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An Electrochemical Approach for the Synthesis of Perfluoroalkylated Purine and Indole Analogues of Plant Growth Regulators

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Abstract—In an effort to prepare new fluorine-containing molecules as analogues of Plant Growth Regulators (PGRs), the indirect electrochemical reduction, by means of an aromatic anion mediator, of perfluoroalkyl halides in the presence of purine and indolyl anions was carried out. The corresponding *C*-perfluoroalkylated products were obtained by an $S_{RN}1$ mechanism, in moderate to good yields, and biological activity of some of the products was evaluated.

Introduction

Nucleophilic substitution by the $S_{RN}1$ mechanism[1,2] is now a well documented reaction not only in its mechanistic aspects but also from a synthetic point of view. For the last ten years some elegant approaches were published for the synthesis of interesting aromatic and heterocyclic compounds, often prepared by a number of difficult chemical steps.[3] Several $S_{RN}1$ substitution reactions, which are triggered chemically or electrochemically, involving fluorinated substrates have been described in the literature;[1,4] as part of our ongoing effort in the synthesis of new fluorinated compounds with potential biological and synthetic applications,[5–16] we wish to report a novel synthetic application of the electrochemical $S_{RN}1$ methodology for preparing F-alkylated analogues of plant hormones such as cytokinins and auxins derivatives, which are not accessible (or requiring a number of steps) by other methods.[17–19]

Cytokinins are plant hormones with a wide range of biological effects.[20] They promote cell division and cell growth and they are involved in retardation of senescence. The cytokinins found in nature are 6-alkylamino purines. Examples of important cytokinins are 6-benzylamino purine, kinetin, and the most potent *trans*-zeatin.[20] So far, very few fluorinated analogues have been synthesised and evaluated for biological testing.[21–25]

The indole nucleus is present in a wide range of natural products, and the synthesis of this important structure has been a steady topic of interest for many years.[26] Among the numerous methods that have been developed for the synthesis of indoles, few practical and mild procedures are available for the construction of 2,3-disubstituted indoles.[27] Among the recent procedures to achieve efficient synthesis of 2,3-disubstituted indoles, we can cite the radical cyclisation of 2-alkenylthioanilides[28] and substituted isonitriles,[29] the titanium cyclised reactions of suitably substituted oxoamides,[30,31] cyclisation reactions of α-thiomethyl ketones,[32] and palladium-catalysed coupling reactions of 2-iodoaniline and the corresponding *N*-substituted derivatives, with a wide variety of internal alkynes.[33] Indole-3-acetic acid (IAA), the first identified plant hormone, has typical auxin activities, including hypocotyl elongation, seeding root development and abscission of fruit and leaves.[34] However, a major drawback which limits the effectiveness of IAA as a plant growth regulator is its ready enzymatic oxidation to hydroxymethyl-2-oxindole and 3-methylene-2-oxindole, with concomitant loss of biological activities.[35] For this reason, designing IAA derivatives that are resistant to enzymatic oxidation has been one important strategy for development of IAA analogues with potent auxin activities.[36] Although various IAA derivatives with auxin activity have been prepared,[37] to our knowledge there are only a few examples of fluorinated analogues, and more generally indole derivatives with a fluorinated substituent.[11,12,15,38–41]

The work presented here is a continuation of our recent efforts towards the synthesis and discovery of new potent fluorinated active plant hormones.[11,12,15,42–46]

Keywords: electrochemistry; fluorine and compounds; $S_{RN}1$; indole; purine.

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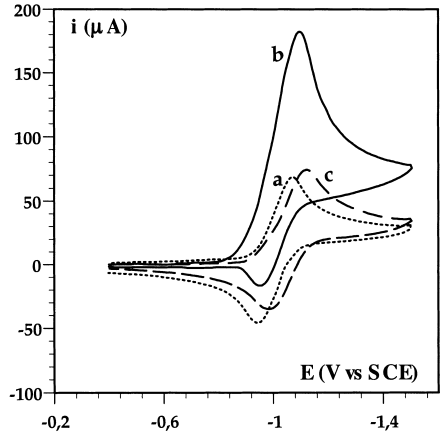


Figure 1. Cyclic voltammetry of the redox catalysed reduction of *n*-C_4F_9I **2** by the anion radical of nitrobenzene in DMSO+0.1 M Et_4NBF_4 in the absence (a, b) and in the presence of 6-benzylamino purine anion $\mathbf{8}^-$ (c). (a) Catalyst alone, C=2.0 mM, (b) a+*n*-C_4F_9I **2** (C=6.0 mM), (c) b+$\mathbf{8}^-$ (C=96.9 mM), scan rate 0.2 V/s, glassy carbon electrode, T=22°C.

The following perfluoroalkyl halides **1**–**4** were used as substrates (CF_3Br (**1**), *n*-C_4F_9I (**2**), *n*-$C_6F_{13}I$ (**3**) and $I(CF_2)_4I$ (**4**)) in the presence of purine and indolyl anions (adenine (**5**), hypoxanthine (**6**), xanthine (**7**), 6-benzylamino purine (**8**), kinetin (6-furfurylamino purine, **9**), 6-chloro purine (**10**), indole-3-acetic acid (IAA, **11**), indole-3-acetic acid methyl ester (IAA–Me, **12**), indole-3-butyric acid (IBA, **13**), 4,4,4-trifluoro-3-(indol-3-yl)butyric acid (TFIBA, **14**), 4,4,4-trifluoro-3-(indol-3-yl)butyric acid methyl ester (TFIBA–Me, **15**)). The corresponding *C*-perfluoroalkylated products are numbered **16**–**35**.

Results and Discussion

Purine as nucleophiles

In all cases, reduction of **1**–**4** in the presence of purine nucleophiles was performed under redox catalysis[47–50] using terephthalonitrile or benzo[c]quinoline for the reduction of **1**, nitrobenzene for the reduction of **2**, **3** and **4**. This approach is made necessary, at the preparative scale, so as to operate under less reducing conditions, to generate the perfluoroalkyl radical in solution and also in order to overcome severe passivation upon direct electrolysis of **3** (due to the formation of some insoluble dimer $C_{12}F_{26}$ on the surface of the electrode). As shown in Fig. 1a, the cyclic voltamogramm of nitrobenzene (**P**, E°=−1.10 V vs SCE) alone is reversible and corresponds to the uptake of one electron per molecule.

$$\mathbf{P} + e \rightleftharpoons \mathbf{P}^{\circ -} \quad (1)$$

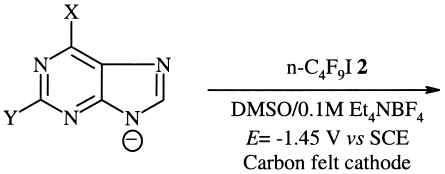
It loses its reversibility and increases in height upon addition of *n*-C_4F_9I (**2**, R_FX) because the reduction of **2** is then redox catalysed by the **P**/**P**°- couple (Fig. 1b). If the nucleophile $\mathbf{8}^-$ is now added to the solution, the peak decreases and reversibility is partially restored (Fig. 1c), demonstrating the occurrence of an $S_{RN}1$ process (the overall electron stoichiometry tends toward zero):

$$\mathbf{P}^{\bullet -} + R_FX \longrightarrow R_F^\circ + X^- + \mathbf{P} \quad (2)$$

$$R_F^\circ + Nu^- \longrightarrow R_FNu^{\circ -} \quad (3)$$

$$R_FNu^{\circ -} + \mathbf{P} \rightleftharpoons R_FNu + \mathbf{P}^{\circ -} \quad (4)$$

In all cyclic voltammetric experiments, we have checked that the decrease of the wave was not due to a reaction between the catalyst (or its reduced form) and the nucleophile. The only exception is with kinetin **9** as nucleophile where a 25% loss of the catalytic wave was observed.



