# Chemistry of Fluorinated Indoles

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## Contents



**Abstract** The chapter is devoted to the synthesis and application of indoles as well as some their azaanalogues bearing fluorine atoms, trifluoromethyl groups, and perfluorinated aryl fragments.

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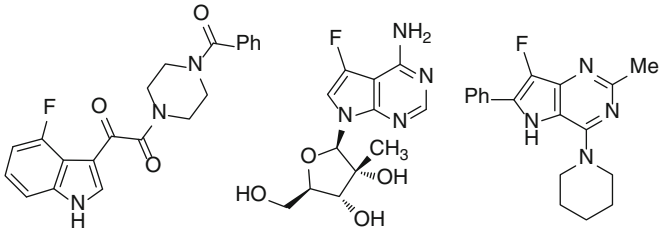
V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_3,

**Keywords** Indole • Fluorine • Trifluoromethyl group • Synthesis • Fluorinated heterocycles

## 1 Introduction

Indoles represent very important subunits of many natural products and pharmacologically active compounds [1]. Fluorinated indole derivatives are inhibitors of HIV-1 [2], CB2 cannabinoid receptor ligands found in the central nervous system [3], and factor Xa preventing thrombus [4]. Some fluorinated azaindoles, for example, fluorinated pyrrolopyrimidines are inhibitors of hepatitis C virus (HCV) RNA replication [5] and Y5 antagonists which are potential antiobesity agents [6]. Herein, we highlighted methods for the synthesis and application of fluoroindoles, trifluromethylpyrroles and some their azaanalogues.

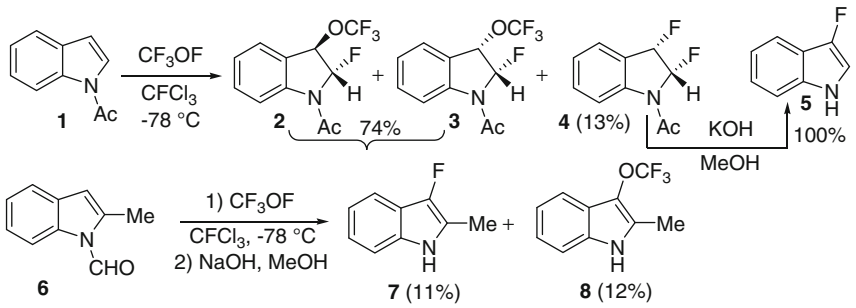



Inhibitor of HIV-1 | Inhibitor of Hepatitis C Virus RNA Replication | Y5 antagonist

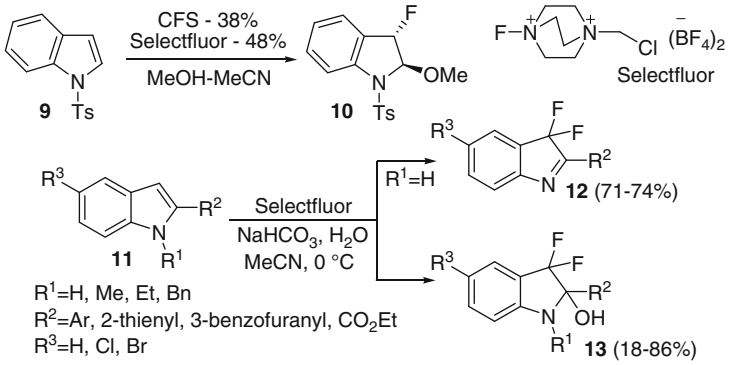
## 2 Synthesis of Fluoroindoles and Deazapurines

### *2.1 Functionalization of the Pyrrole Ring*

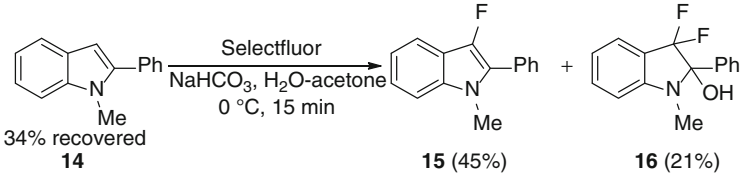
Several reagents were used for the electrophilic fluorination of indole. The first one used for this aim was trifluoromethyl hypofluorite ($CF_3OF$). Treatment of *N*-acylindole **1** with trifluoromethyl hypofluorite in $CF_3Cl$ at −78 °C afforded a mixture of 2-fluoro-3-trifluoromethoxy- and 2,3-difluoroindoline derivatives **2**–**4** in high combined yield. Subsequent treatment of difluoride **4** with potassium hydroxide in methanol afforded quantitatively 3-fluoroindole **5**. Similarly, starting from 1-formyl-2-methylindole reaction with trifluoromethyl hypofluorite resulted in formation of 2-methyl-3-fluoroindole **7** in low yield in mixture with 2-methyl-3-trifluormethoxyindole **8** [7].



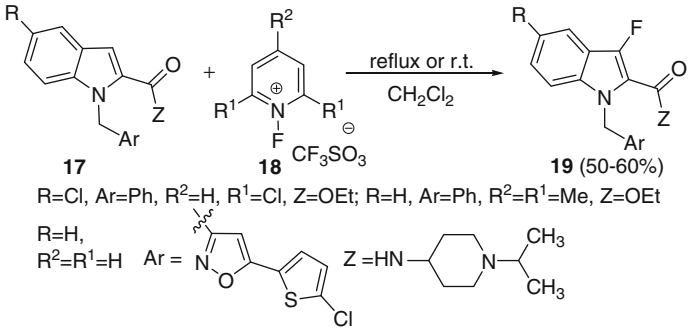

Fluorination of indoles **9** and **11** using cesium fluoroxysulfate ($CsOSO_3F$, CFS) or Selectfluor led to the corresponding 3-fluoroindolines, which are the products of conjugate addition of fluorine and methanol or water. Thus, fluorinated methoxyindolines **10**, and 3-*H*-indoles **12** or hydroxyindolines **13** were obtained in methanolic or aqueous acetonitrile respectively [8a, b].



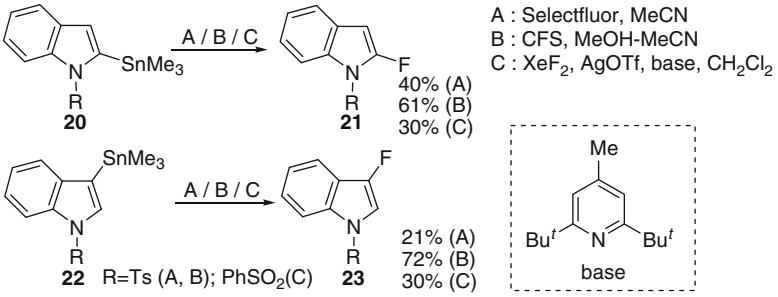

3-Fluoroindole **15** can be also prepared using Selectfluor. When acetonitrile was replaced by acetone and reaction was stopped before the starting *N*-methyl indole **14** was totally consumed, 3-fluoroindole derivative **15** was isolated in 45 % yield together with difluorohydroxyindoline derivative **16**. This experiment led to claim that 3-fluoroindole derivative **15** was a reaction intermediate, subsequent fluorination resulted in the formation of difluoroindolines **12** and **13** [8b].



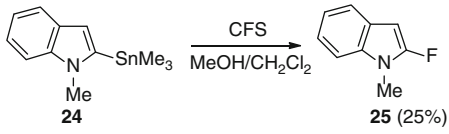

*N*-Fluoropyridinium triflates **18** are another useful type of fluorinating reagents applied for the preparation of fluorinated indoles. Using these reagents a series of 2-(3-fluoroindolyl)carboxylic acid derivatives **19** was prepared in good yields by treatment of indole-2-carboxylates or carboxamides **17** in dichloromethane [4, 9].



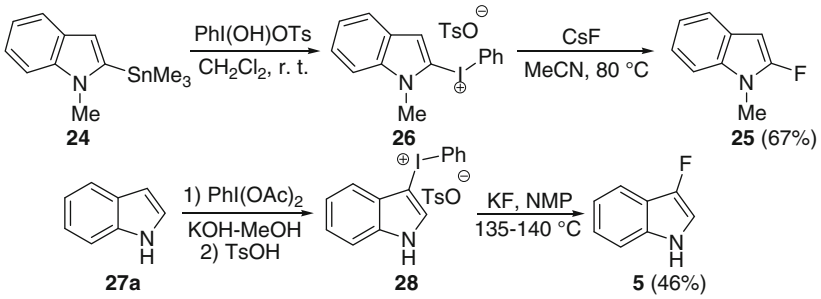

The problem of regioselective installation of fluorine into pyrrole ring of indole was resolved using tin substituted indoles as starting materials. Both 2- and 3-trimethylstannyl-1-(arylsulfonyl)indoles **20** and **22** can be used for fluorination with cesium fluoroxysulfate to afford 2-fluoro and 3-fluoroderivatives in 61 % and 72 % yields correspondingly. Using Selectfluor and xenon difluoride gave fluoroindoles in moderate yields. In addition, reaction of 2-trimethylstannylindole **20** with xenon difluoride afforded admixture of regioisomeric 3-fluoroindole **23** [8, 10].



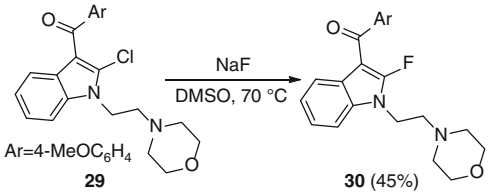

Analogous transformation with cesium fluoroxysulfate in the case of more electron rich 1-methyl-2-(trimethylstannyl)-1*H*-indole **24** leads to 2-fluoro-1-methyl-1*H*-indole **25** in lower yield [8c].



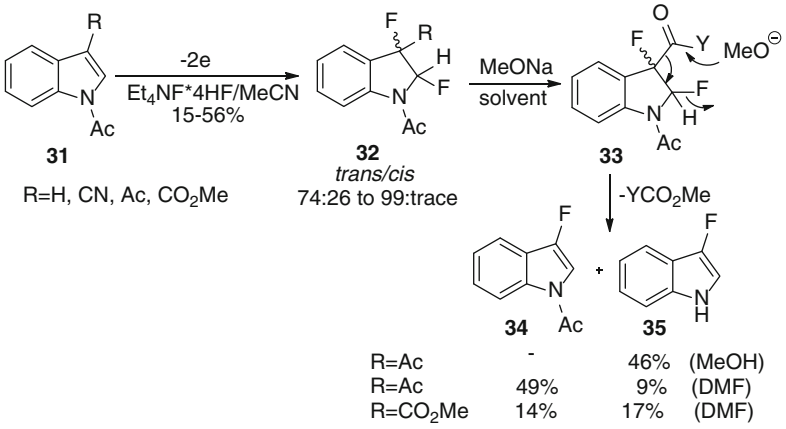

A nucleophilic fluorination approach towards fluoroindoles was also elaborated. Using nucleophilic substitution of phenyliodonium group by fluoride under heating, 2-fluoroindole **25** and 3-fluoroindole **5** were prepared in good yields. The intermediate phenyl(indolyl)iodonium salts **26** and **28** were easily synthesized by treatment of (2-indolyl)trialkylstannane **24** [11] or indole **27a** [12] with the corresponding polyvalent iodine compounds.



