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In Search of Simplicity and Flexibility: A Rational Access to Twelve Fluoroindolecarboxylic Acids

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All twelve indolecarboxylic acids **1**–**12** carrying both a fluorine substituent and a carboxy group at the benzo ring have been prepared either directly from the corresponding fluoroindoles **13**–**16** or from the chlorinated derivatives **22**, **23** and **25** by hydrogen/metal permutation ("metalation"), or from the bromo- or iodofluoroindoles **17**–**20** and **26**, **27**, **29** and **30** by halogen/metal permutation, the organometallic intermediate being each time trapped with carbon dioxide. In most, though not all cases, the nitrogen atom in the five-membered ring had to be protected by a trialkylsilyl group. Some of the bromo- or iodofluoroindoles (**26** and **27**) were successfully subjected to a basicity gradient-driven selective migration of the heavy halogen. An unexpected finding on the way to the target compounds were the rigorously site-selective metalation of the 5-fluoro-*N*-(trialkylsilyl)indole (**14b**; exclusive deprotonation of the 4-position). The fluoroindoles **13**–**16**, although previously known, were accessed more conveniently from suitably substituted nitrobenzenes using the Bartoli or the Leimgruber–Batcho method. A new and very attractive indole synthesis was elaborated consisting of the *ortho*-lithiation of an *N*-acyl-protected aniline followed by *ortho*-formylation, Wittig chloromethylenation and base-catalyzed cyclization accompanied by dehydrochlorination. These five consecutive steps can be contracted to a convenient one-pot protocol.

Introduction

The benzo[*b*]pyrrole ring system is arguably the most frequently occurring heterocyclic motif in natural product chemistry.[1,2] The indole family comprises numerous prominent representatives such as the essential α-amino acid tryptophan, its putrefaction product skatole, the plant growth factor 3-indolylacetic acid (heteroauxin), the neurotransmitter serotonin, the pineal gland hormone melatonin, the *Rauwolfia* alkaloids reserpin and yohimbin, the *Ranunculus* alkaloid ellipticin, the *Nux vomica* alkaloid strychnine, the *Claviceps purpurea* alkaloid ergotamine and the *Catharanthus* alkaloid vincristine. Many of such plant metabolites are highly toxic. However, at the same time they may exhibit valuable medicinal properties. This explains why much effort is devoted to the development of indole-based drugs having optimized therapeutic profiles. Thus, for example, sumatriptan is administered against migraine, pindolol as a β-adrenergic blocker, indomethacin to treat inflammation and, in particular, to attenuate rheumatic pain, whereas ondanseton is taken to suppress nausea and vomiting caused by cancer chemotherapy and radiotherapy.[3]

The synthesis[4–6] of indole derivatives can be classified by the starting materials required, the practically most important aspect. The venerable Fischer cyclization uses arylhydrazines and ketones (or, although rarely, aldehydes) as the determinant components. Two new bonds, the N–C^{α} and the C^{β}–C^{ortho} linkage are formed in the same step. This is equally the case with the Bartoli reaction[7] in the course of which vinylmagnesium bromide adds nucleophilically to a nitrosoarene, generated in situ from a nitroarene precursor. If the nitroarene bears a methyl group in the *ortho* position one can apply the expedient Leimgruber–Batcho procedure.[8] Their almost unrestricted availability puts anilines of course in a privileged position as indole precursors. Two classical methods, the Berlinerblau–Nordlander [9–13] and the Bischler–Möhlau[14] route, alkylate the amino function with a side chain containing a protected or unprotected β-oxo group, which enables an acid catalyst to perform an intramolecular Friedel–Crafts hydroxyalkylation. Alternatively one may begin with an *ortho*-acylation of the aniline. The Sugasawa method [15] employs chloroacetonitrile as the reagent to obtain a 2-aminoaryl chloromethyl ketone, which after reduction with sodium borohydride undergoes smooth cyclization and dehydration. On the other hand, an *ortho* and *N*-doubly-acylated aniline affords also an indole when treated with McMurry low-valent titanium as demonstrated

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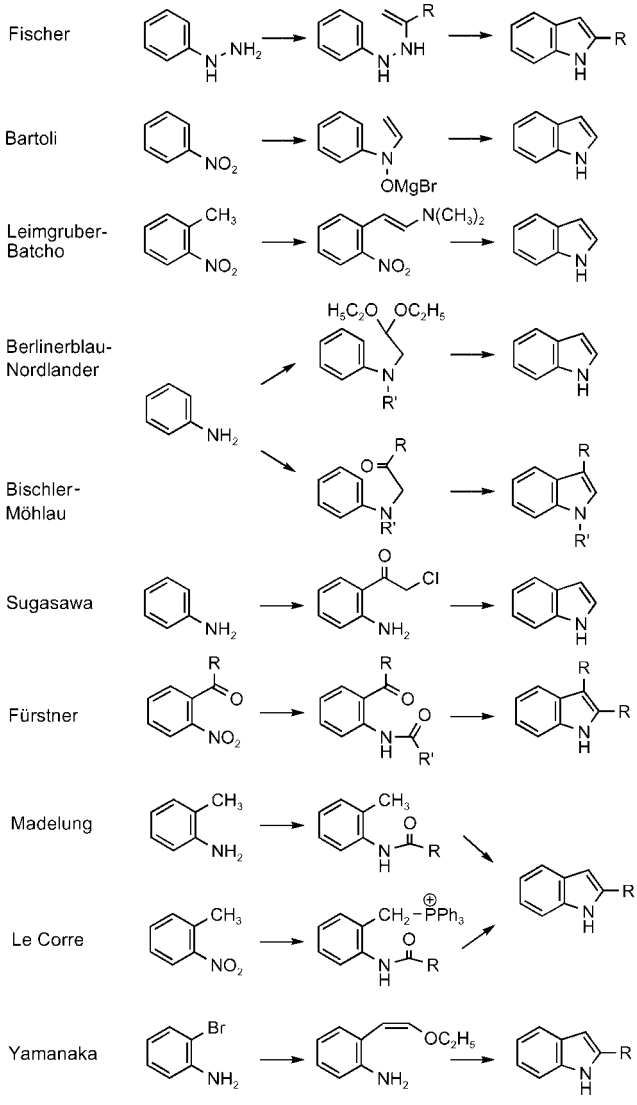
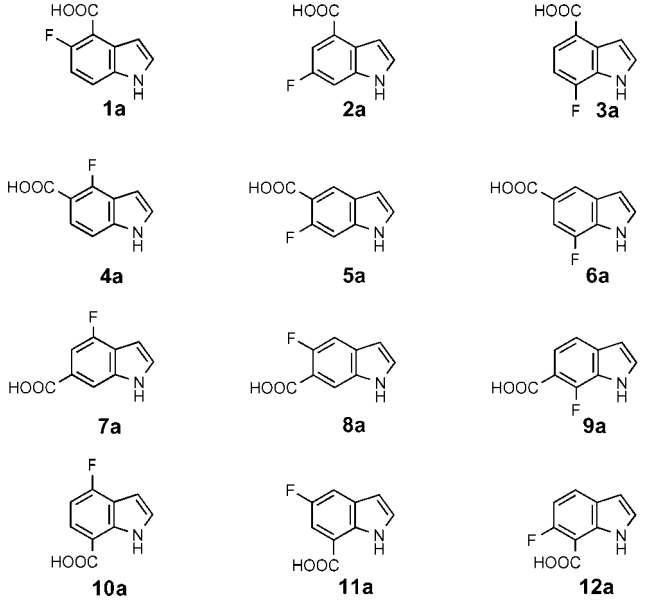
by A. Fürstner et al.[16–19] *N*-Acyl-*o*-toluidines are the typical substrates for the Madelung cyclization which requires elevated temperatures (220–300 °C) unless it is mediated by organometallic bases (e. g. butyllithium) rather than by sodium amide or potassium *tert*-butoxide. An attractive modification has been elaborated by M. Le Corre et al.[20,21] An *ortho*-methylnitroarene is consecutively brominated with *N*-bromosuccinimide and condensed with triphenylphosphane before the nitro group is reduced and the resulting amino function acylated. Treatment with potassium *tert*-butoxide converts ultimately the phosphonium salt into triphenylphosphane oxide and an indole. A final modern method, disclosed by H. Yamanaka et al., is based on the Stille coupling of an *ortho*-bromoaniline with *cis*-(2-ethoxyethenyl)tributyltin and is terminated by an acid-promoted cyclization.[22]

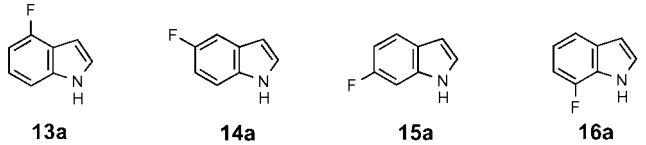


All these procedures suffer from shortcomings. The preparation of the required starting materials and intermediates can be lengthy in quite a few cases. Structural limitations are another concern. Several of the methods described above fail with indoles having a naked, i.e. substituent-free, five-membered ring. Finally, ring-closure by electrophilic attack of the β-carbon at an *ortho*-carbon atom requires the assistance of electron-donating groups and is prevented by electron-withdrawing groups. In other words, although indoles are legion, most of them exhibit familiar structural patterns and mechanism-compatible polarities. For example, not a single fluoroindolecarboxylic acid harboring both the halogen and the carboxy functionality at the benzo ring is known so far. We decided to make all twelve of them (compounds **1a**–**12a**).



This collection of target compounds represents a model case of *regioexhaustive structure variation*. It thus can serve as an ideal test of the "toolbox methods" [23] designed to tackle exactly such kind of problems. The conceptional cornerstone of this bundle of procedures is to introduce an alkali or alkali-earth metal into any vacant substrate position, in the present example into all vacant positions of the fluoroindole benzo ring. All what then remains to be done is to combine the resulting intermediates with carbon dioxide and to isolate the carboxylic acids **1**–**12** after neutralization.

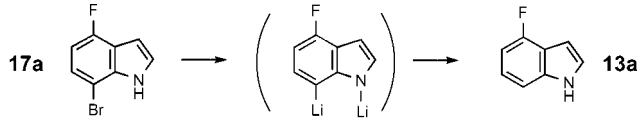
The most straightforward access to organometallic intermediates ("CM species", M = metal) is the permutational hydrogen/metal interconversion ("metalation") of the corresponding CH compounds.[24] Fluorobenzene [25] itself and fluorotoluenes,[26] fluorobiphenyls,[26] fluorochlorobenzenes [27] and fluoroanisoles [28] or fluoro(methoxymethoxy)benzenes [29] as well readily undergo metalation at a fluorine-adjacent position. Therefore, our first objective was to introduce selectively lithium or another alkali metal into 4-, 5-, 6- and 7-fluoroindoles (**13a**–**16a**).



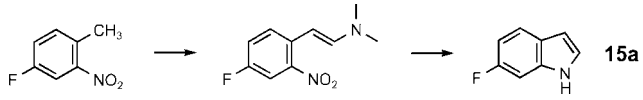
Fluoroindoles

All benzo-ring-substituted fluoroindoles **13a**–**16a** are documented in the literature and the 4-, 5- and 6-fluoro isomers are even commercial. We felt nevertheless compelled to invest time and effort in order to revisit, improve or redesign known syntheses.

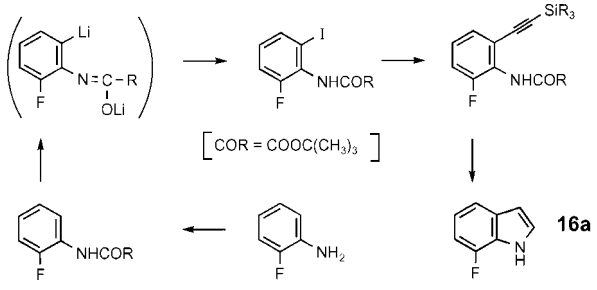
Both 4-fluoroindole [30] and 5-fluoroindole [31] were most easily obtained by consecutive treatment of 7-bromo-4-fluoroindole and 7-bromo-5-fluoroindole (**17a** and **18a**, see below), respectively, with two equiv. of butyllithium and methanol. The satisfactory yields (56 and 46%) confirm that the NH deprotonation step preceded the halogen/metal permutation as expected.[32,33]



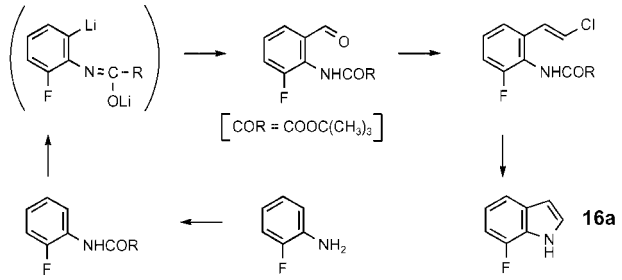
The access to the 6-fluoroindole (**15a**) was also accomplished in a one-flask procedure. By applying the Leimgruber–Batcho method, the commercial 4-fluoro-2-nitrotoluene was directly converted into the product **15a** in 33% yield.



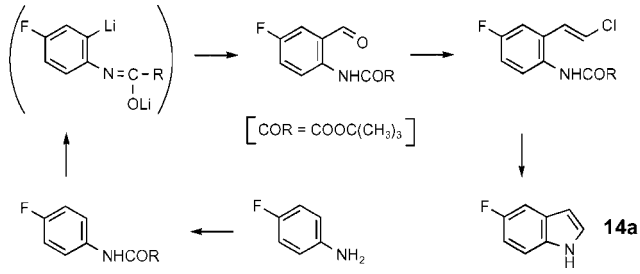
In contrast, the preparation of the 7-fluoroindole (**16a**)[7] proved troublesome. In a first attempt, *N*-*tert*-butoxycarbonyl (BOC) protected 2-fluoroaniline was lithiated at the 6-position[34] and the intermediate trapped with molecular iodine. The iodo compound thus formed was subjected to a Cassar–Sonogashira coupling, [35,36] and the resulting ethinylsilane was simultaneously cyclized and deprotected to afford the 7-fluoroindole (**16a**) in 64% yield.



A major improvement was achieved by replacing the iodination by a formylation stage and the acetylide coupling by a Wittig chloromethylenation.[37,38] The thus modified reaction sequence consisting of aniline acylation, *ortho*-lithiation (using *tert*-butyllithium), formylation (using dimethylformamide), chloroolefination [using chloromethyl(triphenyl)phosphonium chloride] and potassium *tert*-butoxide mediated cyclization followed by deprotection was carried out stepwise and also as a one-flask nonstop procedure. The over-all yield (15–19%) of 7-fluoroindole (**16a**) was acceptable in either case.



The same *ortho*-formylation/chloromethylenation/cyclization sequence was applied to the preparation of 5-fluoroindole (**14a**). The over-all yield (19%) was again satisfactory.