X=NH_2, Y=H, **5**$^-$
X=OH, Y=H, **6**$^-$
X=OH, Y=OH, **7**$^-$
X=-$NHCH_2C_6H_5$, Y=H, **8**$^-$
X=-$NHCH_2$Furyl, Y=H, **9**$^-$
X=Cl, Y=H, **10**$^-$

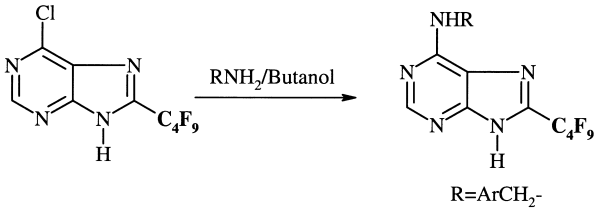
X=NH_2, Y=H, **21** (0.8F/mol), 60%
X=OH, Y=H, **22** (0.8F/mol), 65%
X=OH, Y=OH, **23** (0.70F/mol), 75%
X=-$NHCH_2C_6H_5$, Y=H, **24** (0.80F/mol), 45%
X=-$NHCH_2$Furyl, Y=H, **25** (1.1F/mol), 28%
X=Cl, Y=H, **26** (0.8F/mol), 52%

Scheme 1.

Table 1. Preparative-scale electrolyses of the perfluoroalkylated purine derivatives

Substrate	Nucleophile[a]	Product (isolated yield)
CF_3Br **1**[b]	Adenine **5**	**16** (4.12×10^{-3} mol/h)
CF_3Br **1**[b]	Hypoxanthine **6**	**17** (5.23×10^{-3} mol/h)
CF_3Br **1**[b]	Xanthine **7**	**18** (5.07×10^{-3} mol/h)
CF_3Br 1[b]	6-chloro purine **10**	**19** (3.78×10^{-3} mol/h)
n-C_4F_9I **2**[c]	Adenine **5**	**21** (60%)
n-C_4F_9I **2**[c]	Hypoxanthine **6**	**22** (65%)
n-C_4F_9I **2**[c]	Xanthine **7**	**23** (75%)
n-C_4F_9I **2**[c]	6-benzylamino purine **8**	**24** (45%)
n-C_4F_9I **2**[c]	Kinetin **9**	**25** (28%)
n-C_4F_9I **2**[c]	6-chloro purine **10**	**26** (52%)
n-$C_6F_{13}I$ **3**[c]	6-benzylamino purine **8**	**32** (34%)
n-$C_6F_{13}I$ **3**[c]	6-chloro purine **10**	**33** (48%)
$I(CF_2)_4I$ **4**[c]	Adenine **5**	**34** (40%)
$I(CF_2)_4I$ **4**[c]	Hypoxanthine **6**	**35** (40%)

[a] Tetramethylammonium salt, C=0.21 M.
[b] CF_3Br ($C=5.26\times10^{-2}$ M) was continuously bubbled in the solution in DMF+0.1 M Et_4NBF_4; terephthalonitrile ($C=4.3\times10^{-3}$ M) is used as mediator; electrolysis potential E=−1.75 V vs SCE.
[c] $C=3.61\times10^{-3}$ M in DMSO+0.1 M Et_4NBF_4; $PhNO_2$ ($C=1.44\times10^{-3}$ M) is used as mediator; electrolysis potential E=−1.45 V vs SCE.



Scheme 2.

Using a two-compartment cell, preparative electrolysis of perfluorobutyl iodide **2** in the presence of 6-benzylamino purine anion $\mathbf{8}^-$, at a potential behind the peak potential of the catalyst (E=−1.45 V vs SCE, carbon felt cathode) in DMSO+0.1 M Et_4NBF_4, gave, after the consumption of 0.8 F/mol of starting material, a single product in 45% isolated yield, which was identified as 6-benzylamino-8-(nonafluorobutyl) purine **24**. Perfluorobutyl iodide was chosen as a model substrate and a large spectrum of purine anions was found to be reactive under redox catalysed $S_{RN}1$ reactions (Scheme 1).

Most of the products were precipitated from the reaction mixture by acid hydrolysis of the electrolysis solution followed by careful washings with water (in order to remove any trace of DMSO) and with an organic solvent (Et_2O or EtOAc) to remove the catalyst. By this procedure the products are obtained in high purity as checked by TLC and NMR (Table 1). Higher yields of F-alkylated purines were obtained with adenine **5**, hypoxanthine **6**, xanthine **7** and 6-chloro purine **10**; for the biologically important cytokinins 6-benzylamino purine **8** and kinetin **9** lower yields were obtained, and this is attributed to a lower solubility of these anions in the electrolysis reaction medium (probably due to the presence of the free –NH). Also in the case of kinetin **9**, some decomposition of the substituted product was observed. Nevertheless our procedure allows to obtain in a one pot reaction sufficient amount of F-alkylated analogues of cytokinins for biological testing. The substituted product **26** is a valuable synthon because it could be used as a useful starting material to synthesise more sophisticated 6-substituted purine derivatives, especially cytokinin derivatives with a $-NHCH_2Aryl$ group (Scheme 2).

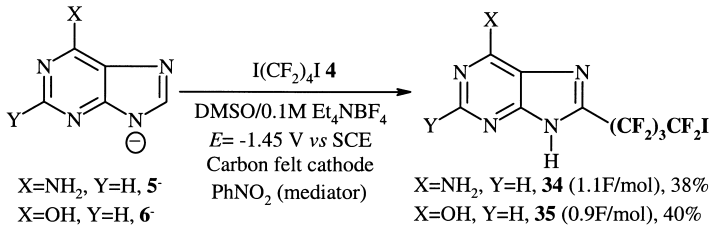
Reactivity of *n*-perfluorohexyl iodide **3** was similar to *n*-perfluorobutyl iodide **2**. For the redox catalysed reduction of $I(CF_2)_4I$ **4**, no disubstituted product was observed. However the isolated yield was not very high, due to some reduction of the terminal $-CF_2I$ bond (observed by ^{19}F NMR of the raw solution, Scheme 3).

With the perfluoroalkyl iodides **2**, **3** and **4**, the other product representing the remaining balance material is always the hydrogenolysis product R_FH, as it was confirmed by fluorine NMR and GC analysis. With CF_3Br **1** as starting material, DMF was chosen as solvent (because of its higher solubility: 4% by weight). CF_3Br was continuously bubbled at a constant concentration during all the electrolysis, therefore isolated yields of substituted products can not be calculated and a production in mol/h is given (Table 1). Because of the lower solubility of the purine anions in DMF, production of trifluoromethyl derivatives is not high and partial basic hydrolysis of the cyano function of the catalyst was also observed.

