Novel Methods for the Facile Construction of 3,3-Disubstituted and 3,3-Spiro-2*H*,4*H*-benzo[*e*]1,2-thiazine-1,1-diones: Synthesis of (11*S*,12*R*,14*R*)-2-Fluoro-14-methyl-11-(methylethyl)spiro[4*H*-benzo[*e*]-1,2-thiazine-3,2′-cyclohexane]-1,1-dione, an Agent for the Electrophilic Asymmetric Fluorination of Aryl Ketone Enolates

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Novel methods for the facile construction of 3,3-disubstituted and 3,3-spiro 2*H*,4*H*-benzo[*e*][1,2]-thiazine-1,1-diones **8a**−**h** are described. *o*-Methyl lithiation of *N*-Boc-*o*-toluenesulfonamide **6** followed by reaction with a variety of ketones gave the corresponding carbinol sulfonamides **7a**−**g**, which underwent cyclization under acidic (methanesulfonic acid) or neutral (NaI/TMSCl/MeCN) conditions to afford the sultams **8a**−**h** in high yields. The chiral spiro sultams **8g**,**h** were subjected to $FClO_3$ fluorination to give the *N*-fluorosultams **11a**,**b**, respectively, which were tested for electrophilic asymmetric fluorination of aryl ketone enolates. As a result, the *N*-fluorosultam **11a** exhibited modest asymmetric inducing abilities with the highest ee, reaching 70% for enantioselective fluorination of the lithium enolate of 2-methyl-1-tetralone.

Introduction

The sulfonamide antibiotics hold the prestigious position of being the first synthetic compounds to have had general utility in human therapy.[1] These exciting developments spawned considerable interest in their use in veterinary practice and in the preparation of many hundreds of cyclic variants (i.e., sultams).[2] In recent years, sultam templates have also become one of the synthetic strategies for the development of novel electrophilic fluorinating agents. Representative examples include nonracemic *N*-fluoro-2,10-camphorsultams **1**[3] and **2**[4] and saccharin-based electrophilic fluorinating agents **3**[5] and **4**[6] (Figure 1). Recently, we reported a novel method for the synthesis of 3-monosubstituted 2*H*,3*H*,4*H*-benzo[*e*]1,2-thiazine-1,1-diones using *orthomethyl lithiation-cyclization* of *N*-acyl-*o*-toluenesulfonamides and proved that the *N*-fluorosultam **5** had some ability for the electrophilic fluorination of aryl ketone enolates.[7] As a part of our continuing research on the development of highly efficient enantioselective fluorinating agents,[8] we were interested in the 3,3-disubstituted 2*H*,4*H*-benzo-[*e*]1,2-thiazine-1,1-diones, especially those with a spiro

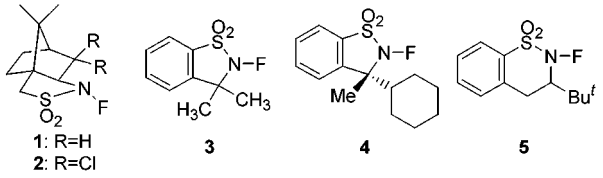

Figure 1.

structure at the 3 position. In this paper, we report novel methods for the construction of these kinds of sultams that led to the synthesis of (11*S*,12*R*,14*R*)-2-fluoro-14-methyl-11-(methylethyl)-spiro[4*H*-benzo[*e*]-1,2-thiazine-3,2′-cyclohexane]-1,1-dione, an agent for the electrophilic asymmetric fluorination of aryl ketone.

Results and Discussion

It is well documented that N-substituted *o*-toluenesulfonamides undergo metalation at the methyl group as well as the nitrogen atom.[7,9] Therefore, it is reasonable to expect that a properly N-protected *o*-toluenesulfonamide will react with ketones after *o*-methyl lithiation to generate tertiary alcohols, which might undergo cyclization to form our target compounds. However, there is only one reported example of *N*-methyl- or *N*-phenyl-substituted *o*-toluenesulfonamides which, when treated with excess butyllithium and reacted with benzophenone, gave carbinol sulfonamides. These were not very stable and

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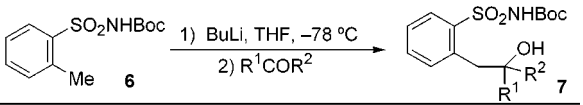
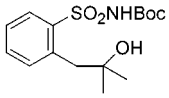
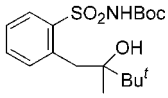
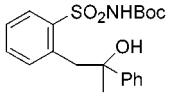
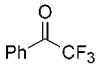
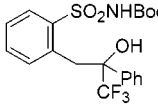
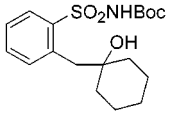
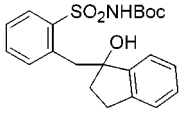
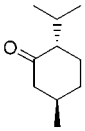
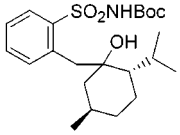
Table 1. Formation of the Carbinol Sulfonamides 7a−g via *o*-Methyl Lithiation of 6 Followed by Reaction with Ketones



entry	ketone	product		yield (%)
1			**7a**	77
2			**7b**	94
3			**7c**	96
4			**7d**	85
5			**7e**	84
6			**7f**	75
7			**7g**	95