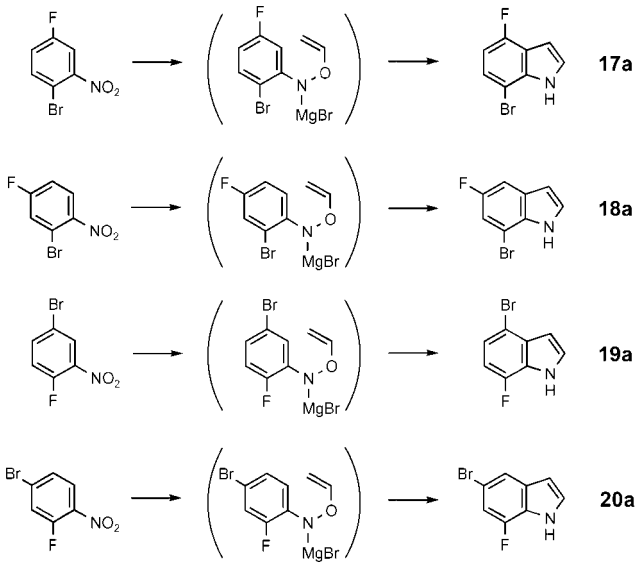


Halofluoroindoles

There is no simpler way to make indoles than by the Bartoli reaction[7] provided that the nitro compound required as the starting material is readily available. The other uncertainty concerns the yields. They are extremely variable, never excellent and sometimes close to zero.

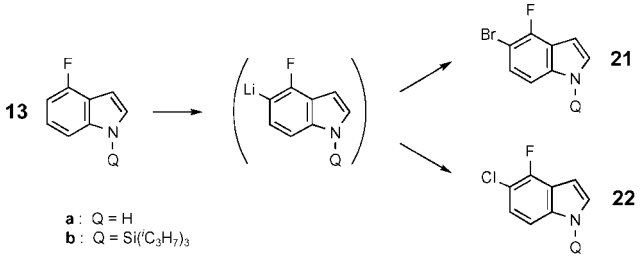
Three bromofluoronitrobenzenes can be purchased. However, these compounds and certain isomers as well can be obtained less expensively by oxidation of the corresponding bromofluoroanilines. Four isomeric bromofluoronitrobenzenes were thus prepared and, under Bartoli conditions, treated with excess vinylmagnesium bromide to afford 7-bromo-4-fluoroindole (**17a**, 52%), 7-bromo-5-fluoroindole (**18a**, 57%), 4-bromo-7-fluoroindole (**19a**, 34%) and 5-bromo-7-fluoroindole (**20a**, 36%).

Obviously, the yields of isolated products (34–57%) fall in the same range regardless whether a small fluorine or a voluminous bromine atom occupies the position adjacent to the nitro group. G. Bartoli et al.[7,39,40] have always considered the presence of a bulky substituent in a nitro-adjacent position as a crucial prerequisite for a successful cyclization step. Steric hindrance emanating from the *ortho* position was believed to reorient the attack of the vinylmagnesium bromide reagent from the nitrogen to the oxygen atom of the nitro group and the transient nitroso substrate. How-

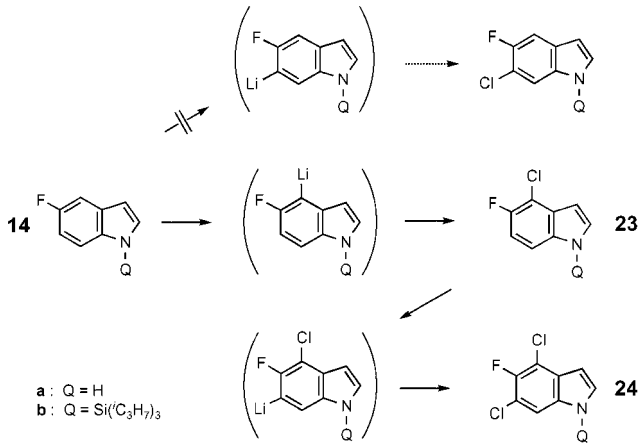


ever, if the reaction mechanism is really single electron-transfer triggered, as the Italian authors plausibly surmise,[39] the vinyl radical has anyway no other choice than to combine with an oxygen rather than the nitrogen atom. Moreover, as G. Köbrich et al. have shown,[41] even nitrobenzene itself reacts with two equiv. of phenyllithium to produce quantitatively (two equiv.!) phenol. All in all, the outcome of the reaction appears to depend not only on the nature of a given substituent, but among other things, the temperature and, in particular, the solvent, all factors which may promote or control the numerous possible side reactions leading to anilines, hydroxylamines, alkenylarylamines, azo and azoxy compounds as by-products.

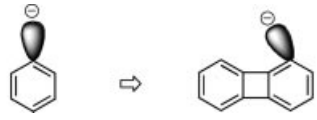
Further halofluoroindoles were prepared on a totally different route by consecutive lithiation and halogenation of 4-, 5- and 6-fluoroindoles. To avoid the ordinary deprotonation of the intrinsically most acidic 2-position,[42–44] the nitrogen had to be protected by bulky groups, in particular triisopropylsilyl (TIPS)[45,46] or 2,2-diethylbutanoyl.[47] The *N*-TIPS-4-fluoroindole (**13b**) was readily converted into the 5-bromo and 5-chloro derivatives **21b** and **22b** and, after deprotection, into the corresponding indoles **21a** and **22a** by consecutive metalation and halogenation.



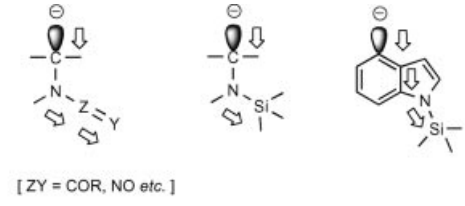
When *N*-TIPS-5-fluoroindole (**14b**) was subjected to an analogous series of reactions, the 4-position was substituted exclusively. Deprotonation of the 6-position occurred only with *N*-TIPS-4-chloro-5-fluoroindole (**23b**) as the substrate, in other words, after the most reactive site had been blocked. Under such circumstances, 4,6-dichloro-5-fluoroindole (**24a**) was obtained in 45% over-all yield.



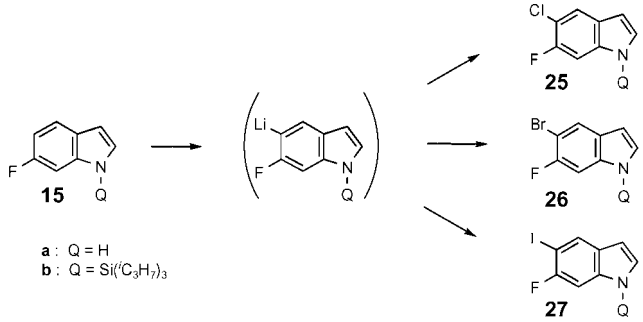
Although much appreciated, the unexpected regioselectivity in favor of the 4-position was puzzling. Eventually we discovered an analogy in the literature. *N*-Silyl-protected 5-(diethylcarbamoyloxy)indole was reported, without comment nor explanation, to undergo metalation also at the 4-position.[48] What kind of phenomenon does provide extra acidification to the 4-position but not to the 6-position? Our tentative explanation focuses, for one thing, on the natural tendency of the nonbonding carbanionic electrons to seek stabilization by expanding beyond their ordinary confinements. Thus, they will invade the empty space surrounding a small carbo- or heterocycle placed in their vicinity.[49] At the same time, the pronounced distortion of the benzene hexagon upon deprotonation [50] or lithiation [51–54] causes relief of strain in a three-, four- or five-membered ring if annulated in the vicinity of the carbanionic center of the benzenide due to the widening of the C–C–C angle. The combination of the two effects increases, for example the statistically corrected kinetic acidity of biphenylene, relative to that of benzene, at the 2-position by a factor of 6.2 but at the 1-position by a factor of 490.[55–57]



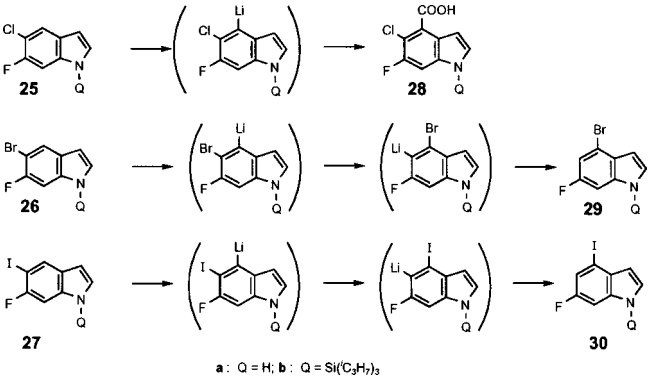
σ/π-Polarization presumably acts as an additional acidity-enhancing effect. *N*-Acyl- or *N*-nitroso-*N*-methylamines readily undergo lithiation of the methyl group.[24,58] The nature of this dipole stabilization has been theoretically investigated.[59,60] Such σ/π-polarization should also lower the energy of carbanions if directly attached to an *N*-silylamino group and perhaps even if located at a vinylogous site like the 4-position of *N*-silylindoles.



Finally, also the *N*-TIPS-protected 6-fluoroindole was regioselectively metalated. The 7-position being sterically screened by the bulky silyl group, deprotonation occurred solely at the 5-position. Trapping of the organometallic intermediate with 1,1,2-trichloro-1,2,2-trifluoroethane, 1,2-dibromo-1,1,2,2-tetrafluoroethane and molecular iodine gave, after deprotection, 5-chloro-6-fluoroindole (**25a**; 85%), 5-bromo-6-fluoroindole (**26a**; 84%) and 6-fluoro-5-iodoindole (**27a**; 79%).

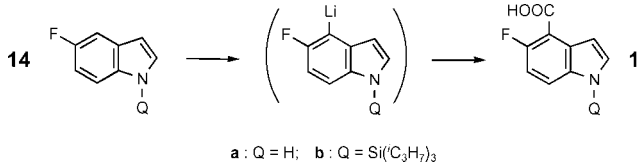


The *N*-TIPS-protected 6-fluoro-5-chloroindole **25** can be lithiated at the 4-position using LITMP (lithium 2,2,6,6-tetramethylpiperidide) as the base. The organometallic intermediate proved perfectly stable as evidenced by its conversion into the carboxylic acid **28a** (75%) by reaction with dry ice, neutralization and deprotection. In contrast, the iodo species **27b** isomerized by basicity gradient-driven halogen migration [61,62] to afford the 6-fluoro-4-iodoindole **30** (88%) after neutralization and deprotection. Under similar conditions, the *N*-TIPS-protected 5-bromo-6-fluoroindole **26b** underwent the bromine/lithium migration more reluctantly. After a reaction time of 6 h followed by neutralization, a 5:1 mixture of, respectively, the 4- and 5-bromo isomers (**26b** and **29b**) was obtained.

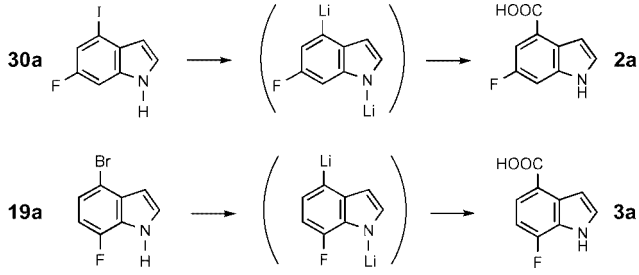


Fluoroindolecarboxylic Acids

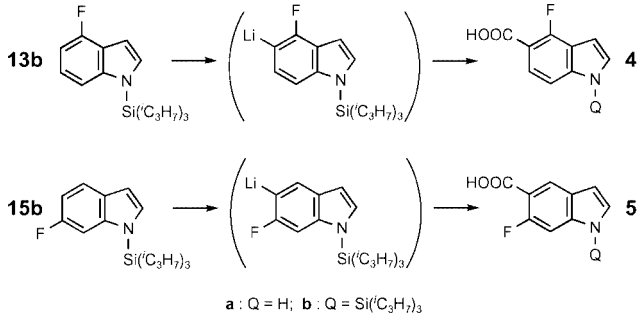
Whenever it was possible to metalate a fluoroindole or an *N*-protected derivative thereof regioselectively, this was the method of choice to access the corresponding fluoroindolecarboxylic acid. In this way, 5-fluoroindole-4-carboxylic acid (**1**) was obtained in high yield (74%) and isomerically pure.



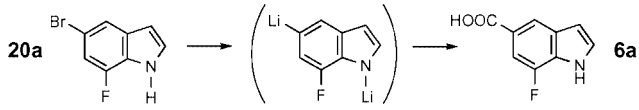
The 6- and 7-fluoroindole-4-carboxylic acids (**2**, 54% and **3**, 67%, respectively) were readily produced by the consecutive treatment of 6-fluoro-4-iodoindole (**30a**) and 7-fluoro-4-bromoindole (**19a**) with two equiv. of butyllithium and dry ice. Again, as testified by the high yields, the halogen/metal permutation, even if very fast, is clearly outpaced by the deprotonation of the NH bonds, which is a diffusion-controlled process by all evidence.



As 4-fluoroindole disposes of just one directly halogen-adjacent position, the site at which deprotonation of its *N*-triisopropylsilyl derivative **13a** would occur was unequivocal. In fact, after trapping with carbon dioxide, 4-fluoroindole-5-carboxylic acid (**4a**, 58%) was formed as the sole detectable product. The outcome of the metalation of 6-fluoro-1-(triisopropylsilyl)indole (**15b**), ultimately providing 6-fluoro-5-carboxylic acid (**5a**), was also predictable as the bulky silyl substituent of course effectively screens the 7-position against any attack of a base (see above).

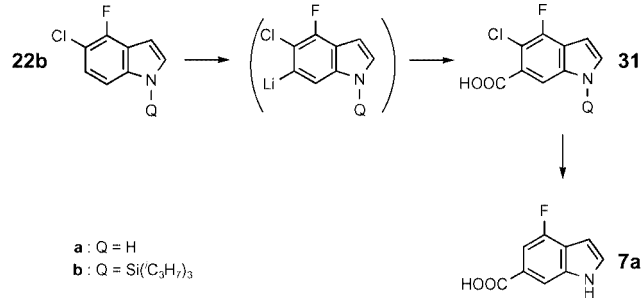


The 7-fluoroindole-5-carboxylic acid (**6a**; 57%) was found to be readily accessible from 5-bromo-7-fluoroindole (**20a**). Once more the NH entity could remain unprotected.