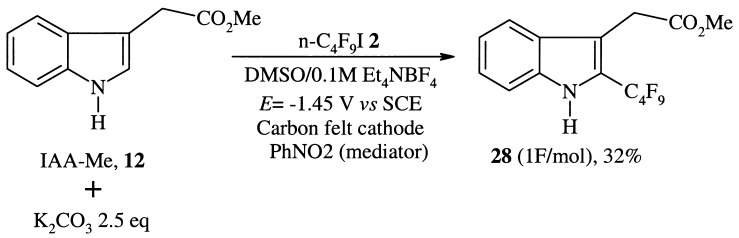
Indole derivatives as nucleophiles

Only recently indolyl anions have been successfully used under $S_{RN}1$ conditions;[51] the electrochemical approach (in liquid ammonia) was used to synthesise β-aryl indole compounds starting from an aromatic chloride and the anion of indole, produced in situ by deprotonation of the acidic form with potassium *tert*-butoxide. However only indole was used as nucleophile.

With indolyl anions **11**–**15**, *n*-C_4F_9I **2** was also chosen as a model substrate; as in the reaction with purine nucleophiles, redox catalysis was preferred so as to operate under less reducing conditions and DMSO was the solvent of choice. The first indole derivative to be tested as a nucleophile was the methyl ester of the IAA, IAA–Me **12**; using a two-compartment cell, preparative electrolysis at a potential behind the peak potential of the catalyst (E=−1.45 V vs SCE, carbon felt cathode) in DMSO+0.1 M Et_4NBF_4 gave, after the consumption of 1 F/mol of starting material, and extraction, a crude product which was shown to contain a mixture of products. Mass spectroscopy analysis of the crude clearly indicated that two new F-alkylated products were obtained, the desired substituted product **28** but also the substituted product **27**; beside these fluorinated products, IAA–Me **12** was recovered with also some IAA **11**. Evidently partial hydrolysis of the anion, as well as of the substituted product **28**, occurred during the electrolysis. The tetramethylammonium hydroxide used as the base to prepare the nucleophile in situ was shown to be too strong for the methyl ester as it was demonstrated that the IAA–Me **12** was completely hydrolysed in DMSO, within 2 h, giving IAA **11** in 75% isolated yield. We then decided to use a milder base such as anhydrous potassium carbonate K_2CO_3; the insoluble base was mixed with IAA–Me **12** in the DMSO+0.1 M Et_4NBF_4 solution and the resulting mixture was stirred for 2 h under nitrogen before introducing the catalyst and substrate. Preparative electrolysis at a potential close to −1.45 V vs SCE gave the desired substituted product **28** in 32% isolated yield after purification by



Scheme 3.



Scheme 4.

column chromatography (Scheme 4). No hydrolysis of IAA–Me **12** or substituted product **28** was observed.

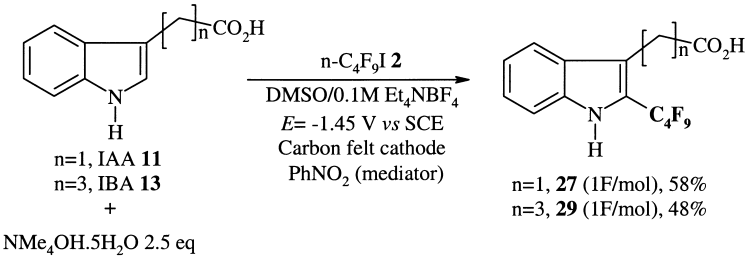
With the indoles having a free acid function **11**, **13** and **14**, 2.5 equiv. of $NMe_4OH.5H_2O$ were used to achieve deprotonation of the –NH and $–CO_2H$ moieties. Perfluoroalkylation of IAA **11** was successful under these conditions and the substituted product **27** was isolated in 58% yield after purification by column chromatography. A 48% isolated yield was obtained with IBA **13** (Scheme 5). Generally, substitution predominantly occurs at the C-2 of the indole ring as it was shown by proton NMR.

Analysis of the crude products by fluorine NMR and mass spectroscopy revealed that some other fluorinated products were formed; as a typical example, fluorine NMR of the crude product obtained from the electrolysis of *n*-C_4F_9I **2** and the anion of IAA **11** revealed, besides the desired substituted product **27** and some other small fluorinated impurities, a major by-product **27′** characterised by a CF_3 at −81.5 ppm/$CFCl_3$, two CF_2 characterised by two complicated AB patterns centred at −114.4 and −120.3 ppm/$CFCl_3$ and a γ-CF_2 at −126.5 ppm/$CFCl_3$. The GC/mass spectrum of the crude revealed for **27′** a molecular peak at 293 (the same as **27**) with a *m/e* at 348 (M^+-CO_2H); however the fragmentation is different from the mass spectrum of the C-2 substituted product **27**. The product **27′** could be a regio-isomer of the C-2 substituted product **27**; such a product could result from a perfluoroalkylation on the benzene ring due to the ambident character of the indolyl anions or at the C-3 of the indole ring (Scheme 6). The two complicated AB patterns accounting each for two fluorine should result from proton–fluorine (^4J) and fluorine–fluorine coupling. Work is under progress to characterise this fluorinated by-product.

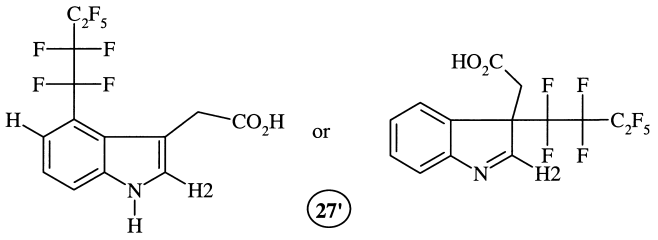
Introduction of a trifluoromethyl group was performed with the IAA **11** anion; the best yield was obtained with benzo[c]quinoline as redox mediator ($E^\circ=-1.44$ V vs SCE) using DMSO as solvent; using terephthalonitrile as redox catalyst, very little amount of substituted product could be detected from analysis of the fluorine NMR of the raw solution. The substituted product **20** (or its ester) has been recently described in the literature[38,40] using two totally different approaches; the first one[38] involves an indole-ring construction by thermolysis of 2-(*N*-acylamino)-benzyl phosphonium salts and introduction of a cyanomethyl group at C-3 of the 2-trifluoromethyl indole, by means of the Mannich reaction. The cyanomethyl group is then hydrolysed to give the expected product. The second one[40] involves the thermolysis of 2-(2-methoxycarbonyl-vinyl)-*N*-(2,2,2-trifluoro-1-tritylazoethylidene)aniline, itself prepared in three steps from the corresponding trifluoroacetylimidoyl chloride, in toluene at 100°C in the presence of PhSH as a hydrogen atom donor. Both approaches gave the trifluoromethyl indole acetic acid in good yields but they suffer from multistep syntheses. Our approach has the advantage to obtain directly the 2-trifluoromethyl-IAA **20** from the commercially available IAA **11** in a one-pot reaction.

We then try our electrochemical approach with TFIBA **14**, a new synthetic analogue of IBA recently prepared in our laboratories; this trifluoromethylated analogue of IBA has shown interesting activities such as root growth-promoting activity in plants (stimulation of the growth of tubers of radish, improved differentiation of female flowers on the cucumber and increase in the yield of potato, among others)[43,44] but unfortunately has shown no auxin activity. Preparative electrolysis at a potential close to −1.45 V vs SCE gave the desired substituted product **30** in 35% isolated yield after purification by column chromatography; product **31** was obtained in 28% isolated yield using K_2CO_3 as the base (Scheme 7).

