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HIGHLY EFFICIENT CONSTRUCTION OF CF_3-CONTAINING 3,3'-PYRROLIDINYL-DISPIROOXINDOLES *VIA* BASE-CATALYZED DIASTEREOSELECTIVE [3+2] ANNULATION

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Abstract – An efficient base-catalyzed diastereoselective [3+2] cyclization of isatin-derived azomethine ylides with methyleneindolinones was developed. The process enables efficient incorporation of CF_3 groups into highly functionalized 3,3'-pyrrolidinyl-dispirooxindoles bearing four contiguous chiral centers, including two adjacent spiro quaternary stereocenters, with high yields and diastereoselectivities.

INTRODUCTION

Spirooxindole is a privileged skeleton frequently existing in many natural products and bioactive compounds.[1] Among various spirocyclic oxindoles, the 3,3'-pyrrolidinyl-spirooxindoles[2] are one of the most valuable synthetic targets because of their remarkable biological and pharmacological activities, such as anticancer agents spirotryprostatin A,[3] strychnofoline,[4] and MI-219[5] (Figure 1, top). As a result, considerable efforts have been devoted to the construction of structurally diverse functionalized pyrrolidinyl-spirooxindoles.[6] Recently, 3,3'-pyrrolidinyl-dispirooxindoles such as A-C have been demonstrated to exhibit promising bioactivities, including anticancer, antifungal, and antimicrobial activities (Figure 1, bottom).[7] However, synthetic methods for these complex dispirooxindoles have less been studied, probably because of the challenges associated with the assembly of this structurally congested and rigid spiroarchitecture containing multiple contiguous stereogenic centers.[8-10]

On the other hand, it is well known that the incorporation of trifluoromethyl groups into bioactive molecules can bring positive effects, such as enhanced binding affinity, lipophilicity, metabolic stability, bioavailability and other properties.[11] Thus, great efforts have been devoted to the synthesis of functionalized molecules with CF_3-containing moieties.

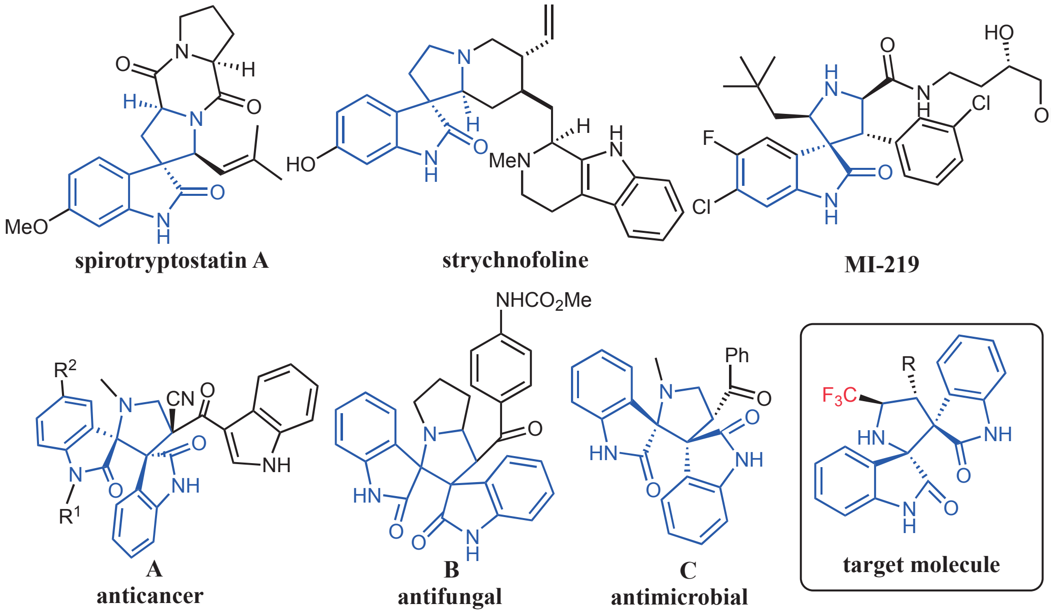


Figure 1. Representative examples of biologically active pyrrolidinyl-spirooxindole derivatives

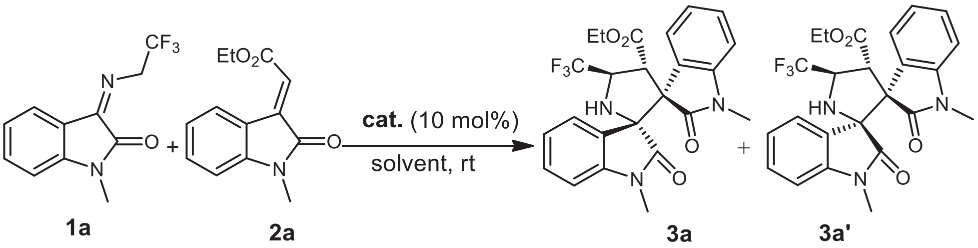
Given the importance of both the 3,3'-pyrrolidinyl-dispirooxindoles and CF_3-containing moieties, herein we report the incorporation of trifluoromethyl groups into 3,3'-pyrrolidinyl-dispirooxindoles via 1,3-dipolar cycloaddition reactions. As we know, the catalytic 1,3-dipolar [3+2] cycloaddition of azomethine ylide with activated alkenes has served as one of the most efficient ways to construct pyrrolidine skeleton.[12] Recently, Wang and coworkers developed a new kind of CF_3-containing azomethine ylides obtained from the condensation of trifluoroethylamine and isatins.[13] As a continuation of our research interest in construction of spirocyclic oxindoles, we envisioned that CF_3-containing dispirooxindole skeletons could be constructed by the 1,3-dipolar cycloaddition reactions between rationally designed isatin-derived CF_3-containing azomethine ylides with methyleneindolinones.[14]

RESULTS AND DISCUSSIONS

Initially, we examined the base-catalyzed reaction employing *N*-2,2,2-trifluoroethylisatin ketimine **1a** and methyleneindolinone **2a** as the substrates in dichloromethane at room temperature. In the presence of 10 mol% Et_3N, the desired 3,3'-pyrrolidinyl-dispirooxindoles **3a** was obtained in 96% yield, albeit with only 3:1 diastereomeric ratio (dr) (Table 1, entry 1). Encouraged by this, various bases (including DABCO, DIPEA, DBU, K_2CO_3 and Cs_2CO_3) were evaluated, and we found that Et_3N was the best choice of base

(Table 1, entries 2−6). Moreover, evaluation of different solvents (including toluene, THF, MeOH, $CHCl_3$ and DCE) indicated that $CHCl_3$ was the optimal solvent which can improve the diastereoselectivity to 4:1 (Table 1, entries 7−11). In addition, whether the catalyst loading was lowered to 5 mol% or increased to 20 mol%, the yield and diastereoselectivity of the product was not further improved, indicating that 10 mol% of Et_3N was the best choice (Table 1, entries 12−13).

