JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX
Note
pubs.acs.org/joc

Diastereoselective α-Fluorination of *N-tert*-Butanesulfinyl Imidates

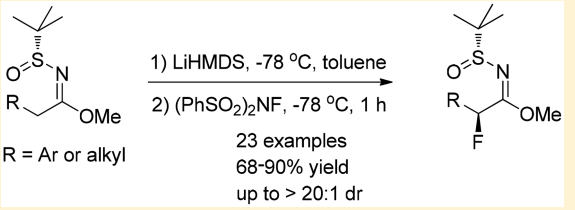
Wei Huang,[‡] Yun Yao,[†] Yan-Jun Xu,[‡] and Chong-Dao Lu*[,†,‡]

[†]School of Chemical Science and Technology, Yunnan University, Kunming 650091, China

[‡]Key Laboratory of Plant Resources and Chemistry of Arid Zones, Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Urumqi 830011, China

Supporting Information

ABSTRACT: A diastereoselective α-fluorination of *N-tert*-butanesulfinyl imidates was developed. Deprotonation of *N-tert*-butanesulfinyl imidates with lithium hexamethyldisilazide generates aza-enolates that can be intercepted, with excellent diastereocontrol, by the inexpensive electrophilic fluorinating agent NFSI. This protocol was applied to the preparation of synthetically useful *trans*-2-fluorocyclohexamine with high enantiomeric purity (99.5% ee).



Organofluorine compounds are important because of their broad applications in pharmaceutical agents[1] and agrochemicals.[2] Diastereoselective C−F bond formation is an effective way to incorporate fluorine into organic compounds with desired stereochemistry.[3] For example, electrophilic fluorination of enolates is broadly used to construct C−F bonds.[3] For this process, catalytic asymmetric protocols have been developed when the substrate is carboxylic derivatives that are easily enolized, such as β-keto acid derivatives or their analogues,[4] oxindoles,[5] α-aryl acetic acid derivatives,[6] and benzofuran-2-(3H)-ones.[7] Enolization of carboxylic acid derivatives with a weakly acidic α-proton is usually carried out using stoichiometric amounts of strong bases or Lewis acids. Diastereoselectivity is controlled by using chiral auxiliaries such as Evans' oxazolidinones or *trans*-Fox (fluorinated oxazolidine).[8] Recent examples of electrophilic fluorination of enolates include Zakarian's $TiCl_4$-promoted diastereoselective electrophilic fluorination of chiral *N*-acyloxazolidinones[9] and Brigaud's enantioselective fluorination of *trans*-Fox-derived amide enolates.[10]

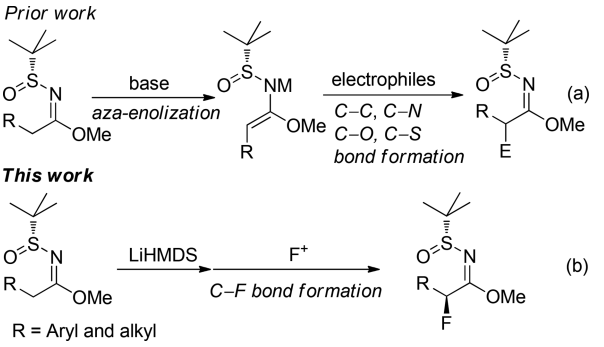
Another approach to achieving diastereoselective fluorination may be to use *N-tert*-butanesulfinyl (*N-t*BS) imidates, which are chiral equivalents of carboxylic acid derivatives and have been used to diastereoselectively construct C−C,[11,12,13,14] C−N,[15] C−O,[16] and C−S[17] bonds in the α-position via reaction between the aza-enolates and suitable electrophiles (Scheme 1a). Diastereoselective α-functionalization of *N-t*BS imidates is synthetically attractive because their chiral starting materials, (R_S)- and (S_S)-enantiomers of *N-tert*-butanesulfinamide,[18] are readily available and because *N-t*BS imidates can be conveniently converted to esters, amides, *N-t*BS imines, and amines.[10,12c,15−17]

Here we report electrophilic α-fluorination of *N-t*BS imidates (Scheme 1b) and demonstrate its synthetic utility by efficiently preparing enantioenriched *trans*-2-fluoro-cyclohexamine.

Initially, we investigated the feasibility of α-fluorination using (R_S)-*N-t*BS imidate **1a** with the inexpensive[9] electrophilic fluorination reagent *N*-fluorobenzenesulfonimide (NSFI, Table 1). Deprotonation of **1a** with lithium hexamethyldisilazide (LiHMDS) in THF at −78 °C and subsequent introduction of NSFI led to complete consumption of **1a** within 1 h and gave α-fluorinated product **2a** with 10:1 dr (entry 1). Changing the reaction solvent to dichloromethane or ether improved diastereoselectivity to 15:1 dr (entries 2−3). When toluene was used as solvent, excellent diastereocontrol was observed (>50:1 dr), and the desired fluorination product **2a** was isolated in 84% yield (entry 4). We also examined the reactions using NaHMDS or KHMDS as base. In these cases, better diastereoselectivities were obtained when the solvent was THF rather than toluene (entry 5 vs 6; entry 7 vs 8).

Using the optimized reaction conditions for the α-fluorination of *N-t*BS imidates (LiHMDS, NSFI, toluene), we evaluated the substrate scope (Table 2). Linear aliphatic-substituted imidates **1b−d** (entries 2−4) and their counterparts containing functionalities such as chlorine (**1e**, entry 5), 4-methoxybenzyloxy group (**1f**, entry 6), vinyl group (**1g**, *ent*-

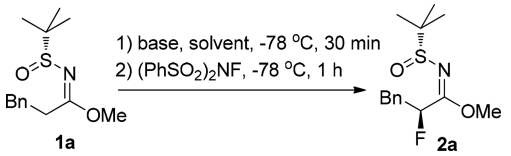
Scheme 1. Electrophilic α-Fluorination of *N-tert*-Butanesulfinyl Imidates



Received: September 13, 2018

DOI: 10.1021/acs.joc.8b02375
J. Org. Chem. XXXX, XXX, XXX−XXX

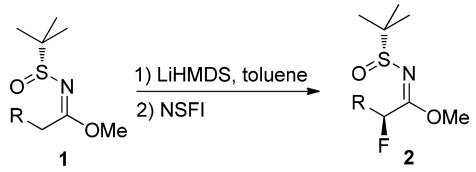
Table 1. Optimization of the Diastereoselectivity of α-Fluorination[a]



entry	base	solvent	dr[b] (yield)[b]
1	$LiN(SiMe_3)_2$	THF	10:1
2[c]	$LiN(SiMe_3)_2$	CH_2Cl_2	15:1
3	$LiN(SiMe_3)_2$	Et_2O	15:1
4	**$LiN(SiMe_3)_2$**	**toluene**	**>50:1 (84%)**[d]
5	$NaN(SiMe_3)_2$	THF	33:1
6	$NaN(SiMe_3)_2$	toluene	9:1
7	$KN(SiMe_3)_2$	THF	40:1
8	$KN(SiMe_3)_2$	toluene	6:1

[a]Reaction conditions: **1a** (0.30 mmol), base (1.2 equiv), and NSFI (1.2 equiv) in anhydrous solvent at −78 °C. Reactions were complete at −78 °C in 1 h. [b]Diastereoselective ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c]Reaction went to completion in 30 min. [d]Isolated yield of single diastereomer after silica gel chromatography.

Table 2. Substrate Scope of the α-Fluorination of *N*-*tert*-Butanesulfinyl Imidates[a]



entry	imidate (R)	product	yield (%)[b]	dr[c]
1	**1b** (Me)	**2b**	84	>20:1
2	**1c** (*n*Pr)	**2c**	86	>20:1
3	**1d** ($BnCH_2$)	**2d**	81	>20:1
4	**1e** [$Cl(CH_2)_3$]	**2e**	71[d]	>20:1
5	**1f** [$PMBO(CH_2)_3$]	**2f**	74	>20:1
6	**1g** (allyl)	**2g**	85 (81)[e]	>20:1 (>20:1)[e]
7	**1h** ($PhC{=}CCH_2$)	**2h**	70[d]	>20:1
8	**1i** ($PhC{\equiv}CCH_2$)	**2i**	75	>20:1
9	**1j** (^{i}Pr)	**2j**	90	>20:1
10	**1k** (cyclohexyl)	**2k**	89	>20:1
11	**1l** (Ph)	**2l**	83 (84)[f]	>20:1 (>20:1)[f]
12	**1m** (4-MeC_6H_4)	**2m**	82	>20:1
13	**1n** (3-MeC_6H_4)	**2n**	73	>20:1
14	**1o** (2-MeC_6H_4)	**2o**	75	>20:1
15	**1p** (4-$MeOC_6H_4$)	**2p**	73	>20:1
16	**1q** (4-FC_6H_4)	**2q**	80	10:1
17	**1r** (4-ClC_6H_4)	**2r**	81	12:1
18	**1s** (4-BrC_6H_4)	**2s**	82	>20:1
19	**1t** (4-$CF_3C_6H_4$)	**2t**	84	16:1
20	**1u** (3,4-diClC_6H_3)	**2u**	79	>20:1
21	**1v** (2,4-diClC_6H_3)	**2v**	68	>20:1
22	**1w** (2-thienyl)	**2w**	81	11:1

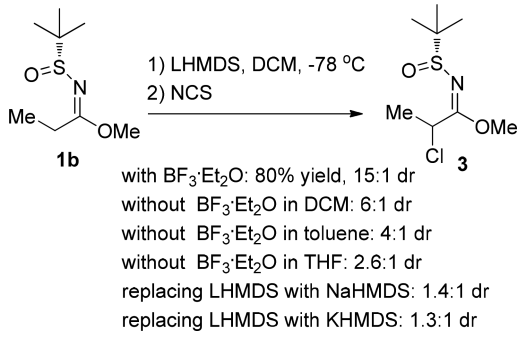
[a]Reaction conditions: **1** (0.30 mmol), LiHMDS (0.36 mmol), and NFSI (0.36 mmol) in anhydrous toluene (4.0 mL) at −78 °C. Reactions were complete within 1 h. [b]Isolated yield after silica gel chromatography. [c]Diastereoselective ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d]Refers to imidate hydrolysis product (*N*-*t*BS amide). [e]The reaction of *ent*-**1g** afforded *ent*-**2g**. [f]Reaction on 1 g scale.

