Synthesis of highly substituted 2-perfluoroalkyl quinolines by electrophilic iodocyclization of perfluoroalkyl propargyl imines/amines†

Pravin R. Likhar,*[a] Madavu Salian Subhas,[a] Sarabindu Roy,[a] Mannepalli Lakshmi Kantam,[a] Balasubramanian Sridhar,[b] Ratanesh Kumar Seth[c] and Sukla Biswas[c]

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A series of highly substituted 2-perfluoroalkyl-3-iodoquinolines are prepared by two different methods in good to excellent yields under mild reaction conditions. The first method involves iodocyclization of perfluoroalkyl propargyl imines with I_2-CAN. The second method involves iodocyclization of perfluoroalkyl propargyl amines using I_2 and ICl. The perfluoroalkyl propargyl amines are prepared in excellent yields *via* Sonogashira coupling of easily accessible imidoyl iodides with alkynes followed by reduction with $NaBH_3CN$. The scope of this methodology is extended by using the resulting 2-perfluoroalkyl-3-iodo quinolines in Suzuki, annulation, dehalogenation and carboxylation reactions. Antimalarial activity of the 2-perfluoroalkyl-3-iodoquinolines is discussed.

Introduction

Recently, fluorinated compounds have attracted considerable attention from the synthetic and medicinal chemists due to the unique physical and biological properties imparted by fluorine. Substitution of an aromatic hydrogen atom by a perfluoroalkyl group has a substantial effect on these characteristics.[1] In particular, trifluoromethylated quinolines have been found to possess special biological properties.[2–5] For example, 2-trifluoromethylated quinolines are of significant pharmacological interest for their use as potent antimalarial agents (mefloquine),[2] PDE4 inhibitors,[3] DPP-IV inhibitors,[4] and leishmanicidal agents.[5]

In view of the importance of fluorine-containing quinoline compounds, considerable effort has been placed in developing an efficient method for the synthesis of trifluoromethylated quinoline derivatives. The usual synthetic methods for the introduction of a CF_3 group into aromatic systems have been fluorination of a suitable functional group[6] (*i.e.* halogen exchange of $-CCl_3$, $-CBr_3$), fluorination of $-CO_2H$[7] upon treatment with a fluorinated Lewis acid (SbF_3, SbF_5, SF_4, *etc.*) or by Ullmann-type reaction of perfluoroalkyl iodides and aryl halides using copper powder.[8] Many other methods are known for the synthesis of 2-perfluoroalkyl-subsituted quinolines but many such methodologies afford the products in low yields.[9]

Baraznenok *et al.*[10] have reported an elegant high yielding synthesis of 2-perfluroalkyl substituted quinolines from anilines and 4-dimethylamino-1,1,1-trifluoro-3-buten-2-one. However this protocol does not provide access to 3- or 4- substituted 2-perfluoroalkylquinolines. In 2001, Amii *et al.* reported one-pot synthesis of highly substituted fluorinated quinolines by Rh(I)-catalyzed cyclization of *N*-aryl trifluoroacetimidoyl chlorides using alkynes.[11] Unfortunately this procedure suffered from poor regioselectivity when unsymmetrical internal alkynes were used. Consequently, the development of an efficient and selective synthesis of 2-perfluoroalkyl substituted quinolines using mild reaction conditions remains an active research area.

The synthesis of carbocycles and heterocycles can be achieved through cyclization of aryl-substituted alkynes *via* intramolecular hydroarylation. Recently, the electrophilic cyclization of functionalized alkenes and alkynes has received considerable attention by organic chemists for synthesizing furans, quinolines, benzo[*b*]furans, benzothiophenes, indoles, isoquinolines and furopyridines *etc.*[12] Such work provides encouragement for the synthesis of 2-perfluoroalkyl quinolines *via* an electrophilic iodocyclization reaction.

Results and discussion

It is assumed that 2-perfluoroalkyl quinolines can be synthesized by electrophilic cyclization of 2-perfluoroalkynyl imines as shown in Scheme 1. Accordingly, the 2-perfluoroalkynyl imine (**3b**) was synthesized *via* Sonogashira coupling[13,14] of imidoyl iodide (**1b**)[15] and phenylacetylene (**2b**) (Scheme 2).

In an attempt to cyclize the imine product, **3b** was treated with I_2 (2.0 equiv) and $NaHCO_3$ (2.0 equiv) in acetonitrile at room temperature. Only a trace amount of the product, **5b** was obtained (Table 1, entry 1). When a strong eletrophile, ICl was employed, the product was isolated in 10% yield (entry 2).

After recent success in iodocyclization of the (2-methoxyaryl)-system,[16] the iodocyclization of **3b** (0.5 mmol) was examined, using I_2 (2.0 mmol)-CAN (1.0 mmol) in 0.1 M CH_3CN at room temperature. Product **5b** was obtained in 65% isolated yield (entry 3). Subsequently, conditions for optimization of I_2 and CAN to afford maximum product yield were tested (Table 1). The

[a]*Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad, 500670, India. E-mail: plikhar@iict.res.in; Fax: +91-40-27160921*
[b]*X-Ray Crystallography Division, Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad, 500670, India*
[c]*National Institute of Malaria Research (ICMR), 22 Shamnath Marg, Delhi, 110 054, India*

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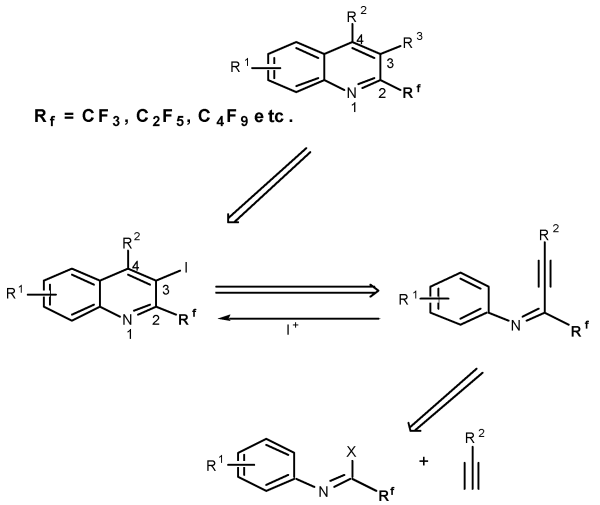
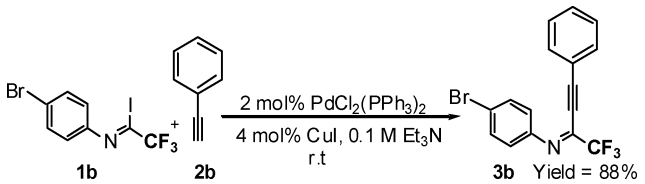
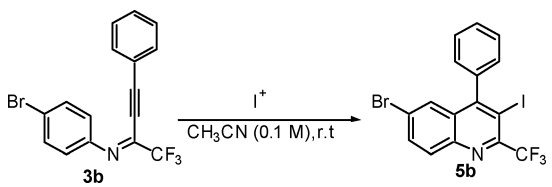


Scheme 1 Retrosynthetic approach for synthesis of 2-perfluoroalkyl-substituted quinolines.