Table 1. Optimization of the reaction conditions[a]

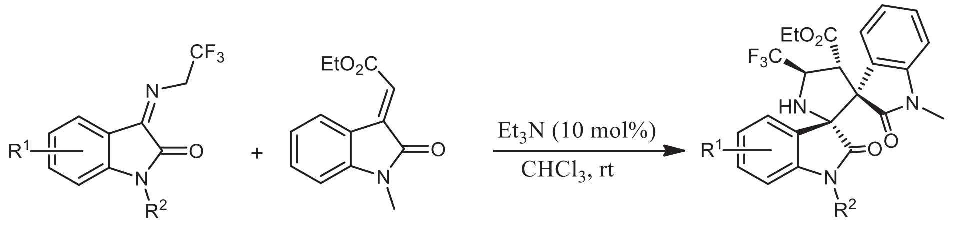


Entry	Cat.	Solvent	Time [h]	Yield [%][b]	*dr* (**3a**/**3a'**)[c]
1	Et_3N	CH_2Cl_2	3	96	3:1
2	DIPEA	CH_2Cl_2	5	89	2:1
3	DBU	CH_2Cl_2	4	93	2:1
4	DABCO	CH_2Cl_2	5	89	1:1
5	K_2CO_3	CH_2Cl_2	7	96	1:1
6	Cs_2CO_3	CH_2Cl_2	4	90	1:1
7	Et_3N	toluene	8	82	1:1
8	Et_3N	THF	3	87	1:1
9	Et_3N	MeOH	2	70	1:1
10	Et_3N	$CHCl_3$	3	98	4:1
11	Et_3N	DCE	3	95	2:1
12[d]	Et_3N	$CHCl_3$	3	96	3:1
13[e]	Et_3N	$CHCl_3$	5	85	2:1

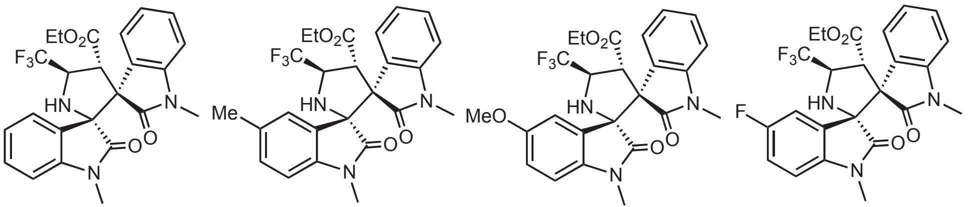
[a] Unless otherwise specified, all reactions were carried out with catalyst (10 mol%), **1a** (0.20 mmol) and **2a** (0.30 mmol) in the indicated solvent (2.0 mL) at room temperature. [b] Isolated yields of diastereomeric mixture. [c] Determined by ^1H NMR analysis of the crude products. [d] 5 mol% catalyst was used. [e] 20 mol% catalyst was used.

With the optimal conditions established in entry 10 of Table 1, we then examined the substrate scope. First, various ketimines **1** derived from different isatines were investigated. As shown in Table 2, the reaction showed excellent functional group tolerance, and a variety of 3,3'-pyrrolidinyl-dispirooxindoles **3a**−**3l** was obtained in high yields and diastereoselectivities. The ketimines bearing electron-donating and electron-withdrawing groups at the 5-position are well suitable substrates, leading to the selective synthesis of dispirooxindoles in high yields and diastereoselectivities (**3a**–**3g**). Besides, the position of the substituent had an obvious effect on the diastereoselectivity. For example, ketimine bearing the chloro group substituted at C-4 position was superior to the C-6 and C-7 substituted counterpart in diastereoselective control (**3h** vs **3i**–**j**). Moreover, the outcome of the reaction did not depend much on the protecting groups at the N1 position. The ketimine substrates with Bn-, Boc- groups or without protection on the nitrogen resulted in the corresponding products **3k**, **3l** and **3m** in high yields and diastereoselectivites.

Table 2. Substrate scope of ketimines **1**[a]