1g, and **1h**, entries 7−8), and alkynyl group (**1i**, entry 9) underwent α-fluorination to afford the corresponding products **2b−i** in 70−86% yields with excellent dr (>20:1). Higher yields (89−90%) were obtained for the imidates **1j** and **1k** bearing a branched alkyl group at the α-position (entries 9−10). In the cases of **1e** and **1h**, we hydrolyzed the initially formed α-fluorinated imidates using aqueous H_2SO_4 in order to remove uncharacterized byproducts that had the same R_f value as the desired product (entries 4 and 7). The hydrolysis products, α-fluorinated *N*-*tert*-butanesulfinyl caboxamides **2e** and **2h**, were quite polar and were easily purified using column chromatography.

A range of α-aryl- and α-heteroaryl-substituted imidates **2l−w** gave products in good yields with high dr (entries 11−22). Steric hindrance from bulky *ortho* substitutions did not compromise diastereoselectivity (entries 14 and 21). The reaction proceeded well in the presence of electron-rich (entry 15) and electron-deficient (entry 19) substitutions on aromatic rings. Yield and dr remained good when the fluorination of **1l** was scaled up to 1 g (entry 11).

Next, we tested the possibility of chlorinating *N*-*t*BS imidate. Reacting aza-enolized imidate **1b** with the chlorinating reagent *N*-chlorosuccinimide (NCS) in dichloromethane in the presence of boron trifluoride gave α-chlorinated imidate **3** in 80% yield with 15:1 dr (Scheme 2).[19] Diastereoselectivity was moderate or poor when the Lewis acid was removed or when the base was changed from LHMDS to NaHMDS or KHMDS (Scheme 2).

Scheme 2. α-Chlorination of *N*-*tert*-Butanesulfinyl Imidate

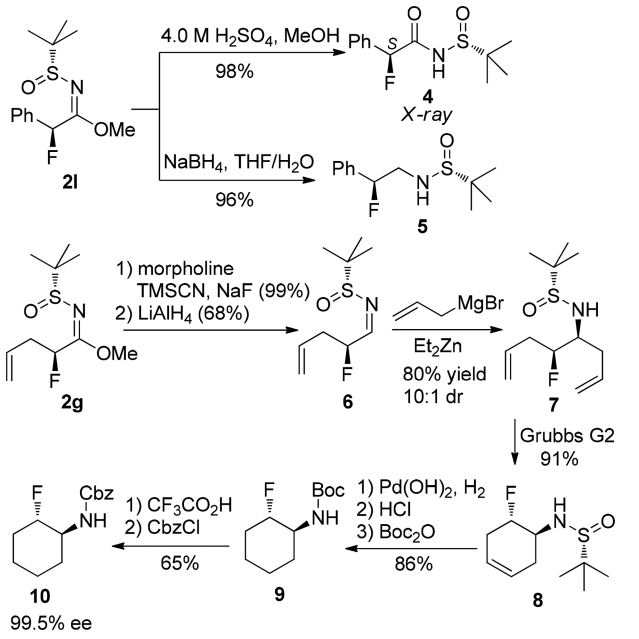


Acidic hydrolysis of α-fluorinated *N*-*t*BS imidate **2l** using 4 M H_2SO_4 in MeOH provided the corresponding *N*-*t*BS caboxamide **4** in nearly quantitative yield (Scheme 3). X-ray crystal diffraction analysis of **4** allowed unambiguous assignment of the absolute configuration of the fluorine-containing stereogenic center, which also enabled the determination of the (2*S*)-configuration of **2l** and its α-fluorinated *N*-*t*BS imidate analogues. $NaBH_4$ reduction easily transformed **2l** to *N*-*t*BS amine **5**.

To demonstrate the synthetic utility of this fluorination protocol, *trans*-2-fluoro-cyclohexamine derivatives[20] were prepared from **2g** (Scheme 3). Cyanide-promoted amidine formation, followed by $LiAlH_4$ reduction, gave *N*-*t*BS imine **6**. Subsequent nucleophilic addition of allylmagnesium bromide in the presence of diethyl zinc provided the vicinal fluoroamine **7** in 80% yield with 10:1 dr. In contrast, 5:1 dr was observed in absence of Et_2Zn. Treatment of diene **7** with second-generation Grubbs catalyst led to ring-closing metathesis, yielding functionalized cyclohexene **8**. Hydrogenation, acid-promoted cleavage of the sulfinyl group, and protection of the

DOI: 10.1021/acs.joc.8b02375
J. Org. Chem. XXXX, XXX, XXX−XXX

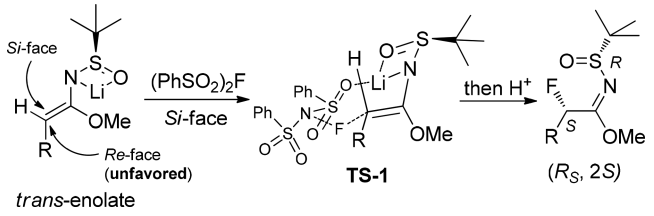
Scheme 3. Transformation of α-Fluorinated *N-tert*-Butanesulfinyl Imidates and Application to Synthesis of Cyclic *trans*-β-Fluoroamine



resulting primary amine with a Boc group provided **9** in 86% yield. The optical rotation of **9** was consistent with the reported data.[21] The *trans*-2-fluoro-cyclohexamine showed 99.5% ee based on chiral HPLC. For this chromatography, we had to replace the Boc protecting group with Cbz in order to render the compound detectable by the UV−vis detector.

The observed stereochemistry of this fluorination can be rationalized by hypothesizing the formation of a chair−chairlike 8/4 bicyclic transition state **TS-1** via sulfone-lithium bonding (Scheme 4).[22] Approach of NFSI from the *Si*-face of

Scheme 4. Rationalization of Stereochemistry



the *trans*-(R_S)-aza-enolate would give (R_S, 2*S*)-fluorination product. Approach of NFSI from the *Re*-face would be less favored since the bulky *t*Bu group of the *trans*-aza-enolate can hinder the *Re*-face attack of NSFI (Scheme 4).

In summary, we have developed a process for diastereoselective α-fluorination of *N-tert*-butanesulfinyl imidates. A range of chiral α-fluorinated imidates can be accessed with high diastereoselectivities. This protocol was used to construct synthetically useful *trans*-2-fluoro-cyclohexamine derivatives with high enantiopurity.

EXPERIMENTAL SECTION

General Experimental Details. All reactions were performed under an argon atmosphere in flame-dried glassware with magnetic stirring using standard Schlenk techniques. All solvents were purified according to the standard procedures. Purification of the reaction products was carried out by flash column chromatography using 200−300 mesh silica gel. Visualization on analytical thin layer chromatography (TLC) was achieved by the use of UV light (254 nm) and treatment with aqueous ceric ammonium molybdate followed by heating. High-resolution mass spectra (HRMS) were measured using electron spray ionization with a time-of-flight mass analyzer (ESI-TOF). Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C{^{1}H} NMR) were recorded on a 400 MHz (^{1}H NMR at 400 MHz and ^{13}C{^{1}H} NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C{^{1}H} NMR: $CDCl_3$ at 77.16 ppm). ^{1}H NMR data are reported as follows: chemical shifts, multiplicity (br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in Hz, integration.

Materials. Toluene and ether were distilled from sodium/benzophenone. Dichloromethane was distilled from CaH_2. (R_S)-*tert*-Butanesulfinamide with ee >99.0% was purchased from a commercial source and used as received. The known compounds **1a−d**, **1f−g**, **1i−j**, and **1l−v** were prepared according to the reported procedure.[11a,b,16,17] The new compounds **1e** and **1h** were prepared via alkylation of α-trimethylsilyl *N-tert*-butanesulfinyl acetimidate and subsequent desilylation according to the reported procedure.[16] The new compound **1k** was prepared by olefination of cyclohexanone with α-triethylsilyl *N-tert*-butanesulfinyl acetimidate and subsequent hydrogenation. The new compound **1w** was prepared by the reaction of *N-tert*-butanesulfinamide with the corresponding orthoester.[11a]

*Methyl (R)-N-(tert-Butylsulfinyl)-5-chloropentanimidate (**1e**).* The reported alkylation−desilylation procedure[16] was followed using α-trimethylsilyl acetimidate (500 mg, 2.0 mmol) and 1-chloro-3-iodopropane (531.4 mg, 2.6 mmol, 1.3 equiv), which provided **1e** as a colorless oil (264.3 mg, 52%). R_f = 0.30 (petroleum ether/ethyl acetate = 4/1); $[\alpha]_D^{25}$ = −86.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.57−3.52 (m, 2H), 2.72−2.68 (m, 2H), 1.83−1.80 (m, 4H), 1.20 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.2, 56.0, 54.3, 44.4, 32.1, 31.9, 23.7, 22.0; HRMS (ESI-TOF) *m*/*z* calcd for $C_{10}H_{21}ClNO_2S$ $[M + H]^+$ 254.0976, found 254.0978.

