JOC The Journal of Organic Chemistry

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Stereoselective Synthesis of *cis*-2-Fluorocyclopropanecarboxylic Acid

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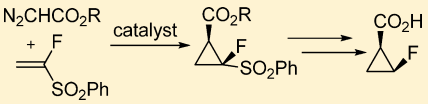
Supporting Information

ABSTRACT: A rhodium-catalyzed cyclopropanation of 1-fluoro-1-(phenylsulfonyl)-ethylene and diazo esters is described as an effective method for the stereoselective synthesis of *cis*-2-fluorocyclopropanecarboxylic acid. This process provides an example of the cyclopropanation of electron-deficient olefin and diazoacetates.



The *N*-1 cyclopropyl group of quinolone antibiotics plays an important role in their potent antibacterial activities. Structure−activity relationship (SAR) studies of a substituent on the cyclopropyl group revealed that a fluoro group at the C-2 position with cis configuration plays a role in the good antibacterial activity.[1−5]

cis-2-Fluorocyclopropanecarboxylic acid (*S*,*S*)-**1** is one of the useful precursors of *cis*-2-fluorocyclopropylamine (*R*,*S*)-**2**, which is a key component of the antibacterial agent sitafloxacin **3** (Figure 1).[3] The fluorine atom in both (*S*,*S*)-**1** and (*R*,*S*)-**2** is

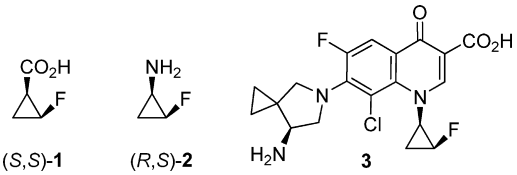


Figure 1. *cis*-Fluorocyclopropanecarboxylic Acid **1**, *cis*-2-Fluorocyclopropylamine **2** and Sitafloxacin **3**

arranged in a cis configuration next to the carboxyl and amine groups, and complicates their stereoselective synthesis. Accordingly, numerous synthetic approaches to control the stereochemistry of the two adjacent stereogenic centers of these fluorine-containing cyclopropanes have been investigated.[6−22]

Representative approaches toward **1** can be categorized into three types (Figure 2). The first type (i) consists of

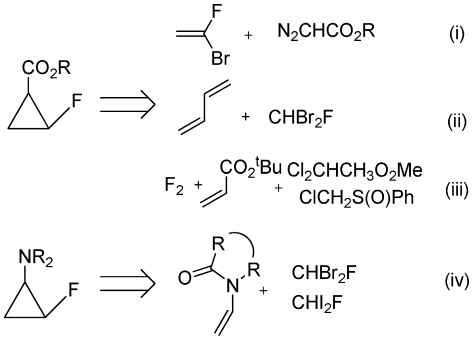
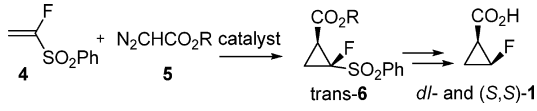


Figure 2. Representative Approaches to **1** and **2**.

cyclopropanations of bromofluoroethene with diazoacetates.[6,7] The second approach (ii) involves the synthesis of precursors of **1** by way of cyclopropanation of butadiene with fluorocarbenoid species,[8,9] and the last approach (iii) includes a fluorination step of suitable intermediates using an F_2 gas.[10,11] The synthesis of optically active (*S*,*S*)-**1** was achieved via enantioselective hydrolysis of the racemic esters of **1** by microorganisms or diastereomeric separation of the racemate **1** by recrystallization with chiral amine.[12,13] On the other site, asymmetric synthesis of *N*-protected **2** (iv) was accomplished with cyclopropanation of optically active *N*-vinyl oxazolidinone or *N*-vinyl lactam with fluorocarbenoid species.[14−17] Though many of the efforts have focused on the stereoselective synthesis of racemic or optically active **1** and **2**, there is room to improve the stereoselectivity. We herein report an efficient synthesis of *dl*- and (*S*,*S*)-**1** via the stereoselective cyclopropanation of sulfonylalkene and diazoacetates. Though a large number of researches on the cyclopropanation of olefins with diazoacetates have been reported and their methods widely applied, due to the electrophilic nature of metal−carbene species, the cyclopropanation with electron-deficient olefins and diazoacetates remains a challenge.[23−34] Indeed, to our knowledge there have been only a few reports of cyclopropanation between sulfonylalkenes and diazoacetates.[35]

The synthesis of **1** is outlined in Scheme 1. Our plan was to install the cis configuration of **1** through metal-catalyzed

Scheme 1. Plan for Synthesis of Cyclopropanecarboxylic Acid 1

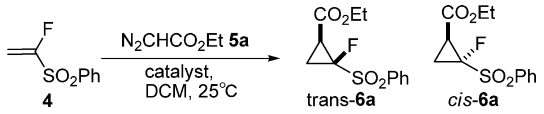


cyclopropanation of 1-fluoro-1-(phenylsulfonyl)ethylene **4**[36−39] and diazoacetates **5**. One of the products of this cyclopropanation, the *tert*-butyl ester *trans*-**6b** (R = ^{t}Bu), was reported as a useful precursor of *dl*-**1**.[11]

Received: May 31, 2014
Published: July 10, 2014

Our initial study of the synthesis of **6a** consisted of a screening of the metal catalysts of cyclopropanation between **4** and ethyl diazoacetate **5a** (runs 1–5, Table 1). Among the