The new F-alkylated indole derivatives were separated from unreacted nucleophile by column chromatography and were obtained in moderate yields (Table 2). It is important to note that fluorine NMR analysis of the crude reactions with indole anions **14** and **15** revealed higher amounts of fluorinated by-products as compared with electrolyses involving **11**, **13** and **14** anions. Such phenomena could be attributed

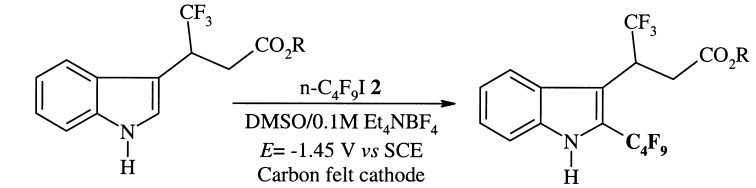


Scheme 5.



for example: C-4 substituted product indolenine substituted product

Scheme 6.



R=H, TFIBA **14**
+ $NMe_4OH.5H_2O$ 2.5 eq
$R=CH_3$, TFIBA-Me **15**
+ K_2CO_3 2.5 eq

R=H, **30** (0.8F/mol), 35%
$R=CH_3$, **31**, (0.8F/mol), 28%

Scheme 7.

to side reactions due to some defluorination at the C-2 perfluoroalkyl group and/or at the CF_3 of the propionic acid chain.

Moderate yields of the F-alkylated indole derivatives could be attributed to an instability of the perfluoroalkyl groups in the basic electrolytic medium; such phenomena have already been observed in previous studies.[52–55] Under these conditions fluoride elimination could give a very reactive intermediate which can be trapped by nucleophiles such as OH^-, H_2O or even the indolyl anion itself (Scheme 8). Most of the C-2 F-alkylated indole derivatives were found to be difficult to separate from the small fluorinated impurities (fluorescent) by column chromatography. In addition, they must be stored in the refrigerator (and in the dark) as they tend to decompose readily at room temperature and under exposure to light.

Some of the products obtained in this work (**21**–**24**, **27**, **28** and **30**) were tested for their biological activity. Compounds **21**–**24** showed low cytokinin activity. Compounds **27** and **28** were examined using two plants, chinese cabbage and lettuce, in petri dish;[44] unfortunately thus far, none of them has shown auxin activities. Further biological investigations are in progress by other plants and/or in the fields.[43]

Table 2. Preparative-scale electrolyses of the perfluoroalkylated indole derivatives

Substrate	Nucleophile[a]	Product (isolated yield)
CF_3Br **1**[b]	IAA **11**	**20** (2.1×10^{-3} mol/h)
n-C_4F_9I **2**[c]	IAA **11**	**27** (58%)
n-C_4F_9I **2**[c]	IAA–Me **12**[d]	**28** (32%)
n-C_4F_9I **2**[c]	IBA **13**	**29** (48%)
n-C_4F_9I **2**[c]	TFIBA **14**	**30** (35%)
n-C_4F_9I **2**[c]	TFIBA–Me **15**[d]	**31** (28%)

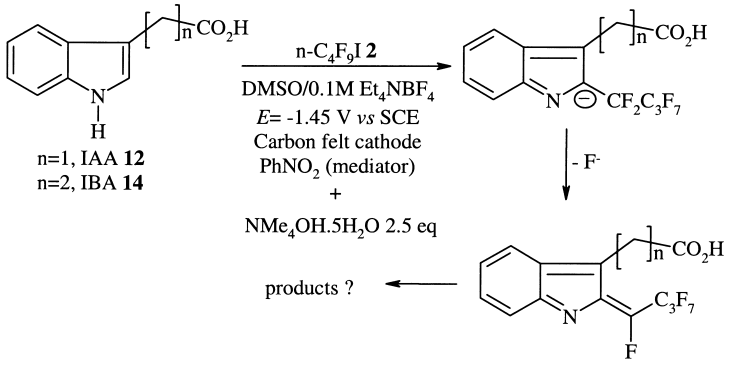
[a] Tetramethylammonium salt, C=0.21 M.
[b] CF_3Br ($C=5.26\times10^{-2}$ M) was continuously bubbled in the solution in DMF+0.1 M Et_4NBF_4; benzo[c]quinoline ($C=4.3\times10^{-3}$ M) is used as mediator; electrolysis potential $E=-1.90$ V vs SCE.
[c] $C=4.33\times10^{-3}$ M in DMSO+0.1 M Et_4NBF_4; $PhNO_2$ ($C=1.45\times10^{-3}$ M) is used as mediator; electrolysis potential $E=-1.45$ V vs SCE.
[d] K_2CO_3 is used as a base.

Conclusions

We have demonstrated that the electrochemical induction of the $S_{RN}1$ mechanism is a useful synthetic tool to obtain new F-alkylated purine and indole derivatives, especially analogues of known plant growth regulators (PGRs). Yields are moderate to good but are not optimised. Work is under progress to characterise the fluorinated impurities obtained during the electrolysis with the indole nucleophiles. The methodology is currently extended to other halogenated fluorinated substrates such as halogenodifluoromethyl heterocycles and ketones.

Experimental

For cyclic voltammetry we used a home-built potentiostat[56] equipped with a positive feedback ohmic drop compensation and a Tacussel GSTP4 signal generator. The working electrode was a glassy carbon (Tokai Corp.) disk (3-mm diameter) and the reference electrode was a saturated calomel electrode (SCE). Electrolyses were carried out in a three-compartment cell with a carbon felt cathode and anode (5×5 cm^2). The cathode compartment was separated from the anolyte with a glass fritt of porosity 4. The system is made gas-tight by means of O-rings. NEt_4BF_4 (Fluka puriss) was used as a supporting electrolyte. Anhydrous DMF and DMSO (Fluka Puriss dried over molecular sieve) were used as received. All reagents are of commercial origin and used as received.



Scheme 8.

The nucleophiles can be prepared as tetramethylammonium salts in the case of purine anions; the corresponding acids were mixed together with appropriate amount of $NMe_4OH.5H_2O$ (Aldrich) in methanol. The resulting solution was vigorously stirred under nitrogen for 1 h and dried over $MgSO_4$, filtered and evaporated to dryness. The resulting oil was carefully dried under vacuum over P_2O_5 and recrystallised from CH_3CN/Et_2O. The resutling hygroscopic solids were kept under vacuum over P_2O_5. For the indolyl anions, the tetramethylammonium salts (or potassium salts) were directly prepared in the DMSO (or DMF) solution, dried over $MgSO_4$ and directly filtered under nitrogen into the electrolysis cell.

Silica gel (MN Kieselgel 60, 70–230 mesh, Macherey–Nagel) was employed for column chromatography. Analytical TLC was performed with 0.25 mm coated commercial plates (Macherey–Nagel, Polygram SIL G/UV_{254}). All the reactions with air-sensitive compounds were carried out under a nitrogen atmosphere.

NMR spectra were taken in acetone-d_6, DMSO-d_6 and $CDCl_3$ using TMS as the internal standard for ^1H (250.133 and 400.132 Hz). ^{19}F NMR (235.323 and 376.498 Hz) used CCl_3F as internal standard. Melting points are uncorrected.