*Methyl N-((R)-tert-Butylsulfinyl)-5-phenylpent-4-enimidate (**1h**).* The reported alkylation−desilylation procedure[16] was followed using α-trimethylsilyl acetimidate (500 mg, 2.0 mmol) and (*E*)-(3-iodoprop-1-en-1-yl)benzene (636.7 mg, 2.6 mmol, 1.3 equiv), which provided **1h** as a colorless oil (381.4 mg, 65%). R_f = 0.30 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ = −84.8 (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.18 (m, 5H), 6.43 (d, *J* = 15.6 Hz, 1H), 6.21−6.14 (m, 1H), 3.77 (s, 3H), 2.86 (t, *J* = 8.0 Hz, 2H), 2.58−2.54 (m, 2H), 1.21 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.0, 137.4, 131.4, 128.6, 128.1, 127.3, 126.2, 55.9, 54.2, 32.6, 29.8, 22.0; HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{24}NO_2S$ $[M + H]^+$ 294.1522, found 294.1525.

Procedure for the Preparation of 1k. To a stirred solution of α-triethylsilyl *N-tert*-butanesulfinyl acetimidate (583.0 mg, 2.0 mmol, 1.0 equiv) in 5.0 mL THF was added LiHMDS (1.2 M in THF, 2.0 mL, 2.4 mmol, 1.2 equiv) at −78 °C. After the reaction mixture was stirred for 30 min at −78 °C, the solution of cyclohexanone (255.2 mg, 2.6 mmol, 1.3 equiv) in 3.0 mL THF was added. The reaction mixture was then stirred at −78 °C for 4 h. After quenching with saturated aqueous ammonium chloride, the reaction mixture was extracted with ethyl acetate for three times. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel to afford *N-tert*-butanesulfinyl cyclohexylideneacetimidate (221.3 mg, 43%, unoptimized) as a colorless oil.

A round-bottom flask containing *N-tert*-butanesulfinyl cyclohexylideneacetimidate (206.0 mg, 0.8 mmol) and 10 wt % of $Pd(OH)_2/C$ (50 mg). MeOH (5.0 mL) was charged, and the flask was evacuated and backfilled with H_2. The reaction was stirred under a balloon of H_2 until TLC indicated complete consumption of the starting material. Upon completion, the reaction was filtered through Celite, rinsing with EtOAc, and concentrated in vacuo. The residue

DOI: 10.1021/acs.joc.8b02375
J. Org. Chem. XXXX, XXX, XXX−XXX

was purified by flash column chromatography on silica gel to afford *N-tert*-butanesulfinyl cyclohexylacetimidate as a colorless oil (203.4 mg, 98%).

*Methyl (R)-N-(tert-Butylsulfinyl)-2-cyclohexylacetimidate (**1k**).* R_f = 0.30 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ = −101.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 2.62−2.46 (m, 2H), 1.87−1.59 (m, 6H), 1.26−1.22 (m, 2H), 1.18 (s, 9H), 1.13−0.92 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.6, 55.8, 54.0, 40.0, 35.9, 33.1, 26.14, 26.11, 26.09, 22.0; HRMS (ESI-TOF) *m*/*z* calcd for $C_{13}H_{26}NO_2S$ $[M + H]^+$ 260.1679, found 260.1681.

Procedure for the Preparation of 1w. The mixture of *N-tert*-butanesulfinamide (1.82 g, 15 mmol, 1.0 equiv), 2-(2,2,2-trimethoxyethyl)thiophene (6.1 g, 30 mmol, 2.0 equiv), and *p*-toluenesulfonic acid (25.8 mg, 0.01 equiv) was stirred at 105 °C for 3 h. Volatile materials were removed in vacuo, and the residue was purified by flash column chromatography on silica gel to afford (thiophen-2-yl)acetimidate as a colorless oil (2.8 g, 72%).

*Methyl (R)-N-(tert-Butylsulfinyl)-2-(thiophen-2-yl)acetimidate (**1w**).* R_f = 0.24 (petroleum ether/ethyl acetate = 6/1); $[\alpha]_D^{25}$ = −127.4 (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.98−6.92 (m, 2H), 4.34 (dd, *J* = 14.8, 0.8 Hz, 1H), 4.08 (dd, *J* = 14.8, 0.8 Hz, 1H), 3.77 (s, 3H), 1.20 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.0, 135.6, 127.3, 127.0, 125.1, 56.4, 54.6, 32.9, 22.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_{11}H_{18}NO_2S_2$ $[M + H]^+$ 260.0773, found 260.0775.

General Procedure for Fluorination. To a stirred solution of *N-tert*-butanesulfinyl imidate (0.30 mmol, 1.0 equiv) in 2.0 mL toluene was added LHMDS (1.0 M in THF, 360 uL, 0.36 mmol, 1.2 equiv) at −78 °C. After the reaction mixture was stirred at −78 °C for 30 min, a solution of NFSI (113.5 mg, 0.36 mmol, 1.2 equiv) in 2.0 mL toluene was added dropwise. After stirring for 1 h at −78 °C, the reaction was quenched with saturated aq. $NaHCO_3$. The solution was warmed to room temperature and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-3-phenylpropanimidate (**2a**).* According to the general procedure, the reaction using imidate **1a** (80.3 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2a** (71.0 mg, 83%) as a colorless oil. R_f = 0.23 (petroleum ether/ethyl acetate = 8:1); $[\alpha]_D^{25}$ = −176.0 (*c* 0.20, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.24 (m, 5H), 6.00 (ddd, *J* = 48.0, 7.2, 6.0 Hz, 1H), 3.75 (s, 3H), 3.26−3.19 (m, 2H), 1.21 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1 (d, J_{C-F} = 20.2 Hz), 135.0 (d, J_{C-F} = 3.6 Hz), 129.6, 128.7, 127.3, 88.7 (d, J_{C-F} = 186.3 Hz), 57.1, 54.6, 38.7 (d, J_{C-F} = 22.3 Hz), 22.2; HRMS (ESI-TOF) *m*/*z* calcd for $C_{14}H_{21}FNO_2S$ $[M + H]^+$ 286.1276, found 286.1273.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoropropanimidate (**2b**).* According to the general procedure, the reaction using imidate **1b** (57.4 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2b** (52.7 mg, 84%) as a colorless oil. R_f = 0.20 (petroleum ether/ethyl acetate = 8:1); $[\alpha]_D^{25}$ = −144.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dq, *J* = 48.0, 6.8 Hz, 1H), 3.81 (s, 3H), 1.61 (dd, *J* = 24.0, 6.8 Hz, 3H), 1.23 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.0 (d, J_{C-F} = 20.1 Hz), 85.2 (d, J_{C-F} = 180.8 Hz), 57.0, 54.7, 22.1, 18.6(d, J_{C-F} = 23.3 Hz); HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{17}FNO_2S$ $[M + H]^+$ 210.0959, found 210.0961.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoropentanimidate (**2c**).* According to the general procedure, the reaction using imidate **1c** (65.8 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2c** (61.2 mg, 86%) as a colorless oil. R_f = 0.23 (petroleum ether/ethyl acetate = 7:1); $[\alpha]_D^{25}$ = −152.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 48.8, 8.8, 4.0 Hz, 1H), 3.80 (s, 3H), 2.01−1.75 (m, 2H), 1.58−1.43 (m, 2H), 1.23 (s, 9H), 0.97 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.6 (d, J_{C-F} = 20.3 Hz), 88.4 (d, J_{C-F} = 183.5 Hz), 57.0, 54.5 (d, J_{C-F} = 6.0 Hz), 34.6 (d, J_{C-F} = 21.7 Hz), 22.2, 18.1, 13.7; HRMS (ESI-TOF) *m*/*z* calcd for $C_{10}H_{21}FNO_2S$ $[M + H]^+$ 238.1272, found 238.1274.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-4-phenylbutanimidate (**2d**).* According to the general procedure, the reaction using imidate **1d** (84.4 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2d** (72.8 mg, 81%) as a colorless oil. R_f = 0.21 (petroleum ether/ethyl acetate = 8:1); $[\alpha]_D^{25}$ = −132.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.27 (m, 2H), 7.22−7.18 (m, 3H), 5.74 (ddd, *J* = 48.4, 8.8, 3.6 Hz, 1H), 3.78 (s, 1H), 2.87−2.74 (m, 2H), 2.34−2.15 (m, 2H), 1.22 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.1 (d, J_{C-F} = 20.5 Hz), 140.2, 128.7, 128.6, 126.4, 88.1 (d, J_{C-F} = 183.7 Hz), 57.0, 54.6, 34.4 (d, J_{C-F} = 22.0 Hz), 31.0 (d, J_{C-F} = 3.6 Hz), 22.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{23}FNO_2S$ $[M + H]^+$ 300.1428, found 300.1430.

