Available online at www.sciencedirect.com
ScienceDirect
Journal of Fluorine Chemistry 129 (2008) 97–107
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Nucleus- and side-chain fluorinated 3-substituted indoles by a suitable combination of organometallic and radical chemistry

Francesca Bellezza [a], Antonio Cipiciani [a], Renzo Ruzziconi [b,*], Sara Spizzichino [b]

[a] *CEMIN, "Centro di Eccellenza Materiali Innovativi Nanostrutturati", via Elce di Sotto, 8, 06123 Perugia, Italy*
[b] *Dipartimento di Chimica, Università di Perugia, via Elce di Sotto, 8, 06123 Perugia, Italy*

Received 27 July 2007; received in revised form 1 September 2007; accepted 9 September 2007
Available online 14 September 2007

Abstract

Regioselectively fluoro-, trifluoromethyl- and trifluoromethoxy-substituted 3-methyleneindolines have been prepared using a four-step procedure involving metalation/bromination of fluorinated Boc-protected anilines, *N*-propargylation of the resulting *o*-bromoarylcarbamate and reductive radical cyclization of the product with tributyltin hydride/AIBN. 3-Methyleneindolines, as valuable, versatile intermediates, can be transformed into highly functionalized 3-substituted indoles by ene-type reactions using different enophiles. Thus, fluoro-, trifluoromethyl- and trifluoromethoxy-substituted diethyl 2-hydroxy-2-[(1*H*-indol-3-yl)methyl]malonates, ethyl 2-hydroxy-3-(1*H*-indol-3-yl)propionates and ethyl 2-hydroxy-3-(1*H*-indol-3-yl)-2-trifluormethylpropionates were obtained in 77–86% yield by simply heating the corresponding *tert*-butyl 3-methyleneindoline-1-carboxylate with an equimolar amount of diethyl ketomalonate, ethyl glyoxalate and ethyl 3,3,3-trifluoropyruvate, respectively, at 100 °C, without solvent, for 0.5–4 h.

Keywords: Fluorinated indolines; Indole derivatives; Arylcarbamate metalation; Radical cyclization; Carbonyl-ene reactions

1. Introduction

It is now recognized that fluorine can change the properties of a biologically active molecule by influencing its metabolism. Its ability to increase lipophilicity, its high electronegativity and its reduced van der Waals radius, which make it like to an OH group, with, however, a scarce propensity to form hydrogen bonds, make fluorine a unique, valuable resource for increasing the therapeutic efficacy of biologically active organic molecules, especially when it is located in specific positions [1]. Besides the fluorine atom, the introduction of a CF_3 [2], or the less common OCF_3 group [3], into an aromatic ring appears to be a successful combination for the biological activity of a molecule to make the undertaking extremely attractive. The indolic nucleus is involved in a variety of natural products also by controlling essential biological functions both in the animal and plant kingdom [4]. For the above reasons, it should not be surprising if the introduction of fluorine or fluorinated substituents into a strategic position of the indole nucleus substantially affects the biological activity of this class of molecules leading to unexpected pharmacokinetic or pharmacodynamic properties [1e,f,5].

Although many methods have been developed to synthesize indole derivatives [6], fluorinated analogues of indole-based, biologically active molecules are not as well known.

Trifluoromethyl-substituted indoles are somewhat rare. Some of them have been prepared starting from commercially available (trifluoromethyl)aniline by complex procedures [7]. Direct electrophilic trifluoromethylation of indoline and oxindoles was recently attempted and gave access to regioselectively substituted 6-(trifluoromethyl)oxindoles, in moderate to good yields [8].

To our knowledge, only two examples of 3-substituted indoles bearing a trifluoromethoxy group are known to date [8,9].

We therefore found attractive to develop a simple, general method for preparing regioselectively nucleous- and side-chain fluoro-, trifluoromethyl- and trifluoromethoxy-substituted indoles functionalyzed at the 3 position, based on a suitable combination of organometallic and radical chemistry. The results of this research are presented in this paper.

* Corresponding author. Fax: +39 075 5855262.
E-mail address: ruzzchor@unipg.it (R. Ruzziconi).

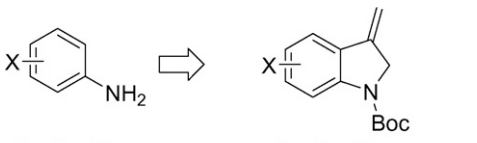
0022-1139/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2007.09.003

2. Results and discussion

3-Methyleneindolines appear the most suitable building block for preparing 3-substituted indoles and other valuable biologically active molecules [10]. Undoubtedly, the radical cyclization appears to be the simplest and most versatile method to prepare substituted indoline and indole derivatives [11], especially when the presence of electron-withdrawing groups like fluoroalkyls or fluoroalkoxy groups in the benzene ring precludes any other approach based on electrophilic cyclization reactions [9]. The decisive step of this strategy, that is common to different cyclization methods, is putting a bromine or iodine atom next to the amino group in a regioselective fashion. To do this, the concept of reagent-controlled optional site selectivity disclosed by M. Schlosser appears to be appropriate [12].

Following this idea, regioselectively fluorinated 3-methyleneindolines **2a–k** (Scheme 1) were prepared in four steps using commercially available anilines **1a–k** as the starting material.

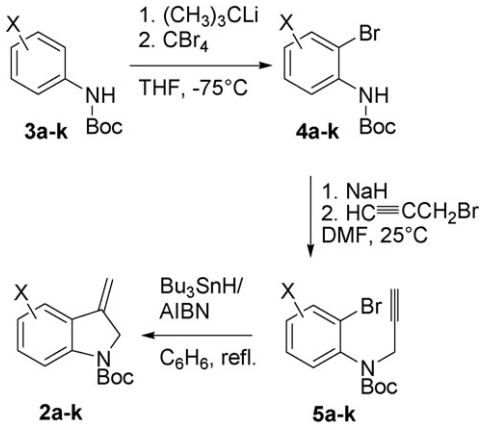
Due to its excellent coordination ability towards alkyllithium reagents, the Boc-amido group can exert a powerful *o*-directing effect on the metalation of Boc-protected aniline [13]. With *tert*-butyllithium, this effect overcomes the acidifying effect of strong electron-withdrawing groups, such as trifluoromethyl or even fluorine, on the position next to halogen. Therefore, Boc-protected fluoro-, trifluoromethyl- or trifluoromethoxy-substituted anilines undergo lithiation at one carbon next to nitrogen, regardless of the position of the substituent in the aromatic ring [13e,14]. Despite the commercial availability of some fluorinated *o*-bromoanilines, aiming at assessing the reliability of the method, the above procedure was adopted to prepare the essential *o*-bromoarylcarbamates used in this work. Thus, commercially available fluoro-, trifluoromethyl-, and trifluoromethoxyanilines **1a–k** were protected as the *tert*-butyl carbamate (**3a–k**) [15]. Metalation of the *N*-Boc-protected anilines with 2 equivalents of *tert*-butyllithium in THF at −75 °C, followed by treatment of the resulting dilithioanilide with CBr_4, allowed the corresponding *o*-bromoanilides **4a–k** to be obtained in good yields (Scheme 2).



1a: X = H
b: X = 2-F
c: X = 3-F
d: X = 4-F
e: X = 2-CF3
f: X = 3-CF_3
g: X = 4-CF_3
h: X = 2-OCF_3
i: X = 4-OCF_3
j: X = 2,4 bis-CF_3
k: X = 2-F-3-OCH_3

2a: X = H
b: X = 7-F
c: X = 6-F
d: X = 5-F
e: X = 7-CF_3
f: X = 6-CF_3
g: X = 5-CF_3
h: X = 7-OCF_3
i: X = 5-OCF_3
j: X = 5,7-bis-CF_3
k: X = 7-F-6-OCH_3

Scheme 1.



Scheme 2.

In virtue of their electronic and steric effects, fluorine, trifluoromethyl or trifluoromethoxy substituents could play a crucial role in determining the orientation of the lithiation at one of the two sites next to the nitrogen atom [12]. Accordingly, when Boc-protected 3-aminobenzotrifluoride (**3f**) was allowed to react with two equivalents of *tert*-butyllithium in THF for 3 h at −50 °C, lithiation occurred exclusively at the most sterically accessible position *ortho* to the amido group. This allowed the corresponding 2-bromo-5-trifluoromethylanilide to be obtained in 81% yield after treatment of the lithium intermediate with CBr_4. Under the above conditions, the *meta* isomer of *N*-(*tert*-butoxycarbonyl)fluoroaniline was easily deprotonated at the double activated position flanked by the two heterosubstituents already at −75 °C, but, as previously reported by Clark and Caroon [16], subsequent elimination of lithium fluoride is rapid generating a transient dehydroarene. Nucleophilic cyclization by the next *tert*-butoxycarbonyl anion gave rise to a 7-lithiobenzoxazole, which can be trapped with any electrophile. This and the above occurrence prevented us from enriching our collection of fluorinated 3-methyleneindoline with the 4-(trifluoromethyl)- and 4-fuoro-substituted regioisomers [17].

Nitrogen deprotonation of the resulting *o*-bromoarylcarbamate with sodium hydride in DMF, followed by treatment with propargyl bromide at room temperature, occurred smoothly allowing the corresponding aryl-*N*-propargyl carbamate **5a–k** to be obtained in good yield (62–88%) [18].

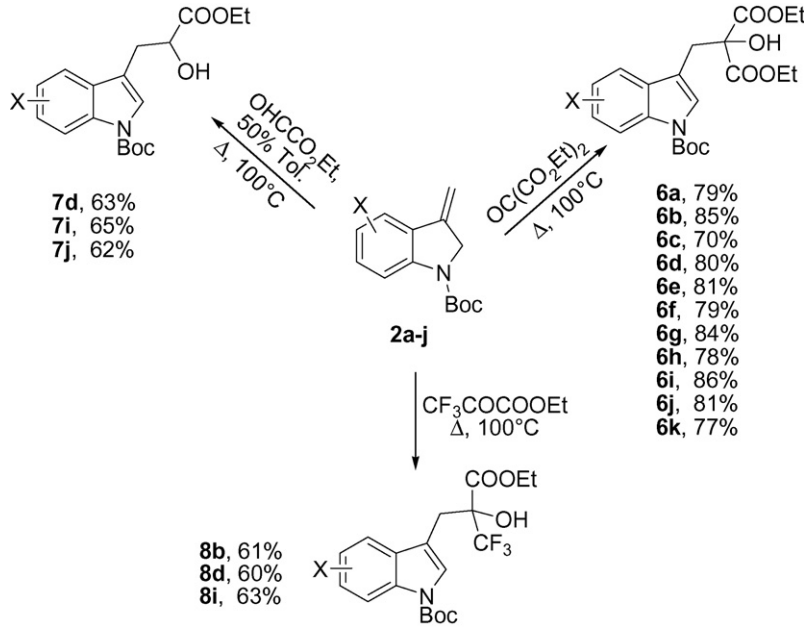
Finally, tributyltin hydride-promoted reductive radical cyclization of bromoaryl-*N*-propargylcarbamate in refluxing benzene, in the presence of AIBN as initiator, allowed the expected 3-methyleneindoline **2a–k** to be obtained in satisfactory yield (45–70%). The results are reported in Table 1.

Surprisingly, they are stable enough to be purified by standard chromatographic methods without any isomerization to the corresponding 3-methylindoles. As shown thoroughly by Buchwald [10b] the remarkable reactivity of the exocyclic carbon-carbon double bond makes 3-methyleneindolines valuable, versatile precursors of several highly functionalized 3-substituted indoles. To test this, we tried to react the above indolines with different enophilic carbonyl compounds. A carbonyl-ene reaction, which is a high activation energy process usually requiring the intervention of a Lewis acid

Table 1
Regioselectively fluorinated 3-methyleneindolines **2a–k** from anilines **1a–k**

Aniline	Aryl carbamate **3**, yield % [a]	*o*-Bromoaryl carbamate, **4**, yield % [a]	*o*-Bromoaryl *N*-(Propargyl)carbamate **5**, yield % [a]	*N*-Boc 3-methyleneindoline **2**, yield % [a]
1a (X = H)	**3a**, 91	**4a**, 78	**5a**, 75	**2a**, 41
1b (X = 2-F)	**3b**, 87	**4b**, 82	**5b**, 82	**2b** (X = 7-F), 58
1c (X = 3-F)	–	**4c**, 75[b]	**5c**, 71	**2c** (X = 6-F), 56
1d (X = 4-F)	**3d**, 99	**4d**, 66	**5d**, 62	**2d** (X = 5-F), 48
1e (X = 2-CF_3)	**3e**, 50	**4e**, 64	**5e**, 88	**2e** (X = 7-CF_3), 70
1f (X = 3-CF_3)	**3f**, 72	**4f**, 77	**5f**, 78	**2f** (X = 6-CF_3), 69
1g (X = 4-CF_3)	**3g**, 84	**4g**, 94	**5g**, 86	**2g** (X = 5-CF_3), 46
1h (X = 2-OCF_3)	**3h**, 76	**4h**, 46	**5h**, 77	**2h** (X = 7-OCF_3), 53
1i (X = 4-OCF_3)	**3i**, 85	**4i**, 81	**5i**, 87	**2i** (X = 5-OCF_3), 57
1j (X = 2,4-bis CF_3)	**3j**, 89	**4j**, 63	**5j**, 74	**2j** (5,7-bis CF_3), 50
1k (X = 2-F-3-OCH_3)	**3k**, 79	**4k**, 62.	**5k**, 84	**2k** (7-F-6-OCF_3), 45

[a] Yield of isolated product.
[b] Prepared from commercial 2-bromo-5-fluoroaniline.