Synthesis of racemic 4,4,4-trifluoro-3-(indol-3-yl)butyric acid (TFIBA, **14**), and 4,4,4-trifluoro-3-(indol-3-yl)butyric acid methyl ester (TFIBA–Me, **15**): a solution of 2,2,2-trifluoro-1-(indol-3-yl)ethanol[15] (10.8 g, 50 mmol) and sodium salt of diethylmalonate (18.2 g, 100 mmol) in dry toluene (250 ml) was heated at reflux for 5 h to give the corresponding diester (85% yield).[45] The diester was subjected to alkaline hydrolysis and subsequent decarboxylation with potassium carbonate in methanol–water under refluxing conditions to give crude acid, which was purified by column chromatography on silica gel eluting with hexane–ethyl acetate (3/1) to give racemic **14** (7.8 g, 61% yield): colourless grains, mp 117–119°C from hexane–ethyl acetate. MS (70 eV) *m/z* (relative intensity %) 257 (86) M^+, 237 (30) M^+-HF, 198 (100) M^+-CH_2COOH, 188 (22) M^+-CF_3. ^1H NMR (acetone-d_6): δ_H=3.04 (1H, dd, *J*=16.1, 9.3 Hz), 3.13 (1H, dd, *J*=16.1, 5.2 Hz), 4.36 (1H, ddq, *J*=8.0, 6.8, 1.1 Hz), 7.09 (1H, ddd, *J*=7.8, 6.8, 1.1 Hz), 7.14 (1H, ddd, *J*=8.0, 6.8, 1.1 Hz), 7.41 (1H, d, *J*=8.0 Hz), 7.47 (1H, s), 7.70 (1H, d, *J*=7.8 Hz), 10.39 (1H, brs). ^{19}F NMR (acetone-d_6): δ_F=−71.2 (3F, d, *J*=9.4 Hz); HRMS found 257.0620, calcd for $C_{12}H_{10}F_3NO_2$ 257.0662. A solution of **14** (5.1 g, 20 mmol) in methanol (300 ml) was saturated with dry HCl gas. After refluxing overnight, the methanol and hydrogen chloride were evaporated to dryness, and the residual material was purified by column chromatography on silica gel eluting with CH_2Cl_2 to give racemic **15** (4.6 g, 85% yield): colourless needles, mp 57–58°C from hexane. MS (70 eV) *m/z* (relative intensity %) 271 (100) M^+, 251 (30) M^+-HF, 198 (75) $M^+-CH_2CO_2CH_3$. ^1H NMR (acetone-d_6): δ_H=2.92 (s, 3H), 3.02 and 3.11 ([AB-d (d′), 2H, *J*=15.7, 9.8 (4.7) Hz, α-CH_2), 4.35 (1H, ddq, *J*=9.8, 4.7, and 9.3 Hz), 7.09 (m, 1H, *J*=7.5, 6.7, and 1.0 Hz, 5-H), 7.15 (m, 1H, *J*=8.4, 6.7, 1.1 Hz, 6-H), 7.43 (m, 1H, *J*=8.4, 1.0, and 0.9 Hz, 7-H), 7.44 (1H, d, *J*=2.4 Hz, 2-H), 7.68 (m, 1H, *J*=7.5, 1.0, and 0.9 Hz, 4-H) 10.39 (1H, brs). ^{19}F NMR (acetone-d_6): δ_F=−71.2 (3F, d, *J*=9.3 Hz). HRMS found 271.0642, calcd for $C_{13}H_{12}F_3NO_2$ 271.0658.

A representative procedure for the synthesis of the perfluoroalkylated purine derivatives is described for the electrolysis of *n*-C_4F_9I (2) in the presence of 6-benzylamino purine anion (8^-)

Into 80 ml of DMSO containing 5.0 g (16.7 mmol) of the tetramethylammonium salt of 6-benzylamino purine **8**, were added under nitrogen, 2.17 g (10 mmol) of NEt_4BF_4, 0.018 g (1.45 mmol) of nitrobenzene and then 1.0 g (2.89 mmol) of *n*-C_4F_9I **2**. Constant potential electrolysis at the reduction potential of the catalyst (*E*=−1.45 V vs SCE) was applied. After 0. 8 F/mol 90–95% of the substrate had reacted (as checked by cyclic voltammetry), the solution was cooled and neutralised with 100 ml of an aqueous 1 N HCl solution. The aqueous solution was cooled in the refrigerator overnight; a precipitate was recovered and washed several times with H_2O, coevaporated with absolute EtOH and finally triturated with hot pentane to afford 0.87 g of a beige powder which was shown (TLC; EtOAc) to contain unreacted nucleophile and a new product. The solid was purified by silica gel chromatography (EtOAc–MeOH 90:10) and finally recrystallised from EtOAc to give in 45% yield (0.58 g, 1.30 mmol) **the 6-benzylamino-8-nonafluorobutyl purine 24**: Off-white powder, mp >260°C. TLC (EtOAc–MeOH 90:10): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−80.1 (3F, CF_3), −109.15 (2F, $CF_2\alpha$), −122.0 (2F, $CF_2\beta$), −125.1 (2F, $CF_2\gamma$). ^1H NMR (DMSO-d_6): δ_H=4.71 (2H, CH_2, broad singlet), 7.43–7.55

(5H, m, arom H), 8.22 (1H, H-2, singlet), 8.29 (1H, NH, singlet), 13.07 (1H, H-9, broad singlet). Mass (CI/NH_3): *m/e*=444 ($M+H^+$), 462 ($M+NH_4^+$). Analysis: Calcd C 43.35, H 2.27, N 15.80. Found. C 43.52, H 2.54, N 15.65.

6-Amino-8-nonafluorobutyl purine 21. After 0.80 F/mol the electrolysis solution was poured into 100 ml of an aqueous 1N HCl solution, the resulting solution was kept in the refrigerator for 2 h and the resulting precipitate was washed several times with H_2O and EtOAc. The cream solid was dried by several coevaporations with absolute EtOH to yield the desired substituted product **21** in 60% yield (0.61 g; 1.75 mmol). Additional product (0.17 g) could be recovered from extraction of the aqueous phase with EtOAc and purification by silica gel chromatography (EtOAc–MeOH 80:20): Cream powder, mp >260°C. TLC (EtOAc–MeOH 75:25): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−80.0 (3F, CF_3), −109.1 (2F, $CF_2\alpha$), −122.0 (2F, $CF_2\beta$), −125.1 (2F, $CF_2\gamma$). ^{1}H NMR (DMSO-d_6): δ_H=8.34 (1H, H-2, singlet), 14.08 (2H, NH_2, broad singlet). Mass (CI/NH_3): *m/e*=354 ($M+H^+$), 371 ($M+NH_4+$). Analysis: Calcd C 30.61, H 1.14, N 19.83. Found. C 30.85, H 1.24, N 19.89.