*(S)-N-((R)-tert-Butylsulfinyl)-5-chloro-2-fluoropentanamide (**2e**).* According to the general procedure, the reaction using imidate **1e** (76.1 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) generated α-fluorinated imidate that was hydrolyzed using 4 M aq. H_2SO_4 to afford **2e** (54.9 mg, 71%) as a colorless gum. R_f = 0.20 (petroleum ether/ethyl acetate = 1:1); $[\alpha]_D^{25}$ = +29.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (br s, 1H), 5.02 (ddd, *J* = 49.2, 7.2, 4.0 Hz, 1H), 3.57 (t, *J* = 6.4 Hz, 2H), 2.26−1.90 (m, 4H), 1.29 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.4 (d, J_{C-F} = 21.4 Hz), 91.4 (d, J_{C-F} = 185.8 Hz), 57.4, 44.0, 29.9 (d, J_{C-F} = 20.1 Hz), 27.6 (d, J_{C-F} = 2.8 Hz), 22.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_9H_{18}ClFNO_2S$ $[M + H]^+$ 258.0725, found 258.0726.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-5-((4-methoxybenzyl)oxy)pentanimidate (**2f**).* According to the general procedure, the reaction using imidate **1f** (106.6 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2f** (82.9 mg, 74%) as a colorless oil; R_f = 0.20 (petroleum ether/ethyl acetate = 5:1); $[\alpha]_D^{25}$ = −94.8 (*c* 0.25, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.24 (m, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.76 (ddd, *J* = 48.4, 8.4, 4.4 Hz, 1H), 4.43 (s 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.52−3.45 (m, 2H), 2.10−1.71 (m, 4H), 1.22 (s 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4 (d, J_{C-F} = 20.4 Hz), 159.3, 130.6, 129.4, 113.9, 88.4 (d, J_{C-F} = 183.3 Hz), 72.7, 69.1, 57.0, 55.4, 54.6, 29.6 (d, J_{C-F} = 23.0 Hz), 25.1 (d, J_{C-F} = 3.2 Hz), 22.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{29}FNO_4S$ $[M + H]^+$ 374.1796, found 374.1799.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoropent-4-enimidate (**2g**).* According to the general procedure, the reaction using imidate **1g** (65.2 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2g** (60.0 mg, 85%) as a colorless oil; R_f = 0.22 (petroleum ether/ethyl acetate = 5:1); $[\alpha]_D^{25}$ = −184.0 (*c* 0.20, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89−5.74 (m, 2H), 5.21−5.14 (m, 2H), 3.78 (s, 3H), 2.78−2.58 (m, 2H), 1.21 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.3 (d, J_{C-F} = 20.2 Hz), 130.9 (d, J_{C-F} = 5.1 Hz), 119.6, 87.6 (d, J_{C-F} = 185.2 Hz), 57.1, 54.5, 36.9 (d, J_{C-F} = 22.4 Hz), 22.2; HRMS (ESI-TOF) *m*/*z* calcd for $C_{10}H_{19}FNO_2S$ $[M + H]^+$ 236.1115, found 236.1117.

*Methyl (R)-N-((S)-tert-Butylsulfinyl)-2-fluoropent-4-enimidate (*ent*-**2g**).* According to the general procedure, the reaction using imidate *ent*-**1g** (80.3 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded *ent*-**2g** (57.2 mg, 81%) as a colorless oil; R_f = 0.22 (petroleum ether/ethyl acetate = 5:1); $[\alpha]_D^{25}$ = +185.0 (*c* 0.20, MeOH). The NMR data of *ent*-**2g** are consistent with those of **2g**. HRMS (ESI-TOF) *m*/*z* calcd for $C_{10}H_{19}FNO_2S$ $[M + H]^+$ 236.1115, found 236.1116.

*(S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-5-phenylpent-4-enamide (**2h**).* According to the general procedure, the reaction using imidate **1h** (88.0 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) generated α-fluorinated imidate that was hydrolyzed using 4 M aq. H_2SO_4 to afford **2h** (62.4 mg, 70%) as a colorless gum; R_f = 0.25 (petroleum ether/ethyl acetate = 1:1); $[\alpha]_D^{25}$ = +27.0 (*c* 0.20,

DOI: 10.1021/acs.joc.8b02375
J. Org. Chem. XXXX, XXX, XXX−XXX

MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (br s, 1H), 7.33−7.21 (m, 5H), 6.53 (d, J = 12.0 Hz, 1H), 6.19−6.11 (m, 1H), 5.14 (ddd, J = 49.2, 5.2, 4.4 Hz), 2.97−2.72 (m, 2H), 1.17 (s 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9 (d, J_{C-F} = 21.5 Hz), 136.4, 135.3, 128.5, 127.8, 126.2, 121.0 (d, J_{C-F} = 2.8 Hz), 91.3 (d, J_{C-F} = 187.4 Hz), 57.3, 35.5 (d, J_{C-F} = 19.7 Hz), 21.7; HRMS (ESI-TOF) m/z calcd for $C_{15}H_{21}FNO_2S$ $[M + H]^+$ 298.1272, found 298.1274.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-5-phenylpent-4-ynimidate (**2i**).* According to the general procedure, the reaction using imidate **1i** (87.4 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2i** 69.6 mg, 75%) as a colorless oil; R_f = 0.25 (petroleum ether/ethyl acetate = 8:1); $[\alpha]_D^{25}$ = −227.0 (c 0.25, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.26 (m, 5H), 6.05 (dt, J = 47.2, 6.4 Hz, 1H), 3.84 (s, 3H), 3.20−3.02 (m, 2H), 1.24 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8 (d, J_{C-F} = 19.9 Hz), 131.8, 128.3, 128.3, 123.0, 85.8 (d, J_{C-F} = 188.0 Hz), 83.8, 82.1 (d, J_{C-F} = 11.0 Hz), 57.3, 54.8, 24.0 (d, J_{C-F} = 27.0 Hz), 22.2; HRMS (ESI-TOF) m/z calcd for $C_{16}H_{21}FNO_2S$ $[M + H]^+$ 310.1272, found 310.1274.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-3-methylbutanimidate (**2j**).* According to the general procedure, the reaction using imidate **1j** (65.6 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2j** (69.6 mg, 90%) as a colorless oil; R_f = 0.25 (petroleum ether/ethyl acetate = 7:1); $[\alpha]_D^{25}$ = −163.8 (c 0.30, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (dd, J = 48.0, 6.4 Hz, 1H), 3.79 (s, 3H), 2.39−2.21 (m, 1H), 1.23 (s, 9H), 1.01 (t, J = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.8 (d, J_{C-F} = 20.6 Hz), 92.6 (d, J_{C-F} = 185.2 Hz), 57.1, 54.4, 31.3 (d, J_{C-F} = 21.0 Hz), 22.2, 18.1 (d, J_{C-F} = 6.2 Hz), 17.2 (d, J_{C-F} = 4.0 Hz); HRMS (ESI-TOF) m/z calcd for $C_{10}H_{21}FNO_2S$ $[M + H]^+$ 238.1272, found 238.1274.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-cyclohexyl-2-fluoroacetimidate (**2k**).* According to the general procedure, the reaction using imidate **1k** (77.8 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2k** (74.1 mg, 89%) as a colorless oil; R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); $[\alpha]_D^{25}$ = −177.0 (c 0.40, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (dd, J = 48.0, 6.4 Hz, 1H), 3.79 (s, 3H), 2.04−1.76 (m, 4H), 1.68−1.58 (m, 2H), 1.39−1.25 (m, 2H), 1.23 (s, 9H), 1.21−1.10 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7 (d, J_{C-F} = 20.6 Hz), 92.1 (d, J_{C-F} = 184.0 Hz), 57.1, 54.4, 40.5 (d, J_{C-F} = 20.6 Hz), 28.0 (d, J_{C-F} = 5.5 Hz), 27.7 (d, J_{C-F} = 3.2 Hz), 26.0, 25.9, 25.6, 22.2; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{25}FNO_2S$ $[M + H]^+$ 278.1585, found 278.1581.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-2-phenylacetimidate (**2l**).* According to the general procedure, the reaction using imidate **1l** (65.6 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2l** (76.0 mg, 83%) as a colorless oil; R_f = 0.20 (petroleum ether/ethyl acetate = 9:1); $[\alpha]_D^{25}$ = −219.0 (c 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.55 (m. 2H), 7.42−7.40 (m, 3H), 6.82 (d, J = 47.2 Hz, 1H), 3.85 (s, 3H), 1.19 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.7 (d, J_{C-F} = 22.1 Hz), 134.2 (d, J_{C-F} = 21.1 Hz), 130.0 (d, J_{C-F} = 2.5 Hz), 129.0, 127.8 (d, J_{C-F} = 5.3 Hz), 88.1 (d, J_{C-F} = 186.1 Hz), 57.2, 54.9, 22.2; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{19}FNO_2S$ $[M + H]^+$ 272.1115, found 272.1117. A scale-up preparation of **2l** was carried out by using imidate **1l** (1.0135 g, 4.00 mmol), LiHMDS (1.0 M in THF, 4.80 mL, 4.80 mmol), and fluorination reagent NFSI (1.5136 g, 4.80 mmol), which afforded **2l** (0.9118 g, 84%) as a colorless oil.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-2-(p-tolyl)-acetimidate (**2m**).* According to the general procedure, the reaction using imidate **1m** (80.2 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2m** (70.1 mg, 82%) as a colorless oil; R_f = 0.26 (petroleum ether/ethyl acetate = 8:1); $[\alpha]_D^{25}$ = −226.0 (c 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 6.8 Hz, 2H), 7.22 (d, J = 7.6 Hz, 2H), 6.76 (d, J = 46.8 Hz, 1H), 3.85 (s, 3H), 2.37 (s, 3H), 1.18 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.0 (d, J_{C-F} = 22.5 Hz), 140.1 (d, J_{C-F} = 2.9 Hz), 131.2 (d, J_{C-F} = 21.0 Hz), 129.7, 127.9 (d, J_{C-F} = 4.9 Hz), 88.1 (d, J_{C-F} = 185.9 Hz), 57.2, 54.9, 22.2, 21.5; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{21}FNO_2S$ $[M + H]^+$ 286.1272, found 286.1274.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-2-(m-tolyl)-acetimidate (**2n**).* According to the general procedure, the reaction using imidate **1n** (80.2 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2n** (62.4 mg, 73%) as a colorless oil; R_f = 0.25 (petroleum ether/ethyl acetate = 8:1); $[\alpha]_D^{25}$ = −197.0 (c 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.21 (m. 4H), 6.78 (d, J = 46.8 Hz, 1H), 3.86 (s, 3H), 2.38 (s, 3H), 1.19 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.8 (d, J_{C-F} = 22.2 Hz), 138.8, 134.1 (d, J_{C-F} = 20.6 Hz), 130.8 (d, J_{C-F} = 2.5 Hz), 128.9, 128.3 (d, J_{C-F} = 5.1 Hz), 124.9 (d, J_{C-F} = 5.3 Hz), 88.1 (d, J_{C-F} = 185.9 Hz), 57.2, 54.9, 22.2, 21.6; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{21}FNO_2S$ $[M + H]^+$ 286.1272, found 286.1275.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-2-(o-tolyl)-acetimidate (**2o**).* According to the general procedure, the reaction using imidate **1o** (80.2 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2o** (64.1 mg, 75%) as a colorless oil; R_f = 0.26 (petroleum ether/ethyl acetate = 8:1); $[\alpha]_D^{25}$ = −156.0 (c 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.29 (m, 2H), 7.24−7.21 (m, 2H), 6.94 (d, J = 47.6 Hz, 1H), 3.92 (s, 3H), 2.49 (s, 3H), 1.16 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.5 (d, J_{C-F} = 21.8 Hz), 138.2 (d, J_{C-F} = 3.4 Hz), 132.1 (d, J_{C-F} = 18.6 Hz), 131.2 (d, J_{C-F} = 2.1 Hz), 130.2 (d, J_{C-F} = 3.6 Hz), 128.3 (d, J_{C-F} = 5.0 Hz), 126.4 (d, J_{C-F} = 2.1 Hz), 86.3 (d, J_{C-F} = 185.0 Hz), 57.1, 54.9, 22.1, 19.2; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{21}FNO_2S$ $[M + H]^+$ 286.1272, found 286.1274.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-2-(4-methoxyphenyl)acetimidate (**2p**).* According to the general procedure, the reaction using imidate **1p** (85.0 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2p** (66.0 mg, 73%) as a colorless oil; R_f = 0.22 (petroleum ether/ethyl acetate = 6:1); $[\alpha]_D^{25}$ = −212.0 (c 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 47.2 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 1.17 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.2 (d, J_{C-F} = 22.9 Hz), 161.0 (d, J_{C-F} = 2.8 Hz), 129.8 (d, J_{C-F} = 4.6 Hz), 126.1 (d, J_{C-F} = 21.4 Hz), 114.4, 88.0 (d, J_{C-F} = 182.0 Hz), 57.1, 55.4, 54.9, 22.2; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{21}FNO_3S$ $[M + H]^+$ 302.1220, found 302.1224.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-2-(4-fluorophenyl)-acetimidate (**2q**).* According to the general procedure, the reaction using imidate **1q** (81.4 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2q** (69.4 mg, 80%) as a colorless oil; R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); $[\alpha]_D^{25}$ = −191.6 (c 0.30, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.54 (m, 2H), 7.10 (t, J = 8.4 Hz, 2H), 6.81 (d, J = 46.8 Hz, 1H), 3.85 (s, 3H), 1.20 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.2 (d, J_{C-F} = 22.7 Hz), 163.7 (dd, J_{C-F} = 247.9, 2.1 Hz), 130.2 (d, J_{C-F} = 3.1 Hz), 130.0 (dd, J_{C-F} = 8.7, 5.0 Hz), 116.1 (d, J_{C-F} = 21.7 Hz), 87.4 (d, J_{C-F} = 186.5 Hz), 57.4, 54.9, 22.2; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{18}F_2NO_2S$ $[M + H]^+$ 290.1021, found 290.1023.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-(4-chlorophenyl)-2-fluoroacetimidate (**2r**).* According to the general procedure, the reaction using imidate **1r** (86.3 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2r** (74.3 mg, 81%) as a colorless oil; R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); $[\alpha]_D^{25}$ = −211.8 (c 0.30, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.50 (m, 2H), 7.39 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 46.4 Hz, 1H), 3.83 (s, 3H), 1.21 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8 (d, J_{C-F} = 22.3 Hz), 136.0 (d, J_{C-F} = 2.8 Hz), 132.7 (d, J_{C-F} = 21.3 Hz), 129.3, 129.1 (d, J_{C-F} = 5.5 Hz), 87.3 (d, J_{C-F} = 186.8 Hz), 57.4, 55.0, 22.2; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{18}FClNO_2S$ $[M + H]^+$ 306.0725, found 306.0728.