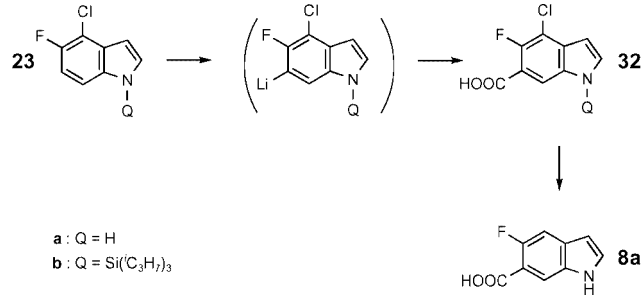


The 4-fluoroindole-6-carboxylic acid (**7a**, 82%) was prepared starting from 5-chloro-4-fluoro-1-(triisopropylsilyl)-indole (**22b**) via the 5-chloro-4-fluoroindole-6-carboxylic acid (**31a**, 79%). The role of the chlorine atom was to

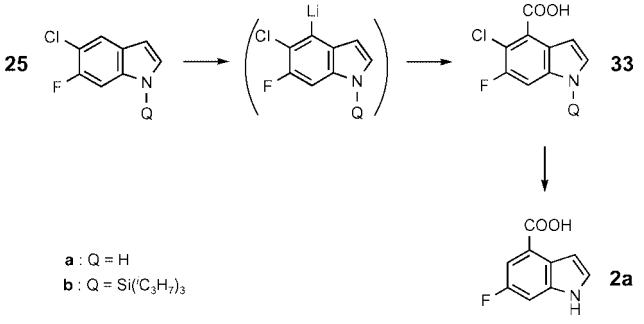
protect the fluorine-adjacent position against lithiation and at the same time to activate the neighboring 6-position toward deprotonation ("deflected metalation" [23]). The heavier halogen was reductively eliminated using ammonium formate in methanol as the hydrogen source and palladium on charcoal as the catalyst.[63]



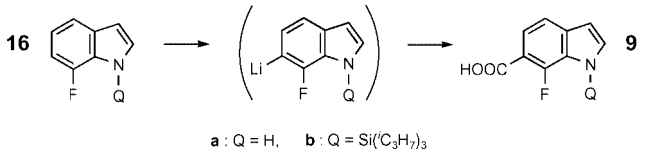
Blockage by a chlorine atom was also the key feature of the synthesis of 5-fluoroindole-6-carboxylic acid (**8**). As already specified for acid **31a**, the 4-chloro-5-fluoro-6-carboxylic acid (**32a**, 74%) resulting from metalation, carboxylation and desilylation was dechlorinated by catalytic hydrogenation.



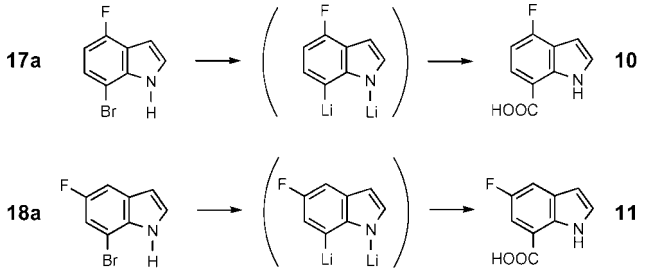
Removal of the chlorine atom, which served as a temporary protecting group, by catalytic hydrogenation was also the last step in the preparation of 6-fluoroindole-4-carboxylic acid (**2a**, 79%) starting from 5-chloro-6-fluoro-1-(triisopropylsilyl)indole (**25**) and passing through 5-chloro-6-fluoro-1-(triisopropylsilyl)indole-4-carboxylic acid (**28**; see above). Acid **2a** (71%) had been independently accessed from 6-fluoro-4-iodoindole (**30a**), as previously mentioned.



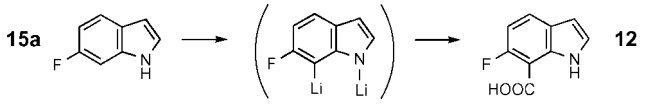
7-Fluoro-1-(triisopropylsilyl)indole (**16b**) underwent smooth metalation at the 6-position to afford, after carboxylation, the 7-fluoroindole-6-carboxylic acid (**9**, 80%). No *C*-deprotonation occurred at all when the free 7-fluoroindole (**16a**) was treated with two equiv. of *sec*-butyllithium. Obviously the electron excess accumulated at the lithiated nitrogen atom spreads out in all directions and deactivates also the benzo ring toward base attack.



The halogen/metal permutation of 7-bromo-4-fluoroindole (**17a**) and 7-bromo-5-fluoroindole (**18a**) proceeded without any problem and provided the 4-fluoroindole-7-carboxylic acid (**10**, 67%) and 5-fluoroindole-7-carboxylic acid (**11**, 55%) after carboxylation and neutralization. Once more, the NH unit could remain unprotected.



Fluoroindole **15a** was found to undergo metalation smoothly at the 7-position (60% of acid **12**, after trapping with dry ice) without prior silylation of the heterocyclic nitrogen atom. Apparently the NLi neighboring group assistance outweighs the deactivating electron donation of the NLi center. All other fluoroindole isomers (**13a**, **14a**, and **16a**) had proven totally inert towards organometallic reagents once the NH site was deprotonated and lithiated.



The unique virtue of this organometallic approach to diversity-oriented synthesis is its product flexibility. Any member of the infinite pool of electrophilic reagents may be selected instead of carbon dioxide in order to open an entry to other classes of functionalized derivatives. To support this claim, also several fluorinated 5-hydroxyindoles and indole-5-carbaldehydes have been prepared.[64]

Experimental Section

Details regarding standard operations and abbreviations can be found in previous publications from this laboratory.[65–67] ^{1}H, ^{13}C (^{1}H-decoupled) and ^{19}F NMR spectra of samples dissolved in deuteriochloroform or, if marked by an asterisk, in hexadeuterioacetone were recorded at 400, 101 and 376 MHz, respectively, chemical shifts being given relative to tetramethylsilane and trichlorofluoromethane as the internal standards. Some of the nitrogen-bound ^{1}H signals were too broad to be unequivocally identified.

Fluoroindolecarboxylic Acids

Most of the twelve fluoroindolecarboxylic acids were prepared by consecutive treatment of the fluoroindoles **13**–**16**, whether they carry a 1-triisopropyl (TIPS) protecting group or not, or of the bromofluoroindoles **17**–**20** and iodofluoroindole **30** with butyllithium and dry ice, a few others by metalation of the TIPS-protected chlorofluoroindoles **22**, **23** and **25** followed by carboxylation and dechlorination. The access to all precursor compounds is described in the sub-chapters "fluoroindoles", "halofluoroindoles" and "chlorofluoroindolecarboxylic acids" appearing below.

5-Fluoro-1-(triisopropylsilyl)indole-4-carboxylic Acid (1b): 2,2,6,6-Tetramethylpiperidine (3.4 mL, 2.8 g, 20 mmol), potassium *tert*-butoxide (2.5 g, 20 mmol) and 5-fluoro-1-(triisopropylsilyl)indole (**14b**, 2.9 g, 10 mmol) were added consecutively to a solution of butyllithium (20 mmol) in tetrahydrofuran (40 mL) and hexanes (10 mL). After 2 h at –75 °C, the mixture was poured onto an excess of freshly crushed dry ice. Water was added (10 mL). The organic phase was decanted and the aqueous one extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with a 1.0 M solution of citric acid (2 × 15 mL) and brine (2 × 10 mL) before the solvents were evaporated. Crystallization from diethyl ether/hexanes (1: 10) gave colorless cubes; m.p. 131–133 °C; yield: 2.48 g (74%). ^{1}H NMR: δ = 7.65 (dd, J = 9.0, 4.0 Hz, 1 H), 7.45 (d, J = 3.0 Hz, 1 H), 7.31 (d, J = 3.0 Hz, 1 H), 6.94 (dd, J = 12.0, 9.0 Hz, 1 H), 1.68 (sept, J = 7.0 Hz, 3 H), 1.14 (d, J = 7.0 Hz, 18 H) ppm. ^{13}C NMR: δ = 170.5, 159.2 (d, J = 255 Hz), 138.0, 135.5, 132.2, 119.7, 110.0 (d, J = 26 Hz), 107.4, 106.5, 18.0 (3 C), 12.2 (6 C) ppm. ^{19}F NMR: δ = –118.3 (d, J = 9 Hz) ppm. MS (c.i.): m/z (%) = 339 (100) [M^+ + 4], 311 (3), 294 (49), 250 (5). $C_{18}H_{26}FNO_2Si$ (335.50): calcd. C 64.44, H 7.81; found C 65.02, H 8.45.

5-Fluoroindole-4-carboxylic Acid (1a): At 25 °C, tetrabutylammonium fluoride hydrate (1.3 g, 5.0 mmol) was dissolved in a solution of 5-fluoro-1-(triisopropylsilyl)-4-indolecarboxylic acid (**1b**, 1.6 g, 5.0 mmol) in tetrahydrofuran (10 mL). After 5 min at 25 °C, the mixture was diluted with diethyl ether, the organic phase washed with brine (2 × 10 mL), dried and filtered and the solvents were evaporated. Crystallization from 90% aqueous methanol afforded colorless platelets; m.p. 225–227 °C; yield: 0.806 g (90%). ^{1}H NMR*: δ = 10.6 (broad s, 1 H), 7.72 (ddd, J = 8.9, 4.1, 1.0 Hz, 1 H), 7.59 (t, J = 3.1 Hz, 1 H), 7.08 (symm. m, 1 H), 7.05 (dd, J = 11.2, 8.7 Hz, 1 H). ^{13}C NMR*: δ = 167.5, 159.5 (d, J = 247 Hz), 148.7, 135.1, 130.0, 118.5, 111.7 (d, J = 23 Hz), 110.5, 105.1. ^{19}F NMR*: δ = –119.6 (broad s) ppm. MS (c.i.): m/z (%) = 197 (86) [M^+ + NH_4], 180 (100), 161 (11), 136 (43), 126 (13). $C_9H_6FNO_2$ (179.15): calcd. C 60.34, H 3.38; found C 60.41, H 3.38.

6-Fluoroindole-4-carboxylic Acid (2a): Palladium (10%) on charcoal (0.21 g, 2.0 mmol) was added to a solution of ammonium formate (0.25 g, 4.0 mmol) and 5-chloro-6-fluoro-4-carboxylic acid (**28a**, 0.43 g, 2.0 mmol) in methanol (5 mL). After 2 h at 25 °C, the reaction mixture was filtered through a celite pad and the solvents evaporated. After crystallization from 75% aqueous methanol, colorless needles were collected; m.p. 222–223 °C; yield: 0.322 g (90%). ^{1}H NMR*: δ = 10.6 (broad s, 1 H), 7.61 (dd, J = 10.5, 2.5 Hz, 1 H), 7.53 (t, J = 3.2 Hz, 1 H), 7.48 (dd, J = 8.9, 2.4 Hz, 1 H), 7.14 (symm. m, 1 H) ppm. ^{13}C NMR*: δ = 169.2, 160.7 (d, J = 235 Hz), 139.1, 129.5, 126.7, 124.2, 112.2 (d, J = 25 Hz), 105.2, 104.1 (d, J = 29 Hz) ppm. MS (c.i.): m/z (%) = 197 (86) [M^+ + NH_4], 180 (100) [M^+ + H], 162 (17), 151 (3), 134 (5), 107 (3). $C_9H_6FNO_2$ (179.15): calcd. C 60.34, H 3.38; found C 60.38, H 4.44. The same acid **2a** was obtained in 54% yield (0.096 g) when a solution of 6-fluoro-4-iodoindole (**30a**, 0.26 g, 1.0 mmol) and butyllithium (3.0 mmol) in tetrahydrofuran (6.0 mL) and hexanes (1.9 mL) was kept for 45 min at –75 °C before being poured on an excess of freshly crushed dry ice and treated with dilute hydrochloric acid.

7-Fluoroindole-4-carboxylic Acid (3a): At –75 °C, butyllithium (15 mmol) in hexanes (10 mL) was added to a solution of 4-bromo-7-fluoroindole (**19a**, 1.1 g, 5.0 mmol) in tetrahydrofuran (30 mL). After having been kept for 2 h in a dry ice/methanol bath, the reaction mixture was poured onto an excess of freshly crushed dry ice. Water was added (50 mL). The organic phase was acidified to pH 1 and extracted with diethyl ether (2 × 15 mL). The solvents were evaporated and the residue was crystallized from 75% aqueous methanol and sublimed; colorless needles; m.p. 203–205 °C; yield: 0.613 g (68%). ^{1}H NMR*: δ = 11.0 (broad s, 1 H), 7.86 (dd, J = 8.5, 5.1 Hz, 1 H), 7.56 (broad s, 1 H), 7.18 (broad s, 1 H), 6.97 (dd, J = 10.5, 8.5 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.2, 159.5 (d, J = 243 Hz), 154.2, 133.7, 127.8, 124.4, 118.1, 105.5 (d, J = 22 Hz), 104.2 ppm. ^{19}F NMR*: δ = –127.8 (dt, J = 11.1, 3.8 Hz) ppm. MS (c.i.): m/z (%) = 197 (100) [M^+ + NH_4], 180 (37) [M^+ + H], 162 (15), 151 (2). $C_9H_6FNO_2$ (179.15): calcd. C 60.34, H 3.38; found C 60.53, H 3.45.

4-Fluoro-1-(triisopropylsilyl)indole-5-carboxylic Acid (4b): A solution containing 4-fluoro-1-(triisopropylsilyl)indole (**13b**, 4.4 g, 15 mmol) and *sec*-butyllithium (15 mmol) in cyclohexane (13 mL) and tetrahydrofuran (30 mL) was kept for 2 h at –75 °C before being poured onto an excess of freshly crushed dry ice. Water was added (10 mL). The organic phase was washed with 1.0 M solution of citric acid (2 × 15 mL) and the solvents evaporated. The residue was crystallized from a 1:10 (v/v) mixture of diethyl ether and hexanes to give colorless cubes; m.p. 155–157 °C; yield: 3.17 g (63%). ^{1}H NMR: δ = 7.80 (t-like dd, J = 8.0 Hz, 1 H), 7.32 (d, J = 8.8 Hz, 1 H), 7.29 (d, J = 3.0 Hz, 1 H), 6.85 (d, J = 3.0 Hz, 1 H), 1.70 (sept, J = 8.0 Hz, 3 H), 1.14 (d, J = 8.0 Hz, 18 H) ppm. ^{13}C NMR δ = 170.2, 157.2 (d, J = 256 Hz), 146.7, 132.1, 124.7, 121.0 (d, J = 21 Hz), 109.9, 107.2, 102.4, 18.0 (3 C), 12.7 (6 C) ppm. ^{19}F NMR: δ = –115.2 (d, J = 7.0 Hz) ppm. MS (c.i.): m/z (%) = 353 (70) [M^+ + NH_4], 336 (37) [M^+ + 1], 318 (11), 292 (30). $C_{18}H_{26}FNO_2Si$ (335.50): calcd. C 64.44, H 7.81; found C 63.41, H 7.73.

4-Fluoroindole-5-carboxylic Acid (4a): Prepared, analogously as acid **1a**, starting from 4-fluoro-1-(triisopropylsilyl)indole-5-carboxylic acid (**4b**, 0.67 g, 2.0 mmol); colorless prisms after crystallization from 90% aqueous methanol; m.p. 225–227 °C; 0.330 g (92%). ^{1}H NMR*: δ = 10.9 (broad s, 1 H), 7.71 (dd, J = 8.6, 6.9 Hz, 1 H), 7.45 (t-like dd, J = 2.8 Hz, 1 H), 7.32 (dd, J = 8.6, 0.8, 1 H), 6.67 (symm. m, 1 H) ppm. ^{13}C NMR δ = 166.6, 157.6 (d, J = 260 Hz), 142.4, 127.9, 125.4, 118.7 (d, J = 19 Hz), 109.2, 108.7, 99.7. ^{19}F NMR: δ = –114.7 (d, J = 5.9 Hz) ppm. MS (c.i.): m/z (%) = 197 (100) [M^+ + NH_4], 180 (26) [M^+ + H], 162 (7), 151 (2). $C_9H_6FNO_2$ (179.15): calcd. C 60.34, H 3.38; found C 60.28, H 3.46.