1 **2a** **3a-3m**

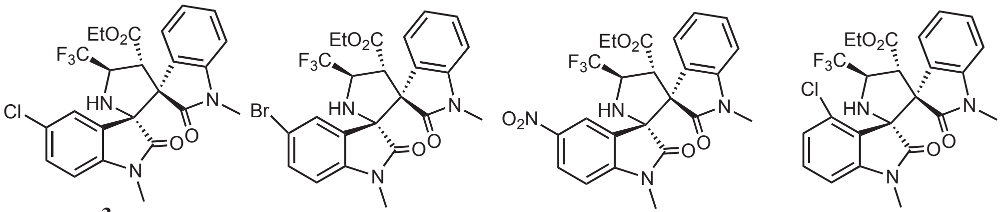


3a
3 h, 98% yield
4:1 *dr*

3b
2 h, 98% yield
3:1 *dr*

3c
3 h, 94% yield
4:1 *dr*

3d
3 h, 96% yield
3:1 *dr*

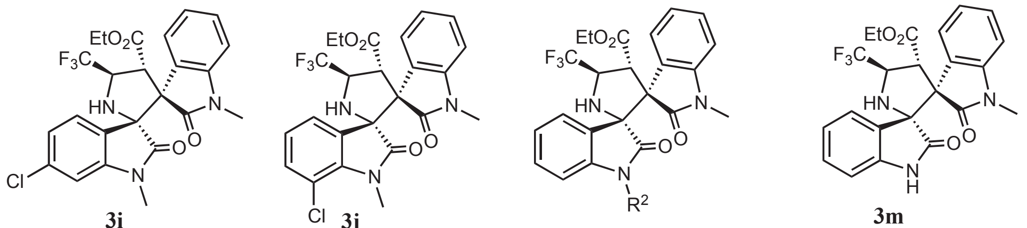


3e
3 h, 94% yield
3:1 *dr*

3f
2 h, 96% yield
4:1 *dr*

3g
5 h, 89% yield
15:1 *dr*

3h
5 h, 95% yield
18:1 *dr*



3i
3 h, 96% yield
3:1 *dr*

3j
3 h, 95% yield
3:1 *dr*

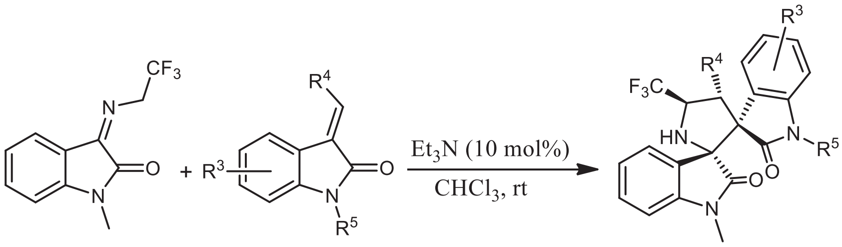
3k: R^2 = Bn, 3 h, 90% yield, 5:1 *dr*
3l: R^2 = Boc, 12 h, 88% yield, 4:1 *dr*

3m
3 h, 90% yield
4:1 *dr*

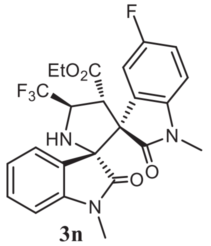
[a] Unless otherwise specified, all reactions were carried out with catalyst (10 mol%), **1a** (0.20 mmol) and **2a** (0.30 mmol) in the indicated solvent (2.0 mL) at room temperature. [b] Isolated yields of diastereomeric mixture. [c] Determined by ^{1}H NMR analysis of the crude products. [d] 5 mol% catalyst was used. [e] 20 mol% catalyst was used.

We next investigated the reaction of ketimine **1a** with various methyleneindolinones. As shown in Table 3, the methyleneindolinones **2** with electron-withdrawing group (F-, Cl-, Br- and -NO_2) or electron-donating substituents (Me- and MeO-) on the indolinone backbone underwent the reaction efficiently, giving high yields (86−98%) and good diastereoselectivities (3:1−4:1 dr). Besides, we examined the effect of the substituents at the N1-position of methyleneindolinone **2**. The substrate bearing

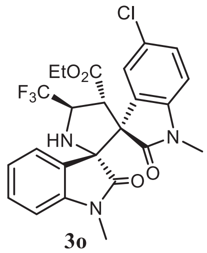
Table 3. Substrate scope of methyleneindolinones **2**[a]



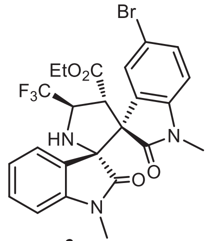
1a **2** **3n-3z**



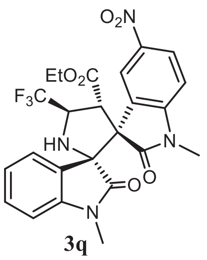
3n
3 h, 95% yield
3:1 *dr*



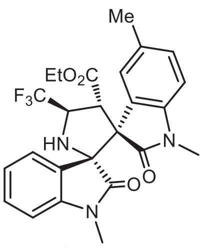
3o
2 h, 94% yield
3:1 *dr*



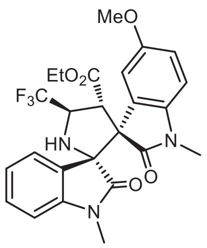
3p
3 h, 95% yield
3:1 *dr*



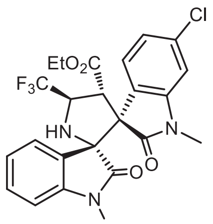
3q
10 h, 86% yield
3:1 *dr*



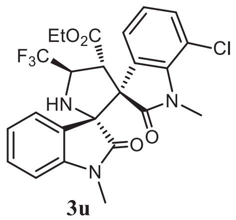
3r
5 h, 98% yield
4:1 *dr*



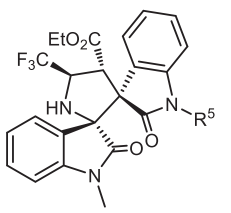
3s
3 h, 96% yield
3:1 *dr*



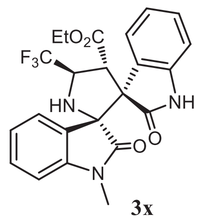
3t
5 h, 96% yield
4:1 *dr*



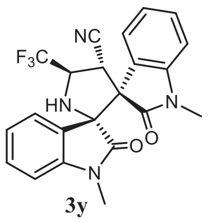
3u
3 h, 98% yield
3:1 *dr*



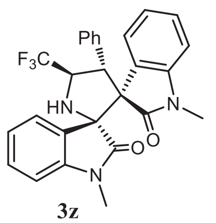
3v: R^5 = Bn, 4 h, 93% yield, 8:1 *dr*
3w: R^5 = Boc, 3 h, 94% yield, 6:1 *dr*



3x
3 h, 98% yield
3:1 *dr*



3y
4 h, 90% yield
10:1 *dr*



3z
N.R.[b]

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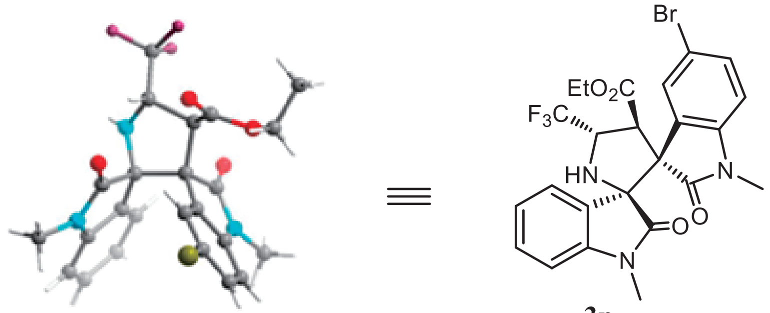
[a] Reaction conditions: all reactions were carried out with catalyst (10 mol%), **1a** (0.20 mmol) and **2** (0.30 mmol) in $CHCl_3$ (2.0 mL) at room temperature. The isolated yields of diastereomeric mixture were determined after column chromatography. The dr value was determined by ^1H NMR analysis of the crude product. [b] No reaction occurred.