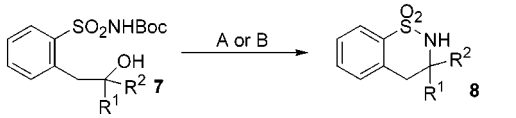
underwent thermal dehydration to afford unsaturated sulfonamides.[9a] Considering that the N-protective group should be easily removable, and inspired by the reports that *N*-Boc-*p*-toluenesulfonamide had shown significant utility as a Mitsunobu N-nucleophile,[10] we chose the readily available *N*-Boc-*o*-toluenesulfonamide **6** as our starting material. In fact, when **6** was treated with 2 equiv of BuLi at −78 °C, *o*-methyl lithiation occurred rapidly. The resulting anion reacted with a variety of ketones to give the corresponding carbinol sulfonamides **7a**−**g** in good yields (Table 1). In the case of *l*-menthone, only one isomer **7g** was isolated. The diastereoselectivity is probably due to the predominant preference for the equatorial attack of the hindered carbanion toward the menthone carbonyl. Thus, the *S* configuration is assumed for the newly created stereogenic center of **7g**.

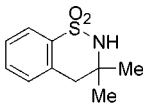
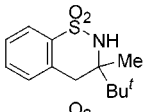
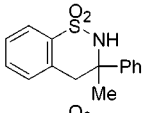
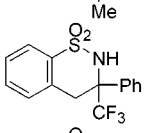
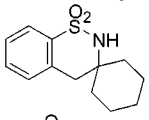
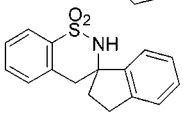
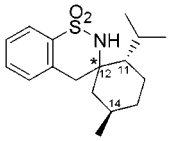
To obtain the sultam structure, we first examined the intramolecular cyclization of the carbinol sulfonamides **7** under Mitsunobu reaction conditions.[10a,11] However, this approach did not work at all, possibly owing to the bulkiness of the various tertiary alcohol groups. We then investigated the cyclization of **7a**−**f** under acidic conditions and found that methanesulfonic acid was effective and the corresponding sultams **8a**−**f** were obtained in high yields (Table 2, method A).

(10) (a) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709−5712. (b) Degerbeck, F.; Fransson, B.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans 1* **1992**, 245−253. (c) Campbell, J. A.; David, J. H. *J. Org. Chem.* **1993**, *58*, 2900−2903. (d) O'Brien, P.; Towers, T. D.; Voith, M. *Tetrahedron Lett.* **1998**, *39*, 8175−8178.

(11) For a review, see: Mitsunobu, O. *Synthesis* **1981**, 1−28.

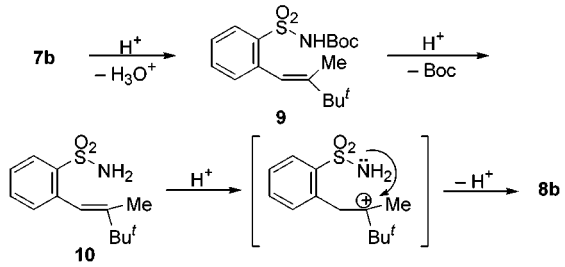
Table 2. Formation of the Sultams 8a−g by Cyclization of the Sulfonamides 7



entry	sulfonamide **7**	sultam **8**		yield (%) A[a]	yield (%) B[b]
1	**7a**		**8a**	94	96
2	**7b**		**8b**	90	93
3	**7c**		**8c**	92	99
4	**7d**		**8d**	89	94
5	**7e**		**8e**	90	95
6	**7f**		**8f**	93	98
7	**7g**		**8g**[c] **8h**[c]	35[d]	91[e]

[a] Method A: $MeSO_3H$, CH_2Cl_2, rt, 24 h. [b] Method B: TMSCl, NaI, MeCN, reflux, 1 h. [c] **8g**:(11*S*,12*R*,14*R*)-isomer. **8h**:(11*S*,12*S*,14*R*)-isomer. [d] **8g**:**8h** = 1:2.5. [e] **8g**:**8h** = 5.5:1.

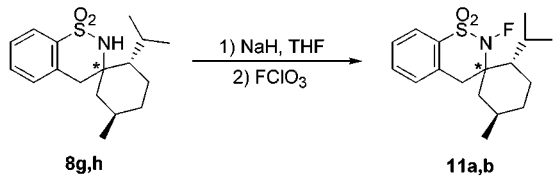
Scheme 1



A sequence of the consecutive N-deprotective cyclization process under acidic conditions is shown in Scheme 1, with the substrate **7b** as an example. When a solution of **7b** in CH_2Cl_2 was treated with 3 equiv of methanesulfonic acid at room temperature, dehydration occurred rapidly to form the unsaturated sulfonamide **9**, which slowly deprotected to give **10**. The intermediate **10** appears to undergo an acid-catalyzed addition process to produce the sultam **8b**. Both intermediates, **9** and **10**, could be isolated, and their structures were confirmed by spectral studies.

However, when this procedure was applied to **7g**, a mixture of two separable diastereomers, **8g** and **8h**, was obtained in only 35% yield, with a ratio of 1:2.5 (Table 2, entry 7, method A). The stereochemistry of the newly created spiro carbon was confirmed by X-ray crystal-

Scheme 2



lographic analysis of a crystalline descendant **11a**. The low yield in the case of **7g** may be due to steric hindrance by the neighboring isopropyl group in the cyclohexane ring and/or the rearrangement of the putative carbocation thus formed. Since the enantiopure sultams **8g**,**h** might be good templates for developing new electrophilic asymmetric fluorinating agents, we examined the reaction conditions for this cyclization.