DOI: 10.1021/acs.joc.8b02375
J. Org. Chem. XXXX, XXX, XXX−XXX

*Methyl (S)-2-(4-bromophenyl)-N-((R)-tert-Butylsulfinyl)-2-fluoroacetimidate (**2s**).* According to the general procedure, the reaction using imidate **1s** (99.7 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2s** (86.1 mg, 82%) as a colorless oil; R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); $[\alpha]_D^{25}$ = −205.5 (*c* 0.20, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.43 (m, 4H), 6.82 (d, *J* = 46.4 Hz, 1H), 3.83 (s, 3H), 1.21 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7 (d, J_{C-F} = 22.3 Hz), 133.3 (d, J_{C-F} = 21.3 Hz), 132.2, 129.4 (d, J_{C-F} = 5.3 Hz), 124.3 (d, J_{C-F} = 3.1 Hz), 87.4 (d, J_{C-F} = 186.7 Hz), 57.4, 55.0, 22.2; HRMS (ESI-TOF) *m*/*z* calcd for $C_{13}H_{18}FBrNO_2S$ $[M + H]^+$ 350.0220, found 350.0221.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-2-(4-(trifluoromethyl)phenyl)acetimidate (**2t**).* According to the general procedure, the reaction using imidate **1t** (96.4 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2t** (85.5 mg, 84%) as a white solid; mp 37.5−38.9 °C; R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); $[\alpha]_D^{25}$ = −180.3 (*c* 0.30, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.66 (m, 4H), 6.96 (d, *J* = 46.4 Hz, 1H); 3.82 (s, 3H), 1,24 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0 (d, J_{C-F} = 22.0 Hz), 138.2 (d, J_{C-F} = 22.1 Hz), 132.3−131.3 (m), 127.8 (d, J_{C-F} = 5.7 Hz), 125.9 (q, J_{C-F} = 3.6 Hz), 123.9 (d, J_{C-F} = 270.8 Hz), 87.1 (d, J_{C-F} = 186.9 Hz), 57.6, 55.0, 22.3; HRMS (ESI-TOF) *m*/*z* calcd for $C_{14}H_{18}F_4NO_2S$ $[M + H]^+$ 340.0989, found 340.0991.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-(3,4-dichlorophenyl)-2-fluoroacetimidate (**2u**).* According to the general procedure, the reaction using imidate **1u** (96.7 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2u** (80.6 mg, 79%) as a colorless oil; R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); $[\alpha]_D^{25}$ = −188.2 (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.50−7.41 (m, 2H), 6.86 (d, *J* = 46.4 Hz, 1H); 3.82 (s, 3H), 1,23 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.8 (d, J_{C-F} = 22.0 Hz), 134.4 (d, J_{C-F} = 21.9 Hz), 134.2 (d, J_{C-F} = 2.5 Hz), 133.3, 131.0, 129.4 (d, J_{C-F} = 6.0 Hz), 126.9 (d, J_{C-F} = 5.6 Hz), 86.5 (d, J_{C-F} = 187.5 Hz), 57.6, 55.0, 22.3; HRMS (ESI-TOF) *m*/*z* calcd for $C_{13}H_{17}FCl_2NO_2S$ $[M + H]^+$ 340.0336, found 340.0340.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-(2,4-dichlorophenyl)-2-fluoroacetimidate (**2v**).* According to the general procedure, the reaction using imidate **1v** (96.7 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2v** (69.4 mg, 68%) as a colorless oil; R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); $[\alpha]_D^{25}$ = −173.6 (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 1.6 Hz, 1H), 7.32 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.05 (d, *J* = 45.2 Hz, 1H), 3.80 (s, 3H), 1.23 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.4 (d, J_{C-F} = 22.2 Hz), 136.2 (d, J_{C-F} = 2.7 Hz), 133.8 (d, J_{C-F} = 4.6 Hz), 131.3 (d, J_{C-F} = 21.8 Hz), 130.0 (d, J_{C-F} = 8.4 Hz), 129.7, 127.7, 85.2 (d, J_{C-F} = 184.1 Hz), 57.4, 55.0, 22.2; HRMS (ESI-TOF) *m*/*z* calcd for $C_{13}H_{17}FCl_2NO_2S$ $[M + H]^+$ 340.0336, found 340.0339.

*Methyl (S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-2-(thiophen-2-yl)-acetimidate (**2w**).* According to the general procedure, the reaction of imidate **1w** (77.8 mg, 0.30 mmol), LiHMDS (1.0 M in THF, 360 uL, 0.36 mmol), and fluorination reagent NFSI (113.5 mg, 0.36 mmol) afforded **2w** as a colorless oil (67.4 mg, 81%); R_f = 0.28 (petroleum ether/ethyl acetate = 7:1); $[\alpha]_D^{25}$ = −233.1 (*c* 0.63, MeOH); ^{1}H NMR (400 MHz, C_6D_6) δ 7.64 (d, *J* = 47.2 Hz, 1H), 7.31−7.29 (m, 1H), 6.82−6.81 (m, 1H), 6.58−6.56 (m, 1H), 3.28 (s, 3H), 1.04 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6) δ 165.8 (d, J_{C-F} = 23.3 Hz),136.1 (d, J_{C-F} = 24.2 Hz), 130.3 (d, J_{C-F} = 5.3 Hz), 128.2 (d, J_{C-F} = 2.8 Hz), 127.1 (d, J_{C-F} = 1.7 Hz), 83.4 (d, J_{C-F} = 186.0 Hz), 57.0, 54.1, 22.1; HRMS (ESI-TOF) *m*/*z* calcd $C_{11}H_{17}FNO_2S_2$ $[M + H]^+$ 278.0679, found 278.0682.