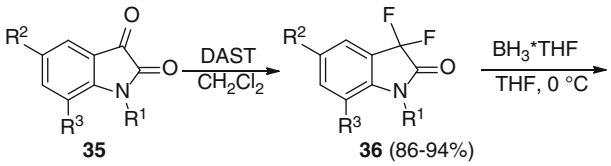

Similarly, 2-fluoroindole **30** derivative was obtained in 45 % yield by nucleophilic substitution of chloride in the 2-chloroindole **29** under heating with sodium fluoride in dimethyl sulfoxide [13]. The nucleophilic substitution proceeds in quite mild conditions for **29** due to the presence of activating nucleophilic substitution keto group in β-position of the indole.



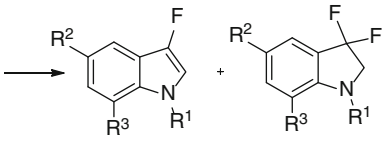

An electrosynthesis of fluorinated indole derivatives was carried out by Fuchigami and co-workers. Anodic fluorination of various *N*-acetyl-3-substituted indole derivatives **31** was performed in acetonitrile to give a mixture of *trans*- and *cis*-2,3-difluoro-2,3-dihydroindoles **32**, which afforded 3-fluoroindoles **35** and **34** after treatment with sodium methoxide [14].



An efficient pathway towards 3-fluoroindoles was proposed starting from isatines **35**. Fluorinated 2-indolinones **36** were obtained in high yields by treatment of isatine derivatives **35** with diethylaminosulfur trifluoride in dichloromethane. In case of electron-donating substituents reduction of **36** with tetrahydrofuran-borane complex led smoothly to 3-fluoroindoles **37** in high yields.



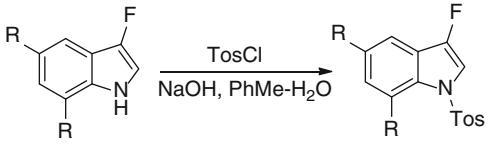

**35** **36** (86-94%)



**37** **38**

| | **37 : 38** | |
|---|---|---|
| $R^1$=$R^2$=$R^3$=H | 76% | - |
| $R^1$=$R^3$=H, $R^2$=Me | 70% | - |
| $R^1$=Bn, $R^2$=$R^3$=H | 86% | - |
| $R^1$=Me, $R^2$=$R^3$=H | 90% | - |
| $R^1$=H, $R^2$=$NO_2$, $R^3$=H | 6% | 85% |
| $R^1$=H, $R^2$=$R^3$=Br | 9% | 79% |

The corresponding difluoroindolines **38** were mostly isolated in case of indoles with electron-withdrawing groups. It was mentioned, that 3-fluoroindoles **5** and **37a** are quite unstable; the much more stable *N*-tosyl derivatives **23** and **39** can be prepared by treatment of **5** and **37a** with tosyl chloride under basic catalysis [15].

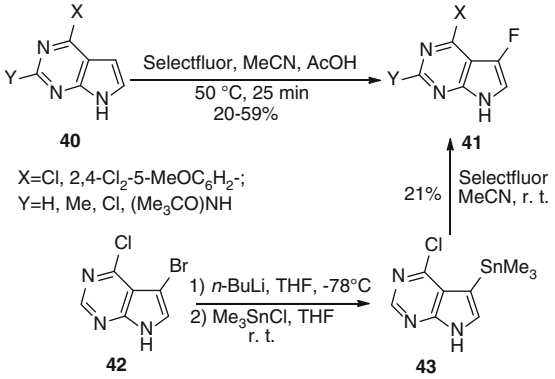



**5** R=H
**37a** R=Me

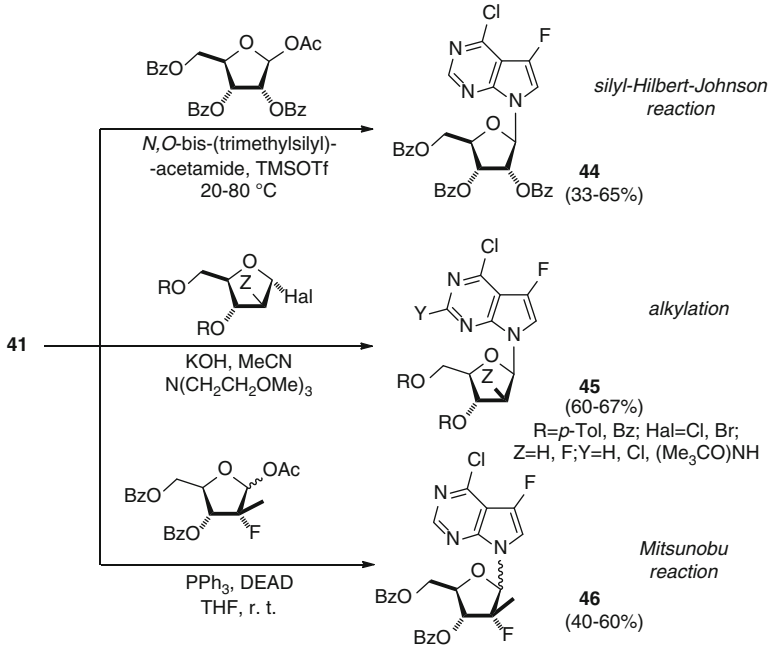
**23** (61%)
**39** (54%)

7-Deazapurines (pyrrolo[2,3-*d*]pyrimidines) are shape mimics of the parent purines. Hence, one might expect the corresponding ribonucleosides can replace naturally occurring RNA-constituents as substrates or inhibitors. As a result, further modifications of the pyrrolo[2,3-*d*]pyrimidine moiety may provide novel pharmacologically active compounds against human immunodeficiency virus [16]. A great effort was devoted to investigations of 7-fluorinated 7-deazapurines. The fluorination of various 7*H*-pyrrolo[2,3-*d*]pyrimidines **40** with Selectfluor gave selectively 7-fluorinated 7-deazapurines **41** in moderate yields [17]. Alternatively, 7-fluorinated 7-deazapurines **41** were prepared by lithiation of 5-bromo-4-chloro-1*H*-pyrrolo[2,3-*d*]pyrimidine **42**, followed by subsequent treatment of the resulting intermediate with trimethylstannane chloride to give

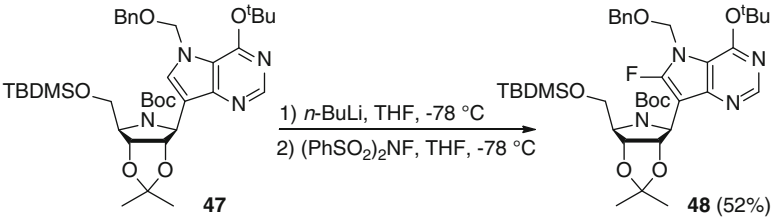
5-trimethylstannane **43**, which affords target 5-fluoroderivative **41** in 21 % yield after the reaction with Selectfluor [5].




The second step of new nucleoside preparation was the modification at the pyrrole nitrogen, using standard techniques of nucleoside synthesis such as the silyl-Hilbert-Johnson (or Vorbrüggen) reaction [17a, c, 18], alkylation under basic conditions [17d, 19] or Mitsunobu reaction [17f, 20]. By means of methods mentioned, a series of nucleosides **44**–**46** was prepared in moderate to good yields.

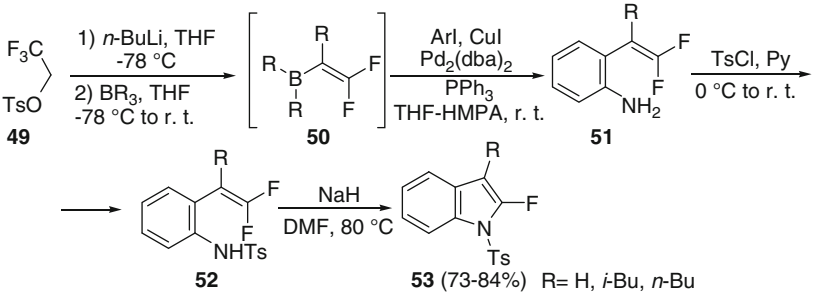


In the case of β-substituted pyrrolo[3,2-*d*]pyrimidines, the fluorine atom can be inserted into the molecule via metallation to α-position to pyrrole ring followed by fluorination. Thus, compound **47** reacted with *n*-butyllithium and *N*-fluorobenzenesulfonimide to produce fluoro derivative **48** in 52 % yield [21].



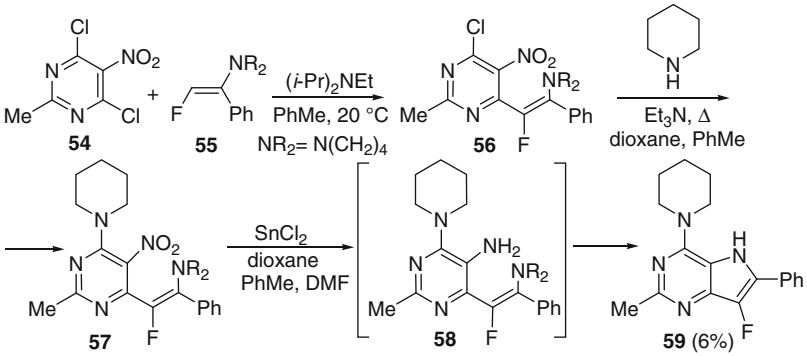

## 2.2 *Heterocyclization*

β,β-Difluorostyrenes **52** bearing a tosylamido group at the *ortho*-position underwent intramolecular nucleophilic substitution of the fluorine atom *via* a 5-*endo* trigonal process leading to 2-fluorinated indoles **53** [22, 23]. The cyclization is promoted by base, for example sodium hydride. The starting β,β-difluorostyrenes **52** were obtained accordingly to scheme below. Firstly, coupling of 2,2-difluorovinylboranes **50**, generated *in situ* from 2,2,2-trifluoroethyl toluene-*p*-sulfonate **49**, with *N*-butylmagnesio-*o*-iodoaniline were performed in the presence of copper(I) iodide and a palladium catalyst to give alkene **51**. Next, alkene **51** was converted into **52** by the reaction with TsCl.




Another intramolecular cyclization of amine **58** is the last step in the pyrrolo[3,2-*d*]pyrimidine analogue **59** synthesis. Intermediate **58** formed *in situ* from nitro precursor **57** by reduction with tin(II) chloride is a key step of this version of Leimgruber–Batcho synthesis leading to formation of **59** finally. This simple three-step route to **59** started from the coupling of electron-poor dichloronitropyrimidine **54** with β-fluoroenamine **55** to form alkene **56**. Regioselective nucleophilic

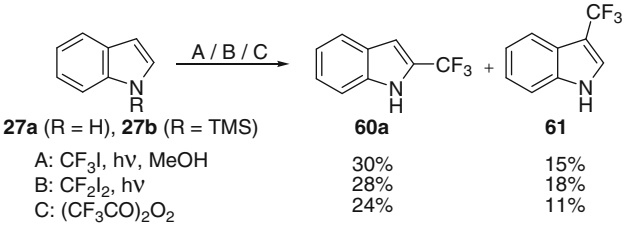
substitution of chlorine with piperidine led to nitro precursor **57**, which transforms into target pyrrolo[3,2-*d*]pyrimidine **59** by reduction in 6 % overall yield [5].