Table 1. Cyclopropanation of 4 with 5a



run[a]	catalyst	yield (%)[b]	*trans*/*cis*[c]
1	$Rh(OAc)_2$	18	86/14
2	$AgSbF_6$	N.D.	
3	$Cu(acac)_2$	N.D	
4	Ru(TPP)(CO)	6	>99/1
5	Co(TPP)	N.D.	
6	$[Rh[O_2CC(Me)_3]_2]_2$	trace	
7	$[Rh(O_2CCF_3)_2]_2$	trace	
8	$[Rh(O_2CC_5H_{11})_2]_2$	13	79/21
9	$[Rh(O_2CC_7H_{15})_2]_2$	32	83/17
10	$Rh_2(esp)_2$	19	84/16
11	$[Rh(O_2CCPh_3)_2]_2$	78	84/16

[a]Reactions were carried out for 1.5 h under Ar with **4** (1.0 equiv), **5a** (2.0 equiv), and catalyst (10 mol %). [b]Total yields. [c]Determined by ^{1}H NMR analysis (400 MHz).

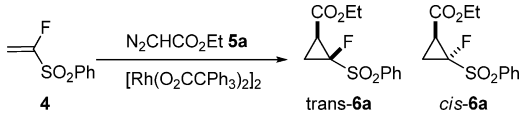
catalysts tested, $Rh_2(OAc)_4$ gave the desired ethyl 2-fluoro-2-phenylsulfonylcyclopropanecarboxylate **6a** in the best yield (18%) with good stereoselectivity (*trans*/*cis* = 86/14, run 1). The relative stereochemistry of **6a** was unambiguously confirmed by NOE experiments (see the Supporting Information [SI]). The ruthenium catalyst Ru(TPP)(CO)[19] also worked to obtain **6a** with good stereoselectivity, albeit in a lower yield (run 4). The other catalysts tested,[40−42] $AgSbF_6$, $Cu(acac)_2$ and Co(TPP) failed to give **6a**. We therefore set out to identify other rhodium catalysts for our purposes (runs 6−11). The use of $[Rh(O_2CCPh_3)_2]_2$ afforded an improved yield of **6a** in dichloromethane at room temperature (78%, *trans*/*cis* = 84/16, run 11).[43,44] The difference in the ligands of the rhodium catalysts would have influence on the stability or reactivity of the carbene species, rather than the stereoselectivity of cyclopropanation.

Both the stereoselectivity and yield of **6a** were little affected by the prolonged reaction time (run 2, Table 2). Either a lower or a higher reaction temperature resulted in decreased yields of **6a** (runs 3−5). Among the solvents tested (runs 6−9), in addition to dichloromethane, heptane was also a suitable solvent for the cyclopropanation to give **6a** in a good yield with similar stereoselectivity (70%, *trans*/*cis* = 85/15, run 6).

In our next experiments, we expected that the larger steric repulsion between the bulky ester and phenylsulfonyl groups would favor trans-stereoselectivity in the cyclopropanation (Table 3). Our results showed that, compared with ethyl ester **5a** (*trans*/*cis* = 85/15, run 6 in Table 3), both *tert*-butyl ester **5b** and *l*-menthyl ester **5c** greatly improved the stereoselectivity and afforded **6b** and **6c** in good yields (*trans*/*cis* = 93/7 and >99/1, runs 3 and 6 in Table 3). The *l*-menthyl ester group of **5c** did not affect the diastereoselectivity of **6c**.

We further confirmed that the steric repulsion between the ester and phenylsulfonyl groups plays an important role in the high stereoselectivity of this cyclopropanation (Table 4). In the case of cyclopropanation of sulfoxide and **5b**, the product was a sulfide rather than the expected sulfoxide. Deoxygenation of the

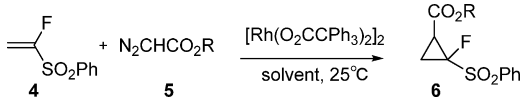
Table 2. Cyclopropanation of 4 and 5a Using $[Rh(O_2CCPh_3)_2]_2$



run[a]	solvent	temp (°C)	yield (%)[b]	*trans*/*cis*[c]
1	DCM	25	78	84/16
2[d]	DCM	25	73	82/18
3	DCM	4	67	82/18
4	DCM	−78	15	79/21
5	DCM	40	61	80/20
6	heptanes	25	70	85/15
7	toluene	25	N.D.	
8	THF	25	N.D	
9	DME	25	N.D.	

[a]Reactions were carried out for 1.5 h under Ar with **4** (1.0 equiv), **5a** (2.0 equiv), and catalyst (10 mol%). [b]Total yields. [c]Determined by ^{1}H NMR analysis (400 MHz). [d]Reaction time was 6 h.

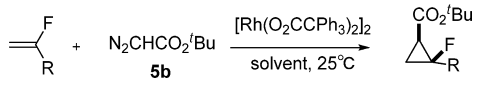
Table 3. Stereoselectivity of Cyclopropanation with Bulky Esters 5b and 5c



run[a]	R	solvent	product	yield (%)[b]	*trans*/*cis* (dr)[c]
1[d]	^{t}Bu **5b**	DCM	**6b**	30	94/6
2	^{t}Bu **5b**	DCM	**6b**	32	95/5
3	^{t}Bu **5b**	heptane	**6b**	80	93/7
4	^{t}Bu **5b**	DCM–heptane	**6b**	51	95/5
5[d]	*l*-menthyl **5c**	DCM	**6c**	76	>99/1 (53/47)
6	*l*-menthyl **5c**	DCM	**6c**	85	>99/1 (51/49)
7	*l*-menthyl **5c**	heptane	**6c**	65	>99/1 (50/50)
8	*l*-menthyl **5c**	DCM–heptane	**6c**	49	>99/1 (51/49)

[a]Reactions were carried out for 6 h under Ar with **4** (1.0 equiv), **5** (2.0 equiv), and $[Rh(O_2CCPh_3)_2]_2$ (10 mol %). [b]Total yields. [c]Determined by ^{1}H NMR analysis (400 MHz). [d]Reaction time was 1.5 h.