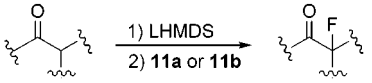
When the TMSCl/NaI/MeCN/reflux system was employed, the cyclization went smoothly to produce the sultams **8g**,**h** in 91% yield, with a ratio of 5.5:1 (Table 2, entry 7, method B). The reversed ratio of **8g** and **8h** can be explained from the mechanistic considerations. As shown in Scheme 1, partial racemization might occur in this acid-mediated cyclization process (Scheme 1), and the major product **8h** retains the *S* configuration of **7g** at the newly formed spiro carbon. In contrast, the TMSCl/NaI/MeCN mediated cyclization (method B) might proceed mainly via an S_N2 process, therefore the major products **8g** should have the reversed configuration of **7g**. The confirmed *R* configuration of the spiro carbon of **8g** also supports the assumed *S* configuration of **7g**.

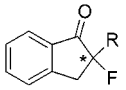
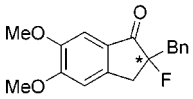
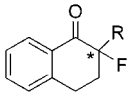
The TMSCl/NaI/MeCN system is well-known as a versatile reagent for reaction with many functional groups.[12] As far as we know, this is the first report of its use to effect a cyclization. In the same way, sultams **8a**−**f** were also obtained in almost quantitative yields (Table 2, method B). Finally, both **8g** and **8h** were separately treated with $FClO_3$[13] in the presence of NaH in THF to give the corresponding diastereomerically pure *N*-fluoro sultams **11a** [(11*S*,12*R*,14*R*)-isomer] and **11b** [(11*S*,12*S*,14*R*)-isomer] in 81% and 44% yields, respectively (Scheme 2).

Asymmetric enolate fluorinations were typically carried out at −50 °C by adding 1.2 equiv of **11a** or **11b** to the preformed enolates generated by treatment of 1.5 equiv of LHMDS with the corresponding ketones. The results are summarized in Table 3. For comparing the asymmetric inducing abilities of **11a** or **11b**, 2-methylindanone and 2-benzylindanone were tested as substrates. In both cases, **11a** gave much better ee's than **11b** (Table 3, entries 1−4). The highest asymmetric induction was observed for the fluorination of 2-methyl-1-tetralone with **11a**, affording the 2-fluoro-2-methyl-1-tetralone (**12e**) in 65% yield with an ee of 70%.

In summary, we have developed two novel methods for the preparation of 3,3-disubstituted and 3,3-spiro-2*H*,4*H*-benzo[*e*]1,2-thiazine-1,1-diones. The TMSCl/NaI/MeCN reagent system (method B) was used for the first time to cause a cyclization. This system gave better results than the method using methanesulfonic acid (method A). The success of this new method led us to synthesize (11*S*,12*R*,14*R*)-2-fluoro-14-methyl-11-(methylethyl)-spiro[4*H*-benzo[*e*]-1,2-thiazine-3,2′-cyclohexane]-1,1-dione (**11a**) for the electrophilic asymmetric fluorination of aryl ketone enolates. This agent exhibited modest asymmetric inducing abilities with the highest ee obtained being 70%. This is comparable to Differding's (**1**) and Davis's (**2**) agents.

Table 3. Asymmetric Fluorination of Aryl Ketone Enolates Using *N*-Fluorosultams 11



entry	*N*-F Sultam	Products	R		ee (%)	config.	isolated yield(%)
1	**11a**		Me	**12a**	40[a]	*S*[d]	76
2	**11b**		Me	**12b**	13[a]	*R*	69
3	**11a**		Bn	**12c**	54[a]	*S*	59
4	**11b**		Bn	**12d**	24[a]	*R*	42
5	**11a**		*p*-OMe-Bn	**12e**	51[b]	ND[e]	52
6	**11a**			**12f**	33[c]	ND[e]	61
7	**11a**		Me	**12g**	70[a]	*S*	65
8	**11a**		Bn	**12h**	56[b]	*S*	61

[a] Chiral OB column (10% *i*-PrOH/hexane). [b] Chiral OJ column (10% *i*-PrOH/hexane). [c] Chiral OJ column (EtOH). [d] References 4 and 6. [e] ND: not determined.

Experimental Section

General Methods. Melting points were determined on a micro-melting point apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on a 1600 FT-IR spectrometer. ^1H NMR (270 MHz) and ^{13}C NMR spectra (75.5 MHz) were recorded at room temperature for $CDCl_3$ solutions, unless otherwise stated. All chemical shifts are reported as δ values (ppm) relative to Me_4Si (0.00 ppm) and $CDCl_3$ (77.0 ppm) as internal standards for ^1H and ^{13}C NMR spectra, respectively. ^{19}F NMR spectra were measured with $CFCl_3$ as an internal standard and were taken with a 254 MHz spectrometer. Upfield shifts are quoted as negative δ values. Mass spectra were obtained by EI method. Column chromatography and preparative TLC were performed on BW-200 (Fuji Silysia) and Kieselgel 60 F-254 plates, respectively. All reactions involving oxygen- or moisture-sensitive compounds were carried out under a dry N_2 atmosphere. Unless otherwise noted, reagents were added by syringe. THF was distilled from sodium/benzophenone immediately prior to use.