6-Fluoro-1-(triisopropylsilyl)indole-5-carboxylic Acid (5b): Prepared, analogously as acid **4b**, starting from 6-fluoro-1-triisopropylsilylindole (**15b**, 1.5 g, 5.0 mmol); colorless cubes after crystallization from a 1:10 (v/v) mixture of diethyl ether and hexanes; m.p. 167–169 °C; yield: 1.33 g (79%). ^{1}H NMR: δ = 8.36 (d, J = 7.6 Hz, 1 H), 7.33 (d, J = 3.2 Hz, 1 H), 7.25 (d, J = 12.9 Hz, 1 H), 6.71 (d, J = 3.2 Hz, 1 H), 1.71 (sept, J = 7.6 Hz, 3 H), 1.15 (d, J = 7.6 Hz, 18 H) ppm. ^{13}C NMR ^{13}C NMR: δ = 170.2, 157.2 (d, J = 256 Hz), 146.7, 132.1, 124.7, 121.0 (d, J = 21 Hz), 109.9, 107.2, 102.4, 18.0 (3 C), 12.7 (6 C) ppm. ^{19}F NMR: δ = –118.3 (dd, J = 12.4, 7.1 Hz) ppm. MS (c.i.): m/z (%) = 353 (0) [M^+ + NH_4], 336 (100) [M^+ + 1], 292 (30), 248 (5), 206 (2). $C_{18}H_{26}FNO_2Si$ (335.50): calcd. C 64.44, H 7.81; found C 63.44, H 7.60.

6-Fluoroindole-5-carboxylic Acid (5a): Prepared, analogously as acid **1a**, starting from 6-fluoro-1-(triisopropylsilyl)indole-5-carboxylic acid (**5b**, 0.67 g, 2.0 mmol); colorless cubes (from 90% aqueous methanol); m.p. 230–231 °C; yield: 0.322 g (90%). ^{1}H NMR*: δ = 10.9 (broad s, 1 H), 8.29 (d, J = 7.1 Hz, 1 H), 7.45 (dd, J = 3.4, 2.3 Hz, 1 H), 7.24 (dd, J = 12.1, 0.9 Hz, 1 H), 6.64 (symm. m, 1 H) ppm. ^{13}C NMR δ = 167.2, 160.7 (d, J = 250 Hz), 140.5, 129.1, 126.7, 126.1, 112.9, 104.5, 99.9 (d, J = 31 Hz) ppm. ^{19}F NMR: δ = –118.9 (dd, J = 12.1, 7.0 Hz) ppm. MS (c.i.): m/z (%) = 197 (20) [$M^+ + NH_4$], 179 (100) [M^+], 162 (43), 134 (18), 121 (9), 107 (16), 99 (8), 81 (12). $C_9H_6FNO_2$ (179.15): calcd. C 60.34, H 3.38; found C 60.41, H 3.44.

7-Fluoroindole-5-carboxylic Acid (6a): Prepared, analogously as acid **3a**, starting from 5-bromo-7-fluoroindole (**20a**, 1.1 g, 5.0 mmol) and purified by sublimation; colorless needles; m.p. 227–228 °C; yield: 0.520 g (58%). ^{1}H NMR*: δ = 10.6 (broad s, 1 H), 8.26 (s, 1 H), 7.62 (d, J = 1.4 Hz, 1 H), 7.56 (dd, J = 5.5, 1.6 Hz, 1 H), 6.75 (dt, J = 2.6, 1.9 Hz, 1 H) ppm. ^{13}C NMR*: δ = 168.7, 151.1 (d, J = 245 Hz), 133.2, 129.3, 128.5, 124.3, 121.2, 108.7 (d, J = 24 Hz), 105.7 ppm. ^{19}F NMR: δ = –135.1 (dd, J = 12.1, 3.0 Hz) ppm. MS (c.i.): m/z (%) = 195 (2) [$M^+ + NH_4$], 179 (100) [M^+], 162 (40), 134 (38), 122 (4), 107 (23), 95 (7), 81 (5). $C_9H_6FNO_2$ (179.15): calcd. C 60.34, H 3.38; found C 60.35, H 3.45.

4-Fluoroindole-6-carboxylic Acid (7a): Prepared, analogously as acid **2a**, from 5-chloro-4-fluoro-6-carboxylic acid (**31a**, 0.43 g, 2.0 mmol) in methanol (5 mL); colorless needles (from 75% aqueous methanol); m.p. 215–217 °C; yield: 0.290 g (81%). ^{1}H NMR*: δ = 10.8 (broad s, 1 H), 7.72 (dd, J = 8.6, 6.9, 1 H), 7.47 (t, J = 2.6, 1 H), 7.33 (d, J = 8.5, 1 H), 6.70 (symm. m, 1 H) ppm. ^{13}C NMR*: δ = 157.7, 158.5 (d, J = 262 Hz), 143.5, 128.7, 128.2, 126.5, 110.2, 109.3, 109.1 ppm. ^{19}F NMR*: δ = –116.1 (d, J = 5.0 Hz) ppm. MS (c.i.): m/z (%) = 179 (84) [M^+], 163 (100), 151 (4), 135 (92), 122 (4), 107 (21), 86 (6). $C_9H_6FNO_2$ (179.15): calcd. C 60.34, H 3.38; found 60.43, H 3.50.

5-Fluoroindole-6-carboxylic Acid (8a): Prepared, analogously as acid **2a**, from 4-chloro-5-fluoroindole-6-carboxylic acid (**32a**, 1.1 g, 5.0 mmol); colorless needles (from 90% aqueous methanol); m.p. 215–217 °C; yield: 0.806 g (90%). ^{1}H NMR*: δ = 11.8 (broad s, 1 H), 8.32 (d, J = 6.4, 1 H), 7.48 (symm. m, 1 H), 7.20 (d, J = 11.6, 1 H), 6.43 (symm. m, 1 H) ppm. ^{13}C NMR*: δ = 168.5, 157.2 (d, J = 240 Hz), 133.2, 131.2, 129.8, 120.1, 115.2, 106.1 (d, J = 23 Hz), 102.3 ppm. ^{19}F NMR*: δ = –116.2 (dd, J = 6.9, 3.1 Hz) ppm. MS (c.i.): m/z (%) = 179 (52) [M^+], 162 (40), 142 (100), 134 (13), 100 (9). $C_9H_6FNO_2$ (179.15): calcd. C 60.34, H 3.38; found C 59.68, H 3.67.

7-Fluoro-1-(triisopropylsilyl)indole-6-carboxylic Acid (9b): Prepared, analogously as acid **4b**, from 7-fluoro-1-(triisopropylsilyl)indole (**16b**) (1.4 g, 5.0 mmol); colorless cubes after crystallization from a 1: 10 (v/v) mixture of diethyl ether and hexanes; m.p. 167–169 °C; yield: 1.49 g (89%). ^{1}H NMR: δ = 7.76 (dd, J = 9.2, 8.1 Hz, 1 H), 7.51 (d, J = 3.2 Hz, 1 H), 7.42 (d, J = 8.1 Hz, 1 H), 6.55 (d, J = 3.4 Hz, 1 H), 1.75 (sept, J = 7.2 Hz, 3 H), 1.15 (d, J = 7.9 Hz, 18 H) ppm. ^{13}C NMR δ = 171.2, 151.7 (d, J = 248 Hz), 139.7, 136.2, 128.2 (d, J = 12 Hz), 123.0, 115.7, 109.0, 105.7, 18.2 (3 C), 13.5 (6 C) ppm. ^{19}F NMR: δ = –119.6 (s) ppm. MS (c.i.): m/z (%) = 353 (39) [$M^+ + NH_4$], 336 (100) [$M^+ + 1$], 318 (5), 292 (15), 274 (7), 248 (15), 206 (9), 178 (7). $C_{18}H_{26}FNO_2Si$ (335.50): calcd. C 64.44, H 7.81; found C 64.44, H 7.62.

7-Fluoroindole-6-carboxylic Acid (9a): Prepared, analogously as acid **1a**, from 7-fluoro-1-(triisopropylsilyl)indole-6-carboxylic acid (**9b**, 1.7 g, 5.0 mmol); tiny colorless needles (from 90% aqueous methanol); m.p. 160–162 °C; yield: 0.824 g (92%). ^{1}H NMR*: δ = 11.1 (broad s, 1 H), 7.71 (m, 2 H), 7.52 (d, J = 8.6 Hz, 1 H), 6.71 (td, J = 2.9, 1.7 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.2, 151.5 (d, J = 260 Hz), 137.2, 130.7, 126.0 (d, J = 16 Hz), 123.2, 117.2, 111.2, 104.5 ppm. ^{19}F NMR*: δ = –129.6 (s) ppm. MS: m/z (%) = 193 (37) [$M^+ + NH_4$], 179 (100) [$M^+ + 1$], 162 (37), 149 (6), 134 (13). $C_9H_6FNO_2$ (179.15): calcd. C 60.34, H 3.38; found C 60.41, H 3.44.

4-Fluoroindole-7-carboxylic Acid (10a): Prepared, analogously as acid **3a**, from 7-bromo-4-fluoroindole (**17a**, 2.1 g, 10 mmol) and purified by sublimation; colorless needles; m.p. 227–228 °C; yield: 1.20 g (67%). ^{1}H NMR*: δ = 10.8 (broad s, 1 H), 7.91 (dd, J = 8.5, 5.3 Hz, 1 H), 7.50 (t-like dd, J = 2.8 Hz, 1 H), 6.89 (dd, J = 10.2, 8.5 Hz, 1 H), 6.66 (dd, J = 3.4, 2.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 169.1, 161.1 (d, J = 252 Hz), 140.5, 128.5, 128.1 (d, J = 9 Hz), 119.2, 112.0, 105.7, 99.5 ppm. ^{19}F NMR*: δ = –114.2 (m) ppm. MS (c.i.): m/z (%) = 179 (100) [M^+], 161 (97), 135 (33). $C_9H_6FNO_2$ (179.15): calcd. C 60.34, H 3.38; found C 60.34, H 3.26.

5-Fluoroindole-7-carboxylic Acid (11a): Prepared, analogously as acid **4b**, from 7-bromo-5-fluoroindole (**18a**, 7.0 g, 33 mmol). The residue was crystallized from 75% aqueous ethanol affording colorless needles; m.p. 210–212 °C; yield: 3.19 g (54%). ^{1}H NMR*: δ = 10.6 (broad s, 1 H), 7.72 (dd, J = 9.0, 2.5 Hz, 1 H), 7.66 (dd, J = 9.8, 2.5 Hz, 1 H), 7.61 (t, J = 2.8 Hz, 1 H), 6.68 (t, J = 2.7 Hz, 1 H) ppm. ^{13}C NMR*: δ = 168.7 (d, J = 232 Hz), 158.1, 134.2, 132.0, 129.9, 115.5 (d, J = 20 Hz), 113.1 (d, J = 15 Hz), 112.5, 103.5 ppm. ^{19}F NMR*: δ = –125.7 (t, J = 8.0 Hz) ppm. MS (c.i.): m/z (%) = 179 (100) [M^+], 161 (89), 134 (12). $C_9H_6FNO_2$ (179.15): calcd. C 60.34, H 3.38; found C 60.20, H 3.47.

6-Fluoroindole-7-carboxylic Acid (12a): Potassium *tert*-butoxide (2.2 g, 20 mmol) and 6-fluoroindole (**15a**, 1.3 g, 10 mmol) were consecutively added to a solution of butyllithium (20 mmol) in hexanes (13 mL) and tetrahydrofuran (40 mL) kept in a dry ice/methanol bath. After 2 h at –75 °C the mixture was poured on an excess of freshly crushed carbon dioxide. Water was added (20 mL), the aqueous phase decanted and washed with diethyl ether (3 × 20 mL) before being acidified to pH 1 and extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried, filtered and the solvents evaporated. Sublimation afforded colorless needles; m.p. 185–187 °C; yield: 1.07 g (60%). ^{1}H NMR*: δ = 10.7 (broad s, 1 H), 7.83 (dd, J = 8.7, 4.8 Hz, 1 H), 7.44 (t, J = 2.5 Hz, 1 H), 6.94 (dd, J = 11.9, 8.6 Hz, 1 H), 6.56 (symm. m, 1 H) ppm. ^{13}C NMR*: δ = 167.1, 160.3 (d, J = 256), 137.1, 127.5 (2 C), 126.6, 109.2 (d, J = 29 Hz), 102.9, 101.8 ppm. ^{19}F NMR*: δ = –115.6 (m) ppm. MS (c.i.): m/z (%) = 197 (68) [$M^+ + NH_4$], 180 (100) [$M^+ + 1$], 162 (13), 152 (3), 136 (6). $C_9H_6FNO_2$ (179.22): calcd. C 60.34, H 3.37; found C 60.64, H 3.40.

Fluoroindoles

The 5- and 7-fluoroindoles were obtained starting from the corresponding *tert*-butyl *N*-(fluorophenyl)carbamates. The preparation of these intermediates and derivatives thereof is described in a subchapter following directly below.

4-Fluoroindole (13a): 7-Bromo-4-fluoroindole (**17a**, 2.1 g, 10 mmol) was added to a solution of butyllithium (20 mmol) in hexanes (16 mL) and tetrahydrofuran (0.10 L) kept in a dry ice/methanol bath. After 15 min at –75 °C, the mixture was treated + 25 °C with water (10 mL). The organic phase was evaporated. Steam distillation furnished a white solid; m.p. 24–25 °C (ref.[15,68] 25–28 °C); yield: 0.757 g (56%). ^{1}H NMR: δ = 8.4 (broad s, 1 H), 7.20 (m, 2 H), 7.10 (ddd, J = 13.4, 9.6, 4.6 Hz, 1 H), 6.79 (dd, J = 10.9, 8.1 Hz, 1 H), 6.64 (symm. m, 1 H) ppm. ^{13}C NMR*: δ = 160.3 (d, J = 247 Hz), 139.0, 124.5, 123.0, 117.5 (d, J = 14 Hz), 107.5, 104.7, 99.0 ppm. MS (c.i.): m/z (%) = 136 (100) [M^+ + H], 124 (5), 108

(21), 81 (4). C_8H_6FN (135.14): calcd. C 71.10, H 4.48; found C 71.06, H 4.60.

4-Fluoro-1-(triisopropylsilyl)indole (13b): At –75 °C, 4-fluoroindole (**13a**, 2.7 g, 20 mmol) and chlorotriisopropylsilane (2.6 mL, 3.8 g, 20 mmol) were added consecutively to a solution of butyllithium (20 mmol) in hexanes (15 mL) and tetrahydrofuran (40 mL). After 15 min at +25 °C, the mixture was partitioned between water (20 mL) and diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL). Distillation afforded a viscous yellow oil; b.p. 115–117 °C/0.2 Torr; yield: 5.21 g (89%). ^{1}H NMR: δ = 7.30 (d, J = 8.1 Hz, 1 H), 7.23 (d, J = 3.0 Hz, 1 H), 7.06 (m, 1 H), 6.78 (dd, J = 11.0, 2.5 Hz, 1 H), 6.71 (d, J = 3.0 Hz, 1 H), 1.70 (sept, J = 8.0 Hz, 3 H), 1.12 (d, J = 8.0 Hz, 18 H) ppm. ^{13}C NMR δ = 156.3 (d, J = 246 Hz), 143.5, 130.9, 121.5, 120.3, 109.9, 104.5 (d, J = 19 Hz), 100.5, 18.0 (3 C), 12.4 (6 C) ppm. ^{19}F NMR: δ = –136.4 (dd, J = 10.0, 5.0 Hz) ppm. MS (c.i.): m/z (%) = 292 (100) [M^+ + H], 268 (24), 248 (42), 206 (12), 174 (8), 147 (12), 130 (20), 102 (8). $C_{17}H_{26}FNSi$ (291.49): calcd. C 70.05, H 8.99; found C 69.49, H 8.86.