Table 4. Impact on Stereoselectivity of Phenylsulfonyl Group



run[a]	R	solvent	yield (%)[b]	*trans*/*cis*[c]
1	SO_2Ph	heptane	80	93/7
2	S(O)Ph	heptane	38[d]	78/22
3	SPh	heptane	86	76/24
4[e]	H	DCM	–	1/3.4

[a]Reactions were carried out for 6 h under Ar with olefin (1.0 equiv), **5b** (2.0 equiv), and $[Rh(O_2CCPh_3)_2]_2$ (10 mol %). [b]Total yields. [c]Determined by ^{1}H NMR analysis (400 MHz). [d]The product was isolated as a sulfide; 59% of SM recovered. [e]Data from ref 44.

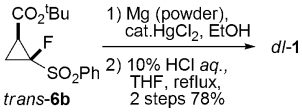
sulfoxide group by carbene species generated from diazoacetate **5b** was assumed to have occurred.[45] In addition, a previously

dx.doi.org/10.1021/jo501219n | J. Org. Chem. 2014, 79, 7226−7231

reported study revealed that cyclopropanation of vinylfluoride and **5b** using $[Rh(O_2CCPh_3)_2]_2$ directly afforded *tert*-butyl ester of **1** with lower stereoselectivity (*trans*/*cis* = 1:3.4, run 4).[39] From the present results shown in Tables 2−4, the stereoselectivity of this cyclopropanation of sulfonylalkene and diazo esters showed a tendency similar to other cyclopropanations such as the cyclopropanation of styrene with diazo esters, in that it could be improved by increasing the bulk of the ester functionality.[46−48]

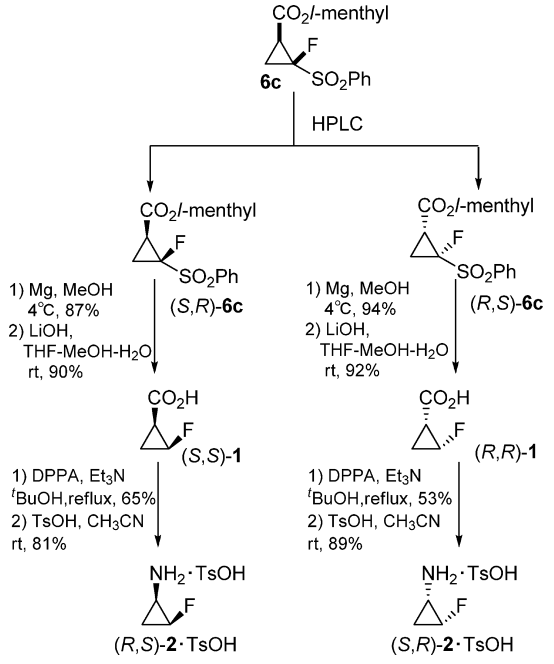
As shown in Scheme 2, the relative stereochemistry of trans-**6b** was elucidated by conversion to *dl*-**1** according to the reported procedure.[11]

Scheme 2. Relative Stereochemistry Elucidation of *trans*-6b



Similarly, the *l*-menthyl ester **6c** was converted to the enantiomeric pair of **1** after diastereomeric HPLC separation (Scheme 3). The dephenylsulfonylation of (*S*,*R*)-**6c** was carried

Scheme 3. Conversion of 6c to Tosylates of Optically Active 2 via Enantiomeric Pair of 1



out successfully using magnesium powder in methanol,[49] and removal of the *l*-menthyl group with aqueous lithium hydroxide solution in tetrahydrofuran and methanol gave (*S*,*S*)-**1** as a colorless solid. The enantiomeric excess (% ee) of (*S*,*S*)-**1** was determined to be >99% ee by chiral HPLC analysis (Chiralpak AD-H). Finally, by employing the previously reported procedure,[14] we demonstrated the synthesis of tosylate of (*R*,*S*)-**2** from (*S*,*S*)-**1**. The antipode (*S*,*R*)-**2** as the tosylate was also prepared from (*R*,*S*)-**6c** in the same manner as described for (*R*,*S*)-**2**.

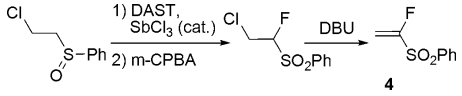
In conclusion, we have accomplished the stereoselective synthesis of *dl*-**1**, (*S*,*S*)-**1**, and (*R*,*S*)-**2**, which are intermediates of quinolone antibiotics. This synthesis involved cyclopropanation of **4** and **5** using a rhodium catalyst to give **6** in good yields with high stereoselectivity. Our results have also provided an example of a metal-catalyzed cyclopropanation employing electron-deficient olefin and diazoacetates.

EXPERIMENTAL SECTION

General Considerations. All reagents were purchased from chemical suppliers and used without additional purification unless noted. Unless otherwise noted, all the experiments were carried out using anhydrous solvents under an atmosphere of argon.