Preparation of *N*-Boc-*o*-toluenesulfonamide 6.[14] *o*-Toluenesulfonamide (8.55 g, 50 mmol) was suspended in CH_2Cl_2 (60 mL) containing Et_3N (7.65 mL, 55 mmol) and DMAP (610 mg, 5 mmol). A solution of di-*tert*-butyl dicarbonate (12.5 g, 57.5 mmol) in CH_2Cl_2 (100 mL) was added dropwise with stirring over 10 min. After 4 h, the solution was concentrated in vacuo and the residue treated with EtOAc (300 mL) and 1 N HCl (200 mL). The EtOAc layer was washed successively with water and brine, dried ($MgSO_4$), and concentrated. Crystallization from hexane provided **6** as a white solid (12.57 g, 93%): mp 109−110 °C; IR (KBr) 3240, 1741, 1710, 1346, 1154, 758 cm^{-1}; ^1H NMR δ 1.34 (s, 9H), 2.67 (s, 3H), 7.35 (m, 2H), 7.44 (br s, 1H), 7.53 (td, J = 7.6, 1.5 Hz, 1H), 8.12 (dd, J = 7.6, 1.5 Hz, 1H); ^{13}C NMR δ 20.4, 28.0, 84.5, 126.1, 131.2, 132.5, 133.8, 136.9, 137.5, 149.7; MS *m*/*z* 271 (M^+), 256 (M^+ − Me); HRMS calcd for $C_{12}H_{17}NO_4S$ 271.0878, found 271.0902. Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16. Found: C, 53.23; H, 6.39; N, 5.13.

(12) For a review, see: Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225−2277.

(13) (a) Takeuchi, Y.; Nagata, K.; Koizume, T. *J. Org. Chem.* **1987**, *52*, 5061−5063. (b) Takeuchi, Y.; Nagata, K.; Koizume, T. *J. Org. Chem.* **1989**, *54*, 5453−5459. See also *J. Org. Chem.* **1988**, *53*, 4160.

(14) Neustadt, B. R. *Tetrahedron Lett.* **1994**, *35*, 379−380.

General Procedure for the Preparation of Carbinol Sulfonamides 7a−g. To a stirred solution of *N*-Boc *o*-toluenesulfonamide (1.09 g, 4 mmol) in THF (20 mL) was added a 1.53 M solution of BuLi in hexane (5.22 mL, 4 mmol) under nitrogen at −78 °C. The reaction mixture was stirred for 10 min and a solution of ketone (4 mmol) in 4 mL THF was added. After 1 h, saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc, the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (30% EtOAc in hexane) to give the carbinol sulfonamide **7** (Table 1).

7a: colorless oil; IR (neat) 3502, 3227, 1740, 1342, 1148, 758 cm^{-1}; ^1H NMR δ 1.31 (s, 6H), 1.35 (s, 9H), 3.30 (s, 2H), 7.42 (d, J = 7.3 Hz, 2H), 7.57 (td, J = 7.3, 1.5 Hz, 1H), 8.17 (m, 2H); ^{13}C NMR δ 28.1, 30.5, 45.2, 71.8, 84.2, 126.8, 131.5, 133.2, 133.9, 137.8, 138.2, 149.9; MS m/z 273 ($M^+ + H - t$-Bu); HRMS calcd for $C_{11}H_{15}NO_5S$ ($M^+ + H - t$-Bu) 273.0671, found 273.0663. Anal. Calcd for $C_{15}H_{23}NO_5S$: C, 54.69; H, 7.04; N, 4.25. Found: C, 54.54; H, 7.16; N, 4.19.

7b: colorless glass; IR ($CHCl_3$) 3420, 1732, 1339, 1161, 758 cm^{-1}; ^1H NMR δ 0.95 (s, 3H), 1.01 (s, 9H), 1.29 (s, 9H), 2.11 (s, 1H), 2.93, 3.68 (ABq, J = 14.2 Hz, 2H), 7.34 (m, 2H), 7.47 (m, 1H), 8.09 (s, 1H), 8.13 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ 21.5, 25.7, 28.1, 38.6, 39.2, 78.0, 84.1, 126.6, 131.4, 132.9, 134.7, 138.6, 138.7, 149.3; MS m/z 371 (M^+), 315 ($M^+ + H - t$-Bu); HRMS calcd for $C_{18}H_{29}NO_5S$ 371.1766, found 371.1763. Anal. Calcd for $C_{18}H_{29}NO_5S$: C, 58.20; H, 7.87; N, 3.77. Found: C, 58.17; H, 7.89; N, 3.59.

7c: colorless glasses; IR ($CHCl_3$) 3679, 3381, 1741, 1343, 1216, 757 cm^{-1}; ^1H NMR δ 1.34 (s, 9H), 1.64 (s, 3H), 3.12 (br s, 1H), 3.38, 3.69 (ABq, J = 14.1 Hz, 2H), 6.85 (m, 1H), 7.21−7.42 (m, 7H), 7.84 (br s, 1H), 8.13 (m, 1H). Anal. Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.37; H, 6.51; N, 3.49.

7d: colorless glasses; IR ($CHCl_3$) 3361, 1725, 1309, 1216, 758 cm^{-1}; ^1H NMR δ 1.34 (s, 9H), 3.50, 4.15 (ABq, J = 14.1 Hz, 2H), 4.83 (s, 1H), 6.40 (d, J = 7.8 Hz, 1H), 7.19 (td, J = 7.6, 1.5 Hz, 1H), 7.31−7.39 (m, 4H), 7.53 (m, 2H), 7.64 (br s, 1H), 8.12 (dd, J = 7.6, 1.5 Hz, 1H); ^{19}F NMR δ −74.9 (s). Anal. Calcd for $C_{20}H_{22}F_3NO_5S$: C, 53.93; H, 4.98; N, 3.14. Found: C, 53.85; H, 4.78; N, 3.06.