Scheme 3.

catalyst [19], in these cases, took place smoothly simply heating a mixture of 3-methylene indolines **2** and the enophilic species at 100 °C, without solvent nor catalyst, for variable periods of time (0.5–2.0 h) depending on the nature of the substituent in the aromatic ring. Thus, diethyl 2-[1-*tert*-butoxycarbonyl-1*H*-indol-3-yl)methyl]malonate **6a–k** and, as demonstrative examples, some ethyl 3-(1-*tert*-butoxycarbonyl-1*H*-indol-3-yl)-2-hydroxypropionates (**7d**,**i**,**j**) and ethyl 2-[(1-*tert*-butoxycarbonyl-1*H*-indol-3-yl)methyl]-2-hydroxy-3,3,3-trifluoropropionates (**8b**,**d**,**i**) were obtained in good yields (77–86%) after the crude reaction mixture was passed through a short column of silica gel (Scheme 3).

3. Conclusion

In conclusion, a simple, general procedure has been devised to prepare regioselectively fluorinated 3-methyleneindolines. The latter, as valuable building blocks, provide a facile access to 3-functionalized nucleous and side-chain regioselectively fluorinated indole derivatives.

4. Experimental

If not specified otherwise, ^{1}H NMR and ^{1}H-decoupled ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solution using tetramethylsilane as an internal standard. ^{19}F NMR spectra were recorded at 376 MHz in $CDCl_3$ solution using $CFCl_3$ as a reference standard. *J* values are in Hz. IR spectra were registered in $CHCl_3$ solution in the 4000–625 cm^{-1} range. Further suggestions about working routine and technical details can be found in previous publications from this laboratory [9,20]. The starting fluoro-, trifluoromethyl- and trifluoromethoxy-substituted anilines and 2-bromo-5-fluoroaniline were commercial products and were used without further purification.

4.1. Standard procedure for preparing fluorinated tert-butyl arylcarbamates (3a–k)

A solution of the fluorinated aniline (0.10 mol) and di-*tert*-butyl dicarbonate (73.4 ml, 0.15 mol) was refluxed in toluene (400 ml). Di-*tert*-butyl dicarbonate was occasionally added and the reflux continued until the aniline had completely disappeared (tlc: SiO_2, eluent petroleum ether/diethyl ether 8:2; $ArNH_2$, R_f 0.1–0.26; ArNHBoc R_f 0.51–0.61). The solvent was evaporated at reduced pressure and the residue was passed through a short SiO_2 column (eluent, petroleum ether/diethyl ether 95:5). Pure *tert*-butyl 3-trifluoromethy-, 4-trifluoromethyl- and 4-trifluoromethoxyphenylcarbamate were obtained by simple crystallization of the crude reaction products from hexane. *tert*-Butyl 2-(trifluoromethyl)- and 2-(trifluoromethoxy)phenylcarbamate were obtained by K_2CO_3-promoted half hydrolysis of the corresponding di-*tert*-butyl dicarbamates in methanol. The latter were prepared by refluxing the aniline with 2 equiv. of di-*tert*-butyl dicarbonate in benzene, in the presence of DMAP as the catalyst [15].

tert-Butyl N-(2-fluorophenyl)carbamate [21] (**3b**, 87%): oil; IR ν_{max} 3442, 3032, 2983, 2935, 1729, 1522, 1238, 1158 cm^{-1}; ^1H NMR δ 8.07 (broad t, J = 7.6, 1 H), 7.0 (m, 2 H), 6.9 (m, 1 H), 6.71 (s, 1 H),1.53 (s, 9 H); ^{13}C NMR δ 152.4, 152.0 (d, J = 240), 126.8 (d, J = 9.9), 124.5 (d, J = 3.6), 122.8 (d, J = 7.4), 120.0, 114.7 (d, J = 19), 80.9, 28.2; ^{19}F NMR δ −133.2 (s).

tert-Butyl N-(4-fluorophenyl)carbamate [21] (**3d**, 99%): mp 125–126 °C (hexane); IR ν_{max} 3441, 3028, 2982, 2935, 1725, 1512, 1254, 1154 cm^{-1}; ^1H NMR δ 7.3 (symmetric m, 2 H), 7.0 (symmetric m, 2 H), 6.54 (broad s, 1 H), 1.50 (s, 9 H); ^{13}C NMR δ 158.7 (d, J = 240), 152.9, 134.3 (d, J = 2.5), 120.3, 115.5 (d, J = 22), 80.6, 28.3; ^{19}F NMR δ −120.6.

tert-Butyl N-[2-(trifluoromethyl)phenyl]carbamate [22] (**3e**, 50%): oil; IR ν_{max} 3463,(free N-H), 3358 (ass. N-H), 2982, 2934, 1743, 1594, 1528, 1159, 1111 cm^{-1}; ^1H NMR δ 8.13 (d, J = 12.4, 1 H), 7.55 (dt, J = 7.9 and 0.6, 1 H), 7.50 (t, J = 8.0, 1 H), 7.12 (tt, J = 7.6 and 0.9, 1 H), 6.79 (broad s, 1 H), 1.52 (s, 9 H); ^{13}C NMR δ 152.5, 136.2, 132.8, 125.9 (q, J = 5.4), 124.1 (q, J = 271), 123.0, 122.3, 118.9 (q, J = 30), 81.3, 28.2; ^{19}F NMR δ −61.3 (s).

tert-Butyl N-[3-(trifluoromethyl)phenyl]carbamate [23] (**3f**, 72%): mp 74–75 °C (hexane); IR ν_{max} 3438,(free N-H), 3311 (ass. N-H), 3098, 2983, 2934, 1729, 1530, 1156, 1133 cm^{-1}; ^1H NMR δ 7.72 (s, 1 H), 7.47 (d, J = 8.0, 1 H), 7.36 (t, J = 7.9, 1 H), 7.26 (d, J = 7.7, 1 H), 6.7 (broad s, 1 H), 1.51 (s, 9 H); ^{13}C NMR δ 152.5, 138.9, 131.3, (q, J = 32), 129.4, 123.9 (q, J = 270), 121.4, 119.5 (d, J = 3.7), 115.1, 81.2, 28.2; ^{19}F NMR δ −63.2.

tert-Butyl N-[4-(trifluoromethyl)phenyl]carbamate [24] (**3g**, 84%): mp 120–121 °C (hexane); IR ν_{max} 3436, 3030, 2983, 2935, 1731, 1530, 1327, 1159, 1118 cm^{-1}; ^1H NMR δ 7.53–7.45 (four peaks AA'XX' system, 4 H), 6.75 (broad s, 1 H), 1.51 (s, 9 H); ^{13}C NMR δ 152.3, 141.5, 126.2 (q, J = 3.7), 124.7 (q, J = 33), 124.2 (q, J = 270), 117.9, 81.2, 28.2; ^{19}F NMR δ −62.4.

tert-Butyl N-[2-(trifluoromethoxy)phenyl]carbamate [14a] (**3h**, 76%): oil IR ν_{max} 3461, 2983, 2935, 1740, 1524, 1252, 1156 cm^{-1} ^1H NMR δ 8.17 (d, J = 8.2, 1 H), 7.2 (m, 2 H), 7.00 (ddd, J = 9.9, 7.4 and 1.6, 1 H), 6.77 (broad s, 1 H), 1.52 (s, 9 H); ^{13}C NMR δ 152.3, 137.6, 131.1, 127.4, 122.7, 120.6 (q, J = 250), 81.2, 28.2; ^{19}F NMR δ −58.0 (s).

tert-Butyl N-[4-(trifluoromethoxy)phenyl]carbamate [14a] (**3i**, 85%): mp 108–109 °C (petroleum ether); IR ν_{max} 3439, 3032, 2983, 2934, 1727, 1522, 1265, 1158 cm^{-1}; ^1H NMR δ 7.38–7.11 (symmetric m, AA'BB' system, 4 H), 6.63 (broad s, 1 H), 1.50 (s, 9 H); ^{13}C NMR δ 152.6, 144.3, 137.0, 121.7, 120.4 (q, J = 255), 119.4, 80.8, 28.2; ^{19}F NMR δ −58.7 (s).

tert-Butyl N-[2,4-bis(trifluoromethyl)phenyl]carbamate (**3j**, 89%): oil; IR ν_{max} 3463, 2985, 2935, 1736, 1634, 1534, 1271, 1142 cm^{-1}; ^1H NMR δ 8.44 (d, J = 8.8, 1 H), 7.81 (s, 1 H), 7.76 (d, J = 8.8, 1 H), 6.99 (broad s, 1 H), 1.54 (s, 9 H); ^{13}C NMR δ 152.1, 139.5, 129.8, 124.6 (q, J = 33), 123.4 (t, J = 4.4), 123.4 (q, J = 272), 123.4 (q, J = 272), 121.3, 117.9 (q, J = 30), 82.2, 28.0; ^{19}F NMR δ −61.9 (s), −62.9 (s).

tert-Butyl N-(2-fluoro-3-methoxyphenyl)carbamate (**3k**, 79%): mp 95–97 °C (petroleum ether); IR ν_{max} 3441, 2983, 1731, 1624, 1539, 1456, 1242, 1156 cm^{-1}; ^1H NMR δ 7.28 (dd, J = 9.0 and 2.2, 1 H), 6.76 (t, J = 8.7, 1 H), 6.06 (broad s, 1 H), 3.87 (s, 3 H), 1.50 (s, 9 H); ^{13}C NMR δ 152.6, 148.4 (d, J = 251), 148.0 (d, J = 10), 126.5, 125.3 (d, J = 12), 112.1, 81.2, 56.6, 28.1; ^{19}F NMR δ −155.9(s).

4.2. Standard procedure for the metalation and subsequent bromination of tert-butyl arylcarbamates (4a–k)

tert-Butyllithium (1.70 M in pentane, 22 ml, 37 mmol) was added dropwise to a solution of *tert*-butyl arylcarbamate (5.0 g, 18 mmol) in anhydrous THF (50 ml) to −75 °C. The mixture was allowed to react 3 h at −50 °C, then it was cooled again at −75 °C and a solution of CBr_4 (5.9 g, 18.05 mmol) in THF (10 ml) was added dropwise. The brown mixture was allowed to react until the starting carbamate disappeared completely (tlc, SiO_2, eluent petroleum ether/diethyl ether 8:2). After a few min, the mixture was poured into icy water and extracted with diethyl ether (3 × 150 ml). The collected organic extracts were dried with Na_2SO_4 and the solvent was evaporated at reduced pressure. Chromatography of the crude product on silica gel (eluent, petroleum ether/diethyl ether 9:1) allowed pure bromoarylcarbamate to be recovered.

tert-Butyl N-(2-bromophenyl)carbamate (**4a**, 78%): oil; IR (film) ν_{max} 3416, 2979, 2932, 1737, 1519, 1156 cm^{-1}; ^1H NMR δ 8.14 (dd, J = 8.3 and 1.1, 1 H), 7.48 (dd, J = 8.0 and 1.5, 1 H), 7.26 (td, J = 8.3 and 1.4, 1 H), 7.00 (broad s, 1 H), 6.87 (ddd, J = 8.0, 7.4 and 1.6, 1 H), 1.53 (s, 9 H); ^{13}C NMR δ 152.3, 136.3, 132.2, 128.2, 123.8, 120.1, 112.4, 81.0, 28.3. Anal. Calcd. for $C_{11}H_{14}BrNO_2$: C, 48.5; H, 5.2; N, 5.1. Found: C, 48.7; H, 5.2; N, 5.1.