The chemical shifts are expressed in parts per million (δ value) downfield from tetramethylsilane, using tetramethylsilane ($\delta = 0$) and/or residual solvents such as chloroform ($\delta = 7.26$) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Unless otherwise noted, all the experiments were carried out using anhydrous solvents under an atmosphere of argon. All melting points were uncorrected. Measurements of optical rotations were carried out by automatic digital polarimeter. High resolution mass spectroscopy (HRMS) was performed on chemical ionization (CI) and TOF instrument with ESI in positive ionization mode. Data for elemental analyses are within ±0.3% of the theoretical values. Analytical and preparative HPLC was carried out using an apparatus equipped with a HPLC pump and oven.

Preparation of 1-Fluoro-1-(phenylsulfonyl)ethylene ***4****.*[36] According to the procedure reported by McCarthy et.al, **4** was prepared from *β*-chloroethyl phenyl sulfoxide as shown below.



General Procedure for Cyclopropanation Reaction. A solution of diazo esters (4.0 mmol) in solvents (5 mL) was added dropwise to a stirred solution of **4** (2.0 mmol) and Rh-catalyst (10 mol % of **4**) in solvents (2 mL) at 25 °C over 1.5 or 6 h. After addition of diazo esters, the solution was concentrated in vacuo. Flash chromatography of the residue gave the desired cyclopropanes. The structure and diastereomer ratio of the products were determined by ^{1}H NMR.

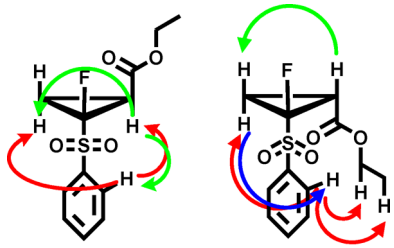
*Ethyl trans-2-Fluoro-2-(phenylsulfonyl)cyclopropane-1-carboxylate (trans-****6a****) and Ethyl cis-2-Fluoro-2-(phenylsulfonyl)cyclopropane-1-carboxylate (cis-****6a****) (Table 1 run 11).* A solution of ethyl diazoacetate (85% CH_2Cl_2 solution, 537.0 mg 4.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of **4** (372.4 mg, 2.0 mmol) and $[Rh(O_2CCPh_3)_2]_2$ (28.9 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) at 25 °C over 1.5 h. After addition of ethyl diazoacetate, the mixture was stirred at room temperature for 1 h and concentrated in vacuo. Flash chromatography (silica, hexane/ethyl acetate = 4:1) of the residue gave a mixture of *trans*- and *cis*-**6a** (423.5 mg, 78%). The mixture of *trans*- and *cis*-**6a** was separated by HPLC [Kanto Mightysil, si 60 (5 μ), ϕ 2.0 cm × 25 cm: hexane/ethyl acetate = 85:15, flow rate 20 mL/min, HPLC analysis; Kanto Mightysil, si 60 (5 μ), ϕ 0.46 cm × 25 cm, hexane/ethyl acetate = 85:15, flow rate 1.0 mL/min; t_R = 16.2 min (*trans*-**6a**) and 19.7 min (*cis*-**6a**)] to give the pure samples of *trans*- and *cis*-**6a**. The relative stereochemistry of **6a** was unambiguously confirmed by NOE experiments as shown below.

trans-**6a**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, J = 7.3 Hz, 3H), 2.02 (dt, J = 7.9, 9.8 Hz, 1H), 2.15 (dt, J = 7.9, 18.4 Hz, 1H), 2.84 (ddd, J = 3.1, 7.9, 10.4 Hz, 1H), 4.11−4.21 (m, 2H), 7.60−7.66 (m, 2H), 7.72−7.77 (m, 1H), 7.94−8.01 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 15.7, 15.8, 24.8, 24.9, 61.9, 89.1, 91.9, 129.2, 129.5, 134.8, 135.9, 165.4, 165.5. IR (ATR): 1735, 1145 cm^{-1}. MS (CI$^+$) m/z: 273 (MH$^+$). HRMS (CI$^+$) for $C_{12}H_{14}FO_4S$ (MH$^+$): calcd, 273.0597; found, 273.0606.

cis-**6a**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, J = 7.3 Hz, 3H), 1.77 (ddd, J = 8.6, 11.0, 18.3 Hz, 1H), 2.34 (ddd, J = 7.9, 9.8, 11.0 Hz, 1H), 2.61 (ddd, J = 9.8, 11.0, 19.0 Hz, 1H), 4.22−4.30 (m, 2H), 7.58−7.64 (m, 2H), 7.70−7.76 (m, 1H), 7.98 (d, J = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 15.2, 15.3, 28.8, 28.9, 62.2,

dx.doi.org/10.1021/jo501219n | J. Org. Chem. 2014, 79, 7226−7231

89.0, 91.7, 129.2, 134.7, 136.4, 164.85, 164.87. IR (ATR): 1736, 1150 cm^{-1}. MS (CI^+) *m/z*: 273 (MH^+). HRMS (CI^+) for $C_{12}H_{14}FO_4S$ (MH^+): calcd, 273.0597; found, 273.0638.