N-Bn and N-Boc resulted in the corresponding products **3v** and **3w** respectively in high yields and diastereoselectivites. In contrast, the substrate without protecting group on the nitrogen resulted in the corresponding products **3x** in moderate diastereoselectivity. In addition, the cyano-substituted methyleneindoliones was also tolerant in the catalytic system to afford the cycloadduct **3y** in 90% yield with 10:1 dr. However, no desired product **3z** was obtained when the phenyl-substituted methyleneindolinone served as substrates, due to its relatively lower reactivity.

To determine the relative configuration of the products, a single crystal of compound **3p** was obtained for X-ray crystallographic analysis (Figure 2).[15] The relative configurations of other products were determined by analogy to **3p**.



3p

Figure 2. X-Ray crystal structure of compound **3p**

In conclusion, we have developed an efficient base-catalyzed diastereoselective [3+2] cyclization reaction of isatin-derived azomethine ylides with methyleneindolinones. The process enables efficient incorporation of CF_3 groups into highly functionalized 3,3'-pyrrolidinyl-dispirooxindoles bearing four contiguous chiral centers, including two adjacent spiro quaternary stereocenters, with high yields and moderate diastereoselectivities. We expect that this method would be of great importance for the drug discovery in terms of the structure diversity of CF_3-containing 3,3'-pyrrolidinyl-dispirooxindoles.

EXPERIMENTAL

General Methods for Procedure of Synthesis

All reactions were carried out in oven dry reaction vessel unless otherwise noted and solvents were dried according to established procedures. Reactions were monitored by thin layer chromatography (TLC). Purification of reaction products was carried out by flash chromatography using Qing Dao Sea Chemical Reagent silica gel (200-300 mesh). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker 400MHz spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm, δ) downfield from the internal standard Me_4Si (TMS, δ = 0 ppm). Chemical shifts in

^{13}C NMR spectra are reported relative to the central line of the chloroform signal (δ = 77.0 ppm). Data are presented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, cm = complex multiplet) and coupling constant in Hertz (Hz). High resolution mass spectra were obtained with a Shimadzu LCMS-IT-TOF mass spectrometer.

General Procedure for Syntheses of the *N*-(2,2,2-Trifluoroethyl) Isatin-derived Imines

Isatin (10 mmol), 2,2,2-trifluoroethylamine hydrochloride (15 mmol) and *p*-toluenesulfonic acid (0.5 mmol) were suspended in toluene (10 mL) in a two-neck flask with a water separator and a condenser. The mixture was then heated to separate the water until complete disappearance of the starting materials. After cooling to room temperature, the mixture was washed with a small quantity of saturated $NaHCO_3$ solution and dried by Na_2SO_4, After evaporation of the organic solvent, the crude residue was purified by flash chromatography (silica gel, hexane/EtOAc) and afforded the resulting ketimine.

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with ketimine (1.60 g, 7.01 mmol), DMAP (122.2 mg, 10 mol%) and MeCN (30 mL) was added via syringe. To the mixture was then added a solution of $(Boc)_2O$ (1.84 g, 8.41 mmol) in MeCN (10 mL) dropwise via syringe over 30 min, and the reaction was allowed to stir at room temperature for 18 h. The solvent was then removed in vacuo and the residue obtained was purified by flash column chromatography, eluting from 100% hexanes to 20% EtOAc in hexanes, to give the product as a yellow solid.

General Procedure for the Synthesis of 3a

To a stirred solution of **1a** (0.2 mmol) and **2a** (0.3 mmol) in $CHCl_3$ (2.0 mL) was added catalyst Et_3N (10 mol%) at room temperature. After the reaction was completed (monitored by TLC), the solution was concentrated under reduced pressure and the residue was subjected to column chromatography (eluted with hexane/EtOAc) to afford the desired product **3a** in 98% yield as a yellow solid; Mp 165.3-166.2 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 (d, J = 7.5 Hz, 1H), 7.25–7.13 (m, 3H), 7.01–6.87 (m, 2H), 6.59 (d, J = 7.7 Hz, 1H), 6.52 (d, J = 7.7 Hz, 1H), 5.69 (dd, J = 16.6, 8.1 Hz, 1H), 3.95 (td, J = 14.1, 7.0 Hz, 1H), 3.89–3.77 (m, 2H), 3.25 (d, J = 10.3 Hz, 1H), 3.01 (s, 3H), 2.89 (s, 3H), 0.80 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.57, 175.20, 168.52, 144.24, 130.68, 129.61, 126.03, 125.55 (q, J_C = 279.2 Hz), 123.78, 122.90, 122.64, 108.30, 74.91, 61.84, 61.34 (q, J_{CF} = 30.3 Hz), 52.12, 26.46, 25.87, 13.90; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.71 (s); HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{23}F_3N_3O_4]^+$: 474.1635, found: 474.1643.

Compound 3b: The product **3b** was obtained in 98% yield as a yellow solid; Mp 181.6-182.5 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (s, 1H), 7.23–7.14 (m, 2H), 6.99 (d, J = 7.8 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 6.58 (d, J = 7.8 Hz, 1H), 6.39 (d, J = 7.9 Hz, 1H), 5.75–5.63 (m, 1H), 3.94 (ddd, J = 14.3, 8.9, 5.4 Hz, 1H), 3.87–3.77 (m, 2H), 3.20 (d, J = 10.5 Hz, 1H), 3.01 (s, 3H), 2.86 (s, 3H), 2.27 (s, 3H), 0.80 (t, J =

7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 177.60, 175.12, 168.55, 144.11, 141.86, 132.52, 130.82, 129.53, 125.58 (q, J_{CF} = 279.0 Hz), 123.72, 122.58, 108.27, 107.96, 74.98, 61.80, 61.29 (q, J_{CF} = 30.4 Hz), 51.90, 26.36, 25.85, 21.26, 13.89; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –73.71; HRMS (ESI): *m/z* [M+H]$^+$ calcd. for [$C_{25}H_{25}F_3N_3O_4$]$^+$: 488.1792, found: 488.1802.

Compound 3c: The product **3c** was obtained in 94% yield as a yellow solid; Mp 185.5-186.9 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.25–7.13 (m, 3H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.73 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 6.42 (d, *J* = 8.5 Hz, 1H), 5.69 (dd, *J* = 17.1, 7.9 Hz, 1H), 3.92 (d, *J* = 7.2 Hz, 1H), 3.83 (dd, *J* = 12.6, 6.0 Hz, 2H), 3.76 (s, 3H), 3.26–3.18 (m, 1H), 3.04 (s, 3H), 2.87 (s, 3H), 0.80 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 177.58, 174.98, 168.47, 156.28, 144.14, 137.66, 129.60, 126.16, 125.57 (q, J_C = 279.1 Hz), 123.82, 122.69, 116.10, 112.02, 108.80, 108.30, 75.04, 61.81, 61.30 (q, J_{CF} = 30.4 Hz), 61.26, 56.32, 52.15, 26.52, 25.96, 13.91; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –73.70; HRMS (ESI): *m/z* [M+H]$^+$ calcd. for [$C_{25}H_{25}F_3N_3O_5$]$^+$: 504.1741, found: 504.1746.