Scheme 2 Synthesis of 2-perfluoroalkynyl imines using coupling of imidoyl iodide and phenylacetylene.

Table 1 Optimization of I_2, ICl, and I_2/CAN in the iodocyclization of **3b**[a]



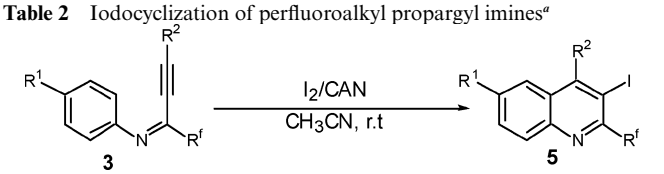
Entry	I^+ (equiv)	CAN (equiv)	Time (h)	Yield (%)[b]
1	I_2 (2.0)	0	24	Trace [c]
2	ICl (2.0)	0	24	10[d]
3	I_2 (2.0)	1.0	5	65
4	I_2 (2.0)	2.0	2	85
5	I_2 (3.0)	2.0	3	85
6	I_2 (1.0)	2.0	5	53

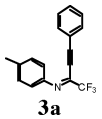
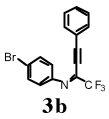
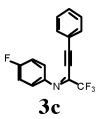
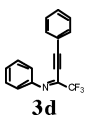
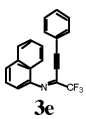
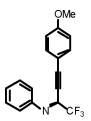
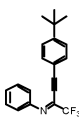
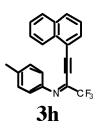
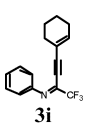
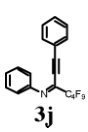
[a] Reaction condition: 0.5 mmol of **3b**, I_2 and CAN in 0.1M of CH_3CN at room temp. [b] Yield of isolated product, **5b**. [c] 2 equiv of $NaHCO_3$ was used. [d] 2 equiv of $NaHCO_3$ in 0.1M CH_2Cl_2 was used.

highest yield (85%) was obtained with 2 equiv of I_2 and 2 equiv of CAN in 0.1 M CH_3CN at room temperature (entry 4).

To investigate the scope of the reaction, the effect of various R^1 groups on the aniline moiety were examined. The electron-donating methyl group afforded corresponding quinoline in 86% yield, while the strongly electron-withdrawing fluorine failed to afford the product (Table 2, entries 1 and 3). The unsubstituted aniline and naphthylamine provided good product yields (entries 4 and 5). The effect of various substitutents on the alkyne moiety was then examined. The substituted aromatic alkynes underwent smooth iodocyclization to afford the corresponding quinolines in

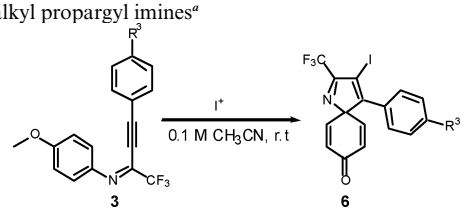
Table 2 Iodocyclization of perfluoroalkyl propargyl imines[a]



Entry	3	Time (h)	5	Isolated yields (%)
1	 **3a**	3	**5a**	86
2	 **3b**	3	**5b**	85
3	 **3c**	24	**5c**	0
4	 **3d**	3	**5d**	82
5	 **3e**	4	**5e**	83
6	 **3f**	2	**5f**	86
7	 **3g**	3	**5g**	78
8	 **3h**	4	**5h**	75
9	 **3i**	4	**5i**	81
10	 **3j**	12	**5j**	86[b]

[a] Reaction conditions: 0.5 mmol of **3**, I_2 (2 equiv) and CAN (2 equiv) in 5 mL of CH_3CN at room temp. [b] I_2 (3 equiv) and CAN (2 equiv) were employed.

Table 3 Electrophilic *ipso* iodocyclization of *para*-methoxy-substituted perfluoroalkyl propargyl imines[a]



Entry	3	R^3	Time (h)	6	% Yield[b]
1	3k	H	0.5	**6a**	92
2	3l	*p*-MeO	0.5	**6b**	90
3	3k	H	24	**6a**	78[c]
4	3l	*p*-MeO	24	**6b**	80[c]

[a] Reaction conditions: 0.5 mmol of **3**, 2 equiv of I_2 and 2 equiv of CAN in 0.1 M CH_3CN at room temp. [b] Isolated yields. [c] 2 equiv of I_2 and 2 equiv of $NaHCO_3$ in 0.1 M CH_3CN at room temp.

excellent yields (entries 6, 7 and 8). The olefin-substituted alkyne gave the desired product with 81% yield (entry 9). A good yield was observed when the perfluoroalkyl chain was changed from CF_3 to C_4F_9 (entry 10).

Surprisingly, when *para*-substituted methoxy perfluoroalkyl propargyl imine **3k** was subjected to iodocyclization, only the azaspiro compound **6a** was obtained in 92% and in 0.5h instead of the desired quinoline product, **5k** (Table 3, entry 1).[17] Similarly, **6b** was obtained in 90% yield from **3l** (entry 2). As an alternative, it was also found that $I_2/NaHCO_3$ was effective for the synthesis of azaspiro compound, however the reaction was more sluggish than the I_2-CAN system (entries 3 and 4). The structure of the azaspiro compound **6a** was confirmed by ^1H NMR, ^{13}C NMR, HRMS and by single-crystal X-ray diffraction study (Fig. 1).[18]

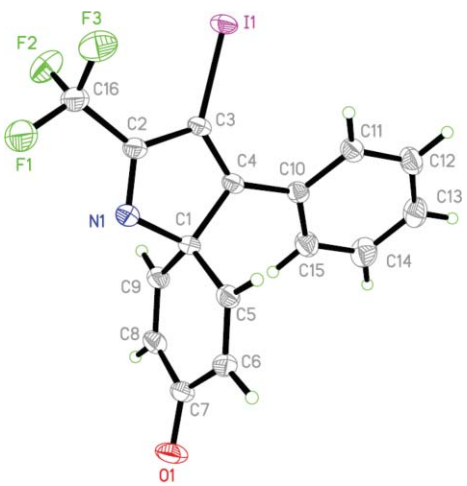
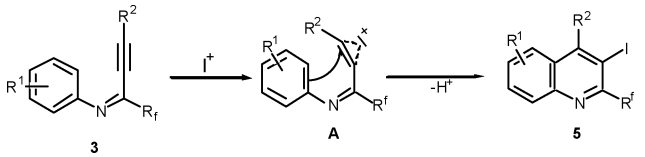


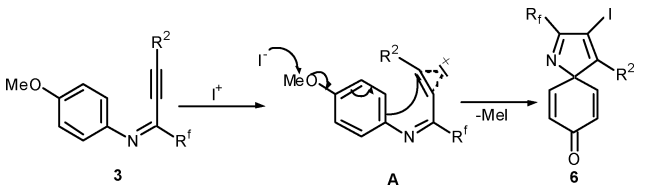
Fig. 1 ORTEP diagram of compound **6a** (see Table 3).