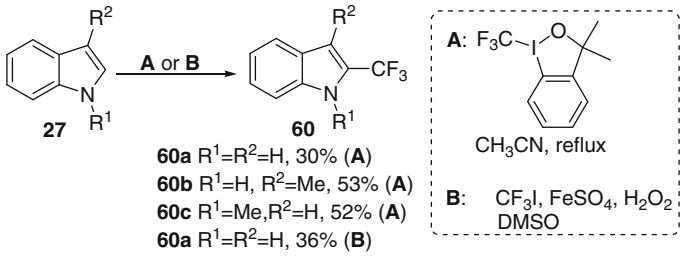

## 3 Synthesis of Trifluoromethylindoles

### *3.1 Direct Trifluoromethylation*

Radical trifluoromethylation of *N*-trimethylsilylindole **27b** with trifluoroiodomethane proceeded nonselectively into both 2- and 3-positions, with a preference for the 2-trifluoromethylindole formation [24]. Quench of the reaction mixture with methanol afforded the 2- and 3-trifluoromethylndoles **60a** and **61** in 2/1 ratio. Similarly, the trifluoromethylation using difluorodiiodomethane [25] and bis(perfluoroalkanoyl) peroxide [26] led to a mixture of the same products. In all cases, the overall yield of isomeric indoles was moderate.

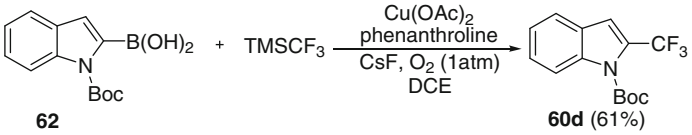



Perfect selectivity was achieved then hypervalent iodine reagent **A** [27] was used for electrophilic trifluoromethylation of indoles. Radical trifluoromethylation using $CF_3I$-$FeSO_4$-$H_2O_2$-DMSO system **B** [28] provided also excellent regioselectivity. However, yields of 2-trifluoromethylindoles **60a–c** in both cases were moderate to good.

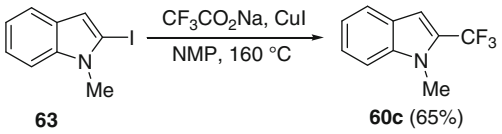



**60a** $R^1$=$R^2$=H, 30% (**A**)
**60b** $R^1$=H, $R^2$=Me, 53% (**A**)
**60c** $R^1$=Me,$R^2$=H, 52% (**A**)
**60a** $R^1$=$R^2$=H, 36% (**B**)

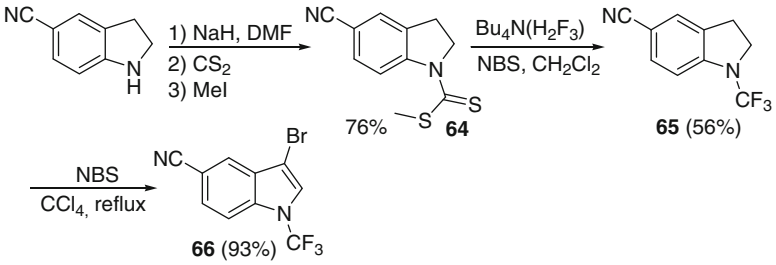
Another selective approach to 2-trifluoromethylindole is copper-mediated oxidative cross-coupling of 2-indolylboronic acid with $TMSCF_3$. Reaction proceeds in mild conditions to give *N*-Boc-2-trifluoromethylindole **60d** in 61 % yield [29].




The nucleophilic trifluoromethylation, which is based on the heating of *N*-methyl-2-iodoindole **63** with 10 equivalents of sodium trifluoroacetate and an equimolar amount of copper(I) iodide in *N*-methylpyrrolidinone, afforded *N*-methyl-2-trifluoromethylindole **60c** in 65 % yield [30].



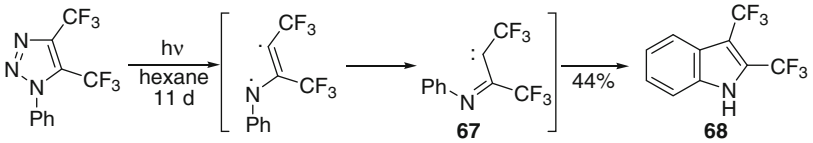

Formal *N*-trifluoromethylation of indole was performed in several steps, starting from indoline. At first step 3-cyanoindoline was treated with NaH, followed by $CS_2$ and then MeI to form thioderivative **64**. The latter was treated with tetrabutylammonium dihydrogen trifluoride, followed by NBS, to give *N*-$CF_3$-indoline **65**. Aromatization of **65** was carried out by reaction with NBS in $CCl_4$ at reflux, leading to *N*-trifluoromethyl-3-bromoindole **66** [31].



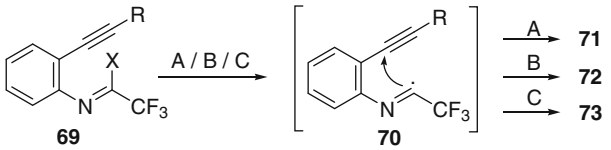
## 3.2 *Heterocyclizations*

### 3.2.1 Formation of the C3-C4 Bond

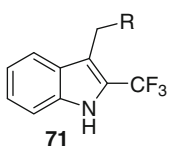
Kobayashi et al. elaborated an unusual pathway for the synthesis of 2,3-bis(trifluoromethyl)indoles [32]. Photolysis of the 1-phenyl-4,5-bis(trifluoromethyl)-1*H*-1,2,3-triazole in hexane proceeded very slowly to afford the indole **68** in 44 % yield. It was proposed, that after homolytic nitrogen extrusion, the carbene **67** was formed. Intramolecular cyclization led to the indole **68**.



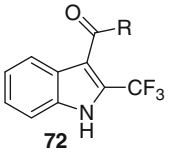

Radical, photochemical and thermolytic generation of *N*-aryltrifluoroacetimidoyl radicals followed by intramolecular cyclization was successfully used to synthesize 2-trifluoromethylindoles [33]. The radical approach was based on treatment of imidoyl iodides **69a** with tributyltin hydride in the presence of 2,2′-azabis(isobutyronitrile) (AIBN). The second method for the generation of *N*-aryltrifluoroacetimidoyl radicals **70** was based on the homolytic cleavage of carbon-iodine or carbon-tellurium bond in imidoyl iodides **69a** and tellurides **69b** under irradiation [34]. The third method involved the thermal homolysis of aza compounds **69c**. All of these methods provided the indoles **71**, **72** and **73**, respectively, in high yields [33, 34].



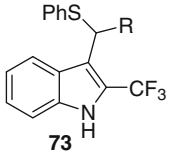

A: (**69a**) X = I; *n*-$Bu_3SnH$, AIBN, benzene, 80 °C
B: (**69b**) X = I or TePh; THF-$H_2O$, hν
C: (**69c**) X = N=N-$CPh_3$; PhSH, toluene, 100 °C




| R | |
|---|---|
| *n*-Bu | 69% |
| Ph | 61% |

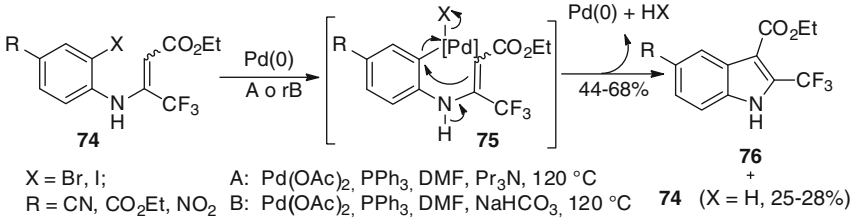



| R | Y = I | Y = Te |
|---|---|---|
| n-Bu | 53% | 68% |
| Ph | 68% | 67% |
| $PhCH_2O$ | 55% | 54% |

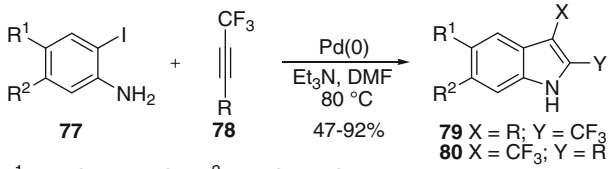



| R | |
|---|---|
| *n*-Bu | 72% |
| Ph | 77% |

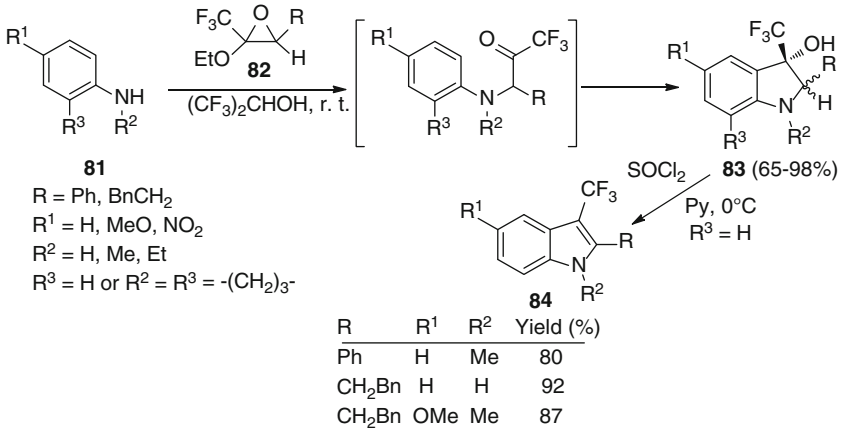
The intramolecular Heck reaction of bromo- or iodoaryl enamines **74** is another versatile key step for the synthesis of indoles. Zero-valent palladium catalysis afforded a mixture of indoles **76** and reduced enamines **74** (X=H) via intermediate formation of **75** depending on the base used [35].



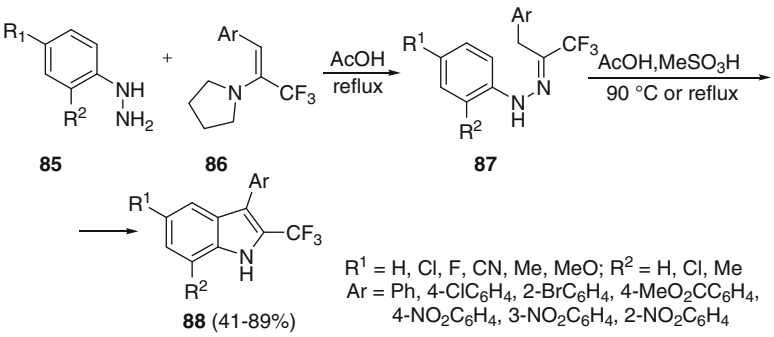

A variation of the intramolecular Heck coupling towards indoles bearing trifluoromethyl and aryl groups in the 2- and 3-positions was described by Chae and co-workers. First the C2-N bond was built, followed by ring closure that forms the C3-C4 bond. Accordingly, the palladium catalyzed addition of the trifluoromethyl(aryl) acetylenes **78** to the *ortho*-iodoanilines **77** afforded a mixture of the indoles **79** and **80** in high overall yield. Depending on the catalyst [20 mol% $Pd(PPh)_3$ or 10 mol% $Pd_2(dba)_3 \cdot CHCl_3$, $P(o\text{-Tol})_3$], one isomeric indole of either **79** or **80** was formed predominantly [36].