Procedure for the Preparation of 3. To a stirred solution of *N*-*tert*-butanesulfinylimidate **1b** (57.4 mg, 0.30 mmol, 1.0 equiv) in 2.0 mL DCM was added LHMDS (1.0 M in THF, 360 uL, 0.36 mmol, 1.2 equiv) at −78 °C. After the reaction mixture was stirred for 30 min at −78 °C, $BF_3{\cdot}Et_2O$ (85.1 mg, 0.6 mmol, 2.0 equiv) in 1.0 mL DCM and NCS (80.1 mg, 0.6 mmol, 2.0 equiv) in 1.0 mL DCM were sequentially added. After stirring for 1 h at −78 °C, the reaction was quenched with 0.2 N aq. HCl and extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel.

*Methyl-N-((R)-tert-Butylsulfinyl)-2-chloropropanimidate (**3**).* Colorless oil (54.2 mg, 80%); R_f = 0.20 (petroleum ether/ethyl acetate = 6:1); $[\alpha]_D^{25}$ = −238.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (q, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 1.68 (d, *J* = 6.8 Hz, 3H), 1.22 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 56.9, 55.0, 49.1, 22.1, 21.8; HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{17}ClNO_2S$ $[M + H]^+$ 226.0663, found 226.0667.

Procedure for Hydrolysis of 2l. To a stirred solution of **2l** (54.3 mg, 0.20 mmol, 1.0 equiv) in 3.0 mL MeOH was added 4.0 M aq. H_2SO_4 (1.0 mL) at rt. After the resultant solution was stirred for 1 h at rt, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate for three times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

*(S)-N-((R)-tert-Butylsulfinyl)-2-fluoro-2-phenylacetamide (**4**).* White solid (50.4 mg, 98%), mp 77.5−79.3 °C; R_f = 0.30 (petroleum ether/ethyl acetate = 1:1); $[\alpha]_D^{25}$ = +123 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.42 (s, 5H), 5.85 (d, *J* = 48.4 Hz, 1H), 1.25 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4 (d, J_{C-F} = 24.6 Hz), 133.8 (d, J_{C-F} = 19.5 Hz), 130.0 (d, J_{C-F} = 2.2 Hz), 129.1, 126.4 (d, J_{C-F} = 6.6 Hz), 91.8 (d, J_{C-F} = 187.6 Hz), 57.7, 22.0; HRMS (ESI-TOF) *m*/*z* calcd for $C_{12}H_{17}FNO_2S$ $[M + H]^+$ 258.0959, found 258.0961 (see Supporting Information).

Procedure for Reduction of 2l. To a stirred solution of **2l** (54.3 mg, 0.20 mmol, 1.0 equiv) in 2.0 mL THF/H_2O (9:1, v/v) was added $NaBH_4$ (30.3 mg, 0.80 mmol, 4 equiv) at rt. The resultant solution was stirred for 2 h at rt before being quenched with saturated aqueous ammonium chloride. The organic layer was separated, and the aqueous layer extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

*(R)-N-((S)-2-Fluoro-2-phenylethyl)-2-methylpropane-2-sulfinamide (**5**).* Colorless oil (46.7 mg, 96%), R_f = 0.20 (petroleum ether/ethyl acetate = 1:1); $[\alpha]_D^{25}$ = −19.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.32 (m, 5H), 5.63 (dt, *J* = 48.0, 5.6 Hz, 1H), 3.63−3.51 (m, 3H), 1.19 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 137.3 (d, J_{C-F} = 19.4 Hz), 128.9, 128.7, 125.7 (d, J_{C-F} = 6.6 Hz), 94.0 (d, J_{C-F} = 172.3 Hz), 56.3, 51.9 (d, J_{C-F} = 25.1 Hz), 22.7; HRMS (ESI-TOF) *m*/*z* calcd for $C_{12}H_{19}FNOS$ $[M + H]^+$ 244.1166, found 244.1167.

Procedure for the Transformation of Imidate 2g to Aldimine 6. To a solution of **2g** (117.7 mg, 0.5 mmol, 1.0 equiv) and morpholine (0.8 mL) in MeOH (0.2 mL) were added NaF (4.2 mg, 1.0 mmol, 0.20 equiv) and TMSCN (12.5 uL, 1.0 mmol, 0.20 equiv) sequentially. The reaction mixture was stirred at 50 °C overnight and then cooled to rt. A 1.0 M solution of KOH was then added, and the mixture was extracted three times with DCM. The combined organic portions were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Column chromatography purification on silica-gel column (50% ethyl acetate-petroleum ether) afforded the desired amidine as a white solid. The amidine product was then dissolved in 5.0 mL anhydrous THF in a round-bottomed flask at 0 °C. $LiAlH_4$ (22.8 mg, 0.60 mmol, 1.5 equiv) was slowly added to the mixture. After complete consumption of starting material, the reaction was quenched by addition of a saturated aqueous solution of potassium sodium tartrate, and the resulting mixture was diluted with ethyl acetate. The organic layer was collected, and the aqueous layer was extracted with ethyl acetate. The combined organic portions were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash column chromatography on silica gel.

DOI: 10.1021/acs.joc.8b02375
J. Org. Chem. XXXX, XXX, XXX−XXX

*(R)-N-((S)-2-Fluoropent-4-en-1-ylidene)-2-methylpropane-2-sulfinamide (**6**).* Colorless oil (69.1 mg, 67.3% for two steps); R_f = 0.25 (petroleum ether/ethyl acetate = 8:1); $[\alpha]_D^{25}$ = −245.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 9.6, 3.2 Hz, 1H), 5.89−5.79 (m, 1H), 5.33−5.18 (m, 3H), 2.73−2.55 (m, 2H), 1.20 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5 (d, J_{C-F} = 30.4 Hz), 131.1 (d, J_{C-F} = 4.9 Hz), 119.6, 92.2 (d, J_{C-F} = 175.5 Hz), 57.3, 37.5 (d, J_{C-F} = 21.4 Hz), 22.5; HRMS (ESI-TOF) *m*/*z* calcd for $C_9H_{17}FNOS$ $[M + H]^+$ 206.1009, found 206.1011.

Procedure for Addition of Grignard Reagent to Imine 6. To a stirred solution of **6** (61.6 mg, 0.30 mmol, 1.0 equiv) in 3.0 mL DCM at −48 °C were added allylmagnesium bromide (0.45 mL, 1.0 M in Et_2O, 0.45 mmol, 1.5 equiv) and Et_2Zn (60.0 uL, 1.0 M in THF, 0.2 equiv) sequentially. After stirring at −48 °C for 5 h and then rt overnight, the reaction was quenched by aqueous ammonium chloride. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The diastereoselectivity (10:1 dr) of the reaction was determined by ^{1}H NMR analysis of the crude product. The crude product was purified by flash column chromatography on silica gel.

*(R)-N-((4S,5S)-5-Fluoroocta-1,7-dien-4-yl)-2-methylpropane-2-sulfinamide (**7**).* Colorless oil (59.4 mg, 80%); R_f = 0.25 (petroleum ether/ethyl acetate = 3:1); $[\alpha]_D^{25}$ = −45.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90−5.72 (m, 2H), 5.25−5.09 (m, 4H), 4.66−4.50 (m, 1H), 3.50−3.29 (m, 2H), 2.67−2.30 (m, 4H), 1.25 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 133.7, 132.7 (d, J_{C-F} = 7.4 Hz), 119.4, 118.7, 93.4 (d, J_{C-F} = 174.7 Hz), 58.0 (d, J_{C-F} = 19.1 Hz), 56.7, 38.2 (d, J_{C-F} = 2.8 Hz), 36.2 (d, J_{C-F} = 21.8 Hz), 22.9; HRMS (ESI-TOF) *m*/*z* calcd for $C_{12}H_{23}FNOS$ $[M + H]^+$ 248.1479, found 248.1481.

Procedure for RCM Reaction of 7. To a stirred solution of 7 (49.5 mg, 0.20 mmol, 1.0 equiv) in 3.0 mL DCM was added Grubbs second-generation catalyst (40 mg, 0.04 mmol, 0.2 equiv) at rt. After complete consumption of starting material, the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride. The organic layer was separated, and the aqueous layer extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

*(R)-N-((1S,6S)-6-Fluorocyclohex-3-en-1-yl)-2-methylpropane-2-sulfinamide (**8**).* Colorless gum (40.0 mg, 91%); R_f = 0.23 (petroleum ether/ethyl acetate = 1:1); $[\alpha]_D^{25}$ = −45.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61−5.54 (m, 2H), 4.70−4.52 (m, 1H), 3.68−3.59 (m, 1H), 3.27 (d, *J* = 6.0 Hz, 1H), 2.67−2.20 (m, 4H), 1.20 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 124.2 (d, J_{C-F} = 1.7 Hz), 123.4 (d, J_{C-F} = 6.8 Hz), 90.5 (d, J_{C-F} = 175.5 Hz), 56.2, 54.5 (d, J_{C-F} = 20.7 Hz), 31.3 (d, J_{C-F} = 4.3 Hz), 30.2 (d, J_{C-F} = 21.2 Hz), 22.6; HRMS (ESI-TOF) *m*/*z* calcd for $C_{10}H_{19}FNOS$ $[M + H]^+$ 220.1166, found 220.1167.