7e: colorless oil; IR (neat) 3506, 3219, 1739, 1341, 1149, 758 cm^{-1}; ^1H NMR δ 1.35 (s, 9H), 1.48−1.68 (m, 10H), 2.44 (br s, 1H), 3.27 (s, 2H), 7.40 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.44 (s, 1H); ^{13}C NMR δ 22.3, 25.9, 28.1, 31.2, 38.4, 72.3, 84.1, 126.7, 131.5, 133.0, 133.9, 137.4, 138.2, 149.3. Anal. Calcd for $C_{18}H_{27}NO_5S$: C, 58.51; H, 7.37; N, 3.79. Found: C, 58.65; H, 7.46; N, 3.62.

7f: colorless oil; IR (neat) 3487, 3222,1739, 1345, 1150, 759 cm^{-1}; ^1H NMR δ 1.36 (s, 9H), 2.06 (m, 1H), 2.44 (ddd, J = 11.2, 7.6, 3.9 Hz, 1H), 2.81−3.20 (m, 2H), 2.93 (br s, 1H), 3.52, 3.69 (ABq, J = 14.2 Hz, 2H), 7.03−7.18 (m, 3H), 7.25−7.27 (m, 3H), 7.38−7.48 (m, 2H), 8.20 (dd, J = 7.6, 1.8 Hz, 1H); ^{13}C NMR δ 28.1, 29.6, 41.3, 41.8, 84.1, 84.4, 123.5, 125.1, 126.6, 126.9, 128.6, 131.4, 133.0, 134.0, 137.2, 138.3, 142.6, 147.0, 149.3. Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.25; N, 3.47. Found: C, 62.61; H, 6.28; N, 3.43.

7g: colorless glass; $[\alpha]^{25}_D$ + 26.7 (c 0.99, $CHCl_3$); IR ($CHCl_3$) 3528, 3214, 1742, 1344, 1150, 758 cm^{-1}; ^1H NMR δ 0.78 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 7.1 Hz, 6H), 1.36 (s, 9H), 1.16−1.80 (m, 8H), 2.24 (br s, 1H), 2.37 (m, 1H), 2.76, 4.15 (ABq, J = 14.2 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.53 (t, J = 7.6 Hz, 1H), 8.19 (d, J = 7.6 Hz, 1H), 8.68 (s, 1H); ^{13}C NMR δ 18.5, 21.3, 22.7, 24.2, 25.9, 28.1, 35.1, 43.8, 46.5, 52.4, 76.3, 83.7, 126.7, 131.4, 132.8, 134.8, 137.8, 138.3, 149.4. Anal. Calcd for $C_{22}H_{35}NO_5S$: C, 62.09; H, 8.29; N, 3.29. Found: C, 61.96; H, 8.50; N, 3.18.

General Procedure for the Preparation of Sultams 8a−g. Method A. Methanesulfonic acid (0.39 mL, 6 mmol) was added to a stirred solution of **7** (2 mmol) in CH_2Cl_2 (10 mL) at room temperature. The reaction mixture was stirred for 24 h. CH_2Cl_2 (20 mL) was added, and the organic layer was washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (30% EtOAc in hexane) to give sultam **8** (Table 2).

Method B. To a stirred solution of **7** (2 mmol) in MeCN (10 mL) was added under nitrogen sodium iodide (0.93 g, 6.2 mmol) and chlorotrimethylsilane (0.76 mL, 6 mmol). The reaction mixture was refluxed for 1 h. It was cooled to room temperature, and 10% sodium thiosulfate aqueous solution was added. The mixture was extracted with EtOAc, and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (30% EtOAc in hexane) to give sultam **8** (Table 2).

3,3-Dimethyl-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (8a): colorless oil; IR (neat) 3262, 1318, 1216, 758 cm^{-1}; ^1H NMR δ 1.36 (s, 6H), 3.02 (s, 2H), 4.23 (s, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.41 (td, J = 7.6, 1.5 Hz, 1H), 7.49 (td, J = 7.6, 1.5 Hz, 1H), 7.80 (dd, J = 7.6, 1.5 Hz, 1H); ^{13}C NMR δ 30.3, 40.5, 56.4, 123.1, 127.6, 129.6, 132.3, 135.3, 138.3; MS m/z 211 (M^+), 196 ($M^+ - Me$); HRMS calcd for $C_{10}H_{13}NO_2S$ 211.0667, found 211.0657. Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.76; H, 6.34; N, 6.59.

3-*tert*-Butyl-3-methyl-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (8b): colorless prisms; mp 204−206 °C; IR (KBr) 3257, 1312, 1216, 756 cm^{-1}; ^1H NMR δ 1.04 (s, 3H), 1.07 (s, 9H), 2.70, 3.46 (ABq, J = 14.9 Hz, 2H), 3.88 (s, 1H), 7.31 (d, J = 7.3 Hz, 1H), 7.41 (td, J = 7.3, 1.5 Hz, 1H), 7.48 (td, J = 7.3, 1.5 Hz, 1H), 7.80 (dd, J = 7.3, 1.5 Hz, 1H); ^{13}C NMR δ 23.0, 25.7, 33.6, 38.0, 65.1, 122.3, 127.3, 130.0, 132.1, 136.5, 138.4; MS m/z 254 ($M^+ + 1$), 253 (M^+), 238 ($M^+ - Me$), 196 ($M^+ - t$-Bu); HRMS calcd for $C_{13}H_{19}NO_2S$ 253.1137, found 253.1129. Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.77; H, 7.60; N, 5.48.