tert-Butyl N-(2-bromo-6-fluorophenyl)carbamate (**4b**, 82%): mp 93–94 °C (petroleum ether); IR ν_{max} 3426, 3038, 2984, 2933, 1733, 1498, 1250, 1159 cm^{-1}; ^1H NMR δ 7.3 (m, 1 H), 7.1 (m, 2 H), 6.12 (broad s, 1 H), 1.48 s (9 H); ^{13}C NMR δ 158.1 (d, J = 252), 152.7, 128.0 (d, J = 5), 127.9, 124.9 (d, J = 15), 122.0, 115.5 (d, J = 21), 81.2, 28.0; ^{19}F NMR δ −115.0 (t, J = 7.7). Anal. Calcd. for $C_{11}H_{13}BrFNO_2$: C, 45.5; H, 4.5; N, 4.8. Found: C, 45.6; H, 4.7; N, 4.9.

tert-Butyl N-(2-bromo-5-fluorophenyl)carbamate (**4c**, prepared from commercial 2-bromo-5-fluoroaniline and di-*tert*-butyl dicarbonate, 75%): oil; IR ν_{max} 3411, 3106, 2984, 2931, 1731, 1606, 1521, 1154 cm^{-1}; major conformer, ^1H NMR δ 7.94 (dd, J = 11 and 2.7, 1 H), 7.35 (dd, J = 8.8 and 5.8, 1 H), 6.96 (broad s, 1 H), 6.56 (ddd, J = 8.8, 7.6 and 3.0, 1 H), 1.46 (s, 9 H); ^{13}C NMR δ 162.3 (d, J = 243), 151.9, 137.5 (d, J = 12), 132.7 (d, J = 9.3), 110.5 (d, J = 23), 107.2 (d, J = 29), 105.9 (d, J = 3.2), 81.5, 28.2; ^{19}F NMR δ −112.0 (s). Anal. Calcd. for $C_{11}H_{13}BrFNO_2$: C, 45.5; H, 4.5; N, 4.8. Found: C, 45.6; H, 4.6; N, 5.0.

tert-Butyl N-(2-bromo-4-fluorophenyl)carbamate [25] (**4d**, 66%): mp 30–32 °C; IR ν_{max} 3417, 3086, 2984, 2935, 2873, 1728, 1516, 1258, 1158 cm^{-1}; ^1H NMR δ 8.07 (dd, J = 9.0 and 5.6, 1 H), 7.24 (dd, J = 7.8 and 2.9, 1 H), 7.00 (dddd, J = 10.7, 7.8, 2.9 and 0.5, 1 H), 6.84 (broad s, 1 H), 1.51 (s, 9 H); ^{13}C NMR δ 157.7 (d, J = 245), 152.5, 132.7, 121.2 (d, J = 7.3), 119.2 (d, J = 26), 115.0 (d, J = 22), 112.4 (d, J = 9.3), 81.2, 28.2; ^{19}F NMR δ −118.9 (s). Anal. Calcd. for $C_{11}H_{13}BrFNO_2$: C, 45.5; H, 4.5; N, 4.8. Found: C, 45.5; H, 4.6; N, 4.8.

tert-Butyl N-[2-bromo-6-(trifluoromethyl)phenyl]carbamate (**4e**, 64%): oil; IR (film) ν_{max} 3433, 3028, 2984, 2934, 1731, 1316, 1169, 1146 cm^{-1}; ^1H NMR δ 7.81 (d, J = 8.0, 1 H), 7.60 (d, J = 7.8, 1 H), 7.24 (t, J = 8.0, 1 H), 6.23 (broad s, 0.7 H), 6.09 (broad s, 0.3 H), 1.50 (s, 6.3 H), 1.37 (s, 2.7 H); ^{13}C NMR δ 152.9, 136.8, 134.0, 130.2 (q, J = 29), 128.4, 126.9, 125.6 (q, J = 4.6), 122.9 (q, J = 272), 81.1, 28.1; ^{19}F NMR δ −62.3 (s). Anal. Calcd. for $C_{12}H_{13}BrF_3NO_2$: C, 42.4; H, 3.8; N, 4.1. Found: C, 42.5; H, 3.9; N, 4.0.

tert-butyl N-[2-bromo-5-(trifluoromethyl)phenyl]carbamate (**4f**, 77%): oil; IR (film) ν_{max} 3416, 3107, 2983, 2935, 1739, 1525, 1157, 1130 cm^{-1}; ^1H NMR δ 8.50 (s, 1 H), 7.60 (d, J = 8.3, 1 H), 7.13 (dq, J = 8.3 and 0.7, 1 H), 7.10 (broad s, 1 H), 1.54 (s, 9 H); ^{13}C NMR δ 152.0, 137.0, 132.7, 130.8 (q, J = 33), 123.6 (q, J = 271), 120.0 (q, J = 3.8), 116.5 (q, J = 4.0), 115.4, 81.8, 28.2; ^{19}F NMR δ −63.3 (s). Anal. Calcd. for $C_{12}H_{13}BrF_3NO_2$: C, 42.4; H, 3.8; N, 4.1. Found: C, 42.5; H, 3.9; N, 4.1.

tert-Butyl N-[2-bromo-4-(trifluoromethyl)phenyl]carbamate (**4g**, 94%): mp 49–51 °C (hexane); IR ν_{max} 3410, 3038, 2984, 2935, 1733, 1530, 1324, 1155 cm^{-1}; ^1H NMR δ 8.31 (d, J = 8.7, 1 H), 7.75 (dq, J = 2.0 and 0.5, 1 H), 7.52 (dq, J = 8.7 and 0.6, 1 H), 7.15 (broad s, 1 H), 1.53 (s, 9 H); ^{13}C NMR δ 151.9, 139.4, 129.3 (q, J = 3.7), 125.4 (q, J = 24), 125.4 (q, J = 3.7), 123.3 (q, J = 270), 119.2, 111.5, 81.9, 28.2; minor conformer (characteristic absorptions): δ 132.6, 112.2, 90.1, 80.9, 28.2; ^{19}F NMR δ −62.5 (s). Anal. Calcd. for $C_{12}H_{13}BrF_3NO_2$: C, 42.4; H, 3.8; N, 4.1. Found: C, 42.3; H, 3.8; N, 4.2.

tert-Butyl N-[2-bromo-6-(trifluoromethoxy)phenyl]carbamate (**4h**, 46%): mp 60–63 °C (hexane); IR ν_{max} 3427, 3030, 2983, 1733, 1496, 1260, 1166 cm^{-1}; ^1H NMR δ 7.54 (dd, J = 8.1 and 1.3, 1 H), 7.25 (d quint., J = 8.3 and 1.4, 1 H), 7.15 (t, J = 8.2, 1 H), 6.05 (broad s, 1 H), 1.48 (s, 9 H); ^{13}C NMR δ 152.6, 145.7, 131.1, 129.7, 128.1, 123.5, 120.4 (q, J = 257), 81.2, 28.0; ^{19}F NMR δ −58.1 (s). Anal. Calcd. for $C_{12}H_{13}BrF_3NO_3$: C, 40.5; H, 3.7; N, 3.9. Found: C, 40.4; H, 3.7; N, 4.0.

tert-Butyl N-[2-bromo-4-(trifluoromethoxy)phenyl]carbamate (**4i**, 81%): mp 47–48 °C (petroleum ether); IR ν_{max} 3414, 3030, 2984, 2934, 1730, 1522, 1259, 1155 cm^{-1}; ^1H NMR δ 8.18 (d, J = 9.1, 1 H), 7.39 (d, J = 2.7, 1 H), 7.16 (dd, J = 9.2 and 2.3, 1 H), 6.97 (broad s, 1 H), 1.52 (s, 9 H); ^{13}C NMR δ 152.2, 143.8, 135.3, 125.1, 121.1, 120.4 (q, J = 256),120.3, 111.9, 81.5, 28.2; ^{19}F NMR δ −58.8 (s). Anal. Calcd. for $C_{12}H_{13}BrF_3NO_3$: C, 40.5; H, 3.7; N, 3.9. Found: C, 40.5; H, 3.7; N, 4.0.

tert-Butyl N-[2-bromo-4,6-bis(trifluoromethyl)phenyl]carbamate (**4j**, 63%): mp 90–92 °C; IR ν_{max} 3429, 2984, 1732, 1622, 1490, 1343, 1147 cm^{-1}; ^1H NMR δ 8.08 (s, 1 H), 7.86 (s, 1 H), 6.26 (broad s, 1 H), 1.47 (s, 9 H); ^{13}C NMR δ 152.2, 137.6, 133.9, 130.6 (q, J = 34), 130.4 (q, J = 31), 127.3, 122.9, 122.2 (q, J = 272), 122.1 (q, J = 272), 81.9, 28.0; ^{19}F NMR δ −62.6 (s), −63.4 (s). Anal. Calcd. for $C_{13}H_{12}BrF_6NO_2$: C, 38.3; H, 3.0; N, 3.4. Found: C, 38.4; H, 3.0; N, 3.5.

tert-butyl N-[6-bromo-2-fluoro-3-methoxyphenyl]carbamate (**4k**, 62%): mp 91–93 °C; IR ν_{max} 3426, 3024, 2983, 2939, 2361, 1732, 1702, 1609, 1492, 1160 cm^{-1}; ^1H NMR δ 7.28 (dd, J = 9.0 and 2.2, 1 H), 6.76 (t, J = 9.0, 1 H), 6.06 (broad s, 1 H), 3.87 (s, 3 H), 1.50 (s, 9 H); ^{13}C NMR δ 152.6, 148.4 (d, J = 251), 148.0 (d, J = 10), 126.5, 125.3 (d, J = 12), 112.1, 81.2, 56.6, 28.1; ^{19}F NMR δ −135.9 (s). Anal. Calcd. for $C_{12}H_{15}BrFNO_3$: C, 45.0; H, 4.7; N, 4.4. Found: C, 45.1; H, 4.8; N, 4.3.

*4.3. Standard procedure for preparing tert-butyl aryl(N-propargyl) carbamates (**5a–k**)*

Arylcarbamate (11.0 mmol) was added to a solution of NaH (0.48 g, 12.1 mmol), in DMF (20 ml) under nitrogen atmosphere. The mixture was allowed to react until the hydrogen evolution ceased (1 h). Propargyl bromide (1.84 ml, 16.5 mmol) was added dropwise and the resulting brown slurry was stirred at 25 °C until the starting arylcarbamate disappeared (tlc, eluent, petroleum ether/diethyl ether 9:1). The mixture was poured into water, extracted with diethyl ether (3 × 100 ml) and the collected organic extracts were dried with Na_2SO_4. The solvent was evaporated at reduced pressure and the residual crude was chromatographed on silica gel (eluent, petroleum ether/diethyl ether 9:1) to recover the pure product.

tert-Butyl N-(2-bromophenyl)-N-(prop-2-ynyl)carbamate (**5a**, 2.8:1 mixture of two conformers, 75%): mp 55–58 °C; IR ν_{max} 3309, 3064, 2982, 2933, 1702, 1478, 1388, 1165 cm^{-1}; major conformer, ^1H NMR δ 7.59 (d, J = 7.7, 1 H), 7.36 (d, J = 6.8, 1 H), 7.30 (t, J = 7.1, 1 H), 7.15 (td, J = 7.4 and 1.7, 1 H), 4.76 (dd, J = 18 and 2.2, 1 H), 3.93 (dd, J = 18 and 2.2, 1 H), 2.18 (s, 1 H), 1.33 (s, 9 H); ^{13}C NMR δ 153.6, 140.0, 132.9, 130.7, 129.0, 127.8, 123.5, 80.9, 79.2, 72.3, 38.0, 28.0; NMR signals identifying the minor conformer, ^1H NMR δ 4.60 (broad d, J = 18, 1 H), 2.21 (broad s, 1 H), 1.53 (s, 9 H); ^{13}C NMR δ 153.5, 140.4, 133.2, 131.0, 129.2, 128.2, 123.5, 81.4, 79.4, 72.0, 39.4, 28.2. Anal. Calcd. for $C_{14}H_{16}BrNO_2$: C, 54.2; H, 5.2; N, 4.5. Found: C, 54.3; H, 5.3; N, 4.4.

tert-Butyl N-(2-bromo-6-fluorophenyl)-N-(prop-2-ynyl)carbamate (**5b**, 3.3:1 mixture of two conformers, 82%): oil; IR