Another versatile approach towards 3-trifluoromethylated indoles was elaborated by Rodrigues et al. Anilines **81** reacted with epoxy ethers **82** (prepared by epoxydation of the corresponding vinyl ethers) in hexafluoropropan-2-ol to form mixtures of diastereomeric indolines **83** in high yields. The ratio of the diastereomers varied between 96:4 and 79:21. These diastereomers can be separated easily by column chromatography. The reaction was general and allowed effective preparation of indolines with both electron-donating and electron-withdrawing substituents. Compounds with fused rings were also prepared by this method. Treatment of the major *trans*-diastereomer of **83** with thionyl chloride in pyridine afforded the 3-trifluoromethylindoles **84** in high yields [37].



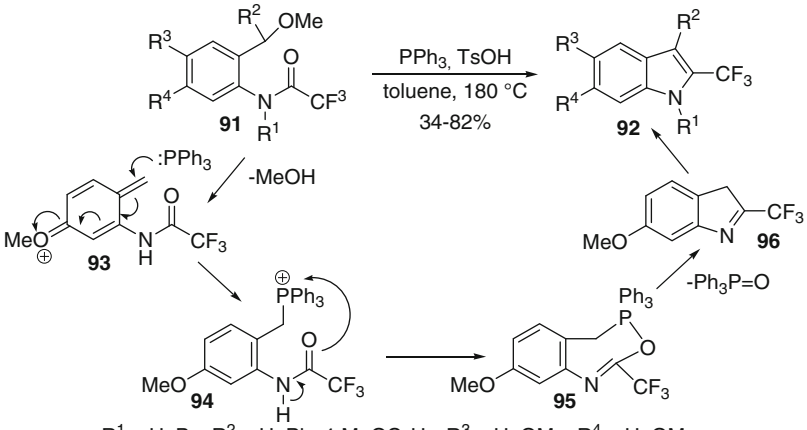

3-Aryl-2-trifluoromethylindoles **88** were prepared regioselectively using trifluoromethyl-2-arylenamines as synthetic equivalents of trifluoromethylated carbonyl compounds in the Fischer indole synthesis. Accordingly, arylhydrazines **85** reacted smoothly with enamines **86** in acetic acid to give the α-trifluoromethylhydrazones **87**. Fischer rearrangement of these hydrazones was performed in refluxing acetic acid the presence of methanesulfonic acid. As a result, a number of 3-aryl-2-trifluoromethylindoles were prepared in moderate to high yields [38]. This approach is first successful example of Fisher rearrangement for trifluoromethylated derivatives.



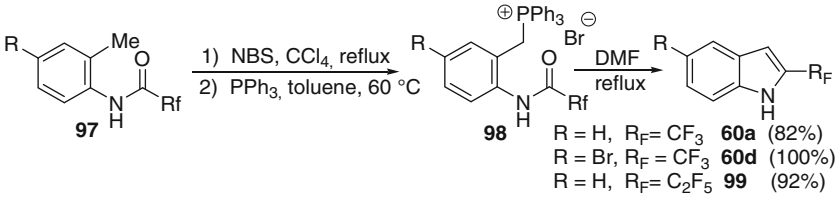

### 3.2.2 Formation of the C2-C3 Bond

Indole **90** was synthesized by a modified Madelung reaction from the amide **89** by treatment with potassium *tert*-butoxide. The presence of two strong electron-withdrawing groups (CN and $CF_3$) in **89** facilitated both the deprotonation to the benzyl anion and its intramolecular cyclization under very mild conditions. Formation of **90** was completed in 10 min at room temperature in 81 % yield [39].

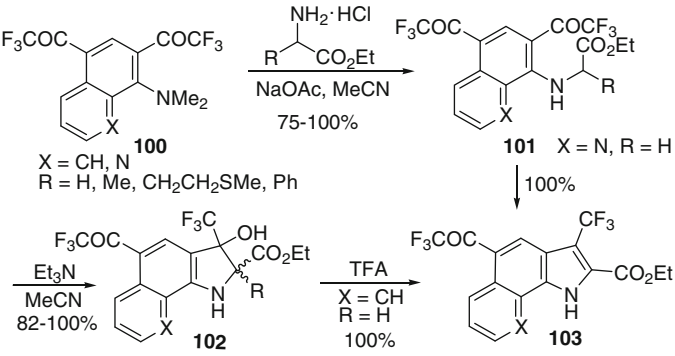

Miyashita and co-workers developed a novel 2-trifluoromethylindole synthesis based on thermolysis of 2-(*N*-acylamino)benzylmethyl ethers **91** in the presence of triphenylphosphine. However, this method has several disadvantages. The presence of a MeO-group in 5-position or 4-methoxyphenyl group at the benzyl carbon atom is necessary for the formation of **92**, otherwise the yields tend to zero. An explanation invokes the necessity of resonance stabilization of the intermediate oxonium ion **93**, which gives the key phosphonium salt **94** after attack by $PPh_3$. Subsequent intramolecular Wittig reaction leads to **95** which affords the 3-*H*-indole **96**. Isomerization of the latter leads to the target indole **92**. Another significant disadvantage of the method is the four-steps synthetic sequence to reach the starting 2-(*N*-acylamino)benzyl methylethers **91** [40].



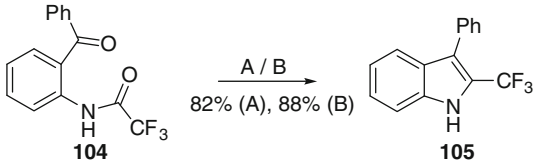

These disadvantages could be overcome by use of the phosphonium salts **98**, which are prepared in two steps from amides **97**. Bromination of **97** with NBS followed by reaction with triphenylphosphine permits to prepare **98** effectively. 2-Perfluoroalkylindoles **60a,d** and **99** were obtained in high yields using this method [40, 41].



Okada and co-workers investigated the reactions of the quinoline and naphthalene bis(trifluoroacetyl) derivatives **100** with amino acid esters in acetonitrile [42]. Two $COCF_3$ groups facilitate extremely nucleophilic substitution in **100** to make dimethylamino group good enough nucleophuge in this case. In the presence of equimolar amounts of sodium acetate (neutral media) the dimethylamino group was substituted with the amino acid ester moiety forming **101**. Subsequent treatment with triethylamine resulted in cyclization of **101** into the condensed dihydropyrrole derivatives **102** as mixtures of diastereomers. Quinoline **101** (X=N) was not isolated, but spontaneously cyclized to give 1*H*-pyrrolo[3,2-*h*]quinoline **102** (X=N). In contrast, naphthalene **101** (X=CH) in basic media was stable enough to be isolated. Treatment of **102** (X=CH) with trifluoroacetic acid gave the 1*H*-benzo[*g*]indole **103** quantitatively.

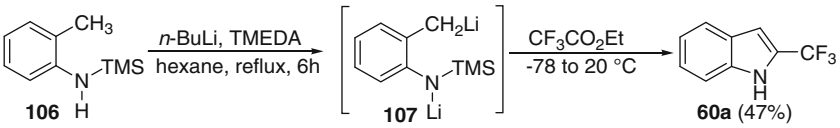



Fürstner and co-workers used the McMurry reaction for the synthesis of 2-trifluoromethyl-3-phenylindole **105** from ketonamide **104**. The reaction was performed either with two equivalents or substoichiometric amounts of titanium(III) chloride. In the latter case, large excesses of trimethylsilyl chloride and zinc were necessary [43].

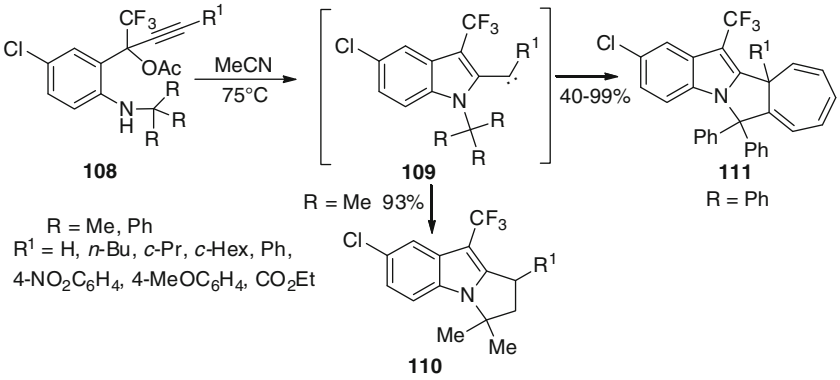



A: 2 equiv. $TiCl_3$, 4 equiv. Zn, THF, reflux
B: 10 mol% $TiCl_3$, 5 equiv. Zn, 5 equiv. TMSCl, MeCN, reflux

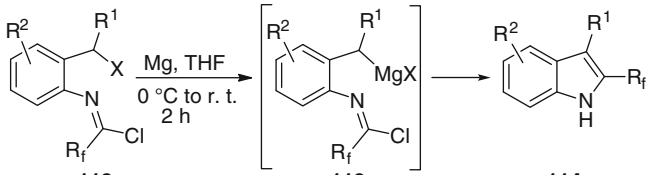
Refluxing of *N*-trimethylsilyltoluidine **106** with *n*-butyllithium in hexane in the presence of TMEDA afforded the dianion **107**, which on treatment with ethyl trifluoroacetate at −78 °C gave 2-trifluoromethylindole **60a** in 47 % yield [30].




An interesting rearrangement was found by Frey et al. Heating the amino alcohol *O*-acetate **108** (R=Me) in acetonitrile led to the tricyclic indole derivative **110**, while the trityl derivative **108** (R=Ph) afforded the dihydrocyclohepta[3,4]pyrrolo[1,2-*a*]indoles **111** in high yields. The authors suggested the carbene **109** as a key reaction intermediate, though the reaction mechanism is still a matter of discussion [44].

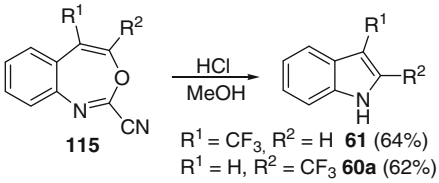



A convenient pathway to 2-fluoroalkyl-substituted indoles **114** was elaborated using the fluorinated *N*-[2-(haloalkyl)aryl]imidoyl chlorides **112** as key intermediates [45]. Treatment of the latter compounds with magnesium in tetrahydrofuran gave the Grignard compounds **113**, which afforded the indoles **114** in high yields by intramolecular cyclization initiated by attack of the nucleophile on imidoyl fragment.

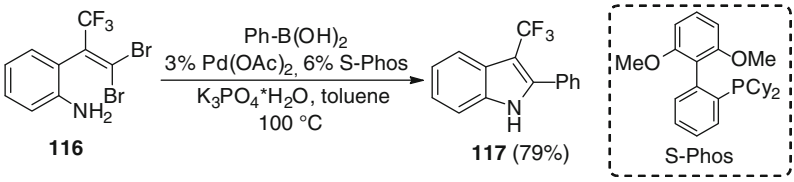


### 3.2.3 Formation of the C2-N Bond

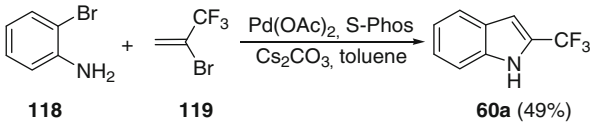
A regioselective pathway to 2- and 3-trifluoromethylindoles based on the ring-opening reaction of compounds **115** was developed by Attanasi and co-workers. After treatment of **115** with HCl in methanol, the corresponding indoles **60a** and **60a** were obtained in good yields. The starting compounds **115** were prepared from trifluoroquinolines in three steps [46].