The observed results can be plausibly explained by electrophilic attack of the iodine cation which is generated in situ by activating with CAN, on the carbon-carbon triple bond of the propargylic aniline to give the iodonium intermediate **A**. It is believed that CAN acts as an efficient and convenient activator for I_2 and during the activation process, reduces Ce(IV) to Ce(III).[19] The intramolecular *ortho* cyclization of the aniline aromatic ring with the activated triple bond results in the formation of perfluoroalkyl quinolines **5** (Scheme 3).



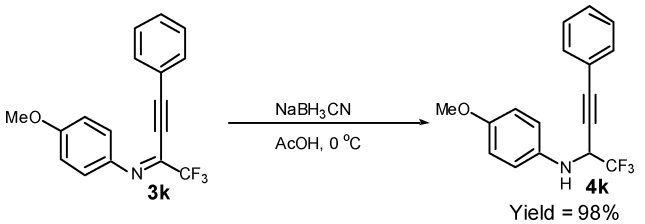
Scheme 3 Plausible mechanism for the formation of compound **5** (Table 2).

In the case of *para*-methoxy substituted aniline, the formation of the azaspiro compound can be explained similarly to above where the iodonium intermediate **A** is generated in the first step. The intermediate **A** can in turn undergo intramolecular *ipso*-cyclization with the electron rich aromatic ring. The removal of the methyl group *via* nucleophilic displacement results into formation of compound **6**[17](Scheme 4).



Scheme 4 Plausible mechanism for the formation of compound **6** (Table 3).

To potentially overcome the limitations of I_2/CAN system in the above iodocyclization process, the iodocyclization of perfluoroalkyl propargyl amines, a reduction product of perfluoroalkyl propargyl imines was examined. Thus 2-trifluoromethyl-substituted propargyl imine **3k** was treated with $NaBH_3CN$ in acetic acid at 0 °C to afford 2-trifluoromethyl-substituted propargyl amine, **4k** in quantitative yields (Scheme 5).

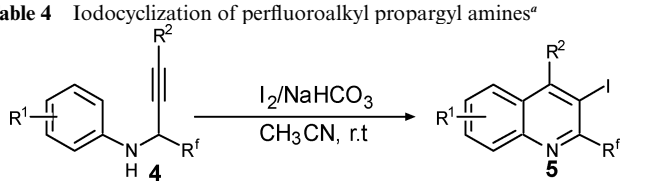


Scheme 5 Reduction of 2-trifluoromethyl-substituted propargyl imine, **3k** to 2-trifluoromethyl-substituted propargyl amine **4k**.

The potentially useful trifluoro propargyl amines were prepared by the addition of acetylenes to trifluoro methyl iminium ions, generated from the corresponding oxazolidines[20] or aminal[21] in the presence of Lewis acid. Recently, another preparation has been reported which describes addition of acetylides to trifluoromethyl aldimines.[22] However, to the best of the authors' knowledge, the synthesis of perfluoroalkyl propargyl amines by the reduction of perfluoroalkyl propargyl imines prepared from Sonogashira coupling reaction of easily accessible corresponding imidoyl iodides and alkynes has not yet been reported.

Next, **4k** was treated with 3 equiv. of iodine in the presence of 2 equiv. of $NaHCO_3$ in 0.1 M acetonitrile and 2-trifluromethyl-substituted quinoline **5k** obtained in 90% yield (Table 4, entry 9).

Table 4 Iodocyclization of perfluoroalkyl propargyl amines[a]



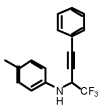
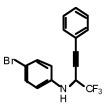
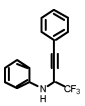
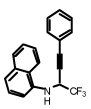
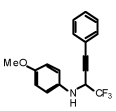
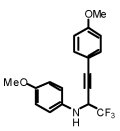
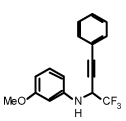
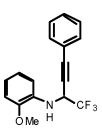
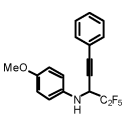
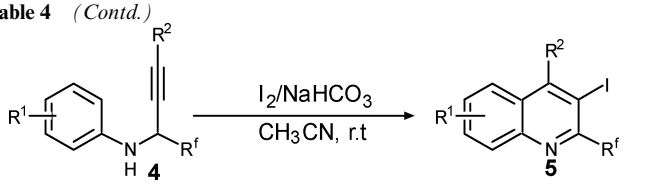
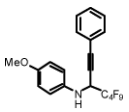
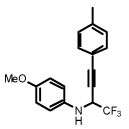
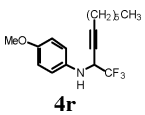
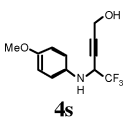
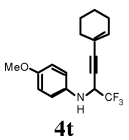
Entry	4	I^+	Time (h)	5	Yield (%)[b]
1	 **4a**	I_2	0.5	**5a**	90
2	 **4b**	I_2	24	**5b**	54
3		ICl	0.5	**5b**	82
4	 **4c**	I_2	24	**5c**	43
5		ICl	0.5	**5c**	74
6	 **4d**	I_2	1	**5d**	0
7		ICl	1	**5d**	38
8	 **4e**	I_2	0.5	**5e**	80
9	 **4k**	I_2	0.5	**5k**	90
10		ICl	0.5	**5k**	92 (79)[c]
11	 **4l**	I_2	0.5	**5l**	57
12		ICl	0.5	**5l**	84
13	 **4m**	I_2	2	**5m**	0, 25[d]
14		ICl	0.5	**5m**	0
15	 **4n**	I_2	2	**5n**	72
16		ICl	0.5	**5n**	74
17	 **4o**	I_2	0.5	**5o**	80

Table 4 *(Contd.)*



Entry	4	I^+	Time (h)	5	Yield (%)[b]
18	 **4p**	I_2	0.5	**5p**	76
19	 **4q**	I_2	0.5	**5q**	81
20	 **4r**	I_2	1	**5r**	64
21	 **4s**	I_2	1	**5s**	58
22		ICl	1	**5s**	64
23	 **4t**	I_2	0.5	**5t**	78

[a] Reaction conditions: 0.5 mmol of **3**, 2 equiv of I_2 and 2 equiv of $NaHCO_3$ in 5 mL of CH_3CN at room temp. [b] Isolated yields. [c] Room temperature. [d] Yield of isolated product, 3,6-diiodo-substituted quinoline.

It can be seen from these experiments that by changing the imine-amine substrates, selective *ipso* or *ortho* cyclization may be realised.

The effect of different solvents and bases on the iodocyclization of **4k** to improve the yield was then examined. It was found that the combination of 0.1 M of acetonitrile and 2 equiv. of $NaHCO_3$ was favourable. (Table 4, entry 9). Encouraged by the results obtained with iodine, the efficacy and generality of the current protocol was studied by employing the stronger electrophile ICl on the cyclization of compound **4k**. It was observed that ICl demonstrated improved results at 0 °C compared to the reaction at room temperature (Table 4, entry 10).