ν_{max} 3304, 2979, 2932, 1712, 1369, 1166 cm^{-1}; major conformer, ^1H NMR δ 7.37 (t, J = 8.0, 1 H), 7.17–7.04 (m, 2 H), 4.57–4.22 (eight peaks, AB portion of an ABX system, 2 H), 2.11 (t, X portion of an ABX system, 1 H), 1.33 (s, 9 H); ^{13}C NMR δ 159.7 (d, J = 252), 153.2, 126.9 (d, J = 8.8), 128.7, 128.2 (d, J = 3.5), 124.8, 115.2 (d, J = 21), 81.3, 78.0, 72.3, 37.3, 27.9; ^{19}F NMR δ −115.3 (dd, J = 8.4 and 5.9); NMR signals identifying the minor conformer, ^1H NMR δ 4.45–4.15 (eight peaks, AB portion of an ABX system, 2 H), 2.15 (t, X portion of an ABX system, 1 H), 1.52 (s, 9 H); ^{13}C NMR δ 160.1 (d, J = 252), 152.8 (129.8 (d, J = 8.8), 128.5, 128.4 (d, J = 3.5), 125.2, 115.6 (d, J = 21), 81.9, 78.3, 72.1, 38.8, 28.2; ^{19}F NMR δ −114.6 (dd, J = 8.3 and 6.0). Anal. Calcd. for $C_{14}H_{15}BrFNO_2$: C, 51.2; H, 4.6; N, 4.3. Found: C, 51.4; H, 4.7; N, 4.2.

tert-Butyl N-(2-bromo-5-fluorophenyl)-N-(prop-2-ynyl)carbamate (**5c**, 2.8:1 mixture of two conformers, 71%): oil; IR (film) ν_{max} 3308, 3088, 2998, 1703, 1588, 1476, 1164 cm^{-1}; major conformer, ^1H NMR δ 7.49 (dd, J = 8.8 and 5.8, 1 H), 7.07 (dd, J = 8.8 and 2.8, 1 H), 4.70 (d, J = 18, 2 H), 3.87 (d, J = 18, 1 H), 2.16 (broad s, 1 H), 1.29 (s, 9 H); ^{13}C NMR δ 161.6 (d, J = 246), 153.2, 141.5, 133.5 (d, J = 8.7), 118.2 (d, J = 23), 118.1, 116.3 (d, J = 22), 81.3, 72.7, 37.8, 28.0; ^{19}F NMR δ 113.9 (s); NMR signals identifying the minor conformer, ^1H NMR δ 4.55 (d, J = 18, 1 H), 1.47 (s, 9 H); ^{13}C NMR δ 78.8, 72.4, 39.3; ^{19}F NMR δ −113.4 (s). Anal. Calcd. for $C_{14}H_{15}BrFNO_2$: C, 51.2; H, 4.6; N, 4.3. Found: C, 51.1; H, 4.5; N, 4.3.

tert-Butyl N-(2-bromo-4-fluorophenyl)-N-(prop-2-ynyl)carbamate (**5d**, 3.1:1 mixture of two conformers, 62%): oil; IR ν_{max} 3306, 2979, 2932, 1709, 1492, 1168 cm^{-1}; major conformer, ^1H NMR δ 7.3 (m, 2 H), 7.02 (dt, J = 8.0 and 2.8, 1 H), 4.76 (dd, J = 18 and 2.4, 1 H), 3.91 (dd, J = 18 and 2.4, 1 H), 2.19 (t, J = 2.4, 1 H), 1.33 (s, 9 H); ^{13}C NMR δ 161.2 (d, J = 250), 153.5, 136.3, 131.6 (d, J = 8.9), 124.0 (d, J = 10.0), 120.0 (d, J = 25.3), 114.9 (d, J = 22.0), 81.0, 79.0, 72.6, 37.9, 28.0; ^{19}F NMR δ −112.4 (q, J = 7.7); NMR signals of the minor conformer, ^1H NMR δ 4.60 (d, J = 18, 1 H), 2.23 (broad s, 1 H), 1.52 (s, 9 H); ^{13}C NMR δ 161.3 (d, J = 250), 153.5, 136.5, 131.9 (d, J = 8.5), 124.0 (d, J = 10), 120.3 (d, J = 25), 115.2 (d, J = 22), 81.6, 78.9, 72.3, 39.3, 28.2; ^{19}F NMR δ −112.1 (q, J = 6.0). Anal. Calcd. for $C_{14}H_{15}BrFNO_2$: C, 51.2; H, 4.6; N, 4.3. Found: C, 51.3; H, 4.6; N, 4.4.

tert-Butyl N-[2-bromo-6-(trifluoromethyl)phenyl]-N-(prop-2-ynyl)carbamate (**5e**, 4.3:1 mixture of two conformers, 88%): oil; IR (film) ν_{max} 3310, 3028, 2983, 2934, 1708, 1315, 1144 cm^{-1}; ^1H NMR δ 7.83–7.80 (m, 1 H), 7.62 (dd, J = 7.9 and 0.9, 1 H), 7.29 (t, J = 8.0, 1 H), 4.48–4.28 (eight peaks, AB portion of an ABX system, J_{AB} = 17, J_{AX} = J_{BX} = 2.6, 2 H), 2.07 (t, X portion of an ABX system, J = 2.6, 1 H), 1.30 (s, 9 H); ^{13}C NMR δ 152.9, 138.1, 136.5, 131.2 (q, J = 30), 129.0, 127.6, 125.9 (q, J = 5.0), 122.7 (q, J = 272), 81.3, 77.2, 73.6, 38.5, 27.8; ^{19}F NMR δ −61.6; NMR signals identifying the minor conformer, ^1H NMR δ 4.37–4.21 (eight peaks, AB portion of an ABX system, J_{AB} = 17, J_{AX} = J_{BX} = 2.6, 2 H), 2.12 (t, X portion of an ABX system, J = 2.6, 1 H), 1.51 (s, 9 H); ^{13}C NMR δ 153.5, 138.6, 136.8, 131.7 (q, J = 30), 129.3, 128.0, 126.1 (q, J = 5.0), 122.7 (q, J = 272), 81.8, 77.7, 73.0, 39.6, 28.1; ^{19}F NMR δ −61.9. Anal. Calcd. for $C_{15}H_{15}BrF_3NO_2$: C, 47.6; H, 4.0; N, 3.7. Found: C, 47.6; H, 4.1; N, 3.6.

tert-Butyl N-[2-bromo-5-(trifluoromethyl)phenyl]-N-(prop-2-ynyl)carbamate (**5f**, 2.5:1 mixture of two conformers, 78%): oil; IR (film) ν_{max} 3079, 2980, 2934, 1719, 1605, 1426, 1289, 1173 cm^{-1}; major conformer ^1H NMR, δ 7.73 (d, J = 8.3, 1 H), 7.62 (s, 1 H), 7.42 (dd, J = 8.4 and 2.2, 1 H), 4.77 (dd, J = 18 and 2.2, 1 H), 3.96 (dd, J = 18 and 2.2, 1 H), 2.22 (broad t, J = 2.3, 1 H), 1.33 (s, 9 H); ^{13}C NMR δ 153.1, 140.6, 133.6, 130.5 (d, J = 34),127.9, 125.6, 123.3 (q, J = 271), 81.6, 73.0, 37.8, 27.9; ^{19}F NMR δ −63.2 (s); NMR signal characterizing the minor conformer, ^1H NMR δ 4.61 (d, J = 18, 1 H), 2.25 (s, 1 H), 1.53 (s, 9 H); ^{13}C NMR δ 84.3, 72.7, 39.3, 28.2; ^{19}F NMR δ −63.1 (s). Anal. Calcd. for $C_{15}H_{15}BrF_3NO_2$: C, 47.6; H, 4.0; N, 3.7. Found: C, 47.8; H, 4.1; N, 3.7.

tert-Butyl N-[2-bromo-4-(trifluoromethyl)phenyl]-N-(prop-2-ynyl)carbamate (**5g**, 2.5:1 mixture of two conformers, 86%): oil; IR (film) ν_{max} 3310, 3074, 2980, 2943, 1710, 1608, 1370, 1321, 1078 cm^{-1}; major conformer, ^1H NMR δ 7.88 (s, 1 H), 7.60–7.48 (four peaks, AB system, J_{AB} = 8.0, 2 H), 4.77 (d, J = 18, 1 H), 3.97 (d, J = 18, 1 H), 2.21 (broad s, 1 H), 1.34 (s, 9 H); ^{13}C NMR δ 153.0, 143.3, 131.1, 131.0, 130.2, 124.1, 122.8 (q, J = 271), 121.6, 81.6, 78.6, 72.8, 37.8, 28.0; ^{19}F NMR δ −63.1 (s); characteristic NMR signal of the minor conformer, ^1H NMR δ 4.67 (d, J = 17, 1 H), 2.24 (broad s, 1 H), 1.54 (s, 9 H); ^{13}C NMR δ 153.0, 143.5, 131.3, 130.3, 125.0, 124.0, 122.8 (d, J = 271), 86.7, 82.0, 72.4, 39.1, 28.0; ^{19}F NMR δ −63.2 (s). Anal. Calcd. for $C_{15}H_{15}BrF_3NO_2$: C, 47.6; H, 4.0; N, 3.7. Found: C, 47.6; H, 4.2; N, 3.8.

tert-Butyl N-[2-bromo-6-(trifluoromethoxy)phenyl]-N-(prop-2-ynyl)carbamate (**5h**, 4.3:1 mixture of two conformers, 77%): oil; IR (film) ν_{max} 3310, 2980, 2932, 1718, 1370, 1252, 1173 cm^{-1}; major conformer, ^1H NMR δ 7.53 (dd, J = 7.9 and 1.5, 1 H), 7.26 (dquint., J = 8.4 and 1.6, 1 H), 7.20 (t, J = 8.3, 1 H), 4.45–4.34 (eight peaks, AB portion of an ABX system, J_{AB} = 17.6, J_{AX} = J_{BX} = 2.5, 2 H, major conformer), 2.11 (t, J = 2.5, X portion of an ABX system, 1 H), 1.33 (s, 9 H); ^{13}C NMR δ 152.9, 147.3, 132.7, 130.7, 129.3, 126.1, 122.9 (q, J = 270), 119.0, 81.3, 77.3, 72.6, 37.4, 27.8; ^{19}F NMR δ −57.3 (s); NMR signals identifying the minor conformer, ^1H NMR δ 4.35–4.18 (eight peaks, AB portion of an ABX system, J_{AB} = 17.6, J_{AX} = J_{BX} = 2.5, 2 H), 2.15 (t, J = 2.5, X portion of an ABX system, 1 H), 1.53 (s, 9 H); ^{13}C NMR δ 153.5, 147.3, 132.9, 130.8, 129.5, 126.2, 123.0 (q, J = 270), 119.0, 81.9, 77.8, 72.1, 38.9, 28.1; ^{19}F NMR δ −57.1 (s). Anal. Calcd. for $C_{15}H_{15}BrF_3NO_3$: C, 45.7; H, 3.8; N, 3.5. Found: C, 45.6; H, 3.8; N, 3.6.

tert-Butyl N-[2-bromo-4-(trifluoromethoxy)phenyl]-N-(prop-2-ynyl)carbamate (**5i**, 3.0:1 mixture of two conformers, 87%): oil; IR (film) ν_{max} 3310, 3098, 2980, 2934, 1714, 1577, 1490, 1258, 1010, 767 cm^{-1}; major conformer, ^1H NMR δ 7.49 (s, 1 H), 7.40 (d, J = 8.3, 1 H), 7.18 (broad d, J = 8.3, 1 H), 4.77 (dd, J = 18 and 2.4, 1 H), 3.92 (dd, J = 18 and 2.4, 1 H), 2.22 (t, J = 2.2, 1 H), 1.34 (s, 9 H); ^{13}C NMR δ 153.3, 148.2, 138.8, 131.5, 125.3, 124.2, 120.6, 120.2, 120.2 (q, J = 257), 84.1, 81.3, 72.7, 37.9, 28.0; ^{19}F NMR δ −58.5 (s); NMR signals characterizing the minor conformer, ^1H NMR δ 4.61 (broad

d, J = 17, 1 H), 2.24 (broad s, 1 H), 1.53 (s, 9 H); ^{13}C NMR δ 153.5, 148.2, 139.0, 131.8, 125.7, 124.1, 120.6, 120.2 (q, J = 257), 84.1, 81.9, 72.4, 39.3, 28.2. Anal. Calcd. for $C_{15}H_{15}BrF_3NO_3$: C, 45.7; H, 3.8; N, 3.5. Found: C, 45.9; H, 3.9; N, 3.6.