3-Methyl-3-phenyl-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (8c): colorless glass; IR ($CHCl_3$) 3267, 1318, 1169, 757 cm^{-1}; ^1H NMR δ 1.58 (s, 3H), 3.22, 3.49 (ABq, J = 15.1 Hz, 2H), 4.50 (s, 1H), 7.29−7.58 (m, 8H), 7.85 (d, J = 7.1 Hz, 1H); ^{13}C NMR δ 29.4, 41.1, 61.5, 122.6, 125.2, 127.5, 127.7, 128.7, 129.6, 132.4, 135.1, 138.6, 145.9; MS m/z 274 ($M^+ + 1$), 273 (M^+), 258 ($M^+ - Me$); HRMS calcd for $C_{15}H_{15}NO_2S$ 273.0823, found 273.0815. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C, 65.89; H, 5.56; N, 5.09.

3-Phenyl-3-trifluoromethyl-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (8d): colorless prisms; mp 194−195 °C; IR (KBr) 3377, 3255, 1316, 1216, 758 cm^{-1}; ^1H NMR (CD_3OD) δ 3.80, 4.20 (ABq, J = 14.9 Hz, 2H), 6.74 (d, J = 7.6 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.31−7.36 (m, 3H), 7.55 (m, 2H), 7.96 (d, J = 7.8 Hz, 1H); ^{19}F NMR δ −78.98 (s); ^{13}C NMR (CD_3OD) δ 37.7, 102.0, 127.8, 128.0, 128.3, 128.8, 129.1, 132.1, 133.4, 134.0, 138.0, 144.0; MS m/z 345 ($M^+ + H_2O$), 327 (M^+), 258 ($M^+ - CF_3$); HRMS calcd for $C_{15}H_{12}F_3NO_2S$ 327.0541, found 327.0552. Anal. Calcd for $C_{15}H_{12}F_3NO_2S \cdot H_2O$: C, 52.16; H, 4.09; N, 4.06. Found: C, 51.94; H, 4.26; N, 4.01.

Spiro(2*H*,4*H*-benzo[*e*][1,2]thiazine-3,1′-cyclohexane) 1,1-dione (8e): colorless prisms; mp 154−155 °C; IR (KBr) 3258, 1323, 1216, 759 cm^{-1}; ^1H NMR δ 1.32 (m, 1H), 1.42−1.82 (m, 9H), 3.01 (s, 2H), 4.13 (s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.39 (td, J = 7.6, 1.5 Hz, 1H), 7.48 (td, J = 7.6, 1.5 Hz, 1H), 7.80 (dd, J = 7.3, 1.5 Hz, 1H); ^{13}C NMR δ 21.6, 25.4, 38.1, 40.0, 58.4, 123.1, 127.4, 129.7, 132.2, 135.0, 138.4; MS m/z 251 (M^+); HRMS calcd for $C_{13}H_{17}NO_2S$ 251.0980, found 253.0977. Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57. Found: C, 61.96; H, 6.91; N, 5.47.

Spiro(2*H*,4*H*-benzo[*e*][1,2]thiazine-3,1′-indane) 1,1-dione (8f): colorless needles; mp 124−126 °C; IR (KBr) 3247, 1315, 1169, 757 cm^{-1}; ^1H NMR δ 2.31 (m, 2H), 2.99 (m, 2H), 3.31 (s, 2H), 4.49 (s, 1H), 7.05 (d, J = 7.6 Hz, 1H), 7.15−7.32 (m, 4H), 7.48 (m, 2H), 7.88 (d, J = 7.3 Hz, 1H); ^{13}C NMR δ 29.5, 37.9, 41.1, 68.8, 122.8, 122.9, 125.2, 127.5, 127.6, 128.9, 129.4, 132.4, 135.4, 139.5, 142.2, 145.9; MS m/z 285 (M^+); HRMS calcd for $C_{16}H_{15}NO_2S$ 285.0823, found 285.0805. Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91. Found: C, 67.25; H, 5.38; N, 4.81.

(11*S*,12*R*,14*R*)-14-Methyl-11-(methylethyl)-spiro(2*H*,4*H*-benzo[*e*][1,2]thiazine-3,2′-cyclohexane) 1,1-dione (8g): colorless needles; mp 96 °C; $[\alpha]^{28}_D$ −44.7 (c 1.22, $CHCl_3$); IR (KBr) 3288, 1316, 1169, 757 cm^{-1}; ^1H NMR δ 0.82 (d, J = 6.6

Hz, 6H), 0.92 (d, J = 7.1 Hz, 3H), 0.81−1.00 (m, 2H), 1.14−1.35 (m, 2H), 1.59−1.82 (m, 4H), 2.62 (m, 1H), 2.65, 3.56 (ABq, J = 15.3 Hz, 2H), 4.12 (s, 1H), 7.29 (d, J = 7.3 Hz, 1H), 7.39 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.3 Hz, 1H), 7.79 (d, J = 7.3 Hz, 1H); ^{13}C NMR δ 18.0, 22.1, 22.3, 24.7, 26.1, 28.0, 34.9, 38.6, 48.8, 51.7, 62.2, 122.5, 127.1, 129.5, 132.2, 136.4, 138.5; MS m/z 307 (M^+), 292 (M^+ − Me); HRMS calcd for $C_{17}H_{25}NO_2S$ 307.1606, found 307.1618. Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.54; H, 8.40; N, 4.54.