5-Fluoroindole (14a): A solution containing *tert*-butyl 2-[(*E*)-2-chloroethenyl]-4-fluorophenyl-carbamate (see paragraph c of the following Section; 7.7 g, 25 mmol) and potassium *tert*-butoxide (8.4 g, 75 mmol) in anhydrous *tert*-butyl alcohol (40 mL) was heated for 5 h at +80 °C. Upon steam distillation a colorless solid was collected and dried in a desiccator; m.p. 46–47 °C (ref.[8,68] 46–47 °C); yield: 1.55 g (46%). ^{1}H NMR: δ = 8.3 (broad s, 1 H), 7.3 (m, 2 H), 7.21 (t, J = 3.2 Hz, 1 H), 6.95 (ddd, J = 12.1, 9.4, 3.7 Hz, 1 H), 6.51 (symm. m, 1 H) ppm. ^{13}C NMR δ = 158.2 (d, J = 235 Hz), 132.5, 128.5, 126.0, 111.7, 110.2 (d, J = 25 Hz), 105.5 (d, J = 23 Hz), 102.5 ppm. MS (c.i.): m/z (%) = 136 (100) [M^+ + 1], 124 (2), 107 (8), 87 (3), 76 (4). C_8H_6FN (135.14): calcd. C 71.10, H 4.48; found C 71.61, H 4.50. 5-Fluoroindole (**14a**) was also obtained, analogously as 4-fluoroindole (**13a**), starting from 7-bromo-5-fluoroindole (**18a**, 5.5 g, 25 mmol); m.p. 46 47 °C; yield: 1.61 g (48%).

5-Fluoro-1-(triisopropylsilyl)indole (14b): Prepared, analogously as 4-fluoro-1-(triisopropylsilyl)indole (**13b**), from 5-fluoroindole (**14a**, 1.3 g, 10 mmol). The product was isolated by distillation as a viscous oil; b.p. 121–123 °C/0.4 Torr; yield: 2.71 g (93%). ^{1}H NMR: δ = 7.41 (dd, J = 9.0, 4.5 Hz, 1 H), 7.27 (d, J = 3.0 Hz, 1 H), 7.25 (dd, J = 6.9, 2.9 Hz, 1 H), 6.90 (dt, J = 9.0, 3.0 Hz, 1 H), 6.58 (d, J = 3.0 Hz, 1 H), 1.69 (sept, J = 8.0 Hz, 3 H), 1.12 (d, J = 8.0 Hz, 18 H) ppm. ^{13}C NMR δ = 157.8 (d, J = 210 Hz), 137.2, 132.9, 131.9, 114.2, 109.5 (d, J = 24 Hz), 105.2 (d, J = 23 Hz), 104.8, 18.0 (3 C), 12.8 (6 C) ppm. ^{19}F NMR: δ = –126.0 (symm. m) ppm. MS (c.i.): m/z (%) = 309 (100) [$M^+ + NH_4^+$], 292 (98) [M^+ + 1], 274 (19), 248 (31), 210 (18), 192 (13). $C_{17}H_{26}FNSi$ (291.49): calcd. C 70.05, H 8.99; found C 70.22, H 9.00.

6-Fluoroindole (15a): A solution of dimethylformamide dimethyl acetal (40 mL, 36 g, 0.30 mol), pyrrolidine (12 mL, 11 g, 0.15 mol) and 4-fluoro-1-methyl-2-nitrobenzene [69] (17 g, 0.15 mol) in dimethylformamide (0.30 L) was heated under reflux for 6 h. At +25 °C, the reaction mixture was diluted with diethyl ether (0.10 L), washed with brine (3 × 25 mL) and the solvents evaporated. The residue was dissolved in 80% aqueous acetic acid (0.30 L). Zinc powder (49 g, 0.75 mol) was added over a period of 1 h under vigorous stirring before the mixture was heated for 5 h at 100 °C. Evaporation and steam distillation afforded colorless platelets; m.p. 74–76 °C (ref.[8,68] 75–76 °C); yield: 6.69 g (33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.0 (broad s, 1 H), 7.54 (dd, J = 8.6, 5.4 Hz, 1 H), 7.11 (dd, J = 3.0, 1.7 Hz, 1 H), 7.02 (dd, J = 10.1, 2.4, Hz, 1 H), 6.90 (ddd, J = 11.1, 8.6, 3.1 Hz, 1 H), 6.51 (symm. m, 1 H) ppm. ^{13}C NMR δ = 160.0 (d, J = 246 Hz), 136.0, 125.2, 124.5, 121.5, 108.7 (d, J = 29 Hz), 102.7, 97.0 (d, J = 27 Hz) ppm. MS (c.i.): m/z (%) = 136 (100) [M^+ + H], 124 (10), 108 (27), 81 (6). C_8H_6FN (135.14): calcd. C 71.10, H 4.48; found C 71.00, H 4.90.

6-Fluoro-1-(triisopropylsilyl)indole (15b): Prepared, analogously as 4-fluoro-1-(triisopropylsilyl)indole (**13b**), from 6-fluoroindole (**15a**, 1.3 g, 10 mmol). The product was isolated after distillation as a viscous yellow oil; b.p. 232–233 °C/2 Torr; yield: 2.13 g (73%). ^{1}H NMR: δ = 7.54 (dd, J = 9.6, 5.9 Hz, 1 H), 7.24 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 10.9, 2.1 Hz, 1 H), 6.91 (td, J = 11.1, 2.2 Hz, 1 H), 6.61 (d, J = 3.6 Hz, 1 H), 1.69 (sept, J = 7.6 Hz, 3 H), 1.15 (d, J = 7.6 Hz, 18 H) ppm. ^{13}C NMR δ = 159.7 (d, J = 210), 141.1, 131.5, 128.2, 120.7, 108.5 (d, J = 27 Hz), 104.7, 100.2 (d, J = 29 Hz), 18.2 (3 C), 12.7 (6 C) ppm. ^{19}F NMR: δ = –122.2 (dt, J = 9.1, 6.1 Hz) ppm. MS (c.i.): m/z (%) = 292 (100) [M^+ + H], 265 (10), 248 (31), 206 (5), 178 (4). $C_{17}H_{26}FNSi$ (291.49): calcd. C 70.05, H 8.99; found C 70.37, H 9.19.

7-Fluoroindole (16a): A solution of *tert*-butyl 6-fluoro-2-[(trimethylsilyl)ethynyl]phenylcarbamate (7.7 g, 25.0 mmol) and potassium *tert*-butoxide (8.4 g, 75.0 mmol) in anhydrous *tert*-butyl alcohol (20 mL) was heated to reflux for 5 h. The product was isolated by steam distillation and extracted with dichloromethane (3 × 0.10 L); colorless needles; m.p. 60–62 °C (ref:[68] 61–62 °C); yield: 2.16 g (64%). ^{1}H NMR: δ = 8.4 (broad s, 1 H), 7.41 (d, J = 8.1 Hz, 1 H), 7.21 (t, J = 3.2 Hz, 1 H), 7.02 (ddd, J = 13.1, 8.4, 4.5 Hz, 1 H), 6.91 (dd, J = 11.5, 8.1 Hz, 1 H), 6.59 (symm. m, 1 H) ppm. ^{13}C NMR δ = 149.5 (d, J = 237 Hz), 131.7, 125.0, 124.5, 119.7, 116.5, 107.0 (d, J = 19 Hz), 103.5 ppm. MS (c.i.): m/z (%) = 153 (7) [$M^+ + NH_4$], 136 (100) [M^+ + H], 124 (12), 108 (35). C_8H_6FN (135.14): calcd. C 71.10, H 4.48; found C 71.50, H 4.60. 7-Fluoroindole (**16a**) was also produced, analogously as described for 5-fluoroindole (**14a**), from *tert*-butyl 2-[(*E*)-2-chloroethenyl]-6-fluorophenylcarbamate (5.3 g, 25 mmol) in a yield of 1.25 g (37%) and, analogously as described for 4-fluoroindole (**13a**), from 4-bromo-7-fluoroindole (**19a**, 5.4 g, 25 mmol) in a yield of 2.53 g (75%).

7-Fluoro-1-(triisopropylsilyl)indole (16b): Prepared, analogously as 7-fluoro-1-(triisopropylsilyl)indole (**13b**), from 7-fluoroindole (**16a**, 1.3 g, 10 mmol). The product was isolated after distillation as a viscous oil; b.p. 121–123 °C/1 Torr; yield: 2.80 g (96%). ^{1}H NMR: δ = 7.41 (d, J = 7.0 Hz, 1 H), 7.34 (d, J = 2.8 Hz, 1 H), 7.03 (ddd, J = 14.1, 9.1, 5.2 Hz, 1 H), 6.88 (dd, J = 7.6, 3.4 Hz, 1 H), 6.64 (t, J = 3.8 Hz, 1 H), 1.71 (sept, J = 7.4 Hz, 3 H), 1.14 (d, J = 7.4 Hz, 18 H) ppm. ^{13}C NMR δ = 150.2 (d, J = 247 Hz), 136.0, 132.5, 128.3, 120.2, 116.5, 107.5 (d, J = 24 Hz), 105.2, 18.5 (3 C), 13.5 (6 C) ppm. ^{19}F NMR: δ = –126.1 (d, J = 13 Hz) ppm. MS (c.i.): m/z (%) = 292 (100) [M^+], 260 (12), 248 (19), 223 (4), 188 (57), 171 (24), 146 (15), 132 (27), 104 (3). $C_{17}H_{26}FNSi$ (291.49): calcd. C 70.05, H 8.99; found C 70.01, H 9.09.

tert-Butyl *N*-(Fluorophenyl)carbamates and Derivatives Thereof

a) *tert*-Butyl *N*-(4-Fluorophenyl)carbamate: A solution of 4-fluoroaniline (19 mL, 22 g, 0.20 mol) and di-*tert*-butyl dicarbonate (65 g, 0.30 mol) in anhydrous toluene (0.20 L) was heated to reflux for 2 h. The mixture was evaporated and the residue crystallized from hexanes; colorless needles; m.p. 124–126 °C (ref.[34] m.p. 125–126 °C); yield: 35.4 g (84%). ^{1}H NMR: δ = 7.31 (dd, J = 8.4, 4.6 Hz, 2 H), 6.95 (t, J = 8.9 Hz, 2 H), 6.5 (broad s, 1 H), 1.51 (s, 9 H) ppm. ^{13}C NMR δ = 199.9 (2 C), 159.1 (d, J = 240), 153.7, 134.5, 119.9, 115.7 (d, J = 26 Hz, 2 C), 28.2 (3 C) ppm. MS (c.i.): m/z (%) = 229 (41) [$M^+ + NH_4$], 212 (66) [M^+ + 1], 173 (61), 156 (19), 137 (6), 156 (19), 137 (6), 111 (100).

b) *tert*-Butyl *N*-(4-Fluoro-2-formylphenyl)carbamate: A solution of *tert*-butyl *N*-(4-fluorophenyl)carbamate [34] (21 g, 0.10 mol) and

tert-butyllithium (0.20 mol) in tetrahydrofuran (0.20 L) and pentanes (70 mL) was kept 3 h at –50 °C before dimethylformamide (7.7 mL, 7.3 g, 0.10 mol) was added. When at +25 °C, the mixture was washed with brine (2 × 0.10 L) and the solvents evaporated. Sublimation afforded tiny colorless prisms; m.p. 58–60 °C; yield: 17.0 g (71%). ^{1}H NMR: δ = 7.7 (broad s, 1 H), 7.51 (d, J = 8.3 Hz, 1 H), 7.42 (t, J = 8.7 Hz, 1 H), 7.31 (d, J = 7.7 Hz, 1 H), 6.6 (broad s, 1 H), 1.55 (s, 9 H) ppm. ^{13}C NMR δ = 187.8, 157.2 (d, J = 245), 153.2, 138.2, 123.5 (d, J = 20 Hz), 121.7, 120.5 (d, J = 25 Hz), 120.3, 81.2, 28.0 (3 C) ppm. ^{19}F NMR: δ = –121.8 (dd, J = 12.3, 7.1 Hz) ppm. MS (c.i.): m/z (%) = 257 (41) [$M^+ + NH_4$], 240 (100) [$M^+ + H$], 201 (70), 184 (45), 139 (48). $C_{12}H_{14}FNO_3$ (239.25): calcd. C 60.24, H 5.90; found C 60.33, H 5.99.

c) *tert*-Butyl 2-[(*E*)-2-Chloroethenyl]-4-fluorophenylcarbamate: At –25 °C, a vigorously stirred suspension of chloromethyl(triphenyl)-phosphonium iodide [70] (7.8 g, 25 mmol) in tetrahydrofuran (0.10 L) was treated dropwise, in the course of 15 min, with *tert*-butyllithium (50 mmol) in pentanes (40 mL) After further 15 min of stirring at –25 °C, *tert*-butyl *N*-(4-fluoro-2-formylphenyl)carbamate (5.3 g, 25 mmol) in tetrahydrofuran (15 mL) was added. The organic phase was absorbed on silica gel (50 mL). The powder, when dry, was put on top of a celite pad (0.10 L). Elution with a 1:9 (v/v) mixture of ethyl acetate and hexanes followed by sublimation afforded colorless needles; m.p. 65–67 °C; yield: 4.47 g, (66%). ^{1}H NMR: δ = 7.13 (dd, J = 9.7, 3.2 Hz, 1 H), 6.97 (ddd, J = 9.6, 8.5, 3.6 Hz, 1 H), 6.79 (dd, J = 17.5, 11.5 Hz, 1 H), 6.3 (broad s, 1 H), 5.69 (dd, J = 12.4, 1.3 Hz, 1 H), 5.44 (dd, J = 11.0, 1.1 Hz, 1 H), 1.52 (s, 9 H) ppm. ^{13}C NMR δ = 159.6 (d, J = 247), 153.3, 129.0, 128.5, 124.5, 118.5, 115.6, 115.2 (d, J = 23 Hz), 112.8 (d, J = 26 Hz), 77.2, 28.4 (3 C) ppm. MS (c.i.): m/z (%) = 289 (4) [$M^+ + NH_4$], 272 (3) [$M^+ + H$], 255 (100), 238 (72), 212 (13), 199 (82), 182 (41), 137 (28). $C_{13}H_{15}ClFNO_2$ (271.72): calcd. C 57.47, H 5.56; found C 57.11, H 5.32.