6-Hydroxy-8-nonafluorobutyl purine 22. After 0.80 F/mol the electrolysis solution was poured into 100 ml of an aqueous 1N HCl solution, the resulting solution was kept in the refrigerator for 2 h and the resulting precipitate was washed several times with H_2O and Et_2O. The orange solid was dried by several coevaporations with absolute EtOH to yield 0.41 g of the desired substituted product **22**; extraction of the aqueous phase with Et_2O–EtOAc left an orange residue which was triturated with hot Et_2O to yield additional 0.25 g of **22**. Total yield is 65% yield (0.66 g; 1.87 mmol): Beige powder, mp >260°C. TLC (EtOAc–MeOH 75:25): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−80.0 (3F, CF_3), −110.21 (2F, $CF_2\alpha$), −122.2 (2F, $CF_2\beta$), −125.0 (2F, $CF_2\gamma$). ^{1}H NMR (DMSO-d_6): δ_H=8.15 (1H, H-2, singlet), 12.57 (1H, H-1, singlet), 14.95 (1H, H-9 broad singlet). Mass (CI/NH_3): *m/e*=355 ($M+H^+$), 371 ($M+NH_4^+$). Analysis: Calcd C 30.53, H 0.85, N 15.82. Found. C 30.58, H 0 87, N 15.90.

2,6-Di-hydroxy-8-nonafluorobutyl purine 23. After 0.70 F/mol the electrolysis solution was poured into 100 ml of an aqueous 1N HCl solution, the resulting solution was kept in the refrigerator for 2 h and the resulting precipitate (unreacted xanthine) was washed several times with H_2O and EtOAc. The orange filtrates were combined and were shown (TLC; EtOAc–MeOH 85:25) to contain the catalyst and the desired substituted product **23**. Evaporation of the solution left an orange solid which was triturated with Et_2O and MeOH to yield the desired product **23** in 75% yield (0.80 g; 2.17 mmol): White powder, mp >260°C. TLC (EtOAc–MeOH 75:25): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−80.03 (3F, CF_3), −110.31 (2F, $CF_2\alpha$), −122.24 (2F, $CF_2\beta$), −125.1 (2F, $CF_2\gamma$). ^{1}H NMR (DMSO-d_6): δ_H=11.19 (1H, H-3, singlet), 11.86 (1H, H-1, singlet). Mass (CI/NH_3): *m/e*=371 ($M+H^+$), 388 ($M+NH_4^+$). Analysis: Calcd C 29.21, H 0.82, N 15.14. Found. C 29.58, H 0.87, N 15.16.

6-Furylamino-8-nonafluorobutyl purine 25. After 1.1 F/mol the electrolysis solution was poured into 100 ml of an aqueous 1N HCl solution, the resulting solution was kept in the refrigerator for 2 h and the resulting precipitate (unreacted kinetin) was washed several times with H_2O and EtOAc. The orange filtrates were combined and were shown (TLC; EtOAc–MeOH 85:15) to contain the catalyst, the desired substituted product **25** and some unreacted kinetin. Evaporation of the solution left a brown solid which was triturated with Et_2O and MeOH to yield the impure desired product **25** which was purified by silica gel chromatography (EtOAc–MeOH 85:15) to yield **25** in 28% yield (0.35 g; 0.81 mmol): Cream powder, mp >260°C. TLC (EtOAc–MeOH 75:25): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−80.02 (3F, CF_3), −108.55 (2F, $CF_2\alpha$), −121.81 (2F, $CF_2\beta$), −124.94 (2F, $CF_2\gamma$). ^{1}H NMR (DMSO-d_6): δ_H=4.75 (2H, CH_2, broad singlet), 6.38 (2H, m, furan H), 7.56 (1H, furan H, singlet), 8.18 (1H, NH, broad singlet), 8.43 (1H, H-2, singlet). Mass (CI/NH_3): *m/e*=434 ($M+H^+$), 451 ($M+NH_4^+$). Analysis: Calcd C 38.81, H 1.86, N 16.17. Found. C 38.58, H 1.87, N 16.45.

6-Chloro-8-nonafluorobutyl purine 26. After 0.8 F/mol the electrolysis solution was poured into 100 ml of an aqueous 1N HCl solution, the resulting solution was kept in the refrigerator for 2 h and the resulting precipitate (unreacted 6-chloro purine) was washed several times with H_2O and EtOAc. The yellow filtrates were combined and were shown (TLC; EtOAc–MeOH 85:15) to contain the catalyst, the desired substituted product **26**. Evaporation of the solution left a yellowish solid which was triturated with Et_2O to yield the desired product **26** in 52% yield (0.65 g; 1.50 mmol): Cream powder, mp >260°C. TLC (EtOAc–MeOH 75:25): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−80.02 (3F, CF_3), −108.55 (2F, $CF_2\alpha$), − 121.81 (2F, $CF_2\beta$), −124.94 (2F, $CF_2\gamma$). ^{1}H NMR (DMSO-d_6): δ_H=8.80 (1H, H-2, singlet). Mass (CI/NH_3): *m/e*=434 ($M+H^+$), 451 ($M+NH_4^+$). Analysis: Calcd C 38.81, H 1.86, N 16.17. Found. C 38.58, H 1 87, N 16.45.

6-Benzylamino purine-8-tridecafluorohexyl purine 32. Same procedure as in the case of compound **24** (1.29 g (2.89 mmol) of **3** was used); evaporation of the organic extracts left an orange solid as crude product which was purified by silica gel chromatography (EtOAc–MeOH 90:10) and finally recrystallised from EtOAc to give **32** in 34% yield (0.53 g; 0.98 mmol): white powder, mp >260°C. TLC (EtOAc–MeOH 90:10): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−80.1 (3F, CF_3), −109.15 (2F, $CF_2\alpha$), −117.0 (2F, $CF_2\beta$), −122.1 (2F, $CF_2\gamma$), −124.1 (2F, $CF_2\delta$), −127.1 (2F, $CF_2\epsilon$). ^{1}H NMR (DMSO-d_6): δ_H=4.71 (2H, CH_2, broad singlet), 7.37–7.58 (5H, m, arom H), 8.22 (1H, H-2, singlet), 8.29 (1H, NH, singlet), 13.07 (1H, H-9, broad singlet). Mass (CI/NH_3): *m/e*=544 ($M+H^+$), 561 ($M+NH_4^+$). Analysis: Calcd C 39.79, H 1.86, N 12.89. Found. C 39.85, H 1.54, N 12.65.

6-Chloro-8-tridecafluorohexyl purine 33. Same procedure as in the case of compound **26** (1.29 g (2.89 mmol) of **3** was used); evaporation of the organic extracts left an orange solid as crude product which was purified by silica gel chromatography (EtOAc–MeOH 90:10) and finally recrystallised from EtOAc to give **33** in 48% yield (0.65 g; 1.38 mmol): white powder, mp >260°C. TLC

(EtOAc–MeOH 90:10): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−80.4 (3F, CF_3), −109.25 (2F, $CF_2\alpha$), −117.12 (2F, $CF_2\beta$), −122.45 (2F, $CF_2\gamma$), −124.25 (2F, $CF_2\delta$), −127.04 (2F, $CF_2\epsilon$). ^{1}H NMR (DMSO-d_6): δ_H=8.80 (1H, H-2, singlet). Mass (CI/NH_3): *m/e*=473 ($M+H^+$), 490 ($M+NH_4^+$). Analysis: Calcd C 27.96, H 0.43, N 11.86. Found. C 27.92, H 0.54, N 11.89.