(11*S*,12*S*,14*R*)-14-Methyl-11-(methylethyl)spiro(2*H*,4*H*-benzo[*e*][1,2]thiazine-3,2′-cyclohexane) 1,1-dione (8h): colorless needles; mp 145−147 °C; $[\alpha]^{28}_D$ −3.1 (*c* 0.30, $CHCl_3$); IR (KBr) 3353, 3271, 1308, 1168, 758 cm^{-1}; ^{1}H NMR δ 0.73−0.98 (m, 2H), 0.79 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 1.25−1.45 (m, 2H), 1.50−1.84 (m, 4H), 2.45 (m, 1H), 2.97, 3.39 (ABq, J = 14.9 Hz, 2H), 3.85 (s, 1H), 7.28 (d, J = 7.3 Hz, 1H), 7.41 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.3 Hz, 1H), 7.80 (d, J = 7.3 Hz, 1H); ^{13}C NMR δ 19.1, 22.4, 23.0, 24.7, 25.4, 29.6, 29.9, 35.0, 48.6, 52.6, 64.5, 122.4, 127.4, 129.4, 132.2, 135.6, 138.9; MS m/z 307 (M^+), 292 (M^+ − Me); HRMS calcd for $C_{17}H_{25}NO_2S$ 307.1606, found 307.1616. Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.51; H, 8.27; N, 4.63.

Intermediates 9,10. Methanesulfonic acid (0.08 mL, 1.2 mmol) was added to a stirred solution of **7b** (148 mg, 0.4 mmol) in CH_2Cl_2 (4 mL) at room temperature. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL). The organic layer was separated, washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative TLC (30% EtOAc in hexane) to give compounds **9** (109 mg, 77.2%) and **10** (16 mg, 15.8%) as a colorless oil, together with **8b** (6.1 mg, 6%) as colorless prisms.

9: IR ($CHCl_3$) 3404, 1744, 1151, 909, 826, 735 cm^{-1}; ^{1}H NMR δ 1.14 (s, 9H), 1.21 (s, 9H), 1.74 (d, J = 1.2 Hz, 3H), 4.37 (s, 1H), 6.81 (s, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.33 (td, J = 7.6, 1.5 Hz, 1H), 7.47 (td, J = 7.6, 1.5 Hz, 1H), 8.03 (dd, J = 7.6, 1.5 Hz, 1H); MS m/z 353 (M^+), 296 (M^+ − *t*-Bu); HRMS calcd for $C_{18}H_{27}NO_4S$ 353.1661, found 353.1682.

10: IR ($CHCl_3$) 3418, 1215, 909, 759 cm^{-1}; ^{1}H NMR δ 1.21 (s, 9H), 1.67 (d, J = 1.0 Hz, 3H), 4.65 (s, 2H), 6.80 (s, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.36 (td, J = 7.6, 1.5 Hz, 1H), 7.53 (td, J = 7.6, 1.5 Hz, 1H), 8.03 (dd, J = 7.6, 1.5 Hz, 1H); MS m/z 253 (M^+), 238 (M^+ − Me); HRMS calcd for $C_{13}H_{19}NO_2S$ 253.1136, found 253.1121.

(11*S*,12*R*,14*R*)-2-Fluoro-14-methyl-11-(methylethyl)-spiro(2*H*,4*H*-benzo[*e*][1,2]thiazine-3,2′-cyclohexane) 1,1-dione (11a). A solution of **8g** (1.8 g, 5.86 mmol) in THF (60 mL) was treated with NaH (60% dispersion in mineral oil, 470 mg, 11.72 mmol) under N_2 at 0 °C, and the mixture was stirred at room temperature for 1 h. To the solution was introduced diluted perchloryl fluoride [$FClO_3$, generated from $KClO_4$ (8.12 g, 58.60 mmol) and FSO_3H (17 mL, 586 mmol)] for 3 h. The reaction was quenched by saturated aqueous NH_4Cl, and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (20% EtOAc in hexane) to give **11a** (1.54 g, 81%) as colorless prisms: mp 114−116 °C; $[\alpha]^{28}_D$ −48.7 (*c* 0.47, $CHCl_3$); IR (KBr) 3027, 1363, 1184, 758 cm^{-1}; ^{1}H NMR δ 0.77 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 7.1 Hz, 3H), 0.76−1.15 (m, 2H), 1.32−1.41 (m, 1H), 1.61−1.78 (m, 2H), 1.82−1.96 (m, 2H), 2.12−2.25 (m, 2H), 2.45 (dd, J = 14.9, 1.2 Hz, 1H), 3.74 (d, J = 14.9 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H); ^{19}F NMR δ −52.9 (s); ^{13}C NMR δ 18.2 (18.3), 22.4, 22.8, 25.8, 26.3, 28.5, 35.6, 35.9 (36.0), 47.0 (47.2), 54.5, 73.5 (73.6), 126.6, 128.1, 129.9, 132.7, 133.6, 136.3; MS m/z 325 (M^+), 306 (M^+ − HF); HRMS calcd for $C_{17}H_{24}FNO_2S$ 325.1512, found 325.1536. Anal. Calcd for $C_{17}H_{24}FNO_2S$: C, 62.74; H, 7.43; N, 4.30. Found: C, 62.48; H, 7.71; N, 4.25.