tert-Butyl N-[2-bromo-4,6-bis(trifluoromethyl)phenyl]-N-(prop-2-ynyl)carbamate (**5j**, 4:1 mixture of two conformers, 74%): oil; IR (film) ν_{max} 3309, 3092, 3029, 2983, 2935, 1714, 1619, 1334, 1174 cm^{-1}; major conformer, ^{1}H NMR δ 8.14 (s, 1 H), 7.93 (broad s, 1 H), 4.56 (dd, J = 17 and 2.6, 1 H), 4.36 (dd, J = 17 and 2.6, 1 H), 2.14 (t, J = 2.6, 1), 1.36 (s, 9); ^{13}C NMR δ 152.7, 142.0, 133.9, 132.5 (q, J = 31), 131.8 (q, J = 34), 129.1, 123.6, 122.6 (q, J = 271), 122.4 (q, J = 272), 82.5, 77.0, 74.7, 38.8, 28.2; ^{19}F NMR δ −62.2 (s), −63.4 (s); minor conformer: ^{1}H NMR δ 8.14 (s, 1 H), 7.93 (s, 1 H), 4.45 (dd, J = 17 and 2.6, 1 H), 4.30 (dd, J = 17 and 2.6, 1 H), 2.18 (t, J = 2.6, 1 H), 1.57 (s, 9 H); ^{13}C NMR δ 152.5, 142.0, 134.2, 133.0 (q, J = 31), 132.2 (q, J = 33), 129.6, 123.6, 123.5 (q, J = 271), 122.8 (q, J = 272), 83.0, 77.0, 74.1, 39.9, 28.5; ^{19}F NMR δ −62.4 (s), −63.6 (s). Anal. Calcd. for $C_{16}H_{14}BrF_6NO_2$: C, 43.1; H, 3.2; N, 3.1. Found: C, 43.2; H, 3.21; N, 3.2.

tert-Butyl N-(6-bromo-2-fluoro-3-methoxyphenyl)-N-(prop-2-ynyl)carbamate (**5k**, 3.6:1 mixture of two conformers, 84%): mp 89–91 °C; IR (film) ν_{max} 3309, 3022, 1707, 1602, 1487, 1369, 1159 cm^{-1}; major conformer, ^{1}H NMR δ 7.33 (dd, J = 9.0 and 2.2, 1 H), 6.85 (dd, J = 8.8 and 8.3, 1 H), 4.57 (dd, J = 18 and 2.5, 1 H), 4.29 (dd, J = 18 and 2.5, 1 H), 3.91 (s, 3 H), 2.15 (t, J = 2.5, 1 H), 1.38 (s, 9 H); ^{13}C NMR δ 153.2, 149.9 (d, J = 251), 147.7 (d, J = 10), 129.1 (d, J = 13), 126.7 (d, J = 4.6), 114.7, 113.3, 81.3, 78.1, 72.3, 56.5, 37.4, 28.0; ^{19}F NMR δ −135.9 (s); minor conformer, ^{1}H NMR δ 7.34 (dd, J = 8.9 and 2.2, 1 H), 6.85 (dd, J = 8.8 and 8.3, 1 H), 4.46 (dd, J = 18 and 2.5, 1 H), 4.21 (dd, J = 18 and 2.5, 1 H), 3.88 (s, 3 H), 2.20 (t, J = 2.5, 1 H), 1.56 (s, 9 H); ^{13}C NMR δ 153.1, 149.9 (d, J = 251), 147.7 (d, J = 10), 129.0 (d, J = 13), 127.0 (d, J = 4.6), 114.9, 113.7, 81.9, 78.1, 72.1, 56.5, 38.9, 28.2; ^{19}F NMR δ −135.1 (s). Anal. Calcd. for $C_{15}H_{17}BrFNO_3$: C, 50.3; H, 4.8; N, 3.9. Found: C, 50.3; H, 4.7; N, 4.0.

4.4. Standard procedure for the synthesis of tert-butyl 3-methyleneindoline-1-carboxylates (2a–k)

Tributyltin hydride (0.9 ml, 32.01 mmol) was added dropwise to a solution of *tert*-butyl (2-bromoaryl)(prop-2-ynyl)carbamates (15 mmol) and AIBN (50 mg, 1.5 mmol) in benzene (150 ml). The solution was refluxed under nitrogen atmosphere and, after 1 h, a second portion of AIBN (50 mg, 1.5 mmol) was added and reflux was continued until the substrate had completely disappeared (TLC, SiO_2, eluent, petroleum ether/diethyl ether 8:2), ca. 2–3 h. The solvent was evaporated at reduced pressure and diethyl ether (20–30 ml) was added to the residual crude. Diazabicycloundecene (DBU, 1.5 eq. with respect to Bu_3SnH) was added and the mixture was stirred for 30 min before 0.1 M iodine in diethyl ether was added until a persistent yellow colour was observed. The mixture was further stirred for 1 h and then filtered through a short silica gel column (eluent, petroleum ether). In some cases, a second treatment with DBU-I_2 was necessary in order to remove the residual organotin derivatives. After the solvent evaporation chromatography of the remaining white product on silica gel (eluent petroleum ether) allowed pure *tert*-butyl 3-methyleneindoline-1-carboxylate to be collected.

tert-Butyl 3-methyleneindoline-1-carboxylate (**2a**, 41%); oil; IR (film) ν_{max} 2976, 2929, 1708, 1390, 1149 cm^{-1}; ^{1}H NMR δ 7.93 (broad s, 0.62 H), 7.51 (broad s, 0.38 H), 7.41 (d, J = 7.6, 1 H), 7.23 (t, J = 7.6, 1 H), 6.96 (td, J = 7.5 and 1.0, 1 H), 5.44 (t, J = 3.0, 1 H), 5.03 (broad s, 1 H), 4.57 (broad s, 2 H), 1.57 (s, 9 H); ^{13}C NMR δ 151.5, 141.1, 129.9, 122.2, 120.3, 115.3, 101.5, 101.1, 80.8, 53.4, 28.4. Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.7; H, 7.4; N, 6.1. Found: C, 72.6; H, 7.4; N, 5.9.

tert-Butyl 7-fluoro-3-methyleneindoline-1-carboxylate (**2b**, 58%): viscous oil; IR ($CHCl_3$) ν_{max} 3026, 2983, 2934, 1694, 1593, 1489, 1377, 1103 cm^{-1}; ^{1}H NMR δ 7.2 (symmetric m, 1 H), 7.0 (symmetric m, 2 H), 5.45 (t, J = 3.0, 1 H), 5.06 (t, J = 2.6, 1 H), 4.61 (t, J = 2.8, 2 H), 1 52 (s, 9 H); ^{13}C NMR δ 151.0 (d, J = 251), 151.9, 141.2 (d, J = 2.2), 133.9 (d, J = 3.0), 131.6 (d, J = 9.9), 124.2 (d, J = 6.9), 117.8 (d, J = 22), 116.0 (d, J = 3.4), 81.5, 72.3, 55.2, 28.1; ^{19}F NMR δ −115.9 (dd, J = 8.6 and 6.0). Anal. Calcd. for $C_{14}H_{16}FNO_2$: C, 67.4; H, 6.5; N, 5.6. Found: C, 67.2; H, 6.5; N, 5.5.

tert-Butyl 6-fluoro-3-methyleneindoline-1-carboxylate (**2c**, 56%): mp 83–85 °C; IR ν_{max} 3024, 2984, 1702, 1614, 1492, 1389, 1170 cm^{-1}; ^{1}H NMR δ 7.68 (broad s, 1 H), 7.34 (dd, J = 8.3 and 5.7, 1 H), 6.66 (td, J = 8.6 and 2.3, 1 H), 5.37 (broad s, 1 H), 4.98 (broad s, 1 H), 4.59 (broad s, 2 H), 1.55 (s, 9); ^{13}C NMR δ 164.1 (d, J = 245), 151.3, 139.9, 125.0, 121.2, 109.2 (d, J = 23), 103.3 (d, J = 29), 101.0, 100.5, 81.3, 54, 28.2; ^{19}F NMR δ −110, 7 (broad s, major conformer), −110.9 (broad s, minor conformer). Anal. Calcd. for $C_{14}H_{16}FNO_2$: C, 67.4; H, 6.5; N, 5.6. Found: C, 67.6; H, 6.4; N, 5.7.

tert-Butyl 5-fluoro-3-methyleneindoline-1-carboxylate (**2d**, 48%): mp 71–73 °C; IR ν_{max} 3034, 2982, 2934, 1698, 1602, 1483, 1391, 1150 cm^{-1}; ^{1}H NMR δ 7.87 (broad s, 0.57 H), 7.42 (broad m, 0.43), 7.06 (dd, J = 8.2 and 2.6, 1 H), 6.91 (t, J = 8.3, 1 H), 5.42 (s, 1 H), 5.06 (s, 1 H), 4.57 (s, 2 H), 1.54 (s, 9 H); ^{13}C NMR δ; 158.8 (d, J = 239), 151.4, 141.4, 140.4, 130.5, 116.4, 116.1 (d, J = 8.0), 106.9 (d, J = 23), 102.4, 80.8, 54.5, 28.3; ^{19}F NMR δ −121.9 (major conformer); −122.1 (minor conformer). Anal. Calcd. for $C_{14}H_{16}FNO_2$: C, 67.4; H, 6.5; N, 5.6. Found: C, 67.3; H, 6.5; N, 5.6.

tert-Butyl 3-methylene-7-(trifluoromethyl)indoline-1-carboxylate (**2e**, 70%): mp 98–100 °C;; IR ν_{max} 2983, 2933, 1724, 1604, 1440, 1157 cm^{-1}; ^{1}H NMR δ 7.56 (d, J = 7.5, 1 H), 7.49 (d, J = 7.4, 1 H), 7.15 (t, J = 7.5, 1 H), 5.52 (t, J = 2.9, 1 H), 5.13 (t, J = 2.4, 1 H), 4.66 (t, J = 2.7, 2 H), 1.52, (s, 9 H); ^{13}C NMR δ 153.6, 142.0 (q, J = 1.6), 141.0, 133.1, 128.4 (q, J = 4.4), 123.8, 123.7 (q, J = 270), 123.2, 120.9 (q, J = 33.1), 102.7, 82.2, 55.7, 27.8; ^{19}F NMR δ −59.8 (s). Anal. Calcd. for $C_{15}H_{16}F_3NO_2$: C, 60.2; H, 5.4; N, 4.7. Found: C, 60.1; H, 5.5; N, 4.8.

tert-Butyl 3-methylene-6-(trifluoromethyl)indoline-1-carboxylate (**2f**, mixture of two conformers, 69%): semi-solid; IR (film) ν_{max} 2980, 2934, 1713, 1615, 1393, 1325, 1166, 1127 cm^{-1}; major conformer; ^1H NMR δ 8.22 (broad s, 0.6 H), 7.63 (broad s, 0.4 H), 7.46 (d, J = 8.0, 1 H), 7.19 (d, J = 8.0, 1 H), 5.56 (broad s, 1 H), 5.15 (broad s, 1 H), 4.60 (broad s, 2 H), 1.55 (s, 9 H); ^{13}C NMR δ 151.4, 145.4, 141.0, 139.7, 128.7, 131.6 (q, J = 34), 124.3 (q, J = 270), 119.2, 112.5, 103.9, 81.6, 53.5, 28.3; ^{19}F NMR δ −63.2. Anal. Calcd. for $C_{15}H_{16}F_3NO_2$: C, 60.2; H, 5.4; N, 4.7. Found: C, 60.2; H, 5.3; N, 4.7.

tert-Butyl 3-methylene-5-(trifluoromethyl)indoline-1-carboxylate (**2g**, 46%): mp 93–95 °C; IR ν_{max} 3031, 2982, 2934, 1706, 1621, 1386, 1274, 1152, 1127 cm^{-1}; ^1H NMR δ 7.99 (broad s, 1 H), 7.59 (s, 1 H), 7.45 (d, J = 8.4, 1 H), 5.51 (t, J = 3.2, 1 H), 5.10 (t, J = 2.5, 1 H), 4.59 (t, J = 2.8, 2 H), 1.56 (s, 9 H); ^{13}C NMR δ 151.3, 147.8, 139.7, 129.4, 127.0 (q, J = 3.4), 124.4 (q, J = 32), 124.3 (q, J = 270), 117.4, 115.2, 103.1, 81.6, 53.7, 28.2 ^{19}F NMR δ −62.2. Anal. Calcd. for $C_{15}H_{16}F_3NO_2$: C, 60.2; H, 5.4; N, 4.7. Found: C, 60.2; H, 5.4; N, 4.7.

tert-Butyl 3-methylene-7-(trifluoromethoxy)indoline-1-carboxylate (**2h**, 53%): oil; IR ν_{max} 3028, 2983, 2934, 1724, 1698, 1371, 1255, 1166 cm^{-1} ^1H NMR δ 7.36 (d, J = 7.5, 1 H), 7.12 (broad d, J = 8.1, 1 H), 7.03 (t, J = 7.7, 1 H), 5.49 (t, J = 3.0, 1 H), 5.10 (t, J = 2.5, 1 H), 4.64 (t, J = 2.7, 2 H), 1 59 (s, 9 H); ^{13}C NMR δ 151.9, 141.0, 137.3 (q, J = 2.1), 137.2, 124.2, 124.1, 120.7 (q, J = 256), 119.2, 102.8, 81.8, 55.5, 27.9; ^{19}F NMR δ −58.3 (s). Anal. Calcd. for $C_{15}H_{16}F_3NO_3$: C, 57.1; H, 5.1; N, 4.4. Found: C, 57.0; H, 5.2; N, 4.5.