6-Amino-8-iodo-nonafluorobutane purine 34. Same procedure as in the case of compound **21** (1.31 g (2.89 mmol) of **4** was used); after aqueous hydrolysis, the precipitate was washed several times with water, EtOAc and finally purified by silica gel chromatography (EtOAc–MeOH 80:20) to yield **34** in 40% yield (0.53 g; 1.15 mmol): Cream powder, mp >260°C. TLC (EtOAc–MeOH 75:25): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−66.8 (2F, CF_2I), −108.1 (2F, $CF_2\alpha$), −114.2 (2F, $CF_2\beta$), −118.1 (2F, $CF_2\gamma$). ^{1}H NMR (DMSO-d_6): δ_H=8.38 (1H, H-2, singlet), 14.28 (2H, NH_2, broad singlet). Mass (CI/NH_3): *m/e*=462 ($M+H^+$), 479 ($M+NH_4^+$). Analysis: Calcd C 28.45, H 0.87, N 15.19. Found. C 28.55, H 0.65, N 15.49.

6-Hydroxy-8-iodo-nonafluorobutane purine 35. Same procedure as in the case of compound **22** (1.31 g (2.89 mmol) of **4** was used); after aqueous hydrolysis, the precipitate was washed several times with water, EtOAc and finally purified by silica gel chromatography (EtOAc–MeOH 85:15) to yield **35** in 40% yield (0.53 g; 1.15 mmol): Cream powder, mp >260°C. TLC (EtOAc–MeOH 85:15): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−67.8 (2F, CF_2I), −109.3 (2F, $CF_2\alpha$), −114.8 (2F, $CF_2\beta$), −119.3 (2F, $CF_2\gamma$). ^{1}H NMR (DMSO-d_6): δ_H=8.14 (1H, H-2, singlet), 12.37 (1H, H-1, singlet), 14.45 (1H, H-9 broad singlet). Mass (CI/NH_3): *m/e*=463 ($M+H^+$), 480 ($M+NH_4^+$). Analysis: Calcd C 23.40, H 0.65, N 12.13. Found. C 23.48, H 0.69, N 12.18.

A representative procedure for the synthesis of the trifluoromethylated purine derivatives is described for the electrolysis of CF_3Br (1) in the presence of adenine anion (5^-)

CF_3Br is soluble in DMF at 4% by weight at atmospheric pressure. From this saturation concentration known concentrations of CF_3Br could be obtained by diluting CF_3Br with N_2 with the help of an Alphagaz mass flow regulator.[57] After saturation of 100 ml of DMF/0.1 M Et_4NBF_4 solution with the CF_3Br/N_2 mixture, 0.055 g (0.43 mmol) of terephthalonitrile and 4.18 g (20.0 mmol) of the tetramethylammonium salt of adenine **5** were added. Constant potential electrolysis at the reduction potential of the catalyst (E=−1.75 V vs SCE) was applied; the electrolysis was arbitrarily stopped after 180 C. The solution was cooled and neutralised with 100 ml of an aqueous 1N HCl solution. The aqueous solution was extracted with $CHCl_3$, and the organic solutions were combined, washed three times with water, and dried over $MgSO_4$. The solvent was evaporated to dryness and the crude product was purified by silica gel chromatography (EtOAc–MeOH 90:10) to give 0.837 g of **the 6-amino-8-trifluoromethyl purine 16**:[58] Cream powder, mp >260°C. TLC (EtOAc–MeOH 75:25): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−82.2 (3F, CF_3). ^{1}H NMR (DMSO-d_6): δ_H=8.34 (1H, H-2, singlet), 14.08 (2H, NH_2, broad singlet). Mass (CI/NH_3): *m/e*=204 ($M+H^+$), 221 ($M+NH_4^+$). Analysis: Calcd C 35.48, H 1.98, N 34.48. Found. C 35.55, H 2.06, N 34.89.

6-Hydroxy-8-trifluoromethyl purine 17.[58] Same procedure as in the case of compound **16**; purification of the crude product by silica gel chromatography (EtOAc–MeOH 90:10) gave 1.067 g of **17**: Cream powder, mp >260°C. TLC (EtOAc–MeOH 75:25): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−81.8 (3F, CF_3). ^{1}H NMR (DMSO-d_6): δ_H=8.15 (1H, H-2, singlet), 12.57 (1H, H-1, singlet), 14.95 (1H, H-9 broad singlet). Mass (CI/NH_3): *m/e*=205 ($M+H^+$), 222 ($M+NH_4^+$). Analysis: Calcd C 35.31, H 1.48, N 27.45. Found. C 35.48, H 1.57, N 27.60.

2, 6-Dihydroxy-8-trifluoromethyl purine 18. Same procedure as in the case of compound **16**; purification of the crude product by silica gel chromatography (EtOAc–MeOH 90:10) gave 1.116 g of **18**: Cream powder, mp >260°C. TLC (EtOAc–MeOH 75:25): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−80.4 (3F, CF_3). ^{1}H NMR (DMSO-d_6): δ_H=11.19 (1H, H-3, singlet), 11.86 (1H, H-1, singlet). Mass (CI/NH_3): *m/e*=221 ($M+H^+$), 238 ($M+NH_4^+$). Analysis: Calcd C 32.74, H 1.37, N 25.45. Found. C 32.81, H 1.57, N 25.66.

6-Chloro-8-trifluoromethyl purine 19. Same procedure as in the case of compound **16**; purification of the crude product by silica gel chromatography (EtOAc–MeOH 90:10) gave 0.841 g of **19**: Cream powder, mp >260°C. TLC (EtOAc–MeOH 75:25): R_f=0.50. ^{19}F NMR (DMSO-d_6): δ_F=−81.5 (3F, CF_3). ^{1}H NMR (DMSO-d_6): δ_H=8.80 (1H, H-2, singlet). Mass (CI/NH_3): *m/e*=223 ($M+H^+$), 240 ($M+NH_4^+$). Analysis: Calcd C 32.38, H 0.91, N 25.27. Found. C 32.54, H 0.74, N 25.45.

A representative procedure for the synthesis of the perfluoroalkylated indole derivatives is described for the electrolysis of *n*-C_4F_9I (2) in the presence of indole-3-acetic acid anion (11^-)

Into 80 ml of DMSO containing 4.14 g (16.7 mmol) of the tetramethylammonium salt of indole-3-acetic acid **11** (prepared in situ as described before), were added under nitrogen, 2.17 g (10 mmol) of NEt_4BF_4, 0.018 g (1.45 mmol) of nitrobenzene and then 1.0 g (2.89 mmol) of *n*-C_4F_9I **2**. Constant potential electrolysis at the reduction potential of the catalyst (E=−1.45 V vs SCE) was applied. After 0.8 F/mol 90–95% of the substrate had reacted (as checked by cyclic voltammetry), the solution was cooled and neutralised with 100 ml of an aqueous 1N HCl solution. The aqueous solution was cooled and extracted with chloroform (3×), the combined organic extracts were washed with water (5×) and dried over $MgSO_4$. Evaporation of the solvent left a red-viscous liquid as crude product which was shown (TLC; Hexane–EtOAc 70:30) to contain unreacted IAA, catalyst and a new product. Mass spectroscopy analysis revealed the formation of the desired substituted product **27**. The crude product was purified by silica gel chromatography (Hexane–EtOAc 80:20) to give in 58% yield (0.64 g; 1.30 mmol) **the 2-nonafluorobutyl-indole-3-acetic acid 27** as a yellowish viscous oil (slowly solidifies on standing). TLC (Hexane–EtOAc 70:30): R_f=0.50. ^{19}F NMR ($CDCl_3$): δ_F=−81.5 (3F, CF_3),

−108.7 (2F, $CF_2\alpha$), −123.4 (2F, $CF_2\beta$), −126.3 (2F, $CF_2\gamma$). ^{1}H NMR ($CDCl_3$): δ_H=4.06 (2H, CH_2, broad singlet), 7.32–7.45 (3H, m, arom H), 7.69 (1H, d, *J*=8.21 Hz, arom H), 8.50 (1H, –NH, broad singlet). GC/Mass: *m/e*=393 (M^+), 348 (M^+-CO_2H). Analysis: Calcd C 42.76, H 2.05, N 3.56. Found. C 42.64, H 2.44, N 3.48.