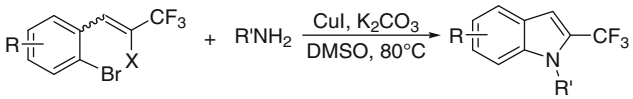

The synthesis of 3-trifluoromethyl-2-phenylindole **117** was accomplished by succeeding palladium catalyzed carbon–carbon cross-coupling of **116** with phenylboronic acid and carbon–nitrogen coupling in the presence of S-Phos [47].




Under similar conditions, 2-trifluoromethylindole **60a** was prepared starting from 2-bromoaniline **118** and 2-bromo-3,3,3-trifluoroprop-1-ene **119** using palladium catalysis [48].



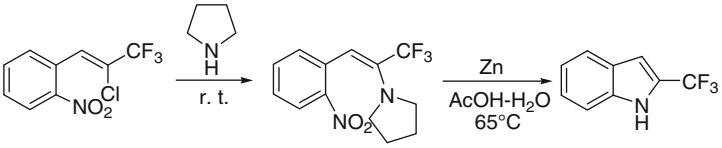

An efficient one-pot synthesis of substituted 2-trifluoromethylindoles was elaborated using copper(I)-catalyzed nucleophilic substitution of vinyl or aryl halogen atoms in styrenes **120** by primary amines. The resulting 2-trifluoromethylindoles **121** were prepared in moderate to good yields. The simplicity of the synthetic procedure and readily available starting materials are significant advantages of this method [49].




**120** **121** (39-74%)

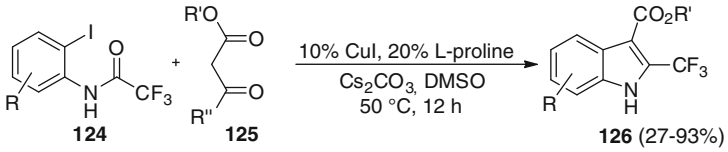
X = Cl, Br; R = H, 5-MeO, 5-EtO, 5,6,7-tri(MeO)
R' = *n*-Hex, *i*-Pr, Et, $Ph(CH_2)_2$, $MeO(CH_2)_2$, $MeO(CH_2)_3$, $3,4\text{-}EtO_2C_6H_3(CH_2)_2$, $3,4\text{-}MeO_2C_6H_3(CH_2)_2$

Another synthetic sequence for the preparation of 2-trifluoromehylindole **60a** was developed. In the first step, the styrene **122** was converted into the enamine **123** in quantitative yield. Subsequent treatment of this enamine with zinc dust under the standard conditions of the Leimgruber-Batcho indole synthesis led to 2-trifluoromethylindole, also in almost quantitative yield. Moreover, a one-pot methodology without isolation of enamine was also applied. In that case, an overall 90 % yield was obtained [50].




**122** **123** (98%) **60a** (93%)

A convenient method for the synthesis of 2-trifluoro-methyl-1*H*-indole-3-carboxylic acid esters **126** was elaborated using a cascade coupling, condensation and deacylation sequence. Starting from aryl trifluoacetamides **124** and ketoesters **125**, the corresponding indoles **126** were prepared in good to excellent yields, using a catalytic system of copper(I) iodide and L-proline [51].




**124** **125** **126** (27-93%)

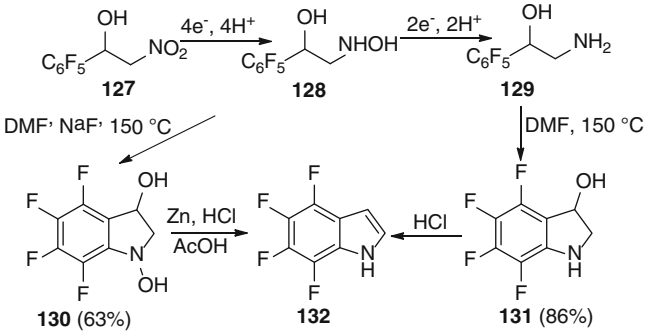
R = $NO_2$, Ac, Cl, Me, $CO_2Me$, I, MeO, $CH_2CH_2OH$
R' = Me, Et, Bn, *t*-Bu, *c*-Hex, allyl
R'' = Me, Ph, *i*-Pr

In conclusion, the synthesis of trifluoromethylated indoles is more difficult and less studied compared to synthesis of indoles bearing C-F bonds, therefore new effective strategies are very desirable to make these compounds to be more accessible building blocks for drug discovery.

## 4 Synthesis of Indoles with Fluorine Atoms in Carbocycle

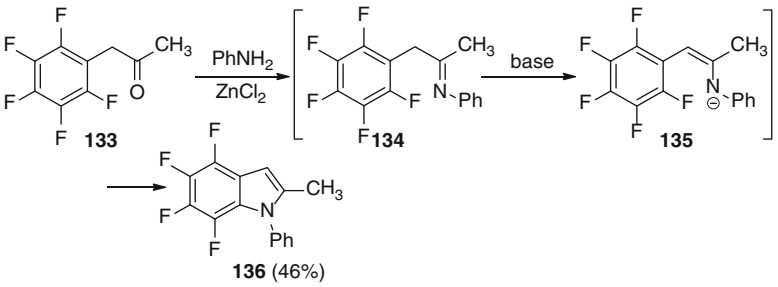
The influence of the fluorine atom on the nature of indole system is lower when fluorine is located on the benzene ring. However, there is significant specificity for indoles having fully fluorinated benzene ring. This part of the chapter is focused on 4,5,6,7-tetrafluoroindole and derivatives.

A common approach to the 4,5,6,7-tetrafluoroindoles is based on the various heterocyclizations starting from pentafluorophenyl precursors. Thus, heating of 1-pentafluorophenyl-2-amino-ethanol **129** in dimethylformamide gives 4,5,6,7-tetrafluoroindole **132** in good yield. The reaction proceeds via intramolecular nucleophilic substitution of the *o*-fluorine atom, followed by dehydration [52].

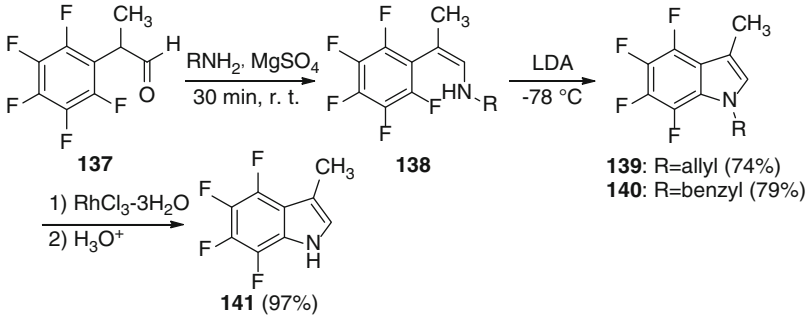



Another possible route for the nucleophilic substitution of the *ortho*-fluorine atom includes intramolecular attack by the hydroxy group of 2-(hydroxyamino)-1-(pentafluorophenyl)ethanol **128**. Heating of compound **128** in *N,N*-dimethylformamide in the presence of sodium fluoride led to cyclizations at the nitrogen to give 1,3-dihydroxy-4,5,6,7-tetrafluoro-indoline **130**. The latter was readily reduced by zinc in acidic media into 4,5,6,7-tetrafluoroindole **132**. The starting amino alcohols **128** and **129** were obtained by the potential-controlled electrochemical reduction of the nitroalcohol **127**, which can be prepared directly from pentafluorobenzaldehyde and nitromethane.

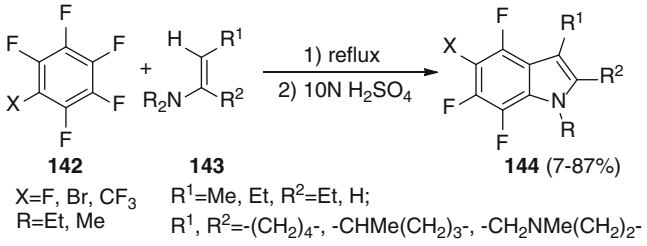
Alternative method for the synthesis of tetrafluoroindole was described in 1968. Ketone **133** was heated under reflux with aniline in the presence of anhydrous zinc chloride in order to prepare the Schiff base **134**. However, the only product isolated was *N*-phenyl-4,5,6,7-tetrafluoro-2-methylindole **136** (<10 %). The yield of **136** was increased up to 47 % by the addition of aniline hydrobromide to the reaction mixture. Thus, the improved synthesis of indole **136** includes heating of the ketone **133**, aniline hydrobromide, anhydrous zinc chloride and aniline under reflux for 2 h [53].



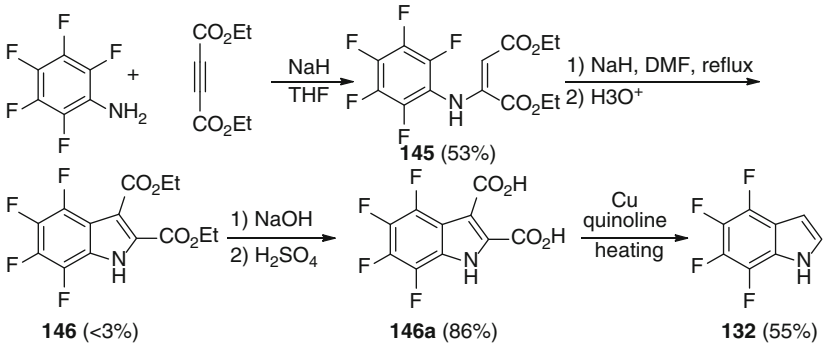

A similar approach was realized by other authors starting from aldehyde **137**. The reaction of the latter one with amines, followed by cyclization of intermediate **138** using lithium diisopropylamide as a base leads to tetrafluoroindole core. Finally, deprotection of **139** or **140** by a rhodium catalyst gave 3-methyl-4,5,6,7-tetrafluoroindole **141**. Overall yield of **141** starting from **138** was 72 % [54].




Intramolecular nucleophilic substitution of fluorine led to the formation of the pyrrole ring in the above mentioned transformations. However, the C-arylation can precede the heterocyclization. For example, condensation of cyclic enamines **143** with perfluorobenzenes **142** gave fluorinated indoles **144** via formation of C-N and C-C bonds. The authors reported that initial C-arylation was in competition with an initial *N*-arylation producing *N*-dialkylaminopoly-fluoroarenes. The "C *versus* N" arylation ratio was found to be dependent upon the nature of the enamine [55].