In an effort to understand the scope of the reaction, the effect of various substituents on the aniline ring was scrutinized. As expected, the electron-rich-substituted anilines promote the reaction and cyclize to give the corresponding quinolines in high yields (Table 4, entry 1). The 4-bromo and 4-fluoro-substituted anilines, in the presence of iodine, afforded moderate yields of the corresponding quinolines with incomplete conversion (entries 2 and 3). Yields were dramatically enhanced when the cyclization was carried out with ICl (entries 3 and 5). Unsubstituted aniline (**4d**) in the presence of iodine yielded iodo-substituted propargyl

amine rather than the quinoline **5d** (entry 6). Replacing the iodine with ICl afforded **5d** in 38% isolated yield. The napthylamine **4h** also provided the corresponding iodoquinoline **5e** in high yield (entry 8). When 3-methoxy-substituted aniline **4m** was treated with iodine, only 25% of the 3,6-diiodo-substituted quinoline was obtained along with uncyclized aromatic iodinated side products (entry 13). No desired quinoline product was observed in this case when ICl was used (entry 14). The iodocyclization of 2-methoxy-substituted aniline, **4n** afforded the corresponding quinoline in good yield when both I_2 and ICl electrophiles were used. (entries 15 and 16).

Attention was then focused on investigating the scope of this cyclization protocol in terms of the perfluoroalkyl chain $\mathbf{R^f}$. It was observed that both the C_2F_5 and C_4F_9-substituted propargyl amines gave high yields of the corresponding quinolines (Table 4, entries 17 and 18). Further, the aryl substitution on the alkyne moiety of the 2-perfluoroalkyl propargyl amines was varied. The iodocyclization of 4-methoxyphenyl-substituted propargyl amines **4l** gave moderate yield (57%) of the quinoline **5l** in the presence of I_2. Yield was further increased to 84% when I_2 was replaced with ICl (Table 4, entry 12). The structure of the 2-trifluoromethylated quinoline **5l** was confirmed by ^{1}H NMR, ^{13}C NMR, HRMS and by single crystal X-ray diffraction study (Fig. 2).[18]

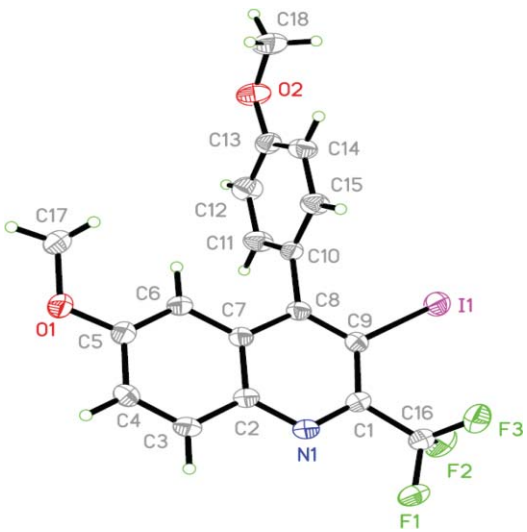
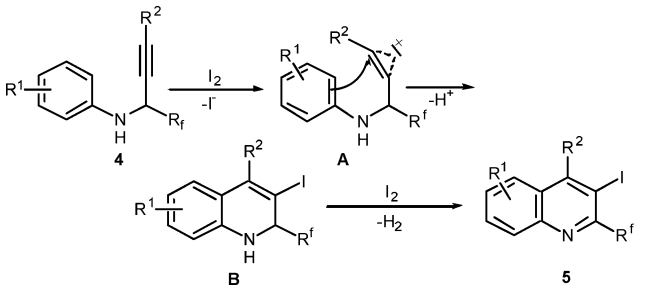


Fig. 2 ORTEP diagram of compound **5l**.

Changing the substitution at the terminal position of the C–C triple bond to alkyl chain afforded a satisfactory yield of the corresponding quinolines (entries 19–23) in the presence of iodine. When ICl was employed in place of iodine in the cyclization of propargyl alcohol **4s**, only a marginal increase in the yield was observed (entry 22). The substrate with vinylic substitution on the terminal alkyne **4t** afforded the desired 2-trifluoromethyl-substituted quinoline **5t** in 78% yield (entry 23).

The plausible mechanism for iodocyclization of perfluoroalkyl propargyl amine **4** presented herein is outlined in Scheme 6. Initially, I_2 coordinates to the alkyne moiety to form the iodonium intermediate **A**. This is followed by intramolecular nucleophilic attack of the aromatic ring of aniline on the activated alkyne moiety leading to formation of intermediate 1,2-dihydroquinoline

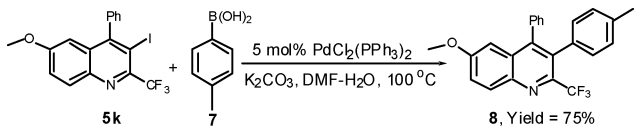


Scheme 6 Plausible mechanism for the iodocyclization of perfluoroalkyl propargyl amine and subsequent dehydrogenation to quinoline.

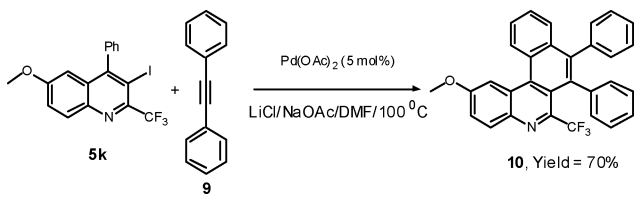
B. Subsequent oxidation of **B** by I_2 produces the corresponding quinoline **5**.[23]

The presence of the iodide functional group at the 3-position of the quinoline ring provides an opportunity to explore the scope of the chemistry. Using 3-iodoquinoline **5k**, some complex 2-perfluoroalkyl-substituted heterocycles have been synthesized in good yields.

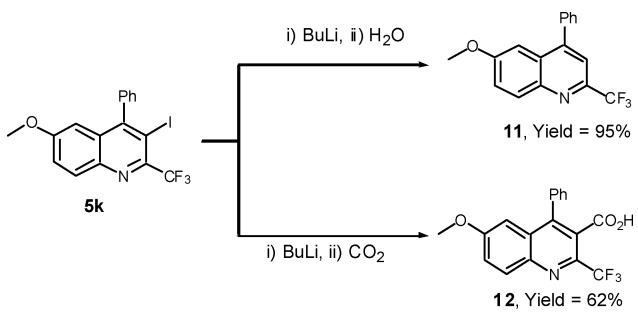
Iodoquinoline **5k** underwent facile Suzuki[24] coupling with *para*-tolylboronic acid to afford the highly substituted 6-methoxy-4-phenyl-3-*p*-tolyl-2-trifluoromethylquinoline **8** in good yield (75%).



Next, **5k** was further subjected to the palladium-catalyzed annulation reaction[25] with the diphenyl acetylene. This yielded trifluoromethyl-substituted benzophenanthridine **10** in 70% yield.