trans-**6a** *cis*-**6a**

*tert-Butyl trans-2-Fluoro-2-(phenylsulfonyl)cyclopropane-1-carboxylate (trans-**6b**) and tert-Butyl cis-2-Fluoro-2-(phenylsulfonyl)-cyclopropane-1-carboxylate (cis-**6b**).* A mixture of *trans*- and *cis*-**6b** was obtained by flash chromatography (silica, hexane/ethyl acetate = 9:1) of the residue of the reaction mixture. The mixture of *trans*- and *cis*-**6b** was further separated by HPLC [Kanto Mightysil, si 60 (5 μ), ϕ 2.0 cm × 25 cm: hexane/ethyl acetate = 95:5, flow rate 20 mL/min, HPLC analysis; Kanto Mightysil, si 60 (5 μ), ϕ 0.46 cm × 25 cm, hexane/ethyl acetate = 95:5, flow rate 1.0 mL/min; t_R = 14.8 min (*trans*-**6b**) and 18.5 min (*cis*-**6b**)] to give pure samples *trans*- and *cis*-**6b**.

trans-**6b**: Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9H), 1.96 (ddd, *J* = 8.0, 9.8, 11.0 Hz, 1H), 2.07 (dt, *J* = 8.0, 18.3 Hz, 1H), 2.76 (ddd, *J* = 3.1, 8.6, 11.0 Hz, 1H), 7.60−7.66 (m, 2H), 7.72−7.77 (m, 2H), 7.94−8.00 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 15.4, 26.0, 26.1, 27.9, 88.9, 91.7, 129.1, 129.4, 134.7, 136.1, 164.18, 164.21. IR (ATR): 1731, 1142 cm^{-1}. MS (CI^+) *m/z*: 301 (MH^+). HRMS (CI^+) for $C_{14}H_{18}FO_4S$ (MH^+): calcd, 301.0910; found, 301.0891.

cis-**6b**: Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 9H), 1.69 (ddd, *J* = 7.9, 11.0, 19.0 Hz, 1H), 2.23 (ddd, *J* = 8.0, 9.8, 11.0 Hz, 1H), 2.57 (ddd, *J* = 9.8, 11.0, 19.6 Hz, 1H), 7.58−7.64 (m, 2H), 7.69−7.75 (m, 2H), 7.98−8.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 15.4, 27.9, 30.0, 30.1, 82.9, 89.1, 91.8, 129.2, 129.3, 134.6, 136.6, 163.70, 163.73. IR (ATR): 1733, 1147 cm^{-1}. MS (CI^+) *m/z*: 301 (MH^+). HRMS (CI^+) for $C_{14}H_{18}FO_4S$ (MH^+): calcd, 301.0910; found, 301.0895.

*(1S,2R)-((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)-2-fluoro-2-(phenylsulfonyl)cyclopropane-1-carboxylate [(S,R)-**6c**] and (1R,2S)-((1R, 2S,5R)-2-Isopropyl-5-methylcyclohexyl)-2-fluoro-2-(phenylsulfonyl)cyclopropane-1-carboxylate [(R,S)-**6c**].* A mixture of the diastereomers of *trans*-**6c** was obtained by flash chromatography (silica, hexane/ethyl acetate = 15:1) of the residue of the reaction mixture. The diastereomers of **6c** were separated by HPLC [Daicel Chiralpak AD-H, ϕ 2.0 cm × 25 cm: hexane/ethanol = 80:20, flow rate 15.0 mL/min, HPLC analysis; Daicel Chiralpak AD-H, ϕ 0.46 cm × 25 cm, hexane/ethanol = 80:20, flow rate 1.0 mL/min; t_R = 5.8 min [(*R*,*S*)-**6c**] and 13.6 min [(*S*,*R*)-**6c**]] to give (*S*,*R*)-**6c** and (*R*,*S*)-**6c**, respectively.

(*S*,*R*)-**6c**: Colorless oil. $[\alpha]_D^{23}$ = −90.3 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.51 (d, *J* = 6.7 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H), 0.78−1.04 (m, 6H), 1.20−1.30 (m, 1H), 1.30−1.52 (m, 2H), 1.58−1.70 (m, 2H), 1.90−2.00 (m, 1H), 2.04−2.24 (m, 2H), 2.74 (ddd, *J* = 3.0, 7.9, 10.3 Hz, 1H), 4.62 (dt, *J* = 4.2, 10.9 Hz, 1H), 7.58−7.65 (m, 2H), 7.71−7.77 (m, 2H), 7.98 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 15.2, 15.8, 20.7, 21.9, 23.2, 25.6, 25.7, 25.9, 31.3, 34.1, 40.6, 46.8, 76.2, 88.9, 91.7, 129.2, 129.4, 134.7, 135.9, 164.71, 164.74. IR (ATR): 1733, 1208, 1146 cm^{-1}. MS (CI^+) *m/z*: 383 (MH^+). HRMS (CI^+) for $C_{20}H_{28}FO_4S$ (MH^+): calcd, 383.1692; found, 383.1651.

(*R*,*S*)-**6c**: Colorless oil. $[\alpha]_D^{23}$ = −19.8 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.72 (d, *J* = 6.7 Hz, 3H), 0.80−0.92 (m, 8H), 0.93−1.09 (m, 1H), 1.25−1.49 (m, 2H), 1.59−1.72 (m, 2H), 1.75−1.92 (m, 2H), 2.00 (ddd, *J* = 7.9, 10.4, 17.7 Hz, 1H), 2.15 (dt, *J* = 7.9, 18.3 Hz, 1H), 2.84 (ddd, *J* = 3.1, 8.6, 11.0 Hz, 1H), 4.62 (dt, *J* = 4.9, 11.0 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.97 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6, 15.7, 16.2, 20.7, 21.9, 23.2, 25.2, 25.3, 26.1, 31.3, 34.1, 40.6, 46.8, 76.3, 89.0, 91.8, 129.1, 129.4, 134.7, 136.0, 164.93, 164.95. IR (ATR): 1733, 1208, 1147 cm^{-1}. MS (CI^+) *m/z*: 383 (MH^+). HRMS (CI^+) for $C_{20}H_{28}FO_4S$ (MH^+): calcd, 383.1692; found, 383.1651.