Compound 3d: The product **3d** was obtained in 96% yield as a white solid; Mp 200.7-201.9 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.31 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.21 (dd, *J* = 12.7, 7.7 Hz, 2H), 6.92 (ddd, *J* = 11.2, 8.0, 2.8 Hz, 2H), 6.63 (d, *J* = 7.8 Hz, 1H), 6.46 (dd, *J* = 8.5, 4.1 Hz, 1H), 5.65 (d, *J* = 8.5 Hz, 1H), 3.93 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.87–3.75 (m, 2H), 3.19 (d, *J* = 10.2 Hz, 1H), 3.05 (s, 3H), 2.89 (s, 3H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 177.16, 175.04, 168.29, 160.50, 158.10, 144.10 (d, J_{CF} = 1.9 Hz), 140.25, 129.80, 125.57 (q, J_{CF} = 279.1 Hz), 123.51 (d, J_{CF} = 7.8 Hz), 122.76, 116.81 (d, J_{CF} = 23.4 Hz), 113.79, 108.79 (d, J_{CF} = 26.3 Hz), 108.43 (d, J_{CF} = 7.8 Hz), 74.61, 61.67, 61.40, 61.00 (q, J_{CF} = 30.5 Hz), 60.75, 52.03 (d, J_{CF} = 1.5 Hz), 26.55, 26.04 (d, J_{CF} = 8.2 Hz), 13.85; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –73.81, –119.59; HRMS (ESI): *m/z* [M+H]$^+$ calcd. for [$C_{24}H_{22}F_4N_3O_4$]$^+$: 492.1541, found: 492.1544.

Compound 3e: The product **3e** was obtained in 94% yield as a white solid; Mp 200.3-201.5 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.52 (d, *J* = 2.0 Hz, 1H), 7.22–7.15 (m, 3H), 6.92 (t, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 8.3 Hz, 1H), 5.72–5.58 (m, 1H), 3.94 (ddd, *J* = 14.3, 8.9, 5.4 Hz, 1H), 3.89–3.76 (m, 2H), 3.19 (d, *J* = 10.1 Hz, 1H), 3.05 (s, 3H), 2.88 (s, 3H), 0.80 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 177.13, 174.83, 168.28, 144.03, 142.78, 130.54, 129.81, 128.43, 125.94, 125.41 (q, J_C = 279.0 Hz), 123.36, 122.70, 109.21, 108.46, 74.54, 61.65, 61.35 (q, J_{CF} = 30.3 Hz), 60.74, 51.72, 26.45, 25.96, 13.82; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –73.79; HRMS (ESI): *m/z* [M+H]$^+$ calcd. for [$C_{24}H_{22}ClF_3N_3O_4$]$^+$: 508.1245, found: 508.1239.

Compound 3f: The product **3f** was obtained in 96% yield as a white solid; Mp 218.8-220.1 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.64 (d, *J* = 1.8 Hz, 1H), 7.33 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 2H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 6.40 (d, *J* = 8.3 Hz, 1H), 5.72–5.60 (m, 1H), 3.95 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.89–3.76 (m, 2H), 3.18 (d, *J* = 10.1 Hz, 1H), 3.06 (s, 3H), 2.87 (s, 3H), 0.80 (t, *J* =

7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 177.20, 174.75, 168.35, 144.08, 143.31, 133.51, 129.82, 128.72, 125.98, 125.43 (q, J_{CF} = 279.1 Hz), 123.41, 122.73, 115.63, 109.70, 108.49, 74.58, 61.72, 61.44, 61.13, 60.97 (q, J_{CF} = 30.7 Hz), 51.69, 26.50, 25.99, 13.89; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –73.78; HRMS (ESI): *m/z* [M+Na]$^+$ calcd. for [$C_{24}H_{21}BrF_3N_3NaO_4$]$^+$: 574.0560, found: 574.0559.

Compound 3g: The product **3g** was obtained in 89% yield as a yellow solid; Mp 222.4-222.9 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.43 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 7.25–7.16 (m, 2H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.69–6.61 (m, 2H), 5.59 (d, *J* = 7.3 Hz, 1H), 3.99–3.87 (m, 2H), 3.80 (dd, *J* = 10.7, 7.2 Hz, 1H), 3.33 (d, *J* = 10.2 Hz, 1H), 3.03 (s, 3H), 2.98 (s, 3H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 176.56, 175.32, 168.05, 149.71, 144.00, 143.74, 130.15, 127.60, 126.03, 125.31 (q, J_{CF} = 279.1 Hz), 123.00, 121.82, 108.73, 108.11, 73.98, 61.56, 61.29 (q, J_{CF} = 30.8 Hz), 52.01, 26.56, 13.85; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –73.72; HRMS (ESI): *m/z* [M+H]$^+$ calcd. for [$C_{24}H_{22}F_3N_4O_6$]$^+$: 519.1486, found: 519.1485.

Compound 3h: The product **3h** was obtained in 95% yield as a yellow solid; Mp 177.9-178.8 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.29 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.97 (dd, *J* = 7.9, 4.8 Hz, 2H), 6.62 (d, *J* = 7.8 Hz, 1H), 6.42 (d, *J* = 7.7 Hz, 1H), 5.30 (d, *J* = 6.1 Hz, 1H), 4.25 (d, *J* = 10.2 Hz, 1H), 3.81–3.70 (m, 2H), 3.44 (d, *J* = 9.4 Hz, 1H), 2.91 (s, 3H), 2.66 (s, 3H), 0.71 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 176.88, 174.94, 167.68, 144.97, 143.84, 133.47, 130.98, 129.75, 127.31, 125.33 (q, J_{CF} = 279.0 Hz), 124.60, 123.45, 121.80, 107.64, 106.52, 64.21, 62.79, 62.48 (q, J_{CF} = 30.8 Hz), 62.18, 61.16, 52.34, 26.66, 26.28, 13.66; ^{19}F NMR (376 MHz,CDCl$_3$) δ: –72.91; HRMS (ESI): *m/z* [M+H]$^+$ calcd. for [$C_{24}H_{22}ClF_3N_3O_4$]$^+$: 508.1245, found: 508.1237.