tert-Butyl 3-methylene-5-(trifluoromethoxy)indoline-1-carboxylate (**2i**, 57%): oil; IR ν_{max} 3019, 2982, 2932, 1698, 1602, 1390, 1255, 1170, 1151 cm^{-1}; ^1H NMR δ 7.92 (broad s, 0.67 H), 7.47 (broad s, 0.33 H), 7.22 (s, 1 H), 7.06 (d, J = 8.6, 1 H), 5.46 (s, 1 H), 5.09 (broad s, 1 H), 4.59 (broad s, 2 H), 1.54 (s, 9 H); ^{13}C NMR δ 151.4, 144.4, 143.7, 140.0, 130.4, 122.7, 120.6 (q, J = 255), 116.0, 113.4, 102.9, 81.2, 53.7, 28.3; ^{19}F NMR δ −58.7. Anal. Calcd. for $C_{15}H_{16}F_3NO_3$: C, 57.1; H, 5.1; N, 4.4. Found: C, 57.3; H, 5.2; N, 4.4.

tert-Butyl 3-methylene-5,7-bis(trifluoromethyl)indoline-1-carboxylate (**2j**, 50%): mp 38–40 °C; IR ν_{max} 3022, 3000, 2936, 1705, 1697, 1623, 1508, 1455, 1371, 1160 cm^{-1}; ^1H NMR δ 7.76 (s, 1 H), 7.74 (s, 1 H), 5.64 (broad s, 1 H), 5.25 (broad s, 1 H), 4.71 (s, 2 H), 1.54 (s, 9 H); ^{13}C NMR δ 152.9, 144.6, 139.5, 134.0, 126.2 (q, J = 33), 123.4 (q, J = 270), 123.0 (q, J = 271), 120.8 (q, J = 34), 120.1, 105.0, 83.0, 56.1, 28.0; ^{19}F NMR δ −60.1 (s), −62.7 (s). Anal. Calcd. for $C_{16}H_{15}F_6NO_2$: C, 52.3; H, 4.1; N, 3.8. Found: C, 50.2; H, 4.1; N, 3.9.

tert-Butyl 7-fluoro-6-methoxy-3-methyleneindoline-1-carboxylate (**2k**, 45%): oil; IR ν_{max} 1729, 1650, 1626, 1352, 1311, 1136 cm^{-1} ^1H NMR δ 7.11 (dd, J = 8.3 and 0.9, 1 H), 6.61 (dd, J = 8.2 and 7.0, 1 H), 5.32 (t, J = 2.9, 1 H), 4.95 (t, J = 2.2, 1 H), 4.60 (t, J = 2.7, 2 H), 3.87 (s, 3 H), 1.52 (s, 9 H); ^{13}C NMR δ 152.0, 150.3 (d, J = 11), 141.5 (d, J = 251), 140.7, 132.4 (d, J = 7.2), 126.0, 115.3 (d, J = 4.2), 108.2, 100.3, 81.7, 56.8, 55.7, 28.1; ^{19}F NMR δ −139.2 (s). Anal. Calcd. for $C_{15}H_{18}FNO_3$: C, 64.5; H, 6.5; N, 5.0. Found: C, 57.3; H, 5.2; N, 4.4.

*4.5. Standard procedure for the synthesis of fluorinated diethyl 2-[(1H-indol-3-yl)methyl]-2-hydroxymalonates (**6a–k**), ethyl 3-[(1H-indol-3-yl)methyl]-2-hydroxypropionates (**7d,i,j**) and ethyl 2-[(1-tert-butoxycarbonyl-1H-indol-3-yl)methyl]-2-hydroxy-3,3,3-trifluoropropionates (**8b,d,i**)*

A mixture of *tert*-butyl 3-methyleneindoline-1-carboxylate (0.33 mmol) and the suitable enophilic species (0.33 mmol) was heated at 100 °C, under nitrogen atmosphere, for 0.5–2 h, until the indoline completely disappeared (tlc, SiO_2, eluent petroleum ether/diethyl ether 9:1). In the case of ethyl glyoxalate, a commercial technical solution, 50% in toluene, was directly used. The crude mixture was taken up with diethyl ether (2 ml) and Chromatographed on silica gel (eluent, petroleum ether/diethyl ether 9:1) to allow the pure malonyl derivative **6**(**a–k**), the propionates **7**(**d**,**i**,**j**) and **8**(**b**,**d**,**i**) to be recovered.

Diethyl 2-[(1-tert-butoxycarbonyl-1H-indol-3-yl)methyl]-2-hydroxymalonate (**6a**, 79%): oil; IR ν_{max} 3518 (broad), 3032, 2984, 2939, 1736, 1453, 1371, 1156, 732 cm^{-1}; ^1H NMR δ 8.02 (broad d, J = 6.6, 1 H), 7.54 (d, J = 7.7, 1 H), 7.43 (s, 1 H), 7.21 (td, J = 7.1 and 1.3, 1 H), 7.14 (td, J = 8.4 and 1.1, 1 H), 4.19–4.08 (m, 4 H), 3.82 (s, 1 H), 3.39 (s, 2 H), 1.58 (s, 9 H), 1.19 (t, J = 7.1, 6 H); ^{13}C NMR δ 169.9, 149.6, 135.1, 130.9, 125.1, 124.2, 122.3, 119.5, 115.0, 113.6, 83.5, 79.1, 62.6, 30.3, 28.2, 14.1. Anal. Calcd. for $C_{21}H_{27}NO_7$: C, 62.2; H, 6.7; N, 3.4. Found: C, 62.4; H, 6.8; N, 3.4.

Diethyl 2-[(1-tert-butoxycarbonyl-7-fluoro-1H-indol-3-yl)methyl]-2-hydroxymalonate (**6b**, 85%): mp 88–89 °C; IR ν_{max} 3689, 3516 (broad), 1737, 1494, 1370, 1235, 1155, 909 cm^{-1}; ^1H NMR δ 7.56 (s, 1 H), 7.41 (dd, J = 7.9 and 0.9, 1 H), 7.17 (td, J = 7.9 and 4.0, 1 H), 7.02 (ddd, J = 12.6, 7.9 and 0.6, 1 H), 4.32–4.18 (symmetric m, 4 H), 3.88 (broad s, 1 H), 3.46 (s, 2 H), 1.65 (s, 9 H), 1.28 (t, J = 7.1, 6 H);^{13}C NMR δ 169.9, 149.9 (d, J = 251), 148.7, 135.2 (d, J = 4.0), 127.5, 123.1, 121.8 (d, J = 10), 115.4, 113.6, 111.5 (d, J = 22), 84.0, 79.1, 62.7, 30.0, 27.9, 13.9; ^{19}F NMR δ −116.8 (dd, J = 13 and 3.8). Anal. Calcd. for $C_{21}H_{26}FNO_7$: C, 59.6; H, 6.2; N, 3.3. Found: C, 59.7; H, 6.2; N, 3.4.

Diethyl 2-[(1-tert-butoxycarbonyl-6-fluoro-1H-indol-3-yl)methyl]-2-hydroxymalonate (**6c**, 70%): oil; IR ν_{max} 3516 (broad), 3024, 2985, 1737, 1619, 1484, 1372, 1158, 909 cm^{-1}; ^1H NMR δ 7.7 (broad s, 1 H), 7.45 (dd, J = 8.6 and 5.4, 1 H), 7.38 (s, 1 H), 6.89 (td, J = 8.6 and 2.3, 1 H), 4.18–4.11 (symmetric m, 4 H), 3.80 (s, 1 H), 3.35 (s, 2 H), 1.58 (s, 9 H), 1.19 (t, J = 7.1, 6 H); ^{13}C NMR δ 169.9, 160.9 (d, J = 238), 149.3, 135.2 (d, J = 13), 125.3 (d, J = 3.5), 120.3 (d, J = 9.8), 113.5, 110.5 (d, J = 24), 102.3 (d, J = 28), 84.0, 79.1, 62.6, 30.0, 28.1, 13.9; ^{19}F NMR δ −118.2 (s). Anal. Calcd. for $C_{21}H_{26}FNO_7$: C, 59.6; H, 6.19; N, 3.3. Found: C, 59.6; H, 6.1; N, 3.3.

Diethyl 2-[(1-tert-butoxycarbonyl-5-fluoro-1H-indol-3-yl)methyl]-2-hydroxymalonate (**6d**, 80%): oil; IR ν_{max} 3519 (broad), 2985, 1736, 1474, 1372, 1278, 1157, 856, 720 cm^{-1}; ^1H NMR δ 7.96 (broad s, 1 H), 7.45 (s, 1 H), 7.19 (dd, J = 9.1 and 2.5, 1 H), 6.92 (td, J = 9.1 and 2.5, 1 H), 4.20–4.11 (m, 4 H),

3.81 (s, 1 H), 3.33 (s, 2 H), 1.57 (s, 9 H), 4.82 (t, J = 7.1, 6 H); ^{13}C NMR δ 169.8, 169.8, 159.2 (d, J = 237), 149.3, 131.7 (d, J = 13), 126.8, 116.0 (d, J = 9.1), 113.4 (d, J = 4.0), 112.0 (d, J = 25), 105.2 (d, J = 24), 83.8, 79.0, 62.7, 30.0, 28.1, 13.9; ^{19}F NMR δ −121.6 (s). Anal. Calcd. for $C_{21}H_{26}FNO_7$: C, 59.6; H, 6.2; N, 3.3. Found: C, 59.8; H, 6.2; N, 3.3.

Diethyl 2-[(1-tert-butoxycarbonyl-7-(trifluoromethyl)-1H-indol-3-yl)methyl]-2-hydroxymalonate (**6e**, 81%): mp 118–120 °C; ^{1}H NMR δ 7.80 (d, J = 7.8, 1 H), 7.58 (d, J = 7.6, 1 H), 7.44 (s, 1 H), 7.30 (t, J = 7.8, 1 H), 4.25–4.15 (symmetric m, 4 H), 3.88 (broad s, 1 H), 3.45, s, 2 H), 1.60 (s, 9 H), 1.24 (t, J = 7.8, 6 H); ^{13}C NMR δ 169.8, 149.7, 133.8, 130.5, 128.8, 124.1 (q, J = 270), 123.6, 123.5, 122.0, 118.1 (q, J = 33.1), 113.1, 84.6, 79.1, 62.7, 29.8, 27.8, 13.9; ^{19}F NMR δ −57.9 (s). Anal. Calcd. for $C_{22}H_{26}F_3NO_7$: C, 55.8; H, 5.5; N, 3.0. Found: C, 55.9; H, 5.6; N, 3.1.

Diethyl 2-[(1-tert-butoxycarbonyl-6-(trifluoromethyl)-1H-indol-3-yl)methyl]-2-hydroxymalonate (**6f**, 79%): mp 46–48 °C; IR ν_{max} 3693, 3524, 3024, 2928, 1735, 1444, 1372, 1276, 1124, 909 cm^{-1}; ^{1}H NMR δ 8.42 (broad s, 1 H), 7.70 (d, J = 8.0, 1 H), 7.61 (s, 1 H), 7.45 (d, J = 8.0, 1 H), 4.27–4.15 (symmetric m, 4 H), 3.89 (s, 1 H), 3.45 (s, 2 H), 1.65 (s, 9 H), 1.25 (t, J = 6.9, 6 H); ^{13}C NMR δ 169.8, 149.1, 134.2, 133.4, 127.6, 124.8 (q, J = 270), 126.3 (q, J = 32.2), 120.1, 119.0 (q, J = 3.5), 113.6, 112.7 (q, J = 4.5), 84.5, 79.0, 62.7, 30.3, 28.1, 13.9; ^{19}F NMR δ −61.5 (s). Anal. Calcd. for $C_{22}H_{26}F_3NO_7$: C, 55.8; H, 5.5; N, 3.0. Found: C, 55.8; H, 5.6; N, 2.8.