*Synthesis of dl- cis-2-Fluorocyclopropanecarboxylic Acid (dl-**1**).*[8,11] To a solution of *trans*-**6b** (660 mg, 2.20 mmol) in ethanol (11 mL) were added magnesium powder (160 mg, 6.59 mmol) and $HgCl_2$ (25.8 mg, 9.50 μmol); the mixture was stirred at room temperature for 16 h. The mixture was poured into a mixture of water (10 mL) and 0.5 mol/L aqueous HCl solution (1 mL), the resulting mixture was extracted with pentane. The organic extracts were dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo (45 °C, 756 mmHg) to give crude *tert*-butyl *cis*-2-fluorocyclopropanecarboxylate (418 mg). To a solution of the crude ester (418 mg) in tetrahydrofuran (6 mL) was added a 10% aqueous HCl solution (1.5 mL), the mixture was heated under reflux for 6 h. After dilution of the mixture with ethyl acetate (10 mL) and water (10 mL), the mixture was extracted with ethyl acetate. The organic layer was extracted with saturated sodium hydrogen carbonate solution, and the aqueous layer was washed with ethyl acetate. The aqueous layer was adjusted to pH 5 by a 10% aqueous HCl solution, and the resulting mixture was extracted with ethyl acetate. The organic extracts were dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, hexane/ethyl acetate = 1:1) of the residue gave *dl*-**1** as colorless solid (185 mg, 78%). An analytic sample was obtained by trituration of the product with hexane. Mp: 71−72 °C (lit.[8] 73−74 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 1.14−1.30 (m, 1H), 1.74−1.91 (m, 2H), 4.80 (ddd, *J* = 6.1, 10.4, 12.2, 64.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 13.2, 19.5, 19.6, 70.9, 73.2, 174.6. IR (ATR): 1686, 1211 cm^{-1}. MS (ESI^-) *m/z*: 103 (MH^-). HRMS (ESI^-) for $C_4H_4FO_2$ (MH^-): calcd, 103.0195; found, 103.0198.

Anal. ($C_4H_5FO_2$) C, H, N. calcd: C, 46.16; H, 4.84. found: C, 46.50; H, 4.83.

*Synthesis of (S,S)-**1**. Step 1. (1S,2S)-((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)-2-fluorocyclopropanecarboxylate.* To a solution of (*S*,*R*)-**6c** (1.03 g, 2.69 mmol) in methanol (13.5 mL) was added magnesium powder (197 mg, 8.08 mmol) at 4 °C, the mixture was stirred at the same temperature for 1.5 h. The mixture was poured into 5% aqueous HCl solution (20 mL), the mixture was extracted with ether. The organic extracts were washed with saturated sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, hexane/ethyl acetate = 20:1) of the residue gave the product as colorless solid (571 mg, 87%). An analytic sample was obtained by trituration of the product with pentane. Mp: 44−46 °C. $[\alpha]_D^{25}$ = −42.6 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.77 (d, *J* = 7.3 Hz, 3H), 0.80−1.16 (m, 10H), 1.34−1.54 (m, 2H), 1.62−1.72 (m, 2H), 1.74−1.94 (m, 3H), 1.96−2.06 (m, 1H), 4.60−4.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.87, 11.97, 20.2, 20.3, 20.7, 22.0, 23.5, 26.3, 31.4, 34.2, 40.9, 47.1, 70.4, 72.7, 74.9, 167.94, 167.97. IR (ATR): 1724, 1179 cm^{-1}. MS (CI^+) *m/z*: 243 (MH^+). HRMS (CI^+) for $C_{14}H_{24}FO_2$ (MH^+): calcd, 243.1760; found, 243.1749. Anal. ($C_{14}H_{23}FO_2$) C, H, N. calcd: C, 69.39; H, 9.57. found: C, 69.19; H, 9.73.

*Step 2. (1S,2S)-2-Fluorocyclopropanecarbocxylic Acid (S,S)-**1**.*[3] To a solution of (1S,2S)-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-2-fluorocyclopropanecarboxylate (558 mg, 2.30mmol) in tetrahydrofuran and methanol (18 mL, 2:1) was added a solution of lithium hydroxide (1.10 g, 46.1 mmol) in water (6 mL) at 4 °C, the mixture was stirred at room temperature for 72 h. The mixture was concentrated in vacuo. After dilution of the residue with water (10 mL) and ether (10 mL), the mixture was extracted with ether. The aqueous layer was adjusted to pH 3 by 2 mol/L aqueous HCl solution and the resulting mixture was extracted with ethyl acetate. The organic extracts were dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, hexane:ethyl acetate = 1:1) of the residue gave (*S*,*S*)-**1** as colorless solid (217 mg, 90%). An analytic sample was obtained by trituration of the product