d) *tert*-Butyl *N*-(2-Fluorophenyl)carbamate: Prepared from 2-fluoroaniline (19 mL, 22 g, 0.20 mol) analogously as *tert*-butyl *N*-(4-fluorophenyl)carbamate. Crystallization from hexanes gave colorless needles; m.p. 45–46 °C (ref.[34] m.p. 46–47 °C); yield: 35.9 g (85%). ^{1}H NMR: δ = 8.07 (t, J = 8.0 Hz, 1 H), 7.11 (t, J = 7.9 Hz, 1 H), 7.04 (d, J = 11.2 Hz, 1 H), 6.9 (m, 1 H), 6.7 (broad s, 1 H), 1.51 (s, 9 H) ppm. ^{13}C NMR δ = 153.2, 151.7 (d, J = 157.5), 127.3, 124.5, 123.2, 121.9, 114.7 (d, J = 12 Hz), 81.1, 28.3 (3 C) ppm. MS (c.i.): m/z (%) = 229 (35) [$M^+ + NH_4$], 212 (43) [$M^+ + 1$], 173 (9), 156 (86), 111 (100).

e) *tert*-Butyl *N*-(2-Fluoro-6-formylphenyl)carbamate: Prepared, analogously as *tert*-butyl *N*-(4-fluoro-2-formylphenyl)carbamate, from *tert*-butyl *N*-(2-fluorophenyl)carbamate[34] (21 g, 0.10 mol). Sublimation afforded tiny colorless prisms; m.p. 58–60 °C; yield: 17.2 g (72%). ^{1}H NMR: δ = 10.0 (s, 1 H), 7.9 (broad s, 1 H), 7.57 (d, J = 7.9 Hz, 1 H), 7.37 (ddd, J = 9.9, 9.1, 1.8 Hz, 1 H), 7.29 (d, J = 7.9, 4.1 Hz, 1 H), 1.51 (s, 9 H) ppm. ^{13}C NMR δ = 191.2, 156.2 (d, J = 252 Hz), 152.7, 129.2, 127.7, 127.2, 125.3, 121.4 (d, J = 25 Hz), 81.7, 28.1 (3 C) ppm. MS (c.i.): m/z (%) = 257 (6) [$M^+ + NH_4$], 240 (26) [$M^+ + 1$], 212 (9), 201 (100), 184 (45), 173 (9), 139 (59), 111 (23). $C_{12}H_{14}FNO_3$ (239.25): calcd. C 60.24, H 5.90; found C 60.85, H 5.81.

f) *tert*-Butyl 2-[(*E*)-2-Chloroethenyl]-6-fluorophenylcarbamate: Prepared, as described above for *tert*-butyl 2-[(*E*)-2-chloroethenyl]-4-fluorophenylcarbamate, from *tert*-butyl *N*-(2-fluoro-6-formylphenyl)carbamate (5.3 g, 25 mmol). Using a 1:9 (v/v) mixture of ethyl acetate and hexanes, the product was eluted from a column filled with silica gel (50 mL) and sublimed; colorless needles; m.p. 65–67 °C; yield: 4.47 g (66%). ^{1}H NMR: δ = 7.0 (m, 3 H), 6.89 (d, J = 13.4 Hz, 1 H), 6.57 (d, J = 13.2, Hz, 1 H), 6.2 (broad s, 1 H), 1.52 (s, 9 H) ppm. ^{13}C NMR δ = 159.7 (d, J = 246 Hz), 153.2, 130.7, 127.7, 124.7, 122.1, 115.9, 115.7 (d, J = 29 Hz), 113.2 (d, J = 27 Hz), 81.7, 28.1 (3 C) ppm. MS (c.i.): m/z (%) = 289 (11) [$M^+ + NH_4$], 272 (2) [$M^+ + 1$], 233 (100), 216 (22), 171 (39), 136 (28), 111 (8). $C_{13}H_{15}ClFNO_2$ (271.72): calcd. C 57.46, H 5.56; found C 57.20, H 5.70.

g) *tert*-Butyl (6-Fluoro-2-iodophenyl)carbamate: At dry-ice temperature, *tert*-butyllithium (0.10 mmol) in pentane (75 mL) was added to a solution of *tert*-butyl *N*-(2-fluorophenyl)carbamate (11 g, 50 mmol) in anhydrous tetrahydrofuran (0.10 L). After 3 h at –50 °C, the mixture was treated with iodine (13 g, 0.10 mol) and, at +25 °C, with a saturated aqueous solution (50 mL) of sodium thiosulfate before being extracted with diethyl ether (3 × 0.10 L). Evaporation and crystallization from hexanes gave colorless prisms: m.p. 88–90 °C; 12.9 g (77%). ^{1}H NMR: δ = 7.61 (dd, J = 8.0, 1.5 Hz, 1 H), 7.10 (ddd, J = 9.5, 9.5, 1.0 Hz, 1 H), 6.95 (ddd, J 11.0, 8.0, 5.5 Hz, 1 H), 6.0 (broad s, 1 H), 1.51 (s, 9 H) ppm. ^{13}C NMR δ = 158.2 (d, J = 254 Hz), 152.8, 134.2, 129.1, 127.8, 116.3 (d, J = 21 Hz), 99.0, 81.1, 28.7 (3 C) ppm. ^{19}F NMR: δ = –111.4 (dd, J = 14.0, 5.0 Hz) ppm. MS (c.i.): m/z (%) = 337 (7) [M^+], 299 (2), 282 (10), 263 (1), 273 (100), 193 (1), 155 (8), 137 (3), 111 (48). $C_{11}H_{13}FINO_2$ (337.13): calcd. C 39.19, H 3.89; found C 39.30, H 3.98.

h) *tert*-Butyl 6-Fluoro-2-[2-(trimethylsilyl)ethynyl]phenylcarbamate: A mixture of *tert*-butyl (2-iodo-6-fluorophenyl)carbamate (17 g, 50 mmol), (trimethylsilyl)acetylene (8.5 mL, 5.9 g, 60.0 mmol), bis(triphenylphosphane)palladium dichloride (35 g, 5.0 mmol), copper(I) iodide (0.9 g, 5.0 mmol) and triethylamine (50 mL) were heated to +50 °C for 5 h. The reaction mixture was poured into a 1.0 M solution (0.10 L) of citric acid, extracted with diethyl ether (3 × 50 mL) and filtered through a celite pad. The combined organic layers were dried and the solvents evaporated. Crystallization from hexanes gave colorless prisms; m.p. 102–104 °C; 11.6 g (75%). ^{1}H NMR: δ = 7.25 (symm. m, 1 H), 7.10 (symm. m, 2 H), 6.3 (broad s, 1 H), 1.52 (s, 9 H), 0.28 (s, 9 H) ppm. ^{13}C NMR δ = 155.4 (d, J = 250 Hz), 152.7, 128.8, 127.6 (d, J = 14 Hz), 127.1, 126.3, 116.9 (d, J = 21 Hz), 101.5, 99.9, 80.8, 28.2 (3 C), 1.2 (3 C) ppm. ^{19}F NMR: δ = –119.2 (t, J = 8.1 Hz) ppm. MS (c.i.): m/z (%) = 307 (3) [M^+], 252 (34), 236 (8), 207 (100), 192 (58), 176 (12), 149 (2), 130 (24), 130 (24). $C_{16}H_{22}FNO_2Si$ (307.44): calcd. C 62.51, H 7.21; found C 62.60, H 7.27.

Halofluoroindoles

7-Bromo-4-fluoroindole (17a): At –40 °C, vinylmagnesium bromide (75 mmol) in tetrahydrofuran (75 mL) was added dropwise, in the course of 30 min, to a solution of 1-bromo-4-fluoro-2-nitrobenzene (see below; 5.5 g, 25 mmol) in tetrahydrofuran (100 mL). After 1 h at –40 °C, the mixture was poured into a saturated aqueous solution (50 mL) of ammonium chloride. The organic layer was evaporated; colorless needles (from pentanes); m.p. 28–29 °C; yield: 2.78 g (52%). ^{1}H NMR: δ = 8.4 (broad s, 1 H), 7.26 (t, J = 1.4 Hz, 1 H), 7.24 (d, J = 4.1 Hz, 1 H), 6.72 (dd, J = 11.6, 6.7 Hz, 1 H), 6.71 (d, J = 1.4 Hz, 1 H) ppm. ^{13}C NMR δ = 156.0 (d, J = 247 Hz), 137.2, 124.7 (d, J = 21 Hz), 118.2, 106.7 (d, J = 19 Hz), 100.2, 99.1, 97.8 ppm. ^{19}F NMR: δ = –124.1 (d, J = 8.0 Hz) ppm. MS (c.i.): m/z (%) = 215 (100) [$M^+ + H$], 191 (10), 150 (6), 136 (33), 124 (14), 112 (19), 98 (24). C_8H_5BrFN (214.04): calcd. C 44.89, H 2.35; found C 44.91, H 2.43.

1-Bromo-4-fluoro-2-nitrobenzene: A mixture of 65% nitric acid (13 mL) and 1-bromo-4-fluorobenzene (28 mL, 44 g, 0.25 mol) in 98% sulfuric acid (0.10 L) was kept 15 min at 0 °C, before being poured onto crushed ice (0.10 kg), and extracted with dichloro-

methane (2 × 50 mL). Evaporation and crystallization of the residue from pentanes gave yellowish needles; m.p. 39–41 °C (ref.[71] 40–41 °C); yield: 39.6 g (72%). ^{1}H NMR: δ = 7.75 (dd, J = 8.9, 5.4 Hz, 1 H), 7.62 (dd, J = 7.8, 3.0 Hz, 1 H), 7.21 (ddd, J = 8.6, 7.0, 2.9 Hz, 1 H) ppm. ^{13}C NMR δ = 161.5 (d, J = 252 Hz), 159.2, 136.7, 121.8 (d, J = 23 Hz), 114.1 (d, J = 25 Hz), 109.2 ppm. MS (c.i.): m/z (%) = 219 (100) [M$^+$ – H], 191 (8), 175 (20), 161 (34), 127 (5), 111 (19), 94 (84). $C_6H_3BrFNO_2$ (220.00): calcd. C 32.76, H 1.37; found C 32.81, H 1.42.

7-Bromo-5-fluoroindole (18a): Prepared, analogously as 7-bromo-4-fluoroindole (**17a**), from 2-bromo-4-fluoro-1-nitrobenzene (see below; 6.6 g, 30 mmol); colorless needles (from pentanes); m.p. 27–28 °C; yield: 3.66 g (57%). ^{1}H NMR: δ = 8.3 (broad s, 1 H), 7.2 (m, 2 H), 7.15 (dd, J = 9.1, 2.6 Hz, 1 H), 6.56 (dd, J = 3.2, 2.4 Hz, 1 H) ppm. ^{13}C NMR 157.5 (d, J = 240 Hz), 132.0, 129.0, 126.7, 113.0 (d, J = 28 Hz), 105.5 (d, J = 26 Hz), 104.2, 103.8 ppm. MS (c.i.): m/z (%) = 215 (100) [M$^+$ + 1], 185 (2), 151 (2), 134 (9), 107 (24). C_8H_5BrFN (214.04): calcd. C 44.89, H 2.35; found C 44.91, H 2.39.

2-Bromo-4-fluoro-1-nitrobenzene: Prepared, analogously as 1-bromo-4-fluoro-2-nitrobenzene, from 3-fluoro-bromobenzene (28 mL, 43 g, 0.25 mol); yellowish needles (from pentanes); m.p. 40–42 °C (ref.[72] 42 °C); yield: 41.8 g (76%). ^{1}H NMR: δ = 7.99 (dd, J = 8.9, 5.1 Hz, 1 H), 7.50 (dd, J = 7.9, 3.7 Hz, 1 H), 7.22 (ddd, J = 8.9, 7.4, 2.5 Hz, 1 H) ppm. ^{13}C NMR δ = 163.5 (d, J = 260 Hz), 145.5, 127.5, 121.5 (d, J = 26 Hz), 115.7, 115.0 (d, J = 29 Hz) ppm. MS (c.i.): m/z (%) = 219 (100) [M$^+$], 205 (15), 191 (90), 173 (32), 161 (66), 111 (18), 94 (100). $C_6H_3BrFNO_2$ (220.00): calcd. C 32.76, H 1.37; found C 32.88, H 1.39.

4-Bromo-7-fluoroindole (19a): Prepared, analogously as 7-bromo-4-fluoroindole (**17a**), from 4-bromo-1-fluoro-2-nitrobenzene (11 g, 50 mmol). Upon distillation a yellowish liquid was collected; m.p. 24–25 °C; yield: 3.61 g (34%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.6 (broad s, 1 H), 7.26 (t, J = 2.9 Hz, 1 H), 7.16 (dd, J = 8.2, 3.9 Hz, 1 H), 6.78 (dd, J = 10.4, 8.3 Hz, 1 H), 6.61 (symm. m, 1 H) ppm. ^{13}C NMR δ = 149.5 (d, J = 243 Hz), 138.2, 126.2, 123.1, 117.5, 108.2 (d, J = 19 Hz), 104.1, 98.5. ^{19}F NMR: δ = –106.1 (t, J = 6.8 Hz) ppm. MS (c.i.): m/z (%) = 215 (100) [M$^+$ + H], 189 (31), 161 (2), 134 (39), 107 (53), 90 (12). C_8H_5BrFN (214.04): calcd. C 44.89, H 2.35; found C 45.07, H 2.30.

4-Bromo-2-fluoroaniline: A suspension containing 2-fluoroaniline (2.1 mL, 2.8 g, 25 mmol) and *N*-bromosuccinimide (4.4 g, 25 mmol) in chloroform (50 mL) was stirred for 2 h at +25 °C. The meanwhile homogeneous mixture was washed with a 0.10 M aqueous solution (2 × 50 mL) of sodium thiosulfate. The organic layer was evaporated and the residue crystallized from hexanes; colorless needles; m.p. 40–42 °C (ref.[73] 41–42 °C); yield: 3.61 g (76%). ^{1}H NMR: δ = 7.14 (dd, J = 10.7, 2.1 Hz, 1 H), 7.05 (ddd, J = 9.1, 0.9, 0.4 Hz, 1 H), 6.66 (t, J = 8.9 Hz, 1 H) ppm. ^{13}C NMR δ = 152.3 (d, J = 242 Hz), 134.2, 127.5, 118.7 (d, J = 18 Hz), 118.2, 109.1 ppm. MS (c.i.): m/z (%) = 191 (100) [M$^+$ + H], 170 (23), 161 (5), 152 (10), 137 (6). C_6H_5BrFN (190.02): calcd. C 37.93, H 2.65; found C 37.82, H 2.75.

4-Bromo-2-fluoro-1-nitrobenzene: At +25 °C, 35% aqueous hydrogen peroxide (56 mL, 0.58 mol) was added to 4-bromo-2-fluoroaniline (15 mL, 19 g, 0.10 mol) in trifluoroacetic acid (0.20 L) over a period of 30 min. The mixture was heated to reflux for 1 h, before being poured onto ice (90 g). The precipitate was collected as yellowish platelets; m.p. 84–86 °C (ref.[74] 85–86 °C); yield: 15.8 g (72%). ^{1}H NMR: δ = 7.99 (t, J = 8.3 Hz, 1 H), 7.88 (dd, J = 10.6, 2.1 Hz, 1 H), 7.49 (dt, J = 9.1, 1.9 Hz, 1 H) ppm. ^{13}C NMR δ = 155.2 (d, J = 270 Hz), 137.2, 129.5, 128.2, 127.1, 121.5 (d, J = 21 Hz) ppm. MS (c.i.): m/z (%) = 219 (63) [M$^+$ – H], 203 (9), 189 (47), 175 (8), 161 (31), 142 (2), 127 (39), 94 (100). $C_6H_3BrFNO_2$ (220.00): calcd. C 32.76, H 1.37; found C 32.81, H 1.59.