Diethyl 2-[(1-tert-butoxycarbonyl-5-(trifluoromethyl)-1H-indol-3-yl)methyl]-2-hydroxymalonate (**6g**, 84%): oil; ^{1}H NMR δ 8.19 (broad d, J = 7.9, 1 H), 7.86 (s, 1 H), 7.59 (s, 1 H), 7.51 (dd, J = 8.7 and 1.7, 1 H), 4.27–4.13 (symmetric m, 4 H), 3.90 (s, 1 H), 3.46 (s, 2 H), 1.65 (s, 9 H), 1.26 (t, J = 7.1, 6 H); ^{13}C NMR δ 169.8, 149.1, 136.7, 130.5, 127.1, 124.9 (q, J = 270), 124.7 (q, J = 32), 120.9, 117.0, 115.4, 113.6, 84.4, 78.7, 62.7, 29.8, 28.2, 13.9; ^{19}F NMR δ −61.3 (s). Anal. Calcd. for $C_{22}H_{26}F_3NO_7$: C, 55.8; H, 5.5; N, 3.0. Found: C, 55.6; H, 5.5; N, 3.0.

Diethyl 2-[(1-tert-butoxycarbonyl-7-(trifluoromethoxy)-1H-indol-3-yl)methyl]-2-hydroxymalonate (**6h**, 78%): mp 96–97 °C; IR ν_{max} 3522 (broad), 3030, 2986, 2936, 1737, 1490, 1356, 1260, 1222, 1155 cm^{-1}; ^{1}H NMR δ 7.58 (dd, J = 7.5 and 0.7, 1 H), 7.51 (s, 1 H), 7.25–7.15 (m, 2 H), 4.25–4.17 (symmetric m, 4 H), 3.89 (s, 1 H), 3.42 (s, 2 H), 1.61 (s, 9 H), 1.23 (t, J = 7.1, 6 H); ^{13}C NMR δ 169.8, 148.4, 135.7, 135.0, 128.3, 126.9, 122.8, 120.9 (q, J = 255), 119.0, 118.9, 113.2, 84.3, 79.1, 62.7, 29.9, 27.9, 13.9; ^{19}F NMR δ −58.4 (s). Anal. Calcd. for $C_{22}H_{26}F_3NO_8$: C, 54.0; H, 5.3; N, 2.9. Found: C, 54.2; H, 5.4; N, 2.8.

Diethyl 2-[(1-tert-butoxycarbonyl-5-(trifluoromethoxy)-1H-indol-3-yl)methyl]-2-hydroxymalonate (**6i**, 86%): oil; IR ν_{max} 3526 (broad), 3036, 2986, 2939, 1736, 1450, 1383, 1258, 1158, 909 cm^{-1}; ^{1}H NMR δ 8.08 (broad d, J = 8.5, 1 H), 7.55 (s, 1 H), 7.45 (s, 1 H), 7.13 (dd, J = 8.5 and 1.4, 1 H), 4.2 (symmetric m, 4 H), 3.91 (s, 1 H), 3.41 (s, 2 H), 1.63 (s, 9 H), 1.25 (t, J = 7.1, 6 H); ^{13}C NMR δ 169.8, 144.8, 133.4, 131.7, 127.0, 120.7 (q, J = 254), 117.7, 115.9, 113.5, 112.2, 84.1, 78.9, 62.7, 30.2, 28.1, 14.1; ^{19}F NMR δ −58.4 (s). Anal. Calcd. for $C_{22}H_{26}F_3NO_8$: C, 54.0; H, 5.3; N, 2.9. Found: C, 54.1; H, 5.3; N, 2.9.

Diethyl 2-[(1-tert-butoxycarbonyl-5,7-bis(trifluoromethyl)-1H-indol-3-yl)methyl]-2-hydroxymalonate (**6j**, 81%): mp 120–122 °C; IR ν_{max} 3514 (broad), 2986, 2936, 1740 (vs, two broad bands), 1625, 1278, 1151, 778, 747 cm^{-1}; ^{1}H NMR δ 8.11 (s, 1 H), 7.85 (s, 1 H), 7.57 (s, 1 H), 4.2 (m, 4 H), 3.92 (s, 1 H), 3.49 (s, 2 H), 1.63 (s, 9 H), 1.28 (t, J = 7.1, 6 H); ^{13}C NMR δ 169.6, 149.0, 133.5, 131.9, 130.6, 124.7 (q, J = 33), 124.0 (q, J = 270), 123.3 (q, J = 270), 120.9, 120.0, 118.5 (q, J = 34), 113.4, 85.5, 78.8, 62.8, 29.6, 27.7, 13.9; ^{19}F NMR δ −58.1 (s), −61.7 (s). Anal. Calcd. for $C_{23}H_{25}F_6NO_7$: C, 51.0; H, 4.6; N, 2.6. Found: C, 51.2; H, 4.7; N, 2.4.

Diethyl 2-[(1-tert-butoxycarbonyl-6-methoxy-7-fluoro-1H-indol-3-yl)methyl]-2-hydroxymalonate (**6k**, 77%): viscous oil; IR ν_{max} 3514 (broad), 2986, 2936, 1737 (vs, broad), 1633, 1510, 1370, 1279, 1238, 1156 cm^{-1}; ^{1}H NMR δ 7.45 (s, 1 H), 7.29 (dd, J = 8.6 and 1.2, 1 H), 6.96 (dd, J = 8.6 and 6.8, 1 H), 4.2 (m, 4 H), 3.94 (s, 3 H), 3.86 (s, 1 H), 3.40 (s, 2 H), 1.63 (s, 9 H), 1.27 (t, J = 7.1 H, 6 H); ^{13}C NMR δ 169.8, 149.0, 145.7 (d, J = 11), 140.9 (d, J = 251), 128.7, 126.7, 122.8 (d, J = 7.0), 114.3 (d, J = 4.6), 113.4, 110.5, 84.0, 79.1, 62.6, 57.8, 29.9, 27.9, 13.9; ^{19}F NMR δ −140.1 (d, J = 6.5). Anal. Calcd. for $C_{22}H_{28}FNO_8$: C, 58.3; H, 6.2; N, 3.1. Found: C, 58.2; H, 6.3; N, 3.0.

(±)-*Ethyl 3-(1-tert-butoxycarbonyl-5-fluoro-1H-indol-3-yl)-2-hydroxypropionates* (**7d**, 63%): viscous oil; IR ν_{max} 3479, 3021, 2984, 2933, 1732, 1474, 1383, 1278, 1157 cm^{-1}; ^{1}H NMR δ 8.07 (broad s, 1 H), 7.52 (s, 1 H), 7.22 (dd, J = 8.9 and 2.5, 1 H), 7.02 (td, J = 9.0 and 2.5, 1H), 4.49 (broad s, X portion of an ABX system, 1 H), 4.2 (symmetric s, 2 H), 3.19–3.03 (eight peaks, AB portion of an ABX system, 2 H), 2.94 (broad s, 1 H), 1.65 (s, 9 H), 1.28 (t, J = 7.2, 3 H); ^{13}C NMR δ 174.1, 159.2 (d, J = 237), 149.3, 131.6 (d, J = 4.5), 125.9, 116.1 (d, J = 9.0), 114.9 (d, J = 3.9), 112.1 (d, J = 25), 104.8 (d, J = 24), 83.8, 70.1, 62.0, 29.8, 28.1, 14.1; ^{19}F NMR −121.5 (broad s). Anal. Calcd. for $C_{18}H_{22}FNO_5$: C, 61.5; H, 6.3; N, 4.0. Found: C, 61.8; H, 6.4; N, 4.0.

(±)-*Ethyl 3-(1-tert-butoxycarbonyl-5-(trifluoromethoxy)-1H-indol-3-yl)-2-hydroxypropionates* (**7i**, 65%): mp 70–72 °C; IR ν_{max} 3538 (broad), 3031, 2985, 2934, 1732, 1450, 1384, 1258, 1158 cm^{-1}; ^{1}H NMR δ 8.12 (broad d, J = 7.6, 1 H), 7.55 (s, 1 H), 7.41 (d, J = 1.0, 1 H), 7.17 (dd, J = 9.0 and 1.1, 1 H), 4.51–4.47 (four peaks, X portion of an ABX system, 1 H), 4.2 (symmetric m, 2 H), 3.21–3.05 (eight peaks, AB portion of an ABX system, 2 H), 2.96 (d, J = 5.6, 1 H), 1.65 (s, 9 H), 1.27 (t, J = 7.1, 3 H); ^{13}C NMR δ 174.0, 149.2, 144.8, 133.6, 131.4, 126.1, 120.6 (q, J = 254), 117.7, 116.0, 115.0, 111.7, 84.1, 70.1, 62.0, 29.6, 28.1, 14.0; ^{19}F NMR δ −58.4 (s). Anal. Calcd. for $C_{19}H_{22}F_3NO_6$: C, 54.7; H, 5.3; N, 3.4. Found: C, 54.7; H, 5.4; N, 3.4.

(±)-*Ethyl 3-(1-tert-butoxycarbonyl-5,7-bis(trifluoromethyl)-1H-indol-3-yl]-2-hydroxypropionates* (**7j**, 62%): mp 98–100 °C; IR ν_{max} 3536 (broad), 3021, 2986, 2936, 1764, 1734, 1332, 1278, 1150, 894 cm^{-1}; ^{1}H NMR δ 8.05 (s, 1 H), 7.86 (s, 1 H), 7.56 (s, 1 H), 4.53–4.49 (four peaks, X portion of an ABX system, 1 H), 4.2 (symmetric m, 2 H), 3.27–3.13 (eight peaks, AB portion of an ABX system, 2 H), 3.02 (d, J = 5.0, 1

H), 1.63 (s, 9 H), 1.28 (t, J = 7.2, 3 H); ^{13}C NMR δ 173.8, 149.1, 133.3, 132.1, 129.7, 124.7 (q, J = 33), 124.0 (q, J = 270), 123.3 (q, J = 271), 120.4, 120.3, 118.6 (q, J = 34), 114.9, 85.5, 70.0, 62.1, 29.1, 27.7, 14.0; ^{19}F NMR δ −58.1 (s), −61.7 (s). Anal. Calcd. for $C_{20}H_{21}F_6NO_5$: C, 51.2; H, 4.5; N, 3.0. Found: C, 51.3; H, 4.6; N, 3.1.

(±)-*Ethyl 2-[(1-tert-butoxycarbonyl-7-fluoro-1H-indol-3-yl)methyl]-2-hydroxy-3,3,3-trifluoropropionates* (**8b**, 61%): mp 105–107 °C; IR ν_{max} 3514 (broad), 3026, 2985, 2933, 1740 (broad), 1494, 1371, 1281, 1155 cm^{-1}; ^{1}H NMR δ 7.55 (s, 1 H), 7.39 (dd, J = 7.9, 1 H), 7.17 (td, J = 7.9 and 4.0, 1 H), 7.02 (ddd, J = 12, 7.9 and 0.9, 1 H), 4.2 (symmetric m, 2 H), 3.93 (d, J = 1.0, 1 H), 3.46–3.21 (four peaks, AB portion of an ABX system, 2 H), 1.64 (s, 9 H), 1.24 (t, J = 7.2, 3 H); ^{13}C NMR δ 168.9, 149.9 (d, J = 251), 148.6, 134.8 (d, J = 3.6), 127.8, 123.3 (q, J = 285), 123.3 (d, J = 7.1), 121.8, 115.2 (d, J = 3.7), 112.0, 111.7 (d, J = 22), 84.3, 75.5 (q, J = 29), 63.9, 27.9, 27.2, 13.8; ^{19}F NMR δ −78.1 (s), -116.5 (dd, J = 12.6 and 4.0). Anal. Calcd. for $C_{19}H_{21}F_4NO_5$: C, 54.4; H, 5.0; N, 3.3. Found: C, 54.4; H, 5.1; N, 3.4.

(±)-*Ethyl 2-[(1-tert-butoxycarbonyl-5-fluoro-1H-indol-3-yl)methyl]-2-hydroxy-3,3,3-trifluoropropionates* (**8d**, 60%): mp 98–100 °C; IR ν_{max} 3508, 3019, 2984, 2939, 1736, 1475, 1381, 1279, 1157 cm^{-1}; ^{1}H NMR δ 8.05 (broad s, 1 H), 7.54 (s, 1 H), 7.27 (dd, J = 8.7 and 2.5, 1 H), 7.02 (td, J = 9.0 and 2.5, 1 H), 4.2 (symmetric m, 2 H), 3.96 (s, 1 H), 3.43–3.18 (four peaks, AB system, J_{AB} = 15, 2 H), 1.65 (s, 9 H), 1.23 (t, J = 7.2, 3 H); ^{13}C NMR δ 168.9, 159.2 (d, J = 237), 149.2, 131.4, 127.1, 123.3 (q, J = 285), 116.1 (d, J = 9), 112.2 (d, J = 25), 111.7, 105.1 (d, J = 24), 84.1, 77.9 (q, J = 28), 63.9, 28.1, 27.3, 13.7; ^{19}F NMR δ −78.7 (s), −121.3 broad (s). Anal. Calcd. for $C_{19}H_{21}F_4NO_5$, C, 54.4; H, 5.0; N, 3.3. Found: C, 54.6; H, 5.1; N, 3.4.