Procedure for the Preparation of 9. Treatment of diene **8** (21.9 mg, 0.10 mmol, 1.0 equiv) in EtOH with 10% $Pd(OH)_2/C$ (5.0 mg) under a H_2 atmosphere for 12 h. Upon completion, the reaction was filtered through Celite, rinsing with EtOAc, and concentrated in vacuo. The crude material was purified by column chromatography to afford the hydrogenation product as an off-white solid. The product was then dissolved in 1.0 mL methanol, followed by the addition of 4 N HCl/MeOH (0.1 mL). The reaction mixture was stirred at rt for 30 min and then concentrated to dryness. A solution of $(Boc)_2O$ (24.0 mg, 0.11 mmol, 1.1 equiv) and NEt_3 (30 uL, 0.22 mmol, 2.2 equiv) in THF (1.0 mL) was added to the residue obtained above, and the resulting mixture was stirred at rt for 6 h. Concentration of the reaction mixture under vacuum and purification of the resultant residue by flash column chromatography on silica gel afforded **9** as a white solid (18.8 mg, 86% for three steps). The NMR spectra and specific rotation of **9** are in agreement with that of the known compound (1*S*, 2*S*)-**9**: $[\alpha]_D^{22}$ = +29.5 (*c* 0.40, $CHCl_3$); lit. $[\alpha]_D^{22}$ = +27.5 (c 1.01, $CHCl_3$).[21]

Procedure for the Preparation of 10. To a solution of compound **9** (21.7 mg, 0.10 mmol, 1.0 equiv) in DCM (1 mL) was added CF_3COOH (0.15 mL, 20.0 equiv). The resulting reaction mixture was stirred at 0 °C for 1 h and then concentrated to dryness. A solution of CbzCl (25.6 mg, 0.15 mmol, 1.5 equiv), DMAP (12.2 mg, 1.0 mmol, 1.0 equiv), and NEt_3 (27 uL, 0.20 mmol, 2.0 equiv) in DCM (1 mL) was added to the residue obtained above, and the mixture was stirred at 0 °C for 2 h. Concentration of the reaction mixture under vacuum and purification of the resultant residue by flash column chromatography on silica gel afforded **10** as a white solid (16.3 mg, 65% for two steps).

*Benzyl ((1S,2S)-2-Fluorocyclohexyl)carbamate (**10**).* Mp 95.8−97.6 °C; R_f = 0.30 (petroleum ether/ethyl acetate = 8:1); $[\alpha]_D^{25}$ = +24.0 (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.16 (m, 5H), 5.12−5.08 (m, 2H), 4.80 (br s, 1H), 4.23 (dddd, *J* = 48.0, 12.0, 8.0, 4.0 Hz, 1H), 3.71−3.61 (m, 1H), 2.13−2.05 (m, 2H), 1.79−1.75 (m, 1H), 1.66−1.50 (m, 2H), 1.38−1.17 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.1, 136.6, 128.6, 128.6, 128.2, 93.5 (d, J_{C-F} = 177.0 Hz), 66.9, 54.4 (d, J_{C-F} = 17.0 Hz), 31.3, 31.2 (d, J_{C-F} = 5.0 Hz), 23.9, 23.4 (d, J_{C-F} = 10.0 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{14}H_{18}FNaNO_2$ $[M + H]^+$ 274.1214, found 274.1215.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02375.

^{1}H and $^{13}C\{^1H\}$ NMR spectra of all new compounds, chiral HPLC analysis of compounds **10**, and X-ray crystal structure of compound **4** (CCDC 1859860) (PDF)

Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: clu@ms.xjb.ac.cn.

ORCID

Chong-Dao Lu: 0000-0001-8968-0134

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (21871292, 21572262, and U1403301) and the Recruitment Program of Global Experts (Xinjiang Program).

■ REFERENCES

(1) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432−2506. (c) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine Containing Pharmaceuticals, Compounds Currently in Phase II−III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422−518.

(2) (a) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315−8359. (b) Fujiwara, T.; O'Hagan, D. Successful Fluorine-Containing Herbicide Agrochemicals. *J. Fluorine*

DOI: 10.1021/acs.joc.8b02375
J. Org. Chem. XXXX, XXX, XXX−XXX

Chem. **2014**, *167*, 16−29. (c) Jeschke, P. Latest generation of halogen-containing pesticides. *Pest Manage. Sci.* **2017**, *73*, 1053−1056.

(3) For reviews, see: (a) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of Fluorine and Fluorine-Containing Functional Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214−8264. (b) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. Advances in Catalytic Enantioselective Fluorination, Mono-, Di-, and Trifluoromethylation, and Trifluoromethylthiolation Reactions. *Chem. Rev.* **2015**, *115*, 826−870. (c) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. Monofluorination of Organic Compounds: 10 Years of Innovation. *Chem. Rev.* **2015**, *115*, 9073−9174. (d) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. Modern Approaches for Asymmetric Construction of Carbon−Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. *Chem. Rev.* **2018**, *118*, 3887−3964.

(4) For catalytic α-fluorination of β-keto acid derivatives and their analogues, see: (a) Hintermann, L.; Togni, A. Catalytic Enantioselective Fluorination of β-Ketoesters. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359−4362. (b) Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. An´ Efficient Enantioselective Fluorination of Various β-Ketoesters Catalyzed by Chiral Palladium Complexes. *J. Am. Chem. Soc.* **2002**, *124*, 14530−14531. (c) Wang, X.; Lan, Q.; Shirakawa, S.; Maruoka, K. Chiral Bifunctional Phase Transfer Catalysts for Asymmetric Fluorination of β-Keto Esters. *Chem. Commun.* **2010**, *46*, 321−323.

(5) For catalytic α-fluorination of oxindoles, see: (a) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. Catalytic Enantioselective Fluorination of Oxindoles. *J. Am. Chem. Soc.* **2005**, *127*, 10164−10165. (b) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. Cinchona Alkaloid Catalyzed Enantioselective Fluorination of Allyl Silanes, Silyl Enol Ethers, and Oxindoles. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157−4161. (c) Li, J.; Cai, Y.; Chen, W.; Liu, X.; Lin, L.; Feng, X. Highly Enantioselective Fluorination of Unprotected 3-Substituted Oxindoles: One-Step Synthesis of BMS 204352 (MaxiPost). *J. Org. Chem.* **2012**, *77*, 9148−9155. (d) Gu, X.; Zhang, Y.; Xu, Z. J.; Che, C. M. Iron(III)-Salan Complexes Catalysed Highly Enantioselective Fluorination and Hydroxylation of β-Keto Esters and *N*-Boc Oxindoles. *Chem. Commun.* **2014**, *50*, 7870−7873.

(6) For catalytic α-fluorination of α-aryl acetic acid derivatives, see: (a) Suzuki, T.; Hamashima, Y.; Sodeoka, M. Asymmetric Fluorination of α-Aryl Acetic Acid Derivatives with the Catalytic System $NiCl_2$−Binap/R_3SiOTf/2,6-Lutidine. *Angew. Chem., Int. Ed.* **2007**, *46*, 5435−5439. (b) Ishimaru, T.; Shibata, N.; Reddy, D. S.; Horikawa, T.; Nakamura, S.; Toru, T. DBFOX-Ph/Metal Complexes: Evaluation as Catalysts for Enantioselective Fluorination of 3-(2-Arylacetyl-2-thiazolidinones. *Beilstein J. Org. Chem.* **2008**, *4*, 16. (c) Reddy, D. S.; Shibata, N.; Horikawa, T.; Suzuki, S.; Nakamura, S.; Toru, T.; Shiro, M. A DBFOX-Ph-Based Combinatorial Catalyst for Enantioselective Fluorination of Aryl Acetyl and 3-Butenoyl Thiazolidinones. *Chem. - Asian J.* **2009**, *4*, 1411−1415.

(7) For catalytic α-fluorination of acid chlorides, see: (a) Paull, D. H.; Scerba, M. T.; Alden-Danforth, E.; Widger, L. R.; Lectka, T. Catalytic, Asymmetric α-Fluorination of Acid Chlorides: Dual Metal-Ketene Enolate Activation. *J. Am. Chem. Soc.* **2008**, *130*, 17260−17261. (b) Erb, J.; Paull, D. H.; Belding, L.; Dudding, T.; Lectka, T. From Bifunctional to Trifunctional (Tricomponent Nucleophile−Transition Metal−Lewis Acid) Catalysis: The Catalytic, Enantioselective α-Fluorination of Acid Chlorides. *J. Am. Chem. Soc.* **2011**, *133*, 7536−7546. For catalytic α-fluorination of benzofuran-2-(3H)-ones, see: (c) Zhu, C.-L.; Fu, X.-Y.; Wei, A.-J.; Cahard, D.; Ma, J.-A. P-Spiro Phosphonium Salts Catalyzed Asymmetric Fluorination of 3-Substituted Benzofuran-2-(3H)-ones. *J. Fluorine Chem.* **2013**, *150*, 60−66.

(8) (a) Davis, F. A.; Han, W. Diastereoselective Fluorination of Chiral Imide Enolates using *N*-Fluoro-*o*-benzenedisulfonimide (NFOBS). *Tetrahedron Lett.* **1992**, *33*, 1153−1156. (b) Davis, F. A.; Kasu, P. V. N.; Sundarababu, G.; Qi, H. Nonracemic α-Fluoro Aldehydes: Asymmetric Synthesis of 4-Deoxy-4-fluoro-D-arabinopyranose. *J. Org. Chem.* **1997**, *62*, 7546−7547. (c) Davis, F. A.; Kasu, P. V. N. Asymmetric Synthesis of α-Fluoro Ketones Using α-Fluoro Oxazolidinone Carboximides. *Tetrahedron Lett.* **1998**, *39*, 6135−6138. (d) Edmonds, M. K.; Graichen, F. H. M.; Gardiner, J.; Abell, A. D. Enantioselective Synthesis of α-Fluorinated β^2-Amino Acids. *Org. Lett.* **2008**, *10*, 885−887. (e) Nakayama, K.; Browne, D. L.; Baxendale, I. R.; Ley, S. V. Studies of a Diastereoselective Electrophilic Fluorination Reaction Employing a Cryo-Flow Reactor. *Synlett* **2013**, *24*, 1298−1302. For enolate intermediates derived from chiral enamides, see: (f) Xu, Y.-S.; Tang, Y.; Feng, H.-J.; Liu, J.-T.; Hsung, R. P. A Highly Regio-and Stereoselective Synthesis of α-Fluorinated Imides via Fluorination of Chiral Enamides. *Org. Lett.* **2015**, *17*, 572−575.