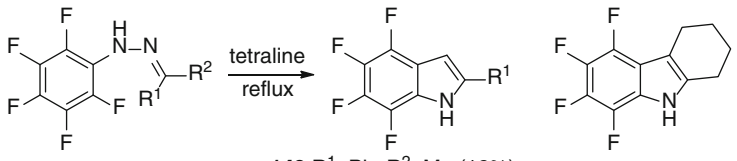


Similar cyclizations based on *N*-arylation are also known. For instance, when pentafluorophenyl substituted aminofumarate **145** (prepared from pentafluoroaniline and diethyl acetylenedicarboxylate) was treated with sodium hydride in dimethylformamide under reflux the indole derivative **146** was isolated. However, the yield of the target indole was very low [56]. Subsequent hydrolysis and decarboxylation provided tetrafluoroindole **132** in 55 % yield.




**145** (53%) **146** (<3%) **146a** (86%) **132** (55%)

An unusual formation of indoles via a formal Fischer cyclization of *N*-pentafluorophenyl hydrazones **147** was discovered by Brooke. Generally, the Fischer reaction demands the *ortho*-position be unoccupied. However, in refluxing tetraline, hydrazones **147** were transformed into polyfluoroindoles accompanying with the loss of one *ortho*-fluorine. Hydrazones of acetophenone and cyclohexanone afforded the corresponding indoles **148** and **149** in 12 and 18 % yields respectively. In case of acetaldehyde hydrazone, only a minor amount of parent tetrafluoroindole **132** were isolated. The mechanism of the reaction has not be clarified [57].



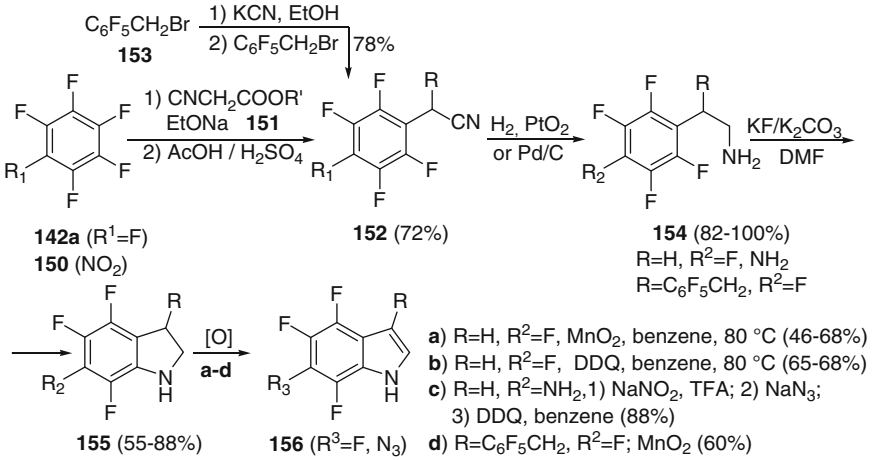

**147**

**148** $R^1$=Ph, $R^2$=Me (12%)
**132** $R^1$=H, $R^2$=Me (1.5%)

**149** (18%)

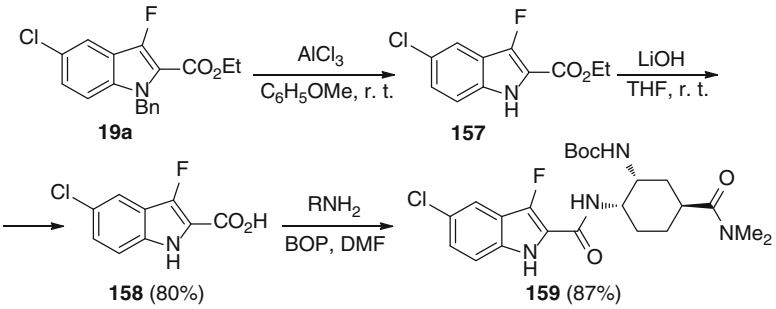
An efficient approach to polyfluoroindole was elaborated starting from hexafluorobenzene **142a** [58] and pentafluoronitrobenzene **150** [59]. In the first step, perfluoroarylacetonitriles **152** were obtained by nucleophilic substitution of fluorine with cyanoacetate **151** followed by acid catalyzed decarboxylation. Alternatively, nitrile **152** could be prepared from pentafluorobenzyl bromide **153** by treatment with potassium cyanide. Next, nitriles **152** were reduced into β-polyfluoroarylethyl amine **154**, which underwent facile cyclizations into fluorinated indolines **155**. The

latter were smoothly aromatized into the corresponding indoles **156** by treatment with manganese (IV) oxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

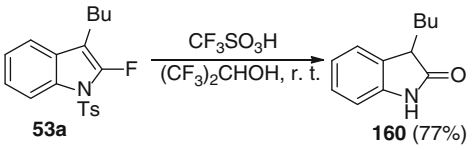



## 5 Properties

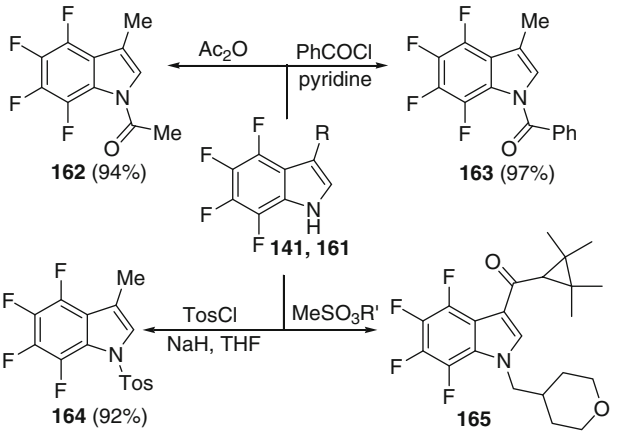
Fluorinated indoles reveal very similar properties in comparison to their non-fluorinated analogues. However, it should be noted that the chemistry of monofluorinated indoles (with fluorine atom attached to both 2 and 3 position) is scarcely studied. For example, 3-fluoroindole derivative **19a** was debenzylated to give indole carboxylic acid ester **157** quantitatively; the latter one was converted into amide **159** by hydrolysis followed by reaction with the corresponding amine in the presence of BOP reagent [9a]. Nitrogen atom in case of 3-fluorosubstituted indole derivatives has usual nucleophilicity and can participate in standard indole reactions, for example reaction with tosyl chloride provided *N*-sulfonylation product in 61 % yield [15].



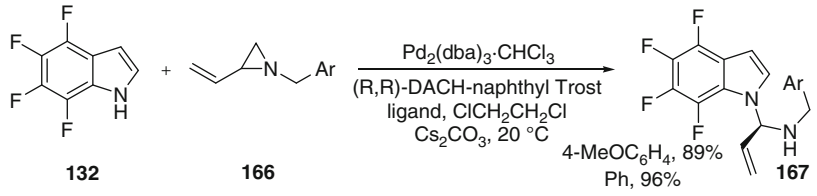
One more example of monofluoroindoles reactivity is hydrolysis of indole derivative **53a** into oxindole **160**, which was achieved under treatment with trifluoromethanesulfonic acid in hexafluoroisopropanol [60].



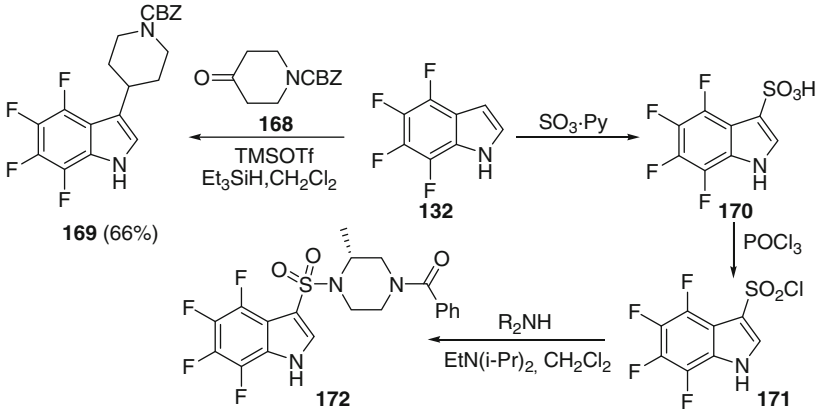

4,5,6,7-Tetrafluoroindoles were also shown to exhibit typical reactivity of indole. N-Substituted 4,5,6,7-tetrafluoroindole derivatives were obtained easily by the reaction of the parent indole with various electrophiles under basic conditions. Reaction of indoles **141** and **161** with acetic anhydride, benzoyl chloride, tosyl chloride and methanesulfonic acid ester afforded the corresponding N-substituted derivatives **162**–**165** in high yields [3, 54b].



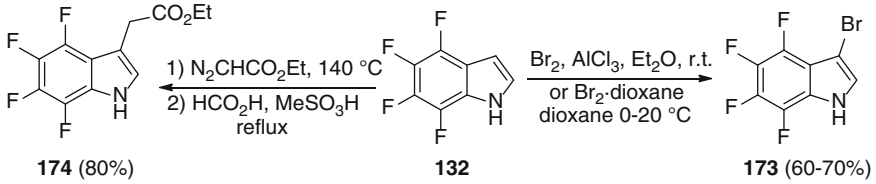

Alternative approach to 4,5,6,7-tetrafluoroindole nitrogen modification was proposed by Trost et al. Reaction of 4,5,6,7-tetrafluoroindole **132** with vinyl azyridines **166** under $Pd_2(dba)_3$ catalysis proceeded with ring-opening to give, stereoselectively, allyl amine derivatives **167** in high yields [61].



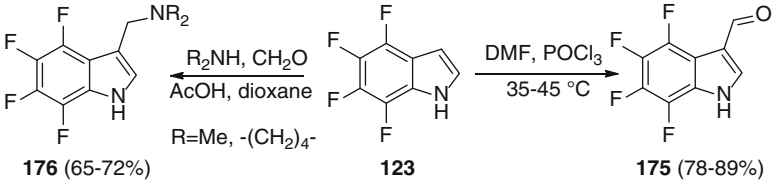
In spite of electron withdrawing action of four fluorine atoms, 4,5,6, 7-tetrafluoroindole **132** reacts with electrophiles under quite mild conditions to give products of substitution at the 3-position. For example, reaction of **132** with *N*-(carbobenzyloxy)piperidin-4-one **168** in the presence of trimethylsilyl triflate and triethylsilane afforded the corresponding piperidine derivative **169** [62]. Using sulfur trioxide-pyridine complex indolyl sulfonic acid **170** was obtained, which was further converted into sulfonyl amide **172** by reaction with phosphorus(V) oxychloride, followed by treatment with derivative of piperazine [2a].




Bromination was carried out using bromine in presence of catalytic amount of aluminum chloride or bromine-dioxane complex at 0–20 °C to form 3-bromoderivative **173** in high yield [63]. Electrophilic carbenoid species, generated at elevated temperature, reacted with polyfluoroindole to form indolyl carboxylic esters **174** after treatment with formic acid [58c].