dx.doi.org/10.1021/jo501219n | J. Org. Chem. 2014, 79, 7226−7231

with pentane. Mp: 55−56 °C. $[\alpha]_D^{25}$ = +15.4 (*c* = 1.0, $CHCl_3$) [lit.[3] $[\alpha]_D$ = +21.6 (*c* = 1.1, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18−1.30 (m, 1H), 1.74−1.90 (m, 2H), 4.80 (dddd, *J* = 5.5, 10.4, 12.8, 68.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 13.2, 19.5, 19.6, 70.9, 73.2, 174.9. IR (ATR): 1723, 1425, 1185 cm^{-1}. MS (EI^+) *m*/*z*: 104 (M^+). HRMS (EI^+) for $C_4H_5FO_2$ (M^+): calcd, 104.0274; found, 104.0290. Anal. ($C_4H_5FO_2$) C, H, N. calcd: C, 46.16; H, 4.84. found: C, 46.25; H, 4.97. The optical purity of (*S*,*S*)-**1** prepared here was determined to be >99% ee by HPLC analysis with a chiral column [Daicel Chiralpak AD-H ϕ 0.46 cm × 25 cm, hexane/2-propanol/TFA = 95:5:0.1, flow rate 1.0 mL/min, t_R = 9.1 min (*S*,*S*)-**1** and 10.4 min (*R*,*R*)-**1**, detection at 230 nm].

*Synthesis of (R,R)-**1**. Step 1. (1R,2R)-((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)-2-fluorocyclopropanecarboxylate.* (1*R*,2*R*)-((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)-2-fluorocyclopropanecarboxylate (576 mg, 94%) was prepared from (*R*,*S*)-**6c** (972 mg, 2.54 mmol) in the same manner as described for step 1 of the synthesis of (*S*,*S*)-**1**. Colorless solid. Mp: 45−46 °C. $[\alpha]_D^{24}$ = −99.9 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (d, *J* = 7.3 Hz, 3H), 0.82−1.18 (m, 10H), 1.34−1.54 (m, 2H), 1.64−1.72 (m, 2H), 1.74−1.84 (m, 2H), 1.86−2.06 (m, 1H), 1.98−2.06, (m, 1H), 4.60−4.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 12.1, 16.2, 20.2, 20.3, 20.8, 22.0, 23.3, 26.0, 31.4, 34.2, 41.0, 47.0, 70.5, 72.8, 75.0, 168.02, 168.05. IR (ATR): 1727, 1169 cm^{-1}. MS (CI^+) *m*/*z*: 243 (MH^+). HRMS (CI^+) for $C_{14}H_{24}FO_2$ (MH^+): calcd, 243.1760; found, 243.1771. Anal. ($C_{14}H_{23}FO_2 \cdot 0.1\ H_2O$) C, H, N. calcd: C, 68.88; H, 9.58. found: C, 68.78; H, 9.43.

*Step 2. (1R,2R)-2-Fluorocyclopropanecarbocxylic Acid (R,R)-**1**.*[3] (1*R*,2*R*)-2-Fluorocyclopropanecarbocxylic acid (*R*,*R*)-**1** (224 mg, 92%) was prepared from (1*R*,2*R*)-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)-2-fluorocyclopropanecarboxylate (570 mg, 2.35 mmol) in the same manner as described for step 2 of the synthesis of (*S*,*S*)-**1**. Colorless solid. Mp: 55−56 °C. $[\alpha]_D^{25}$ = −14.3 ° (*c* = 1.0, $CHCl_3$) [lit.[3] $[\alpha]_D$ = −23.1 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR and IR spectra of this sample were identical to those of (*S*,*S*)-**1**. MS (CI^+) *m*/*z*: 104 (MH^+). HRMS (CI^+) for $C_4H_6FO_2$ (MH^+): calcd, 105.0352; found, 105.0365. Anal. ($C_4H_5FO_2$) C, H, N. calcd: C, 46.16; H, 4.84. found: C46.55; H, 4.80. The optical purity of (*R*,*R*)-**1** prepared here was determined to be >99% ee in the same manner as that described for (1*S*,2*S*)-**1**.

*Synthesis of (R,S)-**2**. Step 1. tert-Butyl N-[(1R,2S)-2-fluorocyclopropyl]carbamate.*[3,14,15] To a solution of (*S*,*S*)-**1** (104 mg, 1.00 mmol) in *tert*-butanol (2.6 mL) were added diphenyl phosphoryl azide (0.28 mL, 1.30 mmol) and triethylamine (0.17 mL, 1.20 mmol); the mixture was heated under reflux for 4 h. The mixture was concentrated in vacuo. After dilution of the residue with ethyl acetate, the mixture was washed with saturated ammonium chloride solution, saturated sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, hexane/ethyl acetate = 5:1) of the residue gave the product as colorless solid (114 mg, 65%). Mp: 74−75 °C (hexane). (lit.[3] Mp: 63 °C, lit.[14]: 77.5−78.5 °C). $[\alpha]_D^{24}$ = −69.4 (*c* = 0.84, $CHCl_3$) [lit.[3] $[\alpha]_D$ = −60.27 (*c* = 0.740, $CHCl_3$), lit.[14] $[\alpha]_D^{25}$= −66.5 (*c* = 0.84, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82−0.98 (m, 1H), 1.00−1.16 (m, 1H), 1.46 (s, 9H), 2.62 (brs, 1H), 4.60 (brd, *J* = 64.2 Hz, 1H), 4.80 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 13.2, 25.76, 25.80, 68.9, 71.1, 79.9, 156.5. IR (ATR): 1691, 1516, 1158 cm^{-1}. MS (CI^+) *m*/*z*: 176 (MH^+). HRMS (CI^+) for $C_8H_{15}FNO_2$ (MH^+): calcd, 176.1087; found, 176.1101. Anal. ($C_8H_{14}FNO_2 \cdot 0.35H_2O$) C, H, N. calcd: C, 52.94; H, 8.16; N, 7.72. found: C, 52.96; H, 7.85; N, 7.69.