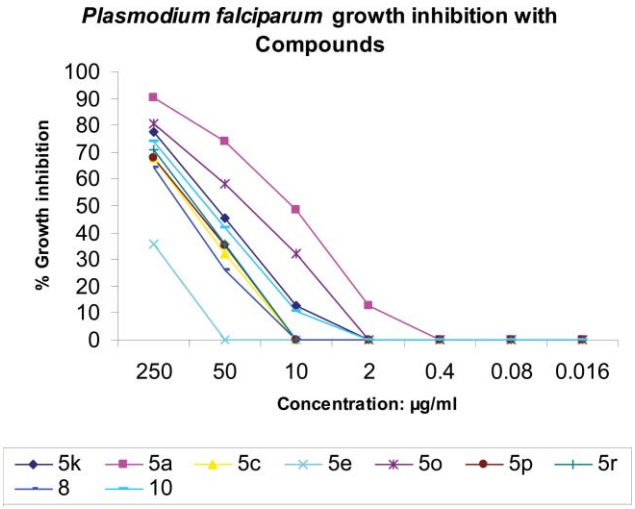
In the metal-halogen exchange reaction,[26] the treatment of n-BuLi with **5k** gave the 2-trifluoromethyl-substituted quinoline **11** in 95% yield, and subsequent treatment with CO_2[27] afforded highly substituted 2-trifluoromethyl quinoline-3-carboxylic acid **12** in 62% yield.



Antimalarial activity of perfluoroalkyl quinolines

The antimalarial activity of some the compounds (**5a**, **5c**, **5e**, **5k**, **5o**, **5p**, **5r**, **8** and **10**) against a *Plasmodium falciparum* strain

(FDL-B) was examined at different doses, starting from 250 μg/ml with 5-fold serial dilutions up to 0.016 μg/ml.[28] The doses were kept constant for all compounds in order to maintain the comparative profile of their activities. The compounds, **5a** and **5o** showed substantial *in vitro* activity for total parasite growth inhibition.



Conclusions

In conclusion, efficient and simple new methodologies for the synthesis of highly substituted perfluoroalkyl quinolines have been developed. These methodologies offer various substitutions at aniline ring or at the terminal alkyne using various perfluoroalkyl groups to allow a diverse range of quinolines to be synthesized. Therefore, such reactions may be distinctly important for pharmacological applications. The iodocyclization processes using I_2/CAN, I_2 and ICl showed considerable synthetic advantages in terms of product diversity, mild reaction conditions, the simplicity of the reaction process and good-to-excellent yields. A new route for the synthesis of 2-perfluoroalkylpropargyl amines, which are the building blocks of perfluoroalkyl heterocycles, have also been demonstrated. Further work is in progress for the synthesis of more complex molecular structures.

Experimental

All reactions were conducted in flame dried glass apparatus. Reactions were followed by TLC analysis using silica plates visualized with a UV lamp. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in Fourier transform mode. Chemical shifts are given in ppm, the internal standard reference is Trimethylsilane for ^{1}H and ^{13}C, and $CFCl_3$ for ^{19}F spectra. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants are reported in Hz. For low (MS) and high (HRMS) resolution mass spectra ion mass/charge (m/z) ratios are reported as values in atomic mass units. Melting points were recorded on a Toshniwal melting point apparatus. CAN was activated at 100°C under vacuum for 1h. All commercially available reagents were purchased and used as supplied. DCM was freshly distilled from P_2O_5.

General procedure for the electrophilic cyclization of *N*-Aryl perfluoroalkyl propargyl imines by I_2–CAN

N-aryl perfluoroalkyl acetylenic imines **3** were prepared by Sonogashira coupling of imidoyl iodide and alkyne according to the literature procedure.[15] To a solution of N-aryl perfluoroalkyl propargyl imine, **3** (0.5 mmol) in CH_3CN (5 mL), was added finely grounded I_2 (2 equiv) and CAN (2 equiv) successively and the mixture was stirred at room temperature. After completion of the reaction as monitored by TLC, the mixture was diluted with 30 mL of EtOAc, and washed with saturated aqueous solution of $Na_2S_2O_3$ (25 mL). The organic layer was separated and the aqueous layer was extracted with fresh EtOAc (30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as eluent unless otherwise stated to get pure **5**.

3-Iodo-6-methyl-4-phenyl-2-(trifluoromethyl)quinoline (5a)

Pale yellow solid: mp 112–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, J = 8.7 Hz, 1H), 7.62-7.52 (m, 4H), 7.22-7.17 (m, 2H), 7.11-7.09 (m, 1H), 2.44 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 156.2, 146.5 (q, J = 32.9 Hz), 143.7, 141.4, 140.0, 133.1, 129.6, 128.93, 128.88, 128.70, 125.6, 121.4 (q, J = 276.6 Hz), 89.7, 21.9, (one sp^2 carbon missing due to overlap). ^{19}F NMR (376.3 MHz, $CDCl_3$) δ –65.20 (s, 3F). MS (ESI): *m/z* = 414 $[M + H]^+$. HRMS: *m/z* calcd for $C_{17}H_{12}NF_3I$ $[M + H]^+$ 413.9966, found 413.9952.

3-Iodo-4-phenyl-2-trifluoromethyl-1-azaspiro[4.5]deca-1,3,6,9-tetraen-8-one (6a)

White solid: mp 162–163 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44-7.24 (m, 5H), 6.48 (d, 2H, J = 10.3 Hz), 6.17 (d, 2H, J = 10.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 184.2, 173.0, 167.7 (q, J = 37.3 Hz), 139.6, 132.6, 131.5, 130.2, 128.8, 127.3, 118.5 (q, J = 276.6 Hz), 83.7, 83.2. ^{19}F NMR (376.3 MHz, $CDCl_3$) δ –67.80 (s, 3F). MS (ESI): *m/z* = 438 $[M + Na]^+$. HRMS: *m/z* calcd for $C_{16}H_9F_3INO$ $[M + Na]^+$ 437.9579, found 437.9581.

3-Iodo-4-(4-methoxyphenyl)-2-trifluoromethyl-1-azaspiro[4.5]deca-1,3,6,9-tetraen-8-one (6b)

White solid: mp 161–162°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, 2H, J = 9.1 Hz), 6.87 (d, 2H, J = 9.1 Hz), 6.49 (d, 2H, J = 10.0 Hz), 6.17 (d, 2H, J = 10.0 Hz), 3.82 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 184.4, 172.0, 167.8 (q, J = 37.3 Hz), 161.0, 140.3, 132.4, 129.0, 123.6, 118.6(q, J = 276.1 Hz), 114.2, 82.7, 81.9, 55.3. ^{19}F NMR (376.3 MHz, $CDCl_3$) δ –67.76 (s, 3F). MS (ESI): *m/z* = 445 $[M + Na]^+$. HRMS: *m/z* calcd for $C_{17}H_{11}F_3INO_2$ $[M + Na]^+$ 467.9684, found 467.9688.