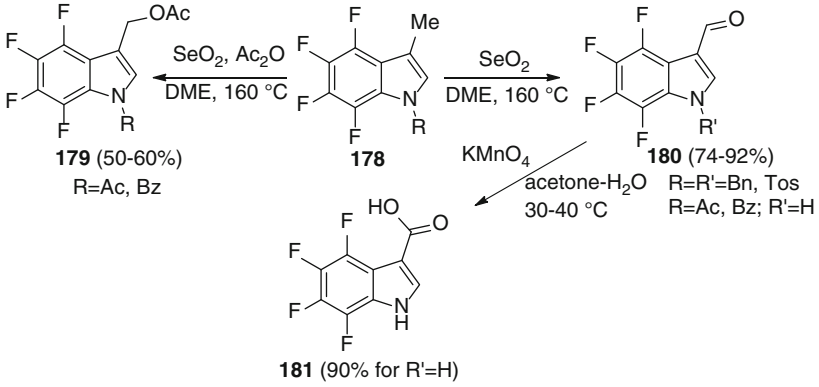



Fluorinated 3-indolyl carbaldehyde **175** was obtained in yields up to 89 % by Vilsmeier-Haack reaction [58c, 63]. Aminomethylation afforded the corresponding fluorinated gramine derivatives **176** in good yields [58c, 63].

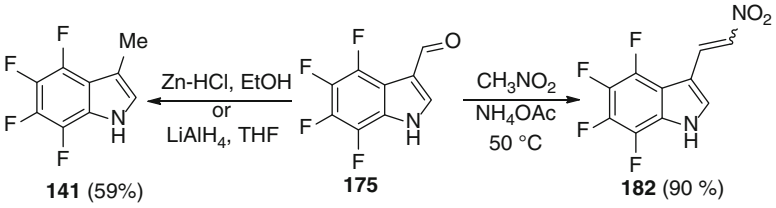


Reaction of chloroacetonitrile with 4,5,6,7-indolyl magnesium bromide, obtained by treatment of tetrafluoroindole with ethylmagnesium bromide, proceeded regioselectively at 3-position to afford the corresponding nitrile **177** in moderate yield [58c].

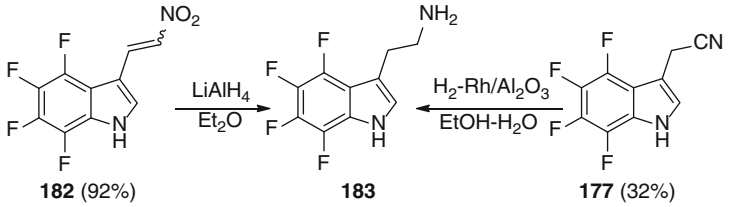

Oxidation of 3-methyltetrafluoroindoles **178** by selenium dioxide in presence of acetic anhydride can be stopped at the alcohol oxidation level step to give acetates **179**. Fluorinated 3-indolylcarbaldehydes **180** were isolated in high yields when the oxidation was performed without addition of acetic anhydride [54]. Further oxidation of aldehyde was achieved by treatment with potassium permanganate to afford 3-indolylcarboxylic acid **181** in high yield [58c].



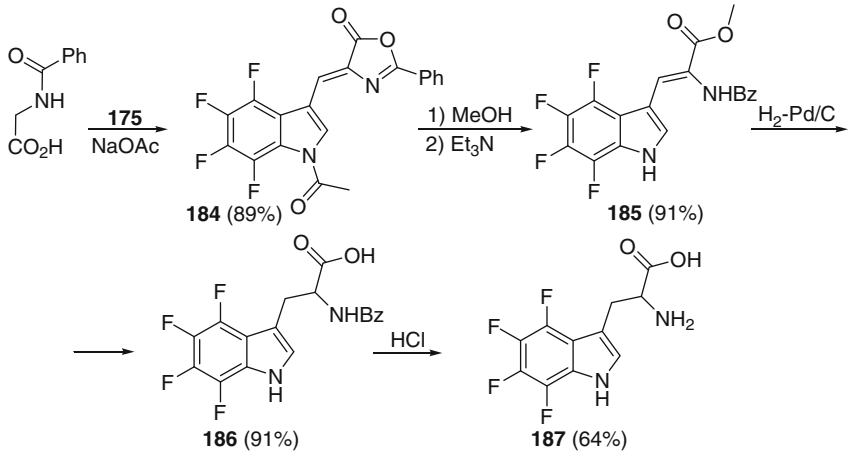

Reduction of the aldehyde **175** with lithium aluminum hydride [63] or zinc in hydrochloric acid [58c] gave fluorinated 3-methylindole **141** in good yield.



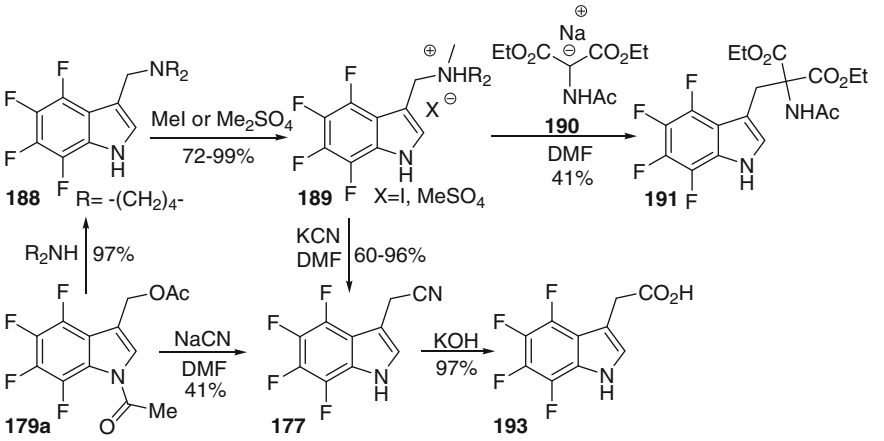
Fluorinated tryptamine **183** was prepared by Rh-catalyzed reduction of the corresponding nitrile **177** by hydrogen [58c]. Alternatively, the compound **183** was synthesized by lithium aluminum hydride reduction of nitroalkene **182**, which was obtained by condensation of aldehyde **175** with nitromethane [54].



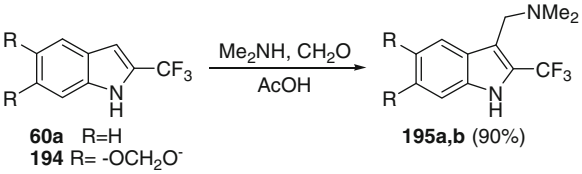

Through a similar reaction sequence, fluorinated tryptophan **187** was synthesized. Condensation of aldehyde **175** with *N*-benzoyl glycine afforded oxazolone **184**, which was converted into unsaturated acid **185**. Reduction of **185** by hydrogen and subsequent acid-catalyzed hydrolysis gave fluorinated tryptophan **187** in good total yield [54].



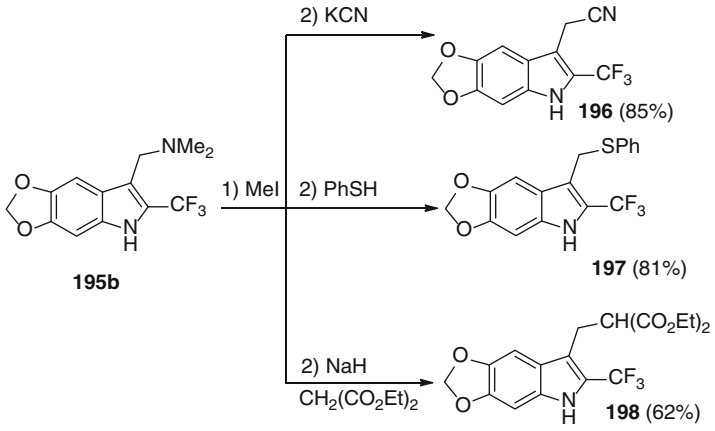

Fluorinated gramine analogue **188** was easily *N*-alkylated by reaction with methyliodide [58c] or dimethylsulfate [54, 63]. The tertiary amine salt **189** and the acetoxy derivative **179a** are suitable substrates for various nucleophilic substitutions. For instance, treatment of **189** or **179a** with potassium cyanide or sodium cyanide afforded the corresponding nitrile **177** [54, 58c] which was hydrolyzed into fluorinated indolyl acetic acid **19**3 [54]. Reaction of acetoxy compound **179a** with secondary amines led to gramine **188**. The corresponding tryptophan derivative **191** was obtained using the sodium salt of diethyl aminomalonate as a nucleophile [58c].



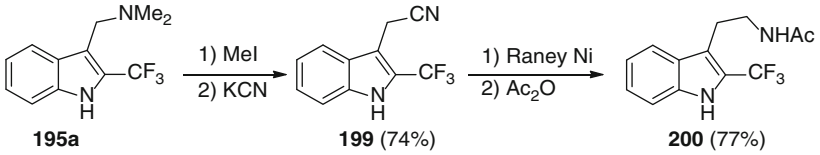

Trifluoromethylindoles undergo similar transformations in comparison to their non-fluorinated analogues as well. Thus, electrophilic substitution at the C-3 position takes place when the C-2 position is occupied by the trifluoromethyl group. The Mannich reaction provided dimethylaminomethyl derivatives in good yields under standard conditions [64].




Quaternization of the compounds **195b** with methyl iodide and subsequent reactions with nucleophiles, e.g. potassium cyanide, thiophenol, and diethyl malonate, gave corresponding products **196**–**198** in 62–85 % yields [64].

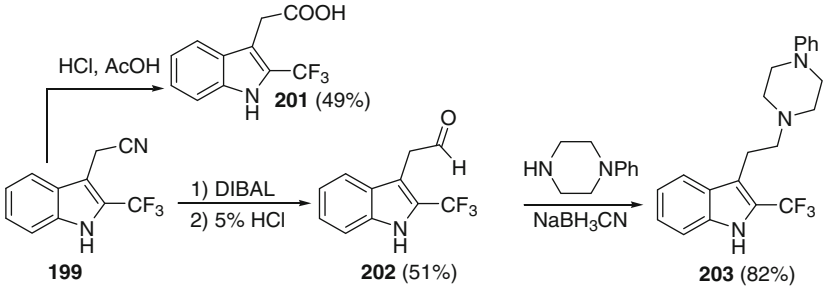


Reduction of the nitrile group of the compound **199** and subsequent reaction with acetic anhydride led to 2-trifluoromethyltryptamine **200** [64]. For the reduction, Raney Ni was used, since hydrides, for example, lithium aluminium hydride, can reduce the trifluoromethyl group as well.



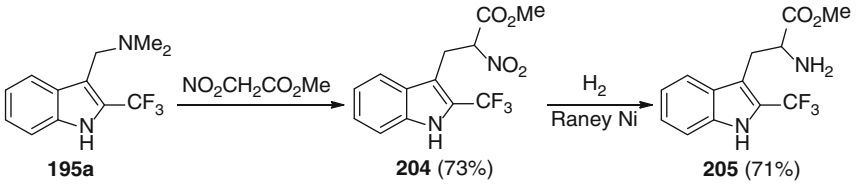

**195a** **199** (74%) **200** (77%)

Hydrolysis of the nitrile **199** gave 2-trifluoromethylindole-3-acetic acid **201** in moderate yield [60]. A partial reduction of the nitrile group in **199** provided indole-3-acetaldehyde **202** in 51 % yield. The latter was used for the synthesis of the 2-trifluoromethylated analogue of oxypertine (an antipsychotic used in the treatment of schizophrenia) **203** upon treatment with *N*-phenylpiperazine and sodium cyanoborohydride [64].