*Step 2. (1R,2S)-2-Fluorocyclopropylammonium p-Toluenesulfonate (R,S)-**2**·TsOH.*[14,15] To a solution of *tert*-butyl *N*-[(1*R*,2*S*)-2-fluorocyclopropyl]carbamate (97.5 mg, 0.56 mmol) in acetonitrile (5 mL) was added *p*-toluenesulfonic acid (317.8 mg, 1.67 mmol); the mixture was stirred at room temperature for 24 h. The mixture was concentrated in vacuo. Treatment of the residue with ether/dichloromethane gave the product as colorless solid (112 mg, 81%). Mp: 169−170 °C (toluene/ethanol) (lit.[15] Mp: 168.5−170.5 C, lit.[16] Mp: 178−179 °C). $[\alpha]_D^{24}$ = −7.3 (*c* = 1.1, MeOH) [lit.[15] $[\alpha]_D^{20}$ = −8.9 ° (*c* = 0.699, MeOH), lit.[16] $[\alpha]_D^{20}$ = −10.7 (*c* = 1.08, MeOH)]. ^{1}H NMR (400 MHz, CD_3OD): δ 1.16−1.28 (m, 2H), 2.62−2.70 (m, 1H), 2.36, (s, 3H), 2.62−2.70 (m, 1H), 4.84 (dtd, *J* = 3.7, 5.5, 63.6 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.69 (d, *J* = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8, 10.9, 21.3, 25.35, 25.44, 68.2, 70.4, 126.9, 129.8, 141.7, 143.5. IR (ATR): 1616, 1545, 1124 cm^{-1}. MS (CI^+) *m*/*z*: 76 ($M-O_2SC_7H_7^+$). HRMS (CI^+) for C_3H_7FN ($M-O_2SC_7H_7^+$): calcd, 76.0563, found, 76.0563. Anal. ($C_3H_6FN \cdot C_7H_8O_3S$) C, H, N. calcd: C, 48.57; H, 5.71; N, 5.66. found: C, 48.58; H, 5.52; N, 5.60. According to the reported procedure,[4] the optical purity of (*R*,*S*)-**2**·TsOH prepared here was determined to be >99% ee by HPLC analysis of its 3,5-dinitrobenzamide. The analysis conditions for HPLC: chiral column [Daicel Chiralpak IA ϕ 0.46 cm × 25 cm, hexane/ethanol = 60:40, flow rate 1.0 mL/min, t_R = 10.4 min (*R*,*S*)-**2**·TsOH and 21.0 min (*S*,*R*)-**2**·TsOH. detection at 254 nm].

*Synthesis of (S,R)-**2**·TsOH. Step 1. tert-Butyl N-[(1S,2R)-2-Fluorocyclopropyl]carbamate.*[3] *tert*-Butyl *N*-[(1*S*,2*R*)-2-fluorocyclopropyl]-carbamate (72 mg, 53%) was prepared from (*R*,*R*)-**1** (80 mg, 0.77 mmol) in the same manner as that described for step 1 of the synthesis of (*S*,*R*)-**2**·TsOH. Colorless solid. Mp: 73−75 °C (lit.[3] Mp: 73 °C). $[\alpha]_D^{25}$ = +69.2 (*c* = 0.84, $CHCl_3$), [lit.[3] $[\alpha]_D$ = +65.57 (*c* = 0.610, $CHCl_3$)]. ^{1}H NMR, IR, and MS spectra of this sample were identical to those of *tert*-butyl *N*-[(1*R*,2*S*)-2-fluorocyclopropyl]carbamate. HRMS (CI^+) for $C_8H_{15}FNO_2$ (MH^+): calcd, 176.1087; found, 176.1116. Anal. ($C_8H_{14}FNO \cdot 0.25H_2O$) C, H, N. calcd: C, 53.47; H, 8.13; N, 7.79. found: C, 53.59; H, 8.03; N, 7.73.

*Step 2. (1S,2R)-2-Fluorocyclopropylammonium p-Toluenesulfonate (S,R)-**2**·TsOH.* (1*S*,2*R*)-2-Fluorocyclopropylammonium *p*-toluenesulfonate (*S*,*R*)-**2**·TsOH (50 mg, 89%) was prepared from *tert*-butyl *N*-[(1*S*,2*R*)-2-fluorocyclopropyl]carbamate (40 mg, 0.23 mmol) in the same manner as described for step 2 of the synthesis of (*R*,*S*)-**2**·TsOH. Colorless solid. Mp: 168−169 °C. $[\alpha]_D^{26}$ = +8.9 (*c* = 1.1, MeOH). ^{1}H NMR, IR, and MS spectra of this sample were identical to those of (*R*,*S*)-**2**·TsOH. HRMS (CI^+) for C_3H_7FN ($M-O_2SC_7H_7^+$): calcd, 76.0563; found, 76.0514. Anal. ($C_3H_6FN \cdot C_7H_8O_3S$) C, H, N. calcd: C, 48.57; H, 5.71; N, 5.66. found: C, 48.48; H, 5.54; N, 5.53. The optical purity of (*S*,*R*)-**2**·TsOH prepared here was determined to be >99% ee in the same manner as that described for (*R*,*S*)-**2**·TsOH.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds and NOE experiments of *trans*-**6a** and *cis*-**6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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