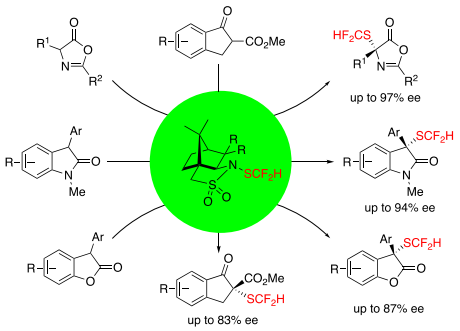
Asymmetric Difluoromethylthiolation of Carbon Nucleophiles with Optically Pure Difluoromethylthiolating Reagents Derived from Camphorsultam

e Zhang, Xiaolong Wan, Qilong Shen*



A family of optically pure electrophilic difluoromethylthiolating reagents based on the camphorsultam skeleton was invented. These reagents reacted with a variety of soft carbon nucleophiles such as oxazolone, oxindole, benzolactone and β-ketoester in good to excellent enantioselectivities.