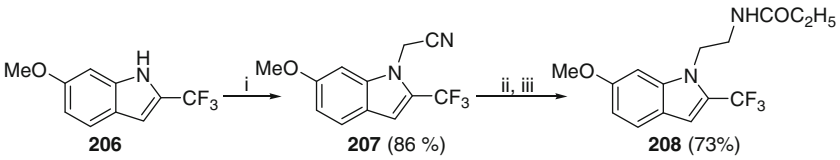

**201** (49%) **199** **202** (51%) **203** (82%)

2-Trifluoromethyltryptophan methyl ester **205** was synthesized from nitro derivative **204** obtained via direct reaction of **195a** with methylnitroacetate. Chemoselective reduction of the nitro group was achieved by hydrogenation in the presence of Raney Ni in methanol [60].




**195a** **204** (73%) **205** (71%)

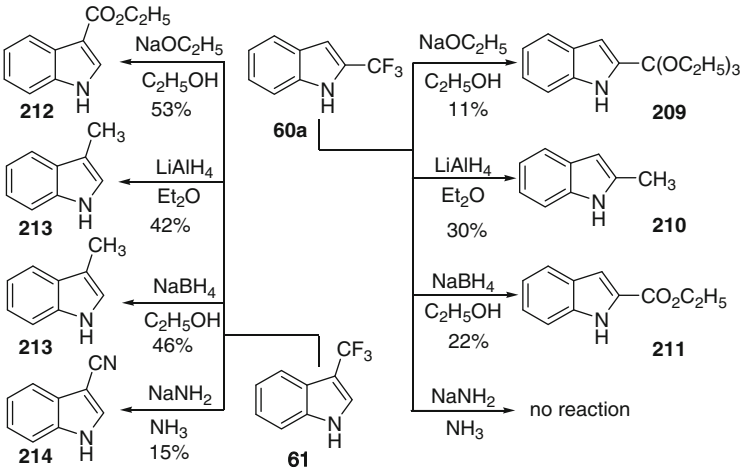
N-Alkylation of indole **206** was achieved by treatment with NaH in DMF, followed by reaction with chloroacetonitrile [65]. Subsequent catalytic reduction of **207** with hydrogen under Raney-Ni followed by reaction with ethylcarbonate led to compound **208**, which was investigated as melatonin receptor ligand.




**206** **207** (86 %) **208** (73%)

(i) NaH, $ClCH_2CN$, DMF, 16h; (ii) Re-Ni, $H_2$, 4 atm; (iii) $(EtCO)_2O$, THF, 50 °C, 6h.

Attanasi et al. investigated reactions of both 2-and 3-trifluoromethylindole involving trifluoromethyl group and leading to loss of fluorine. Treatment of trifluoromethylindoles with $LiAlH_4$ gave methylindoles **210** and **213**.

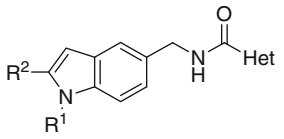


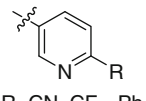

Reaction of 2-trifluoromethylindole with sodium ethoxide led to *ortho*-ether **209**, while ethyl 3-indolylcarboxilate **212** was isolated in case 3-trifluoromethylindole. Reaction of 2-trifluoromethylindole with $NaBH_4$ in ethanol led to ethyl 2-indolylcarboxilate **211**. In contrast, reduction of trifluoromethyl group was observed to form 3-methylindole **213** in case of 3-isomer. Treatment of 3-trifluoromethylindol with sodium amide in liquid ammonia led to 3-cyanoindole **214**, whereas 2-trifluoroindole did not reacted with sodium amide at all [46].

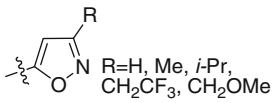
## 6 Pharmacological Properties of Fluorinated Indoles

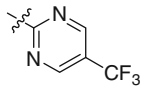
Fluorinated indoles posses a broad scope of physiological activity and they are very prominent candidates for further biological testing and using as drugs. In this part of the chapter pharmacological properties of fluorinated indoles are collected (Table 1). One can see very broad spectrum of biological activity of such structures and synergism bringing both indole fragment and fluorine in a molecule.

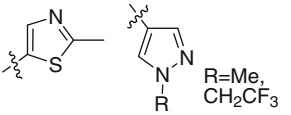
**Table 1** Pharmacological properties of fluorinated indoles



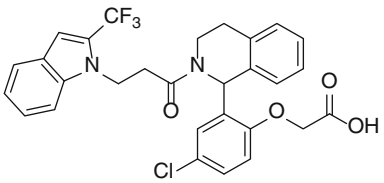



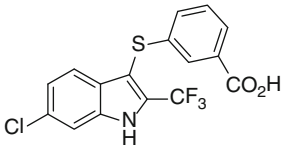



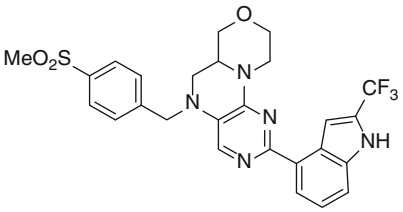

Modulators of nicotinic acetylcholine α7 receptor and KCNQ potassium channel [31]



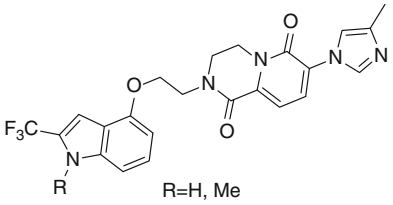

Prostaglandin D2 receptor modulators [66]



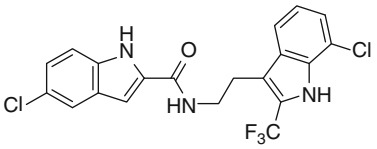

Autotoxin (ATX) inhibitors [67]



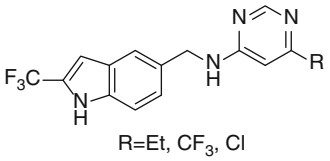

Inhibitor of PI3Kδ [68]



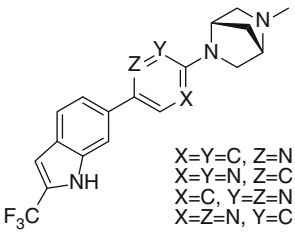

Inhibitor of amyloid beta protein Aβ(1–42) production [69]



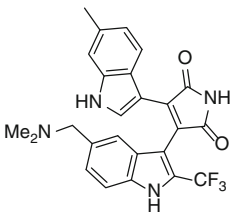

Modulator of human prostaglandin $EP_2$ receptor [70]




Modulator of nicotinic acetylcholine α7 receptor [71]



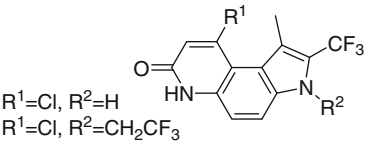

Modulator of α7 neuronal nicotinic receptors (NNRs) [72]




Inhibitor of Protein Kinase Cβ1 (PKCβ1) [73]

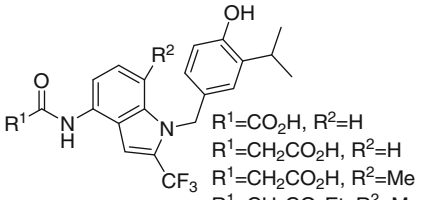
(continued)

**Table 1** (continued)



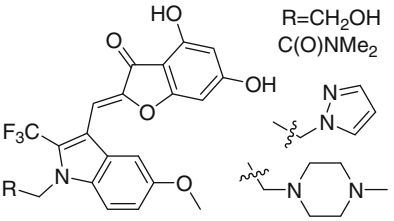

$R^1$=Cl, $R^2$=H
$R^1$=Cl, $R^2$=$CH_2CF_3$
$R^1$=Cl, $R^2$=$CH_2CH(OH)CF_3$
$R^1$=Cl, $R^2$=$CH_2CF_3$
$R^1$=$CF_3$, $R^2$=$CH_2CF_2CF_3$

Androgen receptor modulator [74]

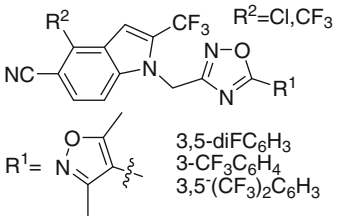



$R^1$=$CO_2H$, $R^2$=H
$R^1$=$CH_2CO_2H$, $R^2$=H
$R^1$=$CH_2CO_2H$, $R^2$=Me
$R^1$=$CH_2CO_2Et$, $R^2$=Me

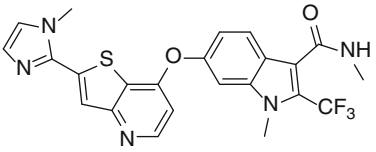
Thyroid hormone receptors (TRα and TRβ) ligand [75]



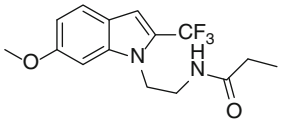

Inhibitor of phosphatidylinositol-3 kinase α (PI3Kα) [76]



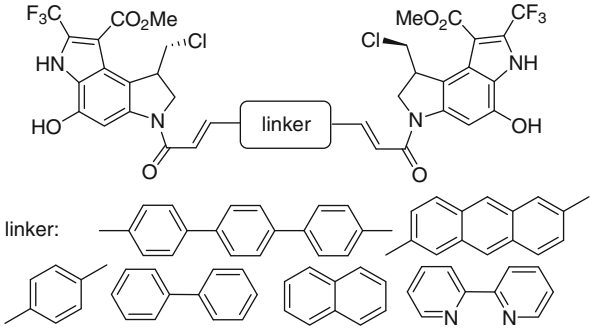

Androgen receptor (AR) agonist [77]




Inhibitor of autophosphorylation receptor [78]



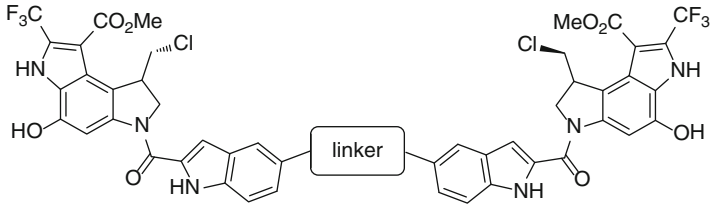

Melatonin receptor ligand [65]




Antiproliferative, antineoplastic, antitumor activity [79]

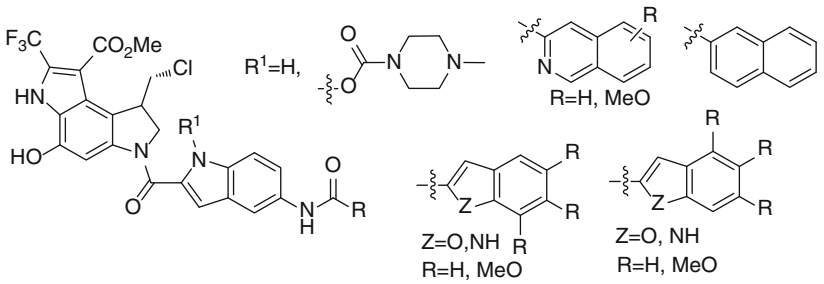
(continued)

**Table 1** (continued)

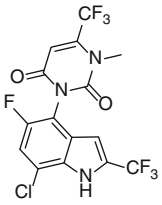



linker: $CH