General procedure for the synthesis of N-Aryl perfluoroalkyl propargyl amines (4)

To a solution of N–aryl perfluoroalkyl acetylenic imine **3** (1 mmol) in glacial acetic acid (4 mL) under nitrogen atmosphere at 0 °C was added $NaBH_3CN$ (3 equiv.) in portions. The mixture was stirred at room temperature for 30 min. The reaction mixture was diluted

with EtOAc (50 mL) and washed with saturated aqueous solution of $NaHCO_3$ until effervescence ceased, followed by saturated aqueous solution of NaCl. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as eluent.

(3-Phenyl-1-trifluoromethyl-prop-2-ynyl)-p-tolylamine (4a)

The indicated compound was obtained in 98% yield as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.37 (m, 2H), 7.34-7.23 (m, 3H), 7.0 (d, 2H, J = 8.2 Hz), 6.65 (d, 2H, J = 8.2 Hz), 4.85-4.74 (m, 1H), 3.80 (d, 1H, J = 9.6 Hz), 2.26 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 142.7, 132.0, 129.9, 129.1, 128.3, 123.8 (q, J = 281.0 Hz), 121.4, 114.9, 86.1, 80.7, 51.1 (q, J = 35.1 Hz), 20.4, (one sp^2 carbon missing due to overlap). ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −76.05 (d, 3F, J = 6.1 Hz).MS (ESI): m/z = 290 $[M + H]^+$. HRMS: m/z calcd for $C_{17}H_{15}F_3N$ $[M + H]^+$ 290.1156, found 290.1163.

Synthesis of 5,5,5-Trifluoro-4-(4-methoxyphenylamino)-pent-2-yn-1-ol (4s)

To **3s** (1 mmol) (prepared by Sonagashira coupling of N-(4-methoxyphenyl)-2,2,2-triflyroacetimidoyl iodide and THP protected propargyl alcohol) in glacial acetic acid (4 mL) under nitrogen atmosphere at 0 °C was added $NaBH_3CN$ (3 equiv.) in portions. The mixture was stirred at room temperature for 30 min. The reaction mixture was again cooled to 0 °C and was added *p*-TsOH (0.01mmol). The reaction mixture was then stirred at room temperature for the required time. After completion of the reaction as monitored by TLC, the reaction mixture was then diluted with EtOAc (50 mL), and washed with saturated aqueous solution of $NaHCO_3$ until effervescence ceased, followed by saturated aqueous solution of NaCl. The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the product was purified by column chromatography on silica gel using 10:2 hexane/EtOAc as eluent to afford the analytically pure product (**4s**) in 236 mg (91%).

Pale brown oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.82-6.76 (m, 2H), 6.73-6.67 (m, 2H), 4.60-4.50 (m, 1H), 4.27 (d, 2H, J = 2.3 Hz), 3.77 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 154.0 138.6, 123.6 (q, J = 281.5 Hz), 116.7, 114.8, 84.6, 77.4, 55.6, 51.3 (q, J = 33.9 Hz), 50.5.^{19}F NMR (376.3 MHz, $CDCl_3$) δ −76.05 (d, 3F, J = 7.4 Hz). MS (ESI): m/z = 260 $[M + H]^+$. HRMS: m/z calcd for $C_{12}H_{13}F_3NO_2$ $[M + H]^+$ 260.0898, found 260.0888.

General procedure for the electrophilic cyclization of N-Aryl perfluoroalkylated propargyl amines by molecular iodine

To a mixture of N-aryl perfluoroalkylated propargylamine **4** (0.5 mmol), $NaHCO_3$ (2 equiv.) and CH_3CN (5 mL) in a 25 mL round-bottomed flask, 3 equiv. of finely grounded iodine was added and the mixture was stirred at room temperature for the required time. After completion of the reaction as monitored by TLC, the mixture was diluted with 30 mL of EtOAc, and washed with saturated aqueous solution of $Na_2S_2O_3$ (25 mL). The organic layer was separated and the aqueous layer was extracted with fresh EtOAc (30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as eluent unless otherwise stated to get pure **5**.

General procedure for the electrophilic cyclization of N-Aryl perfluoroalkylated propargyl amines by ICl

0.5 mmol of the N-aryl perfluoroalkyl propargyl amine **4**, 2 equiv of $NaHCO_3$ and 4 mL of dry CH_2Cl_2 were placed in a 25 mL round bottom flask at 0 °C under the nitrogen atmosphere. 2 Equiv of ICl in 1 mL of dry CH_2Cl_2 were added dropwise to the flask. The mixture was stirred at room temperature for the required time and was then diluted with 30 mL of EtOAc, and washed with 25 mL of saturated aqueous solution of $Na_2S_2O_3$. The organic layer was separated and the aqueous layer was extracted with fresh EtOAc (30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as eluent unless otherwise stated to get pure **5**.

3-Iodo-6-fluoro-4-phenyl-2-(trifluoromethyl)quinoline (5c)

White solid: mp 115–116 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.25 (dd, 1H, J = 9.5, 5.8 Hz), 7.67-7.51 (m, 4H), 7.26-7.19 (m, 2H), 7.01 (dd, 1H, J = 9.5, 2.9 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 162.1 (d, J = 252.5 Hz), 156.5 (d, J = 6.6 Hz), 147.0 (q, J = 32.9 Hz), 142.3, 140.9, 132.8 (d, J = 11 Hz), 129.85 (d, J = 11 Hz), 129.11, 129.0, 128.8, 121.2 (q, J = 276.6 Hz), 121.3 (d, J = 26.3 Hz), 110.5 (d, J = 24.1 Hz), 90.8. ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −65.43 (s, 3F), −107.60–107.68 (m, 1F). MS (ESI): m/z = 418 $[M + H]^+$. HRMS: m/z calcd for $C_{16}H_9F_4IN$ $(M + H)^+$ 417.9715, found 417.9732.

Synthesis of 6-methoxy-4-phenyl-3-*p*-tolyl-2-(trifluoromethyl) quinoline (8)

A 10 mL round bottom flask was charged with iodoquinoline **5k** (107 mg, 0.25 mmol), *p*-tolylboronic acid (54 mg, 0.4 mmol), $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol) and K_2CO_3 (69 mg, 0.5 mmol) in 5 mL of DMF/H_2O (v/v = 4/1). The reaction mixture was stirred under N_2 at 100 °C for 6h. The mixture was cooled to room temperature and diluted with 25 mL of EtOAc, washed with 25 mL of H_2O and 25 mL of saturated aqueous solution of NaCl. The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to get the crude product. The crude product was chromatographed on a silica gel column using 10:1 hexane/EtOAc as eluent to afford the analytically pure product (**8**) in 74 mg (75%).