2-Nonafluorobutyl-indole-3-acetic acid methyl ester 28. Same procedure as in the case of compound **27** (K_2CO_3 was used as base; see text). The crude product was purified by silica gel chromatography (Hexane–EtOAc 75:25) to give **28** in 32% yield (0.38 g; 0.93 mmol) as a yellowish viscous oil (slowly solidifies on standing). TLC (Hexane–EtOAc 75:25): R_f=0.50. ^{19}F NMR ($CDCl_3$): δ_F=−81.4 (3F, CF_3), −108.8 (2F, $CF_2\alpha$), −123.4 (2F, $CF_2\beta$), −126.3 (2F, $CF_2\gamma$). ^{1}H NMR ($CDCl_3$): δ_H=3.56 (3H, CH_3, singlet), 3.92 (2H, CH_2, broad singlet), 7.32–7.45 (3H, m, arom H), 7.69 (1H, d, *J*=8.21 Hz, arom H), 8.49 (1H, –NH, broad singlet). GC/Mass: *m/e*=407 (M^+), 362 (M^+-CO_2H). Analysis: Calcd C 44.24, H 2.48, N 3.44. Found. C 44.54, H 2.58, N 3.65.

2-Nonafluorobutyl-indole-3-butyric acid 29. Same procedure as in the case of compound **27**. The crude product was purified by silica gel chromatography (Hexane–EtOAc 75:25) to give **29** in 48% yield (0.58 g; 1.38 mmol) as a yellowish viscous oil. TLC (Hexane–EtOAc 70:30): R_f=0.50. ^{19}F NMR ($CDCl_3$): δ_F=−81.4 (3F, CF_3), −109.2 (2F, $CF_2\alpha$), −123. 3 (2F, $CF_2\beta$), −126.0 (2F, $CF_2\gamma$). ^{1}H NMR ($CDCl_3$): δ_H=2.11 (2H, CH_2, m), 2.46 (2H, CH_2, t), 2.83 (2H, CH_2, m), 7.00–7.37 (3H, m, arom H), 7.62 (1H, d, *J*=7.84 Hz, arom H), 7.93 (1H, –NH, broad singlet). GC/Mass: *m/e*=421 (M^+), 348 ($M^+-CH_2CO_2H$). Analysis: Calcd C 45.62, H 2.87, N 3.32. Found. C 45.42, H 2.81, N 3.55.

2-Nonafluorobutyl-4,4,4-trifluoro-3-(indol-3-yl)butyric acid 30. Same procedure as in the case of compound **27**. The crude product was purified by silica gel chromatography (Hexane–EtOAc 80:20) to give **30** in 35% yield (0.48 g; 1.01 mmol) as a yellowish viscous oil. TLC (Hexane–EtOAc 80:20): R_f=0.50. ^{19}F NMR ($CDCl_3$): δ_F=−71.3 (3F, d, *J*=9.03 Hz, CF_3), −81.7 (3F, CF_3), −110.03 (2F, $CF_2\alpha$), −122.6 (2F, $CF_2\beta$), −126.0 (2F, $CF_2\gamma$). ^{1}H NMR ($CDCl_3$): δ_H=2.95–3.00 (1H, dd, *J*=16.5, 9.2 Hz), 3.08–3.14 (1H, dd, *J*=16.5, 5.4 Hz), 4.24 (1H, –C*H*CF_3, ddq, *J*=9.1, 6.2, 1.2 Hz), 7.14–7.27 (3H, m, arom H), 7.82 (1H, d, *J*=7.80 Hz, arom H), 8.03 (1H, –NH, broad singlet). GC/Mass: *m/e*=475 (M^+), 416 ($M^+-CH_2CO_2H$). Analysis: Calcd C 40.44, H 1.91, N 2.95. Found. C 40.62, H 2.02, N 2.65.

2-Nonafluorobutyl-4,4,4-trifluoro-3-(indol-3-yl)butyric acid methyl ester 31. Same procedure as in the case of compound **27**. The crude product was purified by silica gel chromatography (Hexane–EtOAc 80:20) to give **31** in 28% yield (0.39 g; 0.81 mmol) as a yellowish viscous oil. TLC (Hexane–EtOAc 80:20): R_f=0.50. ^{19}F NMR ($CDCl_3$): δ_F=−71.2 (3F, d, *J*=9.03 Hz, CF_3), −81.7 (3F, CF_3), −110.03 (2F, $CF_2\alpha$), −122.6 (2F, $CF_2\beta$), −126.0 (2F, $CF_2\gamma$). ^{1}H NMR ($CDCl_3$): δ_H=2.93–2.99 (1H, dd, *J*=16.5, 9.2 Hz), 3.07–3.13 (1H, dd, *J*=16.5, 5.4 Hz), 4.24 (1H, –C*H*CF_3, ddq, *J*=9.1, 6. 2, 1.2 Hz), 7.14–7.27 (3H, m, arom H), 7.79 (1H, d, *J*=7.86 Hz, arom H), 8.03 (1H, –NH, broad singlet). GC/Mass: *m/e*=489 (M^+), 470 (M^+-HF), 430 ($M^+-CH_2CO_2H$), 416 ($M^+-CH_2CO_2Me$). Analysis: Calcd C 41.73, H 2.27, N 2.86. Found. C 41.66, H 2.12, N 2.55.

2-Trifluoromethyl-indole-3-acetic acid 20.[38] Same procedure as for the preparation of compound **16**. The electrolysis was stopped after 535 C. The electrolysis solution was poured into water (400 ml) and extracted with EtOAc (3×200 ml). The combined organic layers were washed with water (5×400 ml), dried over $MgSO_4$ and filtered. Evaporation of solvent left unreacted catalyst. Aqueous solution was acidified (pH 5) with concentrated HCl and extracted with $CHCl_3$ (3×200 ml). The combined organic extracts were washed with water (3×200 ml) and dried over $MgSO_4$. Evaporation of the solvent left a brown solid as crude product which was purified by silica gel chromatography with hexane–EtOAc (70:30) as first eluent to recover benzo[c]quinoline, and then with hexane–EtOAc (50:50) to give 0.51 g of **20** as a yellowish solid. TLC (Hexane–EtOAc 55:45): R_f=0.50. ^{19}F NMR ($CDCl_3$): δ_F=−81.3 (3F, CF_3). ^{1}H NMR ($CDCl_3$): δ_H=3.92 (2H, CH_2, broad singlet), 7.32–7.45 (3H, m, arom H), 8.07 (1H, d, *J*=8.21 Hz, arom H), 8.49 (1H, –NH, broad singlet). GC/Mass: *m/e*=243 (M^+), 198 (M^+-CO_2H). Analysis: Calcd C 54.33, H 3.32, N 5.76. Found. C 54.46, H 3.58, N 5.85.

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