Compound 3i: The product **3i** was obtained in 96% yield as a white solid; Mp 205.1-205.8 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.41 (d, *J* = 8.2 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 2H), 6.93 (t, *J* = 7.8 Hz, 2H), 6.63 (d, *J* = 7.9 Hz, 1H), 6.53 (s, 1H), 5.64 (d, *J* = 7.5 Hz, 1H), 3.98–3.88 (m, 1H), 3.80 (ddd, *J* = 14.3, 12.7, 7.7 Hz, 2H), 3.18 (d, *J* = 10.2 Hz, 1H), 3.03 (s, 3H), 2.87 (s, 3H), 0.78 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 177.34, 175.26, 168.36, 145.58, 144.14, 136.69, 129.84, 126.68, 125.45 (q, J_{CF} = 279.3 Hz), 123.58, 122.80, 122.33, 109.11, 108.54, 74.43, 61.69, 61.32 (q, J_{CF} = 30.4 Hz), 52.10, 30.03, 26.58, 26.05, 13.90; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –73.81; HRMS (ESI): *m/z* [M+H]$^+$ calcd. for [$C_{24}H_{22}ClF_3N_3O_4$]$^+$: 508.1245, found: 508.1234.

Compound 3j: The product **3j** was obtained in 95% yield as a yellow solid; Mp 156.4-157.5 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.43 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 12.2, 7.8 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 7.9 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 5.64 (d, *J* = 7.2 Hz, 1H), 3.98–3.90 (m, 1H), 3.89–3.75 (m, 2H), 3.25 (s, 3H), 3.12 (d, *J* = 9.9 Hz, 1H), 3.00 (s, 3H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 177.09, 175.80, 168.36, 144.08, 140.16, 133.01, 129.90, 126.93, 126.10, 125.48 (q, J_{CF} = 279.1 Hz), 123.55, 122.79, 115.52, 108.50, 74.22, 62.03, 61.42, 60.93 (q, J_{CF} =

30.8 Hz), 51.90, 29.36, 26.55, 13.90; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.89; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{22}ClF_3N_3O_4]^+$: 508.1245, found: 508.1236.

Compound 3k: The product **3k** was obtained in 90% yield as a white solid; Mp 170.6-171.9 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 7.6 Hz, 1H), 7.28–7.07 (m, 6H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 7.2 Hz, 2H), 6.66 (d, *J* = 7.8 Hz, 1H), 6.36 (d, *J* = 7.8 Hz, 1H), 5.67 (dd, *J* = 16.4, 9.1 Hz, 1H), 5.00 (t, *J* = 13.0 Hz, 1H), 4.33 (d, *J* = 16.0 Hz, 1H), 3.98–3.88 (m, 2H), 3.81 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.24 (d, *J* = 10.4 Hz, 1H), 3.02 (s, 3H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.51, 175.28, 168.49, 144.32, 143.71, 135.12, 130.65, 129.56, 128.92, 127.69, 127.15, 126.77, 125.35 (q, J_{CF} = 279.1 Hz), 124.11, 123.09, 74.84, 62.48 (q, J_{CF} = 30.6 Hz), 61.38, 61.10, 52.43, 43.77, 26.58, 13.90; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.74; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{30}H_{27}F_3N_3O_4]^+$: 550.1948, found: 550.1950.

Compound 3l: The product **3l** was obtained in 88% yield as a yellow solid; Mp 215.6-216.4 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.30 (td, *J* = 7.8, 0.9 Hz, 1H), 7.18–7.12 (m, 2H), 6.71–6.61 (m, 3H), 5.04–4.77 (m, 2H), 3.81 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.68 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.98 (s, 3H), 2.71 (d, *J* = 5.3 Hz, 1H), 1.66 (s, 9H), 0.69 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.38, 171.56, 167.85, 149.53, 144.26, 140.44, 130.61, 130.35, 127.05, 126.04, 125.21 (q, J_{CF} = 279.2 Hz), 124.69, 124.25, 123.53, 122.97, 122.52, 115.06, 108.63, 84.59, 72.56, 64.10, 61.35, 60.81, 60.66, 60.33 (q, J_{CF} = 30.6 Hz), 49.95, 28.47, 26.84, 13.85; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –71.10; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{28}H_{29}F_3N_3O_6]^+$: 560.2003, found: 560.1993.

Compound 3m: The product **3m** was obtained in 90% yield as a yellow solid; Mp 136.5-137.3 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.25–7.10 (m, 3H), 6.92 (dt, *J* = 21.0, 7.7 Hz, 2H), 6.66–6.59 (m, 2H), 5.59 (d, *J* = 7.2 Hz, 1H), 3.90 (ddd, *J* = 10.9, 9.7, 5.6 Hz, 2H), 3.77 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.20 (d, *J* = 10.2 Hz, 1H), 3.02 (s, 3H), 0.76 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.36, 168.55, 144.20, 141.45, 130.67, 129.73, 125.50 (q, J_{CF} = 279.8 Hz), 124.54, 123.74, 122.95, 110.23, 108.38, 75.05, 61.79, 61.37, 61.19 (q, J_{CF} = 30.5 Hz), 52.18, 30.02, 26.57, 13.88; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.80; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{23}H_{21}F_3N_3O_4]^+$: 460.1479, found: 460.1487.

Compound 3n: The product **3n** was obtained in 95% yield as a yellow solid; Mp 176.6-177.9 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.47 (d, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.05 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.91 (td, *J* = 8.7, 2.6 Hz, 1H), 6.59–6.50 (m, 2H), 5.75–5.59 (m, 1H), 4.04–3.90 (m, 2H), 3.86 (t, *J* = 9.2 Hz, 1H), 3.27 (d, *J* = 10.5 Hz, 1H), 3.01 (s, 3H), 2.95 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.38, 174.83, 168.23, 160.33, 157.94, 144.31, 140.20 (d, J_{CF} = 2.1 Hz), 130.88, 125.45 (q, J_{CF} = 279.1 Hz), 123.37 (d, J_{CF} = 8.1 Hz), 123.08, 115.79, 114.19 (d, J_{CF} = 23.4 Hz), 108.72 (d, J_{CF} = 26.3 Hz), 108.45 (d, J_{CF} = 7.8 Hz), 74.99, 61.54, 61.35 (q, J_{CF} = 30.6 Hz), 60.90, 52.26 (d, J_{CF} = 1.6 Hz), 26.61, 25.97 (d, J_{CF} = 9.4 Hz), 13.99; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –71.47, –120.08; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{22}F_4N_3O_4]^+$: 492.1541, found: 492.1545.