White solid: mp 239–240 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, 1H, J = 9.1 Hz), 7.39 (dd, 1H, J = 9.1, 3.0 Hz), 7.28-7.21 (m, 3H), 7.06-7.00 (m, 2H), 6.97-6.89 (m, 4H), 6.66 (d, 1H, J = 3.0 Hz), 3.69 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 159.4, 148.9, 143.7 (q, J = 32.9 Hz), 141.9, 136.8, 136.1, 132.4, 132.1, 131.7, 130.3, 129.8, 129.6, 127.9, 127.5, 122.1 (q, J = 276.3 Hz), 122.9, 104.2, 55.4, 21.2, (one sp^2 carbon missing due to overlap).^{19}F NMR (376.3 MHz, $CDCl_3$) δ −61.63 (s, 3F). MS (ESI): m/z = 394 $[M + H]^+$. HRMS: m/z calcd for $C_{24}H_{19}F_3NO$ $[M + H]^+$ 394.1418, found 394.1432.

Synthesis of 2-methoxy-7,8-diphenyl-6-(trifluoromethyl)benzo[*k*]phenanthridine (10)

A 10 mL round-bottomed flask was charged with iodoquinoline **5k** (107 mg, 0.25 mmol), diphenylacetylene (89 mg, 0.5 mmol), $Pd(OAc)_2$ (2.8 mg, 0.012 mmol), NaOAc (41 mg, 0.5 mmol) and LiCl (11 mg, 0.25 mmol) in 5 mL of DMF The reaction mixture was stirred at 100 °C under the atmosphere of nitrogen for 20h. The mixture was cooled to room temperature and diluted with 25 ml of EtOAc, washed with H_2O (25 mL) and saturated aqueous solution of NaCl (25 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The reaction mixture was chromatographed on a silica gel column using 10:1 hexane/EtOAc as eluent to afford the analytically pure product (**10**) in 84 mg (70%).

White solid: mp 214–215 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.03 (d, 1H, J = 8.3 Hz), 8.30 (d, 1H, J = 2.3 Hz), 8.23 (d, 1H, J = 9.1 Hz), 7.75-7.56 (m, 3H), 7.49 (dd, 1H, J = 9.1, 3.0 Hz), 7.29-7.21 (m, 3H), 7.12-7.00 (m, 5H), 6.98-6.92 (m, 2H), 4.03 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 159.8, 144.1 (q, J = 32.9 Hz), 139.6, 139.4, 138.6, 138.3, 135.1, 134.8, 133.7, 132.6, 131.2, 130.8, 128.5, 127.83, 127.75, 127.70, 126.91, 126.85, 126.6, 125.3, 121.4, 121.2 (q, J = 276.6 Hz), 119.5, 108.0, 55.8, (two sp^2 carbon missing due to overlap). ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −59.34 (s, 3F). MS (ESI): *m/z* 480 $[M + H]^+$. HRMS: *m/z* calcd for $C_{31}H_{21}F_3NO$ $[M + H]^+$ 480.1575, found 480.1597.

Synthesis of 6-methoxy-4-phenyl-2-(trifluoromethyl)quinoline (11)

To a two-neck round-bottomed flask, under nitrogen, containing a solution of **5k** (107 mg; 0.25 mmol) in dry THF (2 mL) at −78 °C was added n-BuLi (0.16 mL of a 1.6 M solution in hexane, 0.25 mmol) dropwise. The reaction mixture was stirred for 10 min and allowed to stir at room temperature. Then water (2 mL) was added and the reaction mixture was diluted with 25 mL of EtOAc and washed with 25 mL saturated aqueous solution of NaCl. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using 10:1 hexane/EtOAc as the eluent to afford the pure product (**11**) in 72 mg (95%).

Pale brown solid: mp 75–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, 1H, J = 9.8 Hz), 7.58 (s, 1H), 7.57-7.48 (m, 5H), 7.42 (dd, 1H, J = 9.8, 2.6 Hz), 7.15 (d, 1H, J = 2.6 Hz), 3.80 (s, 3H) ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 159.4, 149.0, 145.1 (q, J = 32.9 Hz), 143.9, 137.5, 131.9, 129.2, 128.9, 128.7, 123.3, 121.8 (q, J = 274.4 Hz), 117.4, 103.4, 55.5 (one sp^2 carbon missing due to overlap). ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −67.44 (s, 3F). MS (ESI): *m/z* = 304 $[M + H]^+$. HRMS: *m/z* calcd for $C_{17}H_{13}F_3NO$ $(M + H)^+$ 304.0949, found 304.0950.

Data for 6-methoxy-4-phenyl-2-(trifluoromethyl)-3-uinolinecarboxylic acid (12)

To a two-neck round-bottomed flask, under nitrogen, containing a solution of n-BuLi (0.16 mL of a 1.6 M solution in hexane, 0.25 mmol) was added a solution of **5k** (107 mg; 0.25 mmol) in dry THF (2 mL) at −78 °C. The reaction was stirred for 45 min. and then poured on to an excess of freshly crushed dry ice. The reaction mixture was diluted with water (10 mL) and the aqueous phase was washed with diethyl ether (3 × 25 mL). The aqueous layer was acidified with hydrochloric acid to pH 2 and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure to get the crude product, which was crystallized from mixture of chloroform and hexane 1:2 (v/v) to afford the analytically pure product (**12**) in 54 mg (62%). White solid; mp 196–197 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.13 (d, 1H, J = 9.4 Hz), 7.57-7.43 (m, 4H), 7.42-7.33 (m, 2H), 6.82 (d, 1H, J = 3.1 Hz), 3.72 (s, 3H). ^{13}C NMR (75.5 MHz, CD_3OD + CH_3OH): δ 169.4, 161.6, 147.8, 143.8, 141.5 (q, J = 35.1 Hz), 136.0, 132.4, 130.6, 130.4, 130.1, 129.6, 127.2, 125.5, 123.0 (q, J = 274.4 Hz), 105.0, 56.0. ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −58.62 (s, 3F). MS (ESI): *m/z* 348 $[M + H]^+$. HRMS: *m/z* calcd for $C_{18}H_{13}F_3NO_3$ $[M + H]^+$ 348.0847. The structure of 12 was further confirmed by preparing the methyl ester derivative (**13**) of corresponding acid using CH_2N_2. White solid; mp 75–76 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.15 (d, 1H, J = 8.5 Hz), 7.62-7.28 (m, 6H), 6.78 (d, 1H, J = 3.1 Hz), 3.73 (s, 3H), 3.58 (s, 3H).