5-Bromo-7-fluoroindole (20a): Prepared, analogously as 7-bromo-4-fluoroindole (**17a**), from 4-bromo-2-fluoro-1-nitrobenzene (see below; 5.5 g, 25 mmol); colorless needles (from pentanes); m.p. 24–25 °C; yield: 1.92 g (36%). ^{1}H NMR: δ = 8.4 (broad s, 1 H), 7.54 (dd, J = 1.0, 0.5 Hz, 1 H), 7.24 (t, J = 2.5 Hz, 1 H), 7.06 (dd, J = 10.6, 2.0 Hz, 1 H), 6.53 (dt, J = 2.9, 2.1 Hz, 1 H) ppm. ^{13}C NMR 150.2, 146.5 (d, J = 237 Hz), 132.3, 124.7, 119.1, 111.7, 110.2 (d, J = 23 Hz), 102.7 ppm. ^{19}F NMR: δ = –112.9 (d, J = 10.2 Hz) ppm. MS (c.i.): m/z (%) = 231 (6) [M$^+$ + NH$_4$], 215 (100) [M$^+$], 189 (5), 150 (3), 134 (50), 107 (36). C_8H_5BrFN (214.04): calcd. C 44.89, H 2.35; found C 45.34, H 2.30.

5-Bromo-4-fluoro-1-(triisopropylsilyl)indole (21b): *sec*-Butyllithium (10 mmol) in pentanes (8.0 mL) was added to a solution of 4-fluoro-1-(triisopropylsilyl)indole (**13b**, 2.9 g, 10 mmol) and *N*,*N*,*N*′,*N*″,*N*″′-pentamethyldiethylenetriamine (2.1 mL, 1.7 g, 10 mmol) in tetrahydrofuran (20 mL) cooled in a dry ice/methanol bath. After 6 h –75 °C, the mixture was treated with 1,2-dibromo-1,1,2,2-tetrafluoroethane (2.6 g, 1.7 mL, 10 mmol) before being evaporated. Elution with hexanes from a column filled with silica gel (50 mL) gave a colorless liquid; m.p. –11 to –12 °C; yield: 3.11 g (84%). ^{1}H NMR: δ = 7.2 (m, 2 H), 7.04 (d, J = 8.7 Hz, 1 H), 6.71 (d, J = 3.1 Hz, 1 H), 1.66 (sept, J = 7.6 Hz, 3 H), 1.12 (d, J = 7.6 Hz, 18 H) ppm. ^{13}C NMR 152.3 (d, J = 247 Hz), 142.3, 131.9, 124.9, 121.5 (d, J = 21 Hz), 110.7, 100.7, 97.8 (d, J = 19 Hz), 18.0 (3 C), 12.7 (6 C). ^{19}F NMR: δ = –116.4 (d, J = 6.4 Hz) ppm. MS (c.i.): m/z (%) = 371 (100) [M$^+$ + H], 327 (10), 292 (3), 247 (3), 204 (2), 130 (2). $C_{17}H_{25}BrFNSi$ (370.38): calcd. C 55.13, H 6.80; found C 56.19, H 7.21.

5-Bromo-4-fluoroindole (21a): Tetrabutylammonium fluoride hydrate (0.10 g, 2.0 mmol) was added to a solution of 5-bromo-4-fluoro-1-(triisopropylsilyl)indole (**21b**, 0.37 g, 1.0 mmol) in tetrahydrofuran (5 mL). After 5 min at +25 °C, the reaction mixture was diluted with diethyl ether (15 mL), washed with brine (2 × 5 mL), dried and the solvents evaporated. Crystallization from hexanes gave colorless needles; m.p. 33–34 °C; yield: 0.190 g (89%). ^{1}H NMR: δ = 8.9 (broad s, 1 H), 7.35 (dd, J = 8.6, 6.9 Hz, 1 H), 7.16 (t, J = 2.8 Hz, 1 H), 7.06 (dd, J = 8.4, 1.1 Hz, 1 H), 6.61 (symm. m, 1 H) ppm. ^{13}C NMR 153.2 (d, J = 247 Hz), 138.2, 131.7, 129.5, 126.5, 126.1, 109.2, 99.2 (d, J = 27 Hz) ppm. ^{19}F NMR: δ = –114.2 (d, J = 6.8 Hz) ppm. MS (c.i.): m/z (%) = 213 (80) [M$^+$], 174 (4), 149 (15), 134 (100), 107 (84). C_8H_5BrFN (214.04): calcd. C 44.89, H 2.35; found C 45.07, H 2.30.

5-Chloro-4-fluoro-1-(triisopropylsilyl)indole (22b): Prepared, analogously as the bromo analog **21b**, from 4-fluoro-1-(triisopropylsilyl)-indole (**13b**) (2.9 g, 10 mmol) using 1,1,2-trichloro-1,2,2-trifluoroethane (1.3 mL, 1.5 g, 10 mmol) as the reagent. The same work-up gave again a colorless liquid; m.p. 35–36 °C; yield: 2.12 g (65%). ^{1}H NMR: δ = 7.2 (m, 2 H), 7.09 (dd, J = 8.9, 7.1 Hz, 1 H), 6.71 (d, J = 3.1 Hz, 1 H), 1.65 (sept, J = 7.5 Hz, 3 H), 1.11 (d, J = 7.2 Hz, 18 H) ppm. ^{13}C NMR 151.5 (d, J = 249 Hz), 141.7, 133.3, 132.1, 122.7, 121.7 (d, J = 19 Hz), 110.5, 100.5, 18.1 (3 C), 12.7 (6 C) ppm. ^{19}F NMR: δ = –115.6 (d, J = 6.9 Hz) ppm. MS (c.i.): m/z (%) = 326 (100) [M$^+$ + H], 308 (3), 274 (8), 240 (5), 205 (6), 174 (11). $C_{17}H_{25}ClFNSi$ (325.93): calcd. C 62.65, H 7.73; found C 62.91, H 7.72.

5-Chloro-4-fluoroindole (22a): Prepared, analogously as the bromo analog **21a**, from 5-chloro-4-fluoro-1-(triisopropylsilyl)indole (**22b**, 0.33 g, 1.0 mmol); colorless needles (from hexanes); m.p. 22–23 °C; yield: 0.149 g (88%). ^{1}H NMR: δ = 8.3 (broad s, 1 H), 7.31 (t, J =

3.1 Hz, 1 H), 7.26 (dd, *J* = 8.9, 3.5 Hz, 1 H), 7.05 (t, *J* = 8.4 Hz, 1 H), 6.66 (symm. m, 1 H) ppm. ^{13}C NMR 153.7 (d, *J* = 237 Hz), 135.7, 132.5, 126.7, 111.5 (d, *J* = 19 Hz), 110.9, 110.2, 102.1. ^{19}F NMR: δ = –112.4 (t, *J* = 6.9 Hz) ppm. MS (c.i.): *m*/*z* (%) = 169 (100) [M$^+$], 151 (3), 134 (11), 115 (3), 107 (22), 91 (3). C_8H_5ClFN (169.58): calcd. C 56.66, H 2.97; found 56.56, H 3.03.

4-Chloro-5-fluoro-1-(triisopropylsilyl)indole (23b): 2,2,6,6-Tetramethylpiperidine (1.7 mL, 1.4 g, 10 mmol), *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (2.1 mL, 1.7 g, 10 mmol) and 5-fluoro-1-(triisopropylsilyl)indole (**14a**, 1.45 g, 5.0 mmol) were added consecutively to a solution of butyllithium (10 mmol) in tetrahydrofuran (20 mL) and hexanes (6.0 mL) cooled in a dry ice/methanol bath. After 6 h at –75 °C, the mixture was treated with 1,1,2-trichloro-1,2,2-trifluoroethane (0.62 mL, 0.78 g, 5.0 mmol) before it was allowed to reach +25 °C. The organic phase was absorbed on silica gel (10 mL). The powder, when dry, was put on the top of a wet column filled with more silica (0.10 L). Elution with hexanes gave a colorless liquid; m.p. –14 to –13 °C; yield: 1.01 g (62%). ^{1}H NMR: δ = 7.3 (m, 2 H), 6.97 (t, *J* = 9.4 Hz, 1 H), 6.72 (d, *J* = 3.2 Hz, 1 H) 1.67 (sept, *J* = 7.5 Hz, 3 H), 1.12 (d, *J* = 7.5 Hz, 18 H) ppm. ^{13}C NMR 154.1 (d, *J* = 238 Hz), 138.2, 134.5, 131.9, 113.2, 110.8 (d, *J* = 31 Hz), 105.7 (d, *J* = 29 Hz), 103.4, 19.2 (3 C), 13.2 (6 C) ppm. ^{19}F NMR: δ = –119.6 (m) ppm. MS (c.i.): *m*/*z* (%) = 325 (100) [M$^+$], 282 (76), 248 (58), 206 (34), 178 (34), 157 (28), 130 (79), 102 (31). $C_{17}H_{25}ClFNSi$ (325.92): calcd. C 62.65, H 7.73; found C 62.97, H 7.67.

4-Chloro-5-fluoroindole (23a): Prepared, analogously as the bromofluoroindole **21a**, from 5-chloro-4-fluoro-1-(triisopropylsilyl)indole (**23b**, 0.33 g, 1.0 mmol); colorless needles (from hexanes); m.p. 21–22 °C; yield: 0.160 g (94%). ^{1}H NMR: δ = 8.3 (broad s, 1 H), 7.29 (t, *J* = 3.8 Hz, 1 H), 7.24 (dd, *J* = 8.7, 3.6 Hz, 1 H), 7.01 (t, *J* = 8.4 Hz, 1 H), 6.66 (symm. m, 1 H) ppm. ^{13}C NMR 153.7 (d, *J* = 237 Hz), 147.7, 132.7, 126.1, 111.5 (d, *J* = 26 Hz), 110.7, 109.7, 101.5 ppm. ^{19}F NMR: δ = –112.6 (t, *J* = 7.0 Hz) ppm. MS (c.i.): *m*/*z* (%) = 169 (93) [M$^+$], 160 (11), 134 (14), 107 (23), 84 (100). C_8H_5ClFN (169.58): calcd. C 56.66, H 2.97; found C 56.76, H 3.05.

4,6-Dichloro-5-fluoro-1-(triisopropylsilyl)indole (24b): Prepared, analogously as 5-chloro-4-fluoro-1-(triisopropylsilyl)indole (**22b**), from 4-chloro-5-fluoro-1-(triisopropylsilyl)indole (**23b**, 3.25 g, 10 mmol); colorless oil; m.p. –5 to –4 °C; yield: 2.71 g (75%). ^{1}H NMR: δ = 7.39 (d, *J* = 5.4 Hz, 1 H), 7.30 (d, *J* = 3.2 Hz, 1 H), 6.69 (d, *J* = 3.1 Hz, 1 H), 1.66 (sept, *J* = 7.9 Hz, 3 H), 1.14 (d, *J* = 7.7 Hz, 18 H) ppm. ^{13}C NMR 149.1 (d, *J* = 240 Hz), 136.7, 133.7, 129.7, 115.5 (d, *J* = 21 Hz), 113.1, 105.5 (d, *J* = 23 Hz), 103.7, 18.5 (3 C), 13.1 (6 C) ppm. ^{19}F NMR*: δ = –131.0 (d, *J* = 4.9 Hz) ppm. MS (c.i.): *m*/*z* (%) = 360 (100) [M$^+$], 316 (29), 292 (6), 248 (20), 174 (16), 157 (30), 130 (36). $C_{17}H_{24}Cl_2FNSi$ (360.37): calcd. C 56.66, H 6.71; found C 57.88, H 6.74.

4,6-Dichloro-5-fluoroindole (24a): Prepared, analogously as the bromofluoroindole **21a**, from 4,6-dichloro-5-fluoro-1-(triisopropylsilyl)indole (**24b**, 0.71 g, 2.0 mmol); colorless needles; m.p. 89–91 °C; 0.391 g (96%). ^{1}H NMR: δ = 8.3 (broad s, 1 H), 7.36 (d, *J* = 5.5 Hz, 1 H), 7.29 (t, *J* = 2.5 Hz, 1 H), 6.64 (d, *J* = 2.2 Hz, 1 H) ppm. ^{13}C NMR 149.6 (d, *J* = 239 Hz), 131.4, 127.1, 126.4, 117.1 (d, *J* = 25 Hz), 112.3, 111.2, 102.1 ppm. ^{19}F NMR*: δ = –131.2 (d, *J* = 5.9 Hz) ppm. MS (c.i.): *m*/*z* (%) = 203 (100) [M$^+$ – 1], 168 (16), 141 (28), 105 (9), 91 (3). $C_8H_4Cl_2FN$ (204.03): calcd. C 47.09, H 1.98; found C 47.00, H 1.85.

5-Chloro-6-fluoro-1-(triisopropylsilyl)indole (25b): Prepared, analogously as 5-chloro-4-fluoro-1-(triisopropylsilyl)indole (**22b**), from 6-fluoro-1-(triisopropylsilyl)indole (**15b**, 2.9 g, 10 mmol); colorless cubes (from hexanes); m.p. 55–56 °C; yield: 2.77 g (85%). ^{1}H NMR: δ = 7.69 (d, *J* = 7.9 Hz, 1 H), 7.41 (d, *J* = 10.9 Hz, 1 H), 7.32 (d, *J* = 2.9 Hz, 1 H) 6.74 (d, *J* = 3.1 Hz, 1 H), 1.72 (sept, *J* = 7.6 Hz, 3 H), 1.21 (d, *J* = 7.9 Hz, 18 H) ppm. ^{13}C NMR δ = 154.2 (d, *J* = 240 Hz), 139.2, 132.7, 128.5, 120.7, 113.2, 104.2, 101.3 (d, *J* = 28 Hz), 18.1 (3 C), 12.7 (6 C) ppm. MS (c.i.): *m*/*z* (%) = 326 (100) [M$^+$], 308 (2), 282 (14), 240 (3), 212 (5). $C_{17}H_{25}ClFNSi$ (325.93): calcd. C 62.65, H 7.73; found C 62.87, H 7.90.

5-Bromo-6-fluoro-1-(triisopropylsilyl)indole (26b): Prepared, analogously as the isomer **21b**, from 6-fluoro-1-(triisopropylsilyl)indole (**15b**, 2.9 g, 10 mmol); colorless liquid; m.p. –14 to –13 °C; yield: 3.11 g (84%). ^{1}H NMR: δ = 7.75 (d, *J* = 7.1 Hz, 1 H), 7.29 (d, *J* = 10.6 Hz, 1 H), 7.23 (d, *J* = 3.1 Hz, 1 H), 6.54 (d, *J* = 3.2 Hz, 1 H), 1.66 (sept, *J* = 7.4 Hz, 3 H), 1.14 (d, *J* = 7.4 Hz, 18 H) ppm. ^{13}C NMR 155.1 (d, *J* = 237 Hz), 139.7, 132.5, 129.3, 123.7, 104.2, 101.2 (d, *J* = 27 Hz), 100.7, 17.3 (3 C), 12.5 (6 C) ppm. ^{19}F NMR: δ = –116.3 (dd, *J* = 10.4, 7.0 Hz) ppm. MS (c.i.): *m*/*z* (%) = 396 (7), 371 (1) [M$^+$ + H], 328 (24), 291 (18), 248 (100), 206 (45), 178 (54). $C_{17}H_{25}BrFNSi$ (370.38): calcd. C 55.13, H 6.80; found C 55.84, H 6.86.