(9) Alvarado, J.; Herrmann, A. T.; Zakarian, A. Stereoselective α-Fluorination of *N*-Acyloxazolidinones at Room Temperature within 1 h. *J. Org. Chem.* **2014**, *79*, 6206−6220.

(10) Lubin, H.; Dupuis, C.; Pytkowicz, J.; Brigaud, T. Crystallization-Induced Dynamic Resolution of Fox Chiral Auxiliary and Applications to the Diastereoselective Electrophilic Fluorination of Amide Enolates. *J. Org. Chem.* **2013**, *78*, 3487−3492.

(11) For alkylation reactions of *N*-*t*BS imidates or amidines, see: (a) Kochi, T.; Ellman, J. A. Asymmetric α-Alkylation of *N*′-*tert*-Butanesulfinyl Amidines. Application to the Total Synthesis of (6*R*,7*S*)-7-Amino-7,8-dihydro-α-bisabolene. *J. Am. Chem. Soc.* **2004**, *126*, 15652−15653. (b) Colpaert, F.; Mangelinckx, S.; Verniest, G.; De Kimpe, N. Asymmetric Synthesis of α-Alkylated *N*-Sulfinyl Imidates as New Chiral Building Blocks. *J. Org. Chem.* **2009**, *74*, 3792−3797. (c) Colpaert, F.; Mangelinckx, S.; De Kimpe, N. Asymmetric Synthesis of Chiral *N*-Sulfinyl 3-Alkyl- and 3-Arylpiperidines by α-Alkylation of *N*-Sulfinyl Imidates with 1-Chloro-3-iodopropane. *J. Org. Chem.* **2011**, *76*, 234−244.

(12) For aldol reactions of *N*-*t*BS imidates, see: (a) Bartrum, H. E.; Viceriat, A.; Carret, S.; Poisson, J.-F. Sulfinylimidates as Chiral Amide Equivalents for Irreversible, Asymmetric Aldol Reactions. *Org. Lett.* **2014**, *16*, 1972−1975. (b) Li, C.-T.; Liu, H.; Xu, Y.-J.; Lu, C.-D. Aldol Reaction of *N*-*tert*-Butanesulfinyl Imidates under Basic Conditions for Diastereoselective Synthesis of *anti*-Aldols. *J. Org. Chem.* **2017**, *82*, 11253−11261. (c) Huang, W.; Liu, H.; Lu, C.-D.; Xu, Y.-J. Diastereoselective Synthesis of 2-Methoxyimidoyloxiranes via Dimethyl Phosphite-mediated Coupling of α-Keto *N*-sulfinyl imidates with Aldehydes. *Chem. Commun.* **2016**, *52*, 13592−13595. (d) Huang, W.; Liu, H.; Xu, Y.-J.; Lu, C.-D. Reaction of Silyllithium, α-Keto *N*-*tert*-Butanesulfinyl Imidates and Aldehydes for Asymmetric Synthesis of α-Substituted β-(Silyloxy)-α-hydroxy Acid Derivatives. *J. Org. Chem.* **2017**, *82*, 10748−10755.

(13) For Mannich reactions of *N*-*t*BS imidates, see: (a) Colpaert, F.; Mangelinckx, S.; De Kimpe, N. Asymmetric Synthesis of New Chiral β-Amino Acid Derivatives by Mannich-type Reactions of Chiral *N*-Sulfinyl Imidates with *N*-Tosyl Aldimines. *Org. Lett.* **2010**, *12*, 1904−1907. (b) Colpaert, F.; Mangelinckx, S.; De Brabandere, S.; De Kimpe, N. Asymmetric Synthesis of α-Chloro-β-amino-*N*-sulfinyl Imidates as Chiral Building Blocks. *J. Org. Chem.* **2011**, *76*, 2204−2213. (c) Semina, E.; Colpaert, F.; Van Hecke, K.; De Kimpe, N.; Mangelinckx, S. Asymmetric Synthesis of δ-Chloro-β-Amino-*N*-Sulfinyl Imidates as Versatile Chiral Building Blocks for the Synthesis of 2,3-Disubstituted Piperidines. *Eur. J. Org. Chem.* **2015**, *2015*, 4847−4859.

(14) For 1,4-addition involving *N*-*t*BS imidates, see: (a) Wang, J. F.; Zhou, Y.; Zhang, L.; Li, Z.; Chen, X. J.; Liu, H. Asymmetric Michael Addition of *N*-*tert*-Butanesulfinyl Imidate with α,β-Unsaturated Diesters: Scope and Application to the Synthesis of Indanone Derivatives. *Org. Lett.* **2013**, *15*, 1508−1511. (b) Wang, H.-J.; Tang, P.; Zhou, Q.-L.; Zhang, D.; Chen, Z.-T.; Huang, H.-X.; Qin, Y. One-Pot Synthesis of Multisubstituted Butyrolactonimidates: Total Synthesis of (−)-Nephrosteranic Acid. *J. Org. Chem.* **2015**, *80*, 2494−2502. (c) Huang, H.-X.; Wang, H.-J.; Tan, L.; Wang, S.-Q.; Tang, P.; Song, H.; Liu, X.-Y.; Qin, Y. Asymmetric Michael Addition Induced by *(R)*-*tert*-Butanesulfinamide and Syntheses of Chiral Pyrazolidinone Derivatives. *J. Org. Chem.* **2016**, *81*, 10506−10516.

DOI: 10.1021/acs.joc.8b02375
J. Org. Chem. XXXX, XXX, XXX−XXX

(15) For α-amination of *N*-*t*BS imidates, see: Ma, P.-J.; Liu, H.; Lu, C.-D.; Xu, Y.-J. Diastereoselective Electrophilic α-Hydroxyamination of *N*-*tert*-Butanesulfinyl Imidates. *Org. Lett.* **2017**, *19*, 670−673.
(16) For α-hydroxylation of *N*-*t*BS imidates/amidines, see: Ma, P.-J.; Liu, H.; Xu, Y.-J.; Aisa, H. A.; Lu, C.-D. Diastereoselective α-Hydroxylation of *N*-*tert*-Butanesulfinyl Imidates and *N*′-*tert*-Butanesulfinyl Amidines with Molecular Oxygen. *Org. Lett.* **2018**, *20*, 1236−1239.
(17) For α-hydroxylation of *N*-*t*BS imidates, see: Niu, S.-T.; Liu, H.; Xu, Y.-J.; Lu, C.-D. Diastereoselective α-Sulfenylation of *N*-*tert*-Butanesulfinyl Imidates. *J. Org. Chem.* **2018**, *83*, 10580−10588.
(18) For reviews of *tert*-butanesulfonamide, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *N*-*tert*-Butanesulfinyl Imines: Versatile Intermediates for the Asymmetric Synthesis of Amines. *Acc. Chem. Res.* **2002**, *35*, 984−995. (b) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *tert*-Butanesulfinimines: Structure, Synthesis and Synthetic Applications. *Chem. Soc. Rev.* **2009**, *38*, 1162−1186. (c) Robak, M. T.; Herbage, M. A.; Ellman, J. A. Synthesis and Applications of *tert*-Butanesulfinamide. *Chem. Rev.* **2010**, *110*, 3600−3740.
(19) The absolute configuration of chlorinated stereogenic center was not assigned.
(20) For selected examples of enantioselective synthesis of β-fluoroamines (1,2-fluoroamines), see: (a) Schulte, M. L.; Lindsley, C. W. Highly Diastereoselective and General Synthesis of Primary β-Fluoroamines. *Org. Lett.* **2011**, *13*, 5684−5687. (b) Appayee, C.; Brenner-Moyer, S. E. Organocatalytic Enantioselective Olefin Amino-fluorination. *Org. Lett.* **2010**, *12*, 3356−3359. (c) Kong, W.; Feige, P.; de Haro, T.; Nevado, C. Regio- and Enantioselective Amino-fluorination of Alkenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 2469−2473. (d) Vara, B. A.; Johnston, J. N. Enantioselective Synthesis of β-Fluoro Amines via β-Amino α-Fluoro Nitroalkanes and a Traceless Activating Group Strategy. *J. Am. Chem. Soc.* **2016**, *138*, 13794−13797. (e) Trost, B. M.; Saget, T.; Lerchen, A.; Hung, C. I. Catalytic Asymmetric Mannich Reactions with Fluorinated Aromatic Ketones: Efficient Access to Chiral β-Fluoroamines. *Angew. Chem., Int. Ed.* **2016**, *55*, 781−784. (f) Mennie, K. M.; Banik, S. M.; Reichert, E. C.; Jacobsen, E. N. Catalytic Diastereo- and Enantioselective Fluoroamination of Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 4797−4802.
(21) Kalow, J.; Schmitt, D. E.; Doyle, A. G. Synthesis of β-Fluoroamines by Lewis Base Catalyzed Hydrofluorination of Aziridines. *J. Org. Chem.* **2012**, *77*, 4177−4183.
(22) For reactions involving a chelated, chairlike 6/4 bicyclic transition state, see: (a) Kochi, T.; Tang, T. P.; Ellman, J. A. Development and Application of a New General Method for the Asymmetric Synthesis of *syn*- and *anti*-1,3-Amino Alcohols. *J. Am. Chem. Soc.* **2003**, *125*, 11276−11282. For discussion of a closed chair−chairlike eight-membered transition state for α-fluorination using NSFI, see: (b) Beeson, T. D.; Macmillan, D. W. C. Enantioselective Organocatalytic α-Fluorination of Aldehydes. *J. Am. Chem. Soc.* **2005**, *127*, 8826−8828.

DOI: 10.1021/acs.joc.8b02375
J. Org. Chem. XXXX, XXX, XXX−XXX