Compound 3o: The product **3o** was obtained in 94% yield as a yellow solid; Mp 149.3-150.9 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, *J* = 7.6 Hz, 1H), 7.25–7.13 (m, 3H), 6.97 (t, *J* = 7.7 Hz, 1H), 6.54 (dd, *J* = 15.5, 8.1 Hz, 2H), 5.67 (dd, *J* = 17.5, 7.4 Hz, 1H), 4.04–3.93 (m, 2H), 3.82 (d, *J* = 8.3 Hz, 1H), 3.30–3.21 (m, 1H), 3.00 (s, 3H), 2.95 (s, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.18, 174.91, 168.20, 144.28, 142.73, 130.91, 129.50, 128.27, 126.47, 125.46 (q, J_{CF} = 279.0 Hz), 125.29, 123.29, 123.06, 109.20, 108.49, 75.02, 61.61, 61.09 (q, J_{CF} = 30.2 Hz), 60.94, 52.05, 30.02, 26.58, 14.01; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.62; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{22}ClF_3N_3O_4]^+$: 508.1245, found: 508.1232.

Compound 3p: The product **3p** was obtained in 95% yield as a white solid; Mp 144.4-145.1 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, *J* = 7.6 Hz, 1H), 7.33 (dt, *J* = 9.9, 3.5 Hz, 2H), 7.22 (t, *J* = 7.7 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.57 (dd, *J* = 13.4, 7.9 Hz, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 5.73–5.61 (m, 1H), 4.03–3.94 (m, 2H), 3.81 (d, *J* = 8.2 Hz, 1H), 3.28–3.21 (m, 1H), 2.99 (s, 3H), 2.95 (s, 3H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.08, 174.95, 168.20, 144.29, 143.21, 132.43, 130.92, 129.17, 125.85, 125.47 (q, J_{CF} = 279.3 Hz), 123.27, 123.06, 115.42, 109.71, 108.50, 75.07, 61.42 (q, J_{CF} = 30.4 Hz), 61.27, 52.02, 30.03, 26.56, 25.92, 14.06; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.62; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{22}BrF_3N_3O_4]^+$: 552.0740, found: 552.0749.

Compound 3q: The product **3q** was obtained in 86% yield as a yellow solid; Mp 190.4-191.8 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21–8.08 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 5.68 (d, *J* = 8.3 Hz, 1H), 4.12–3.93 (m, 2H), 3.87 (d, *J* = 8.1 Hz, 1H), 3.24 (d, *J* = 10.0 Hz, 1H), 3.09 (s, 3H), 2.92 (s, 3H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.51, 174.75, 167.77, 149.59, 144.15, 143.52, 131.20, 126.54, 125.37 (q, J_{CF} = 279.0 Hz), 124.84, 123.21, 122.35, 108.76, 108.03, 74.89, 62.06, 61.43, 61.39 (q, J_{CF} = 30.3 Hz), 52.35, 26.97, 26.09, 14.11; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.65; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{22}F_3N_4O_6]^+$: 519.1486, found: 519.1487.

Compound 3r: The product **3r** was obtained in 98% yield as a white solid; Mp 170.7-171.2 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.04 (s, 1H), 6.95 (t, *J* = 7.9 Hz, 2H), 6.52 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 1H), 5.68 (dt, *J* = 10.3, 7.8 Hz, 1H), 3.91 (ddd, *J* = 18.6, 9.0, 3.6 Hz, 2H), 3.83 (d, *J* = 8.3 Hz, 1H), 3.27 (d, *J* = 10.6 Hz, 1H), 2.98 (s, 3H), 2.90 (s, 3H), 2.24 (s, 3H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz,$CDCl_3$) δ 176.15, 173.84, 167.24, 142.96, 140.46, 130.86, 129.29, 128.45, 125.64, 125.29, 124.25 (q, J_{CF} = 279.2 Hz), 122.44, 121.52, 106.91, 106.65, 73.62, 60.56, 60.39 (q, J_{CF} = 30.8 Hz), 59.95, 50.66, 28.68, 25.12, 24.47, 19.96, 12.55; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.63; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{25}H_{25}F_3N_3O_4]^+$: 488.1792, found:

488.1798.

Compound 3s: The product **3s** was obtained in 96% yield as a yellow solid; Mp 152.8-153.5 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.49 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 7.7 Hz, 1H), 6.96 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 2.3 Hz, 1H), 6.72 (dd, J = 8.5, 2.4 Hz, 1H), 6.51 (dd, J = 18.6, 8.1 Hz, 2H), 5.74–5.62 (m, 1H), 3.95 (d, J = 7.1 Hz, 1H), 3.87 (dd, J = 10.5, 7.8 Hz, 2H), 3.71 (s, 3H), 3.28 (d, J = 10.7 Hz, 1H), 2.98 (s, 3H), 2.93 (s, 3H), 0.85 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 177.40, 175.04, 168.48, 156.06, 144.34, 137.65, 130.70, 125.53 (q, J_{CF} = 279.2 Hz), 124.89, 123.66, 122.96, 114.95, 112.75, 108.70, 108.29, 75.01, 62.01, 61.09 (q, J_{CF} = 30.5 Hz), 56.25, 52.32, 26.54, 25.92, 13.97; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –73.62; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{25}H_{25}F_3N_3O_5]^+$: 504.1741, found: 504.1734.

Compound 3t: The product **3t** was obtained in 96% yield as a white solid; Mp 194.8-195.5 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.45 (d, J = 7.6 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 6.97 (s, 1H), 6.90 (dd, J = 8.2, 1.3 Hz, 1H), 6.62–6.54 (m, 2H), 5.65 (d, J = 8.9 Hz, 1H), 3.99 (dq, J = 10.7, 7.1 Hz, 1H), 3.90–3.79 (m, 2H), 3.19 (d, J = 10.3 Hz, 1H), 2.99 (s, 3H), 2.92 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 176.56, 174.12, 167.31, 144.45, 143.30, 134.65, 129.92, 126.20, 124.46 (q, J_{CF} = 279.0 Hz), 122.54, 122.11, 121.38, 108.12, 107.56, 73.88, 60.51, 60.02 (q, J_{CF} = 30.1 Hz), 51.20, 29.04, 25.63, 25.00, 13.06; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –73.77; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{22}ClF_3N_3O_4]^+$: 508.1245, found: 508.1230.