(±)-*Ethyl 2-[(1-tert-butoxycarbonyl-5-(trifluomethoxy)-1H-indol-3-yl)methyl]-2-hydroxy-3,3,3-trifluoropropionate* (**8i**, 63%): mp 90–93 °C; IR ν_{max} 3506, 3024, 2985, 2938, 1737, 1451, 1381, 1258, 1158 cm^{-1}; ^{1}H NMR δ 8.12 (broad d, J = 8.6, 1 H), 7.58 (s, 1 H), 7.45 (d, J = 1.1, 1 H), 7.18 (dd, J = 9.1 and 1.1, 1 H), 4.2 (symmetric m, 2 H), 3.96 (d, J = 1.0, 1 H), 3.45–3.21 (four peaks, AB system, J_{AB} = 15, 2 H), 1.66 (s, 9 H), 1.24 (t, J = 7.1, 3 H); ^{13}C NMR δ 168.9, 149.0, 144.9, 133.3, 131.2, 127.3, 123.3 (q, J = 285), 117.9, 116.0, 112.0, 111.8, 84.4, 64.0, 28.1, 27.1, 13.7; ^{19}F NMR δ −58.4 (s), −78.7 (s). Anal. Calcd. for $C_{20}H_{21}F_6NO_6$: C, 49.5; H, 4.4; N, 2.9. Found: C, 49.6; H, 4.3; N, 3.0.

Acknowledgements

Thanks are due to MIUR (Ministero dell'Università e Ricerca), to CEMIN (Centro di Eccellenza per Materiali Innovativi Nanostrutturati and to University of Perugia for financial support (PRIN 2004 contract no. 2004033322). We also wish to express our sincere gratitude to the Institute of Chemical Sciences and Engineering (ISIC) of the ''Ecole Polytechnique Fédérale de Lausanne'' (Epfl) through its Dean, Professor Thomas Rizzo, for the useful donation of laboratory equipment.

References

[1] (a) M. Schlosser, in: V.A. Soloshonok (Ed.), Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets, Wiley, Chichester, 1999;
(b) M. Schlosser, Angew. Chem. 110 (1998) 1538–1556;
(c) M. Schlosser, Angew. Chem. Int. Ed. Engl. 37 (1998) 1496–1513;
(d) M. Schlosser, D. Michel, Tetrahedron 52 (1996) 99–108;
(e) R. Filler, Y. Kobayashi, L.M. Yagupolskii (Eds.), Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications, Elsevier, Amsterdam, 1993;
(f) G. Resnati, Tetrahedron 49 (1993) 9385–9445;
(g) T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, Wiley, New York, 1991;
(h) R. Filler, Y. Kobayashi (Eds.), Biomedical Aspects of Fluorine Chemistry, Kodansha, Ltd./Elsevier Biomedical, Tokio/Amsterdam, 1982

[2] (a) W. Hofheinz, H. Bürgin, H. Gocke, C. Jacquet, R. Masciadri, G. Schmid, H. Stohler, H. Urwyler, Trop. Med. Parasitol. 45 (1994) 261–265;
(b) W. Hofheinz, H. Bürgin, H. Gocke, C. Jacquet, R. Masciadri, G. Schmid, H. Stohler, H. Urwyler, Chem. Abs. 122 (1995) 71406k;
(c) K. Sestanj, F. Bellini, S. Fung, N. Abraham, A. Treasurywala, L. Humber, N. Sinard-Dequesne, D. Dvornik, J. Med. Chem. 27 (1984) 255–256;
(d) A. Thompson, E.G. Corley, M.F. Huntington, E.J.J. Grabowski, J.F. Remenar, D.B. Collum, J. Am. Chem. Soc. 120 (1998) 2028–2038.

[3] (a) L.M. Yagupolskii, L.Z. Gandelsman, Zh. Obshch. Khim. 33 (1963) 2301–2307;
(b) L.M. Yagupolskii, L.Z. Gandelsman, J. Gen. Chem. USSR 33 (1963) 2240–2245;
(c) L.M. Yagupolskii, L.Z. Gandelsman, Chem. Abstr. 60 (1964) 692a;
(d) S. Ghosh, Y. Zheng, X. Jun, R.K. Narla, S. Mahajan, C. Navara, C. Mao, E.A. Sudbeck, F.M. Uckun, Clin. Cancer Res. 4 (1998) 2657–2668;
(e) S. Ghosh, Y. Zheng, X. Jun, R.K. Narla, S. Mahajan, C. Navara, C. Mao, E.A. Sudbeck, F.M. Uckun, Chem. Abstr. 130 (1999) 177207b;
(f) T.J. Rosen, K.J. Coffman, S. McLean, R.T. Crawford, D.K. Bryce, Y. Gohda, M. Tsuchiya, A. Nagahisa, M. Nakane, J.A. Lowe, Bioorg. Med. Chem. Lett. 8 (1998) 281–284;
(g) S. Gonsalves, J. Watson, C. Ashton, Eur. J. Pharmacol. 305 (1996) 181–185.

[4] (a) O. Vandeputte, S. Oden, A. Mol, D. Vereecke, K. Goethals, M. El Jaziri, E. Prinsen, Appl. Envir. Microbiol. 71 (2005) 1169–1177;
(b) V.A. Marinos, M.E. Tate, P.J. Williams, Phytochemistry 31 (1992) 2755–2759.

[5] (a) I. Ojima, ChemBioChem 5 (2004) 628–635;
(b) A.E. Klopffer, J.W. Engels, ChemBioChem 5 (2004) 707–716;
(c) G. Beck, Synlett (2002) 837–850;
(d) B.E. Smart, J. Fluorine Chem. 109 (2001) 3–11;
(e) J.T. Welch, Tetrahedron 43 (1987) 3123–3197.

[6] See for example:
(a) G.R. Humphrey, J.T. Kuethe, Chem. Rev. 106 (2006) 2875–2911;
(b) S. Cacchi, G. Fabrizi, Chem. Rev. 105 (2005) 2873–2920;
(c) R. Dalpozzo, G. Bartoli, Curr. Org. Chem. 9 (2005) 163–178;
(d) G.W. Gribble, J. Chem. Soc. Perkin Trans (2000) 1045–1075.

[7] (a) S.M. Bromidge, S. Dabbs, D.T. Davies, S. Davies, D.M. Duckworth, I.T. Forbes, P. Ham, G.E. Jones, F.D. King, D.V. Saunders, S. Starr, K.M. Thewlis, P.A. Wyman, F.E. Blaney, C.B. Naylor, F. Bailey, T.P. Blackburn, V. Holland, G.A. Kennett, G.J. Riley, M.D. Wood, J. Med. Chem. 41 (1998) 1598–1612;
(b) A.N. Tischler, T.J. Lanza, Tetrahedron Lett. 27 (1986) 1653–1656.

[8] S. Debarge, K. Kassou, H. Carreyre, B. Violeau, M.-P. Jouannetaud, J.-C. Jacquesy, Tetrahedron Lett. 45 (2004) 21–23.

[9] S. Leconte, R. Ruzziconi, J. Fluorine Chem. 117 (2002) 167–172.

[10] (a) S.N. Osipov, N.M. Kobel'kova, A.F. Kolomiets, K. Pumpor, B. Koksch, K. Burger, Synlett (2001) 1287–1289;
(b) J.H. Tidwell, S.L. Buchwald, J. Am. Chem. Soc. 116 (1994) 11797–11810.

[11] (a) Y. Ueno, K. Chino, M. Watanabe, O. Moriya, M. Okawara, J. Am. Chem. Soc. 104 (1982) 5564–5566;

(b) G. Stork, in: H. Nozaki (Ed.), Current Trends in Organic Synthesis, Pergamon Press, Oxford, 1983, p. 359;
(c) G. Stork, N.H. Baine, J. Am. Chem. Soc. 104 (1982) 2321–2323;
(d) C.P. Jasperse, D.P. Curran, T.L. Fevig, Chem. Rev. 91 (1991) 1237–1286;
(e) B. Quiclet-Sire, B. Sortais, S.Z. Zand, Chem. Commun. (2002) 1692–1693;
(f) X.J. Salom-Roig, F. Dénès, P. Renaud, Synthesis (2004) 1903–1928.

[12] (a) M. Schlosser, Angew. Chem. Int. Ed. Engl. 44 (2005) 376–439;
(b) M. Schlosser, Eur. J. Org. Chem. (2001) 3975–3984.

[13] (a) J.M. Muchowski, M.C. Venuti, J. Org. Chem. 45 (1980) 4798–4801;
(b) L.R. Hillis, S.J. Gould, J. Org. Chem. 50 (1985) 718–719;
(c) I.S. Cho, L. Gong, J.M. Muchowski, J. Org. Chem. 56 (1991) 7288–7291;
(d) P. Stanetty, H. Koller, M. Mihovilovic, J. Org. Chem. 57 (1992) 6833–6837;
(e) S. Takagishi, G. Katsoulos, M. Schlosser, Synlett (1992) 360–362;
(f) J.I. Ubeda, M. Villacampa, C. Avendaño, Synlett (1997) 285–286.

[14] (a) F. Leroux, E. Castagnetti, M. Schlosser, J. Org. Chem. 68 (2003) 4693–4699;
(b) M. Schlosser, M. Marull, Eur. J. Org. Chem. (2003) 1569–1575;
(c) M. Schlosser, E. Castagnetti, Eur. J. Org. Chem. (2001) 3991–3997.

[15] The protection of the amino group by the classical treatment with di-tert-butyl dicarbonate is anything but a foregone, operation., In the cases where the amino group is adjacent to the bulky CF3 or OCF3 group, the recourse to the DMAP-catalysed double amidation, successive K2CO3-promoted solvolysis of the resulting, *N,N*-di-Boc derivative in methanol was, required S. Darnbrough, M. Mervic, S.M. Condon, C.J. Burns, Synth. Commun. 31 (2001) 3273–3280.

[16] (a) R.D. Clark, J.M. Caroon, J. Org. Chem. 47 (1982) 2804–2806;
(b) S. Takagishi, G. Katsoulos, M. Schlosser, Synlett (1992) 360–362.

[17] As suggested by Schlosser [16b] a plausible access to *N*-(2-bromo-3-fluorophenyl)carbamate could be realized by treating *N*-(3-fluorophenyl)-carbamate with butyllithium and pentamethyldiethylentriamine (PMDTA) in THF for 2 h at −75 °C before the addition of a brominating reagent.

[18] Actually, the ^{1}H, ^{13}C, and ^{19}F NMR spectra point out a mixture of two conformers. Accordingly, the ^{1}H NMR spectrum exhibits two AB systems in varying intensity ratios at δ 4.8–3.7 ppm, attributable to CH_2 protons of the propargylic group, as well as two triplets ($J = 2.5$), in the same ratios at δ 2.1 ppm assignable to the acetylenic protons and two singlet at δ 1.6–1.5 ppm, again in the same intensity ratio, ascribed to *tert*-butyl group. Most probably, the two conformers originate from the hindered rotation around the carbonyl-nitrogen bond due to the zwitterionic nature of the amide group. The two propargylic protons are most likely rendered diastereotopic due to atropoisomerism around the aryl-nitrogen bond.

[19] (a) G. Jenner, R.B. Salem, B. El'yanov, E.M. Gonikberg, J. Chem. Soc. Perkin Trans. 2 (1989) 1671–1675;
(b) B.B. Snider, Acc. Chem. Res. 13 (1980) 426–432;
(c) G. Jenner, M. Papadopoulos, J. Org. Chem. 47 (1982) 4201–4204;
(d) O. Achmatowicz, E. Białecka-Florjańczyk, Tetrahedron 52 (1996) 8827–8834.

[20] (a) G. Ricci, R. Ruzziconi, J. Org. Chem. 70 (2005) 611–623;
(b) R.W. Hartmann, A. Palusczak, F. Lacan, G. Ricci, R. Ruzziconi, J. Enzyme Inhib. Med. Chem. 19 (2004) 145–155.

[21] M. Schlosser, A. Ginanneschi, F. Leroux, Eur. J. Org. Chem. (2006) 2956–2969.

[22] P. Hewawasam, W. Fan, J. Knipe, S.L. Moon, C.G. Boissard, V.K. Gribkoff, J.E. Starrett Jr., Bioorg. Med. Chem. Lett. 12 (2002) 1779–1783.

[23] Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, J. Am. Chem. Soc. 127 (2005) 10164–10165.

[24] R.E. Swenson, T.J. Sowin, H.Q. Zhang, J. Org. Chem. 67 (2002) 9182–9185.

[25] A. Kessler, C.M. Coleman, P. Charoenying, D.F. O'Shea, J. Org. Chem. 69 (2004) 7836–7846.