6-Fluoro-5-iodo-1-(triisopropylsilyl)indole (27b): Prepared, analogously as 5-bromo-4-fluoro-1-(triisopropylsilyl)indole (**21b**), from 6-fluoro-1-(triisopropylsilyl)indole (**15b**, 2.9 g, 10 mmol) using elemental iodine (1.3 g, 10 mmol) as the reagent. The product was eluted with hexanes from a silica gel column as a colorless liquid; m.p. –8 to –7 °C; yield: 3.14 g (75%). ^{1}H NMR: δ = 7.95 (d, *J* = 6.6 Hz, 1 H), 7.27 (s, 1 H), 7.21 (d, *J* = 3.2 Hz, 1 H), 6.52 (d, *J* = 2.9 Hz, 1 H), 1.65 (sept, *J* = 7.4 Hz, 3 H), 1.21 (d, *J* = 7.4 Hz, 18 H) ppm. ^{13}C NMR 157.5 (d, *J* = 235 Hz), 140.5, 132.3, 129.9, 104.1, 100.5 (d, *J* = 31 Hz), 85.1, 72.0 (d, *J* = 29 Hz), 18.5 (3 C), 13.1 (6 C) ppm. ^{19}F NMR: δ = –128.1 (d, *J* = 9.1 Hz) ppm. MS (c.i.): *m*/*z* (%) = 417 (100) [M$^+$], 374 (24), 346 (2), 291 (8), 248 (9), 204 (13), 130 (16). $C_{17}H_{25}FINSi$ (417.45): calcd. C 48.92, H 6.04; found C 49.20, H 6.21.

6-Fluoro-5-iodoindole (27a): Prepared, analogously as 5-bromo-4-fluoroindole (**21a**), from 6-fluoro-5-iodo-1-(triisopropylsilyl)indole (**27b**, 1.2 g, 3.0 mmol); colorless cubes (from hexanes); m.p. 37–39 °C; yield: 0.412 g (79%). ^{1}H NMR: δ = 8.2 (broad s, 1 H), 7.35 (dd, *J* = 8.9, 2.1 Hz, 1 H), 7.27 (symm. m, 2 H), 6.65 (dd, *J* = 3.1, 2.2 Hz, 1 H) ppm. ^{13}C NMR 158.0 (d, *J* = 240 Hz), 135.0, 128.1, 126.5, 119.2 (d, *J* = 27 Hz), 106.7 (d, *J* = 29 Hz), 104.5, 72.2 ppm. ^{19}F NMR*: δ = –104.4 (t-like dd, *J* = 7.0, 9.0 Hz) ppm. MS (c.i.): *m*/*z* (%) = 278 (9) [M$^+$ + NH$_4$], 262 (100) [M$^+$ + H], 238 (3), 161 (14), 134 (17), 107 (11), 81 (3). C_8H_5FIN (261.03): calcd. C 36.81, H 1.93; found C 36.82, H 1.95.

4-Bromo-6-fluoro-1-(triisopropylsilyl)indole (29b): 2,2,6,6-Tetramethylpiperidine (0.34 mL, 0.28 g, 2.0 mmol), *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (0.42 mL, 0.35 g, 2.0 mmol) and 5-bromo-6-fluoro-1-(triisopropylsilyl)indole (**26b**, 0.74 g, 2.0 mmol) were added consecutively to a solution of butyllithium (2.0 mmol) in tetrahydrofuran (5.0 mL) and hexanes (2.0 mL) cooled in a dry ice/methanol bath. After 6 h at –75 °C, the mixture was treated with water (5.0 mL). The organic phase was washed with brine (3 × 10 mL), dried and the solvents evaporated. NMR analysis of the reaction mixture using dioxane as an internal standard, revealed a 5:1 ratio between the 4- and 5-bromo-6-fluoro-1-(triisopropylsilyl)indoles (**29b** and **26b**); yield: 0.585 g (79%). ^{1}H NMR*: δ = 7.62 (dd, *J* = 8.6, 5.8 Hz, 1 H), 7.31 (d, *J* = 3.3 Hz, 1 H), 6.99 (dt, *J* = 9.3, 2.2 Hz, 1 H), 6.69 (dt, *J* = 19.8, 3.3 Hz, 1 H), 1.75 (sept, *J* = 7.5 Hz, 3 H), 1.24 (d, *J* = 7.6 Hz, 18 H) ppm. MS (c.i.): *m*/*z* (%) = 371 (100) [M$^+$], 328 (70), 247 (77), 205 (28).

6-Fluoro-4-iodoindole (30a): 2,2,6,6-Tetramethylpiperidine (0.34 mL, 0.28 g, 2.0 mmol), *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethyl-

enetriamine (0.42 mL, 0.35 g, 2.0 mmol) and 6-fluoro-5-iodo-1-(triisopropylsilyl)indole (**27b**, 0.81 g, 2.0 mmol) were added consecutively to a solution of butyllithium (2.0 mmol) in tetrahydrofuran (5.0 mL) and hexanes (2.0 mL) cooled in a dry ice/methanol bath. After 6 h at –75 °C, the mixture was treated with water (5.0 mL). The organic phase was washed with brine (3 × 10 mL), dried and the solvents were evaporated. The residue was treated at 25 °C with tetrabutylammonium fluoride hydrate (0.20 g, 4.0 mmol) in tetrahydrofuran (10 mL). After 5 min at 25 °C, the reaction mixture was diluted with diethyl ether (5.0 mL), washed with brine (2 × 5 mL), dried, and the solvents evaporated. The product was eluted from a column filled with silica using a 1:9 (v/v) mixture of ethyl acetate and hexanes; colorless cubes (from hexanes); m.p. 69–70 °C; yield: 0.460 g (88%). ^{1}H NMR*: δ = 8.2 (broad s, 1 H), 7.97 (d, J = 5.9 Hz, 1 H), 7.17 (t, J = 2.9 Hz, 1 H), 7.11 (d, J = 8.9 Hz, 1 H), 6.46 (symm. m, 1 H) ppm. ^{13}C NMR 157.7 (d, J = 238 Hz), 135.7, 130.8, 127.2, 125.5, 102.1, 98.2 (d, J = 29 Hz), 71.2 (d, J = 32 Hz) ppm. ^{19}F NMR*: δ = –123.2 (t, J = 9.9 Hz) ppm. MS (c.i.): m/z (%) = 261 (100) [M$^+$], 135 (2), 107 (3). C_8H_5FIN (261.03): calcd. C 36.81, H 1.93; found C 36.61, H 2.05.

Chlorofluoroindolecarboxylic Acids

5-Chloro-6-fluoro-1-(triisopropylsilyl)indole-4-carboxylic Acid (28b): 2,2,6,6-Tetramethylpiperidine (3.4 mL, 2.8 g, 20 mmol), *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (4.2 mL, 3.4 g, 20 mmol) and 5-chloro-6-fluoro-1-(triisopropylsilyl)indole (**25b**, 3.2 g, 10 mmol) were added consecutively to a solution of butyllithium (20 mmol) in tetrahydrofuran (40 mL) and hexanes (13 mL) cooled in a dry ice/methanol bath. After 2 h at –75 °C, the mixture was poured onto an excess of freshly crushed dry ice. Water was added (10 mL), the aqueous phase decanted and washed with diethyl ether (3 × 10 mL). The combined organic layers were washed with 1.0 M solution of citric acid (2 × 15 mL) and brine (2 × 10 mL), dried, filtered and the solvents evaporated. Crystallization from hexanes gave colorless prisms; m.p. 181–183 °C; yield: 2.93 g (79%). ^{1}H NMR: δ = 7.48 (d, J = 10.3 Hz, 1 H), 7.38 (d, J = 3.0 Hz, 1 H), 7.02 (d, J = 3.6 Hz, 1 H), 1.69 (sept, J = 7.9 Hz, 3 H), 1.15 (d, J = 7.1 Hz, 18 H) ppm. ^{13}C NMR 172.2, 154.3 (d, J = 237 Hz), 139.1, 134.2, 128.4, 120.8, 109.2, 105.4, 104.3 (d, J = 27 Hz), 17.6 (3 C), 12.5 (6 C) ppm. ^{19}F NMR*: δ = –121.8 (d, J = 14.9 Hz) ppm. MS (c.i.): m/z (%) = 370 (39) [M$^+$ + H], 330 (23), 274 (28), 231 (10), 192 (8), 174 (24), 148 (93), 117 (22), 93 (11), 76 (100). $C_{18}H_{25}ClFNO_2Si$ (369.94): calcd. C 58.44, H 6.81; found C 57.65, H 6.61.

5-Chloro-6-fluoroindole-4-carboxylic Acid (28a): A solution containing tetrabutylammonium fluoride hydrate (1.3 g, 5.0 mmol) and 5-chloro-6-fluoro-1-(triisopropylsilyl)indole-4-carboxylic acid (**28b**, 1.8 g, 5.0 mmol) in tetrahydrofuran (10 mL) was kept 5 min at 25 °C, before being diluted with diethyl ether (10 mL), washed with brine (2 × 10 mL), dried and the solvents evaporated. Crystallization from 90% aqueous methanol afforded colorless platelets; m.p. 202–203 °C; yield: 0.886 g (83%). ^{1}H NMR*: δ = 7.56 (d, J = 9.5 Hz, 1 H), 7.52 (t, J = 2.9 Hz, 1 H), 6.72 (symm. m, 1 H) ppm. ^{13}C NMR*: 171.1, 166.2, 154.2 (d, J = 237 Hz), 134.5, 128.2, 124.2, 112.2, 102.2, 101.1 (d, J = 29 Hz) ppm. ^{19}F NMR*: δ = –121.8 (d, J = 10.6 Hz) ppm. MS (c.i.): m/z (%) = 231 (100) [M$^+$ + NH$_4$], 213 (32), 196 (7), 174 (9), 150 (6), 118 (6). $C_9H_5ClFNO_2$ (213.59): calcd. C 50.61, H 2.36; found C 50.82, H 2.58.

5-Chloro-4-fluoro-1-(triisopropylsilyl)indole-6-carboxylic Acid (31b): Prepared, analogously as acid **28b**, from 5-chloro-4-fluoro-1-(triisopropylsilyl)indole (**22b**, 3.2 g, 10 mmol). Crystallization from hexanes gave colorless prisms; m.p. 121–123 °C; yield: 2.93 g (79%). ^{1}H NMR: δ = 8.21 (s, 1 H), 7.44 (d, J = 3.4, 1 H), 6.79 (d, J = 3.5, 1 H), 1.71 (sept, J = 7.5 Hz, 3 H), 1.16 (d, J = 7.9 Hz, 18 H) ppm. ^{13}C NMR 170.7, 152.2 (d, J = 247 Hz), 140.2, 135.5, 124.7 (d, J = 21 Hz), 120.5, 114.5, 111.7, 101.5, 18.1 (3 C), 12.7 (6 C) ppm. ^{19}F NMR*: δ = –124.9 (d, J = 5.1 Hz) ppm. MS (c.i.): m/z (%) = 370 (100) [M$^+$ + 1], 326 (41), 231 (26), 214 (36), 196 (65), 168 (15), 148 (23), 134 (17), 102 (6). $C_{18}H_{25}ClFNO_2Si$ (369.94): calcd. C 58.44, H 6.81; found C 58.70, H 6.84.

5-Chloro-4-fluoroindole-6-carboxylic Acid (31a): Prepared, analogously as acid **28a**, from 5-chloro-4-fluoro-1-(triisopropylsilyl)indole-6-carboxylic acid (**31b**, 1.85 g, 5.0 mmol); colorless prisms (from hexanes); m.p. >250 °C; yield: 0.84 g (79%). ^{1}H NMR*: δ = 8.05 (t, J = 0.9 Hz, 1 H), 7.69 (t, J = 2.7, 1 H), 6.69 (symm. m, 1 H) ppm. ^{13}C NMR 168.7, 152.7 (d, J = 245 Hz), 147.7, 138.1, 131.2, 125.7, 121.7 (d, J = 24 Hz), 113.2, 99.1 ppm. ^{19}F NMR*: δ = –122.6 (d, J = 4.9 Hz) ppm. MS (c.i.): m/z (%) = 213 (19) [M$^+$], 186 (7), 153 (4), 133 (4), 107 (3). $C_9H_5ClFNO_2$ (213.59): calcd. C 50.61, H 2.36; found C 50.89, H 2.44.

4-Chloro-5-fluoro-1-(triisopropylsilyl)indole-6-carboxylic Acid (32b): Prepared from 4-chloro-5-fluoro-1-(triisopropylsilyl)indole (**23b**) (1.3 g, 10 mmol) as described for (**28b**); m.p. 177–179 °C; yield: 2.66 g (72%). ^{1}H NMR: δ = 8.19 (d, J = 4.9 Hz, 1 H), 7.51 (d, J = 3.1 Hz, 1 H), 6.79 (d, J = 3.5 Hz, 1 H), 1.73 (sept, J = 7.9 Hz, 3 H), 1.15 (d, J = 7.9 Hz, 18 H) ppm. ^{13}C NMR 170.2, 152.5 (d, J = 255 Hz), 137.5, 136.1, 135.5, 116.7, 112.3 (d, J = 22 Hz), 111.2, 104.2, 18.1 (3 C), 12.5 (6 C) ppm. ^{19}F NMR*: δ = –127.8 (d, J = 4.9 Hz) ppm. MS (c.i.): m/z (%) = 378 (0) [M$^+$ + NH$_4$], 360 (100) [M$^+$], 326 (20), 292 (8), 256 (3), 231 (15), 170 (13), 148 (48), 130 (24). $C_{18}H_{25}ClFNO_2Si$ (369.94): calcd. C 58.44, H 6.81; found C 56.44, H 6.62.

4-Chloro-5-fluoroindole-6-carboxylic Acid (32a): Prepared, analogously as acid **28a**, from 4-chloro-5-fluoro-1-(triisopropylsilyl)indole-6-carboxylic acid (**32b**, 1.8 g, 5.0 mmol); colorless needles (from 90% aqueous methanol); m.p. 213-214 °C; yield: 0.748 g (70%). ^{1}H NMR*: δ = 8.12 (d, J = 5.1 Hz, 1 H), 7.74 (t, J = 2.9 Hz, 1 H), 6.65 (t, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR*: 167.2, 154.2 (d, J = 248 Hz), 133.8, 133.1, 118.1, 115.1, 112.7 (d, J = 21 Hz), 102.2, 101.2. ^{19}F NMR*: δ = –125.6 (d, J = 4.9 Hz) ppm. MS (c.i.): m/z (%) = 231 (100) [M$^+$ + NH$_4$], 213 (75) [M$^+$], 196 (27), 186 (13), 150 (6), 107 (3). $C_9H_5ClFNO_2$ (213.59): calcd. C 50.61, H 2.36; found C 50.82, H 2.58.

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