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References

1 (*a*) M. Schlosser, *Angew. Chem. Int. Ed.*, 2006, **45**, 5432; (*b*) M. Hudlicky, *Chemistry of Organic Fluorine Compounds*, Ellis Horwood Ltd, Chichester, 1992; (*c*) I. Ojima, J. R. McCarthy, J. T. Welch, *Biomedical Frontiers of Fluorine Chemistry*, ACS Symposium Series, no. 639, Washington, 1996.
2 C. J. Ohnmatch, A. R. Patel and R. E. Lutz, *J. Med. Chem.*, 1971, **14**, 926–928.
3 (*a*) H. J. Dyke, J. G. Montana, WO 2000026208, 2000; (*b*) R. Kuang, D. Blythin, N. Y. Shih, H. J. Shue, X. Chen, J. Cao, D. Gu, Y. Huang, J. H. Schwerdt, P. C. Ting, S. C. Wong, L. Xiao, WO 2005116009, 2005.
4 H. Sakashita, T. Yoshida, H. Kitajima, M. Takeuchi, Y. Tanaka, T. Yoshimura, F. Akahoshi, Y. Hayashi, WO 2003024942, 2003.
5 J. Dade, O. Provot, H. Moskowitz, J. Mayrargue and E. Prina, *Chem. Pharm. Bull.*, 2001, **49**, 480–483.
6 J. B. Dickey, J. G. McNally, US 2432393, 1947.
7 M. S. Raasch, *J. Org. Chem.*, 1962, **27**, 1406–1409.
8 Y. Kobayashi and I. Kumadaki, *Tetrahedron Lett.*, 1969, **10**, 4095–4097.
9 (*a*) R. J. Linderman and K. S. Kirollos, *Tetrahedron Lett.*, 1990, **31**, 2689–2692; (*b*) I. I. Gerus, L. V. Kropachev, M. G. Gorbunova, A. Y. Ilchenko and V. P. Kukhar, *Ukr. Khim. Zh. (Russ. Ed.)*, 1993, **59**, 408–411; (*c*) H. Keller and M. Schlosser, *Tetrahedron*, 1996, **52**, 4637–4644; (*d*) M. Schlosser, H. Keller, S. Sumida and J. Yang, *Tetrahedron Lett.*, 1997, **38**, 8523–8526; (*e*) M. Hojo, R. Masuda, Y. Kokuryo, H. Shioda and S. Matsuo, *Chem. Lett.*, 1976, 499–502; (*f*) T. Moriguchi, T. Endo and T. Takata, *J. Org. Chem.*, 1995, **60**, 3523–3528; (*g*) A. Colla, M. A. P. Martins, G. Clar, S. Krimmer and P. Fischer, *Synthesis*, 1991, 483–486; (*h*) S. I. Vdovenko, I. I. Gerus and M. G. Gorbunova, *J. Chem. Soc. Perkin Trans. 2*, 1993, 559–562.
10 I. L. Baraznenok, V. G. Nenajdenko and E. S. Balenkova, *Eur. J. Org. Chem.*, 1999, 937–941.
11 H. Amii, Y. Kishikawa and K. Uneyama, *Org. Lett.*, 2001, **3**, 1109–1112.
12 (*a*) A. Sniady, K. A. Wheeler and R. Dembinski, *Org. Lett.*, 2005, **7**, 1769–1772; (*b*) X. Zhang, M. A. Campo, T. Yao and R. C. Larock, *Org. Lett.*, 2005, **7**, 763–766; (*c*) A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli and L. Moro, *Synlett.*, 1999, **9**, 1432–1434; (*d*) D. Yue and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 1905–1909; (*e*) D. Yue and R. C. Larock, *Org. Lett.*, 2004, **6**, 1037–1040; (*f*) Q. Huang, J. A. Hunter and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 3437–3444; (*g*) A. Arcadi, S.

Cacchi, S. Di, Giuseppe, G. Fabrizi and F. Marinelli, *Org. Lett.*, 2002, **4**, 2409–2412.
13 (*a*) R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874–922; (*b*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285–2310.
14 (*a*) Y. M. Wu, M. Zhang and Y. Q. Li, *J. Fluorine Chem.*, 2006, **127**, 218–222; (*b*) H. B. Yu and W. Y. Huang, *J. Fluorine Chem.*, 1998, **87**, 69–73; (*c*) K. Uneyama and H. Watanabe, *Tetrahedron Lett.*, 1991, **32**, 1459–1462.
15 (*a*) H. Amii, M. Kohda, M. Seo and K. Uneyama, *Chem. Commun.*, 2003, 1752–1753; (*b*) K. Tamura, H. Mizukami, K. Maeda, H. Watanabe and K. Uneyama, *J. Org. Chem.*, 1993, **58**, 32–35; (*c*) Y. M. Wu, Y. Li and J. Deng, *J. Fluorine Chem.*, 2005, **126**, 791–795; (*d*) K. Uneyama, H. Amii, T. Katagiri, T. Kobayashi and T. Hosokawa, *J. Fluorine Chem.*, 2005, **126**, 165–171; (*e*) K. Uneyama, *J. Fluorine. Chem.*, 1999, **97**, 11–25; (*f*) H. B. Yu and W. Y. Huang, *Tetrahedron Lett.*, 1996, **37**, 7999–8000.
16 P. R. Likhar, M. S. Subhas, M. Roy, S. Roy and M. L. Kantam, *Hel. Chim. Acta*, 2008, **91**, 259–264.
17 (*a*) For *ipso* iodocyclizations see:Q. F. Yu, Y. H. Zhang, Q. Yin, B. X. Tang, R. Y. Tang, P. Zhong and J. H. Li, *J. Org. Chem*, 2008, **73**, 3658–3661; (*b*) X. Zhang and R. C. Larock, *J. Am. Chem. Soc.*, 2005, **127**, 12230–12231; (*c*) C. W. Li, C. I. Wang, H. Y. Liao, R. Chaudhuri and R. S. Liu, *J. Org. Chem.*, 2007, **72**, 9203–9207.
18 CCDC 696933 (**6a**) and 696932 (**5l**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
19 (*a*) For molecular iodine as a oxidising agent seeH. Togo and S. Iida, *Synlett.*, 2006, **14**, 2159–2175and references cited therein; (*b*) C. Lin, P.-T. Lai, S. K.-S. Liao, W.-T. Hung, W.-B. Yang and J.-M. Fang, *J. Org. Chem.*, 2008, **73**, 3848–3853.
20 N. Lebouvier, C. Laroche, F. Huguenot and T. Brigaud, *Tetrahedron Lett.*, 2002, **43**, 2827–2830.
21 Y. Xu and W. R. Dolbier, Jr., *J. Org. Chem.*, 2000, **65**, 2134–2137.
22 G. Magueur, B. Crousse and D. B. Delpon, *Tetrahedron Lett.*, 2005, **46**, 2219–2221.
23 (*a*) M. I. Rodrı'guez-Franco, I. Dorronsoro, A. I. Herna'nde-Higueras and G. Antequera, *Tetrahedron Lett.*, 2001, **42**, 863–865; (*b*) V. Nair and A. Deepthi, *Chem. Rev.*, 2007, **107**, 1862–1891.
24 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483.
25 R. C. Larock, M. J. Doty, Q. Tian and J. M. Zenner, *J. Org. Chem.*, 1997, **62**, 7536.
26 (*a*) M. Aso, T. Kaneko, M. Nakamura, N. Koga and H. Suemune, *Chem. Commun.*, 2003, 1094–1095; (*b*) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis and V. A. Vu, *Angew. Chem. Int. Ed.*, 2003, **42**, 4302–4320.
27 F. Cottet, M. Marull, O. Lefebvre and M. Schlosser, *Eur. J. Org. Chem.*, 2003, 1559–1568.
28 (*a*) W. Trager and J. B. Jensen, *Science*, 1976, **193**, 673–675; (*b*) S. Biswas, *J. Postgrad. Med.*, 2001, **47**, 240–243.