(11*S*,12*S*,14*R*)-2-Fluoro-14-methyl-11-(methylethyl)-spiro(2*H*,4*H*-benzo[*e*][1,2]thiazine-3,2′-cyclohexane)1,1-Dione (11b). In the same way, **11b** was obtained from **8h** as colorless prisms (44%): mp 114−116 °C; $[\alpha]^{28}_D$ −4.6 (*c* 1.00, $CHCl_3$); IR (KBr) 3027, 1455, 1361, 1180, 757 cm^{-1}; ^{1}H NMR δ 0.79 (d, J = 6.1 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.01−1.16 (m, 1H), 1.32−1.54 (m, 4H), 1.70−1.85 (m, 3H), 2.46 (m, 1H), 3.14, 3.43 (ABq, J = 14.9 Hz, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H); ^{19}F NMR δ −75.5 (s); ^{13}C NMR δ 19.0, 22.6, 23.1, 24.8, 25.5, 29.2 (29.3), 30.9, 34.6, 38.8 (39.1), 49.5, 76.9, 125.7, 128.0, 129.4, 133.8, 134.7, 135.8; MS m/z 325 (M^+), 306 (M^+ − HF); HRMS calcd for $C_{17}H_{24}FNO_2S$ 325.1512, found 325.1521. Anal. Calcd for $C_{17}H_{24}FNO_2S$: C, 62.74; H, 7.43; N, 4.30. Found: C, 62.79; H, 7.47; N, 4.24.

General Procedure for Asymmetric Fluorination of Ketone Enolates with 11a and 11b. To a stirred solution of ketone (0.15 mmol) in THF (2.0 mL) was added a 1.0 M solution of LiHMDS in THF (0.225 mL, 0.225 mmol) under nitrogen atmosphere at −78 °C. The mixture was stirred for 10 min at −78 °C, warmed to 0 °C, stirred for an additional 1 h, and cooled to −40 °C. A solution of **11** (58.5 mg, 0.18 mmol) in THF (2 mL) was added to the reaction mixture. After the reaction was complete, as indicated by TLC, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl. EtOAc (10 mL) was added. The aqueous layer was extracted with EtOAc, the combined organic phases were washed with water and brine, dried ($MgSO_4$), and concentrated to give an oil that was purified by preparative TLC (Table 3).

(*S*)-2-Methyl-2-fluoro-1-indanone (12a): (76%) oil; 40% ee; $[\alpha]^{28}_D$ −21.6 (*c* 0.47, $CHCl_3$). Its spectral properties were in agreement with literature values.[4−6]

(*R*)-2-Methyl-2-fluoro-1-indanone (12b): (69%) oil; 13% ee; $[\alpha]^{28}_D$ +6.3 (*c* 0.51, $CHCl_3$). **12b** exhibited the same spectral properties (IR, MS, ^{1}H NMR, and ^{19}F NMR) as **12a**.

(*S*)-2-Benzyl-2-fluoro-1-indanone (12c): (59%) oil; 54% ee; $[\alpha]^{28}_D$ −57.5 (*c* 0.42, $CHCl_3$). Its spectral properties were in agreement with literature values.[4−6]

(*R*)-2-Benzyl-2-fluoro-1-indanone (12d): (42%) oil; 24% ee; $[\alpha]^{28}_D$ +27.2 (*c* 0.62, $CHCl_3$). **12d** exhibited the same spectral properties (IR, MS, ^{1}H NMR, and ^{19}F NMR) as **12c**.

(−)-2-*p*-Methoxybenzyl-2-fluoro-1-indanone (12e): (52%) oil; 51% ee; $[\alpha]^{28}_D$ −44.3 (*c* 0.41, $CHCl_3$); IR (neat) 3018, 1726, 1610, 1513, 1250, 917, 836, 757 cm^{-1}; ^{19}F NMR δ −154.8 (m); ^{1}H NMR δ 2.92 (dd, J = 29.7, 14.3 Hz, 1H), 3.15 (dd, J = 22.8, 17.3 Hz, 1H), 3.35 (m, 2H), 3.78 (s, 3H), 6.82 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 7.39 (dd, J = 13.2, 7.6 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H); MS m/z 271 (M^+ + 1), 270 (M^+), 250 (M^+ − HF); HRMS calcd for $C_{17}H_{15}FO_2$ 270.1056, found 270.1051.

(−)-5,6-Dimethoxy-2-benzyl-2-fluoro-1-indanone (12f): (61%) oil; 33% ee; $[\alpha]^{28}_D$ −33.8 (*c* 0.65, $CHCl_3$); IR (neat) 3021, 1710, 1593, 1501, 1283, 919, 866, 756 cm^{-1}; ^{1}H NMR δ 2.89 (dd, J = 29.8, 14.1 Hz, 1H), 2.98 (dd, J = 22.9, 17.5 Hz, 1H), 3.23 (dd, J = 17.5, 12.0 Hz, 1H), 3.33 (t, J = 13.5 Hz, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 6.68 (s, 1H), 7.13 (s,1H), 7.20 (m, 5H); ^{19}F NMR δ −153.5 (m); MS m/z 301 (M^+ + 1), 300 (M^+), 280 (M^+ − HF); HRMS calcd for $C_{18}H_{17}FO_3$ 300.1162, found 300.1174.

(*S*)-2-Fluoro-2-methyl-1-tetralone (12g): (65%) oil; 70% ee; $[\alpha]^{28}_D$ −15.1 (*c* 0.62, $CHCl_3$). Its spectral properties were in agreement with literature values.[4−6]

(*S*)-2-Benzyl-2-fluoro-1-tetralone (12h): (61%) oil; 56% ee; $[\alpha]^{28}_D$ −28.2 (*c* 0.49, $CHCl_3$). Its spectral properties were in agreement with literature values.[4−6]

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Supporting Information Available: ORTEP diagram of **11a**, its details of crystallographic information, and ^{1}H NMR spectra for compounds **9**, **10**, and **12a**,**c**,**e**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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