Compound 3u: The product **3u** was obtained in 98% yield as a white solid; Mp 168.5-169.3 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.43 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.13 (dd, J = 16.4, 7.9 Hz, 2H), 6.99 (s, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.57 (d, J = 7.7 Hz, 1H), 5.66 (dd, J = 16.3, 8.3 Hz, 1H), 4.06–3.92 (m, 1H), 3.91–3.75 (m, 2H), 3.37 (s, 3H), 3.26 (d, J = 8.1 Hz, 1H), 2.89 (s, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 177.90, 174.94, 168.29, 144.21, 140.13, 132.01, 130.96, 126.60, 125.45 (q, J_{CF} = 279.0 Hz), 124.73, 123.49, 123.16, 115.62, 108.54, 75.28, 61.55, 61.27, 61.11 (q, J_{CF} = 30.5 Hz), 52.55, 30.08, 25.97, 14.03; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –73.69; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{22}ClF_3N_3O_4]^+$: 508.1245, found: 508.1234.

Compound 3v: The product **3v** was obtained in 93% yield as a white solid; Mp 201.1-201.8 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.53 (d, J = 7.5 Hz, 1H), 7.34–7.15 (m, 5H), 7.06 (td, J = 7.7, 0.8 Hz, 1H), 6.91 (t, J = 7.4 Hz, 2H), 6.82 (d, J = 6.8 Hz, 2H), 6.59 (d, J = 7.8 Hz, 1H), 6.42 (d, J = 7.8 Hz, 1H), 5.81–5.62 (m, 1H), 4.97–4.84 (m, 1H), 4.65 (d, J = 16.0 Hz, 1H), 3.99 (d, J = 8.8 Hz, 1H), 3.87 (dq, J = 10.8, 7.1 Hz, 1H), 3.74 (dq, J = 10.7, 7.2 Hz, 1H), 3.18 (d, J = 10.0 Hz, 1H), 2.90 (s, 3H), 0.70 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 177.68, 175.76, 168.35, 144.39, 143.54, 135.12, 130.58, 129.63, 128.97, 127.75, 127.00, 126.30, 124.24 (q, J_{CF} = 278.6 Hz), 123.37, 122.73, 109.55, 108.35, 74.61, 61.86, 61.32 (q, J_{CF} = 30.3 Hz), 61.06, 53.25, 44.07, 26.01, 13.77; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –73.89; HRMS

(ESI): *m/z* $[M+H]^+$ calcd. for $[C_{30}H_{27}F_3N_3O_4]^+$: 550.1948, found: 550.1952.

Compound 3w: The product **3w** was obtained in 94% yield as a yellow solid; Mp 210.2-210.9 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.26–7.18 (m, 3H), 6.99 (dt, *J* = 18.1, 7.5 Hz, 2H), 6.53 (d, *J* = 7.8 Hz, 1H), 5.70 (d, *J* = 6.8 Hz, 1H), 3.95 (qd, *J* = 7.1, 3.6 Hz, 2H), 3.85–3.75 (m, 1H), 3.03 (d, *J* = 9.5 Hz, 1H), 2.83 (s, 3H), 1.59 (s, 9H), 0.79 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.37, 175.22, 168.33, 148.67, 144.32, 140.16, 130.98, 129.85, 126.80, 125.82, 125.59 (q, J_{CF} = 279.0 Hz), 124.23, 124.02, 123.08, 122.70, 114.83, 108.44, 84.96, 75.81, 62.34, 61.56, 61.33, 61.03 (q, J_{CF} = 30.5 Hz), 52.04, 28.37, 25.92, 13.90; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.98; HRMS (ESI): *m/z* $[M+Na]^+$ calcd. for $[C_{28}H_{28}F_3N_3NaO_6]^+$: 582.1822, found: 582.1801.

Compound 3x: The product **3x** was obtained in 88% yield as a yellow solid; Mp 189.0-190.0 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.57 (dd, *J* = 20.7, 7.7 Hz, 1H), 7.24 (dd, *J* = 14.8, 6.8 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.94 (dt, *J* = 21.6, 7.5 Hz, 2H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 5.68 (d, *J* = 7.3 Hz, 1H), 3.92 (dd, *J* = 14.9, 9.4 Hz, 2H), 3.87–3.73 (m, 1H), 3.14 (d, *J* = 9.7 Hz, 1H), 2.92 (s, 3H), 0.79 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 179.28, 175.53, 168.37, 144.34, 141.30, 130.72, 129.68, 126.61, 125.84 (q, J_{CF} = 278.8 Hz), 124.43, 124.03, 123.23, 122.68, 110.05, 108.37, 74.65, 62.07, 61.46, 61.25 (q, J_{CF} = 30.4 Hz), 60.95, 52.37, 26.00, 13.88; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.86; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{23}H_{21}F_3N_3O_4]^+$: 460.1479, found: 460.1481.

Compound 3y: The product **3y** was obtained in 90% yield as a white solid; Mp 222.4-222.9 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.25 (dd, *J* = 12.7, 4.8 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 5.55–5.42 (m, 1H), 3.83 (d, *J* = 7.0 Hz, 1H), 3.65 (d, *J* = 11.2 Hz, 1H), 3.07 (s, 3H), 3.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.64, 174.27, 144.49, 144.23, 131.28, 130.49, 127.07, 124.63 (q, J_{CF} = 279.6 Hz), 123.65, 123.33, 121.40, 117.25, 108.83, 75.57, 64.08 (q, J_{CF} = 30.2 Hz), 59.61, 37.85, 26.48, 25.96; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –73.25; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{22}H_{18}F_3N_4O_2]^+$: 427.1376, found: 427.1374.

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14. For our recent work on the enantioselective synthesis of trifluoromethyl-substituted 3,3'-pyrrolidinyl-dispirooxindoles, see: J. Weng, W. J. Huang, Q. Chen, N. Lin, X. W. Long, W. G. Pan, Y. S. Xiong, and G. Lu, *Org. Chem. Front.*, 2017, **4**, 472; The major products in this article are the minor diastereomers of the current study.
15. CCDC 1502692 (**3p**) contains the supplementary crystallographic data for this paper. The relative configuration of the minor isomers was determined by the X-ray crystallographic analysis of the epimer of **3f** (**3f'**, CCDC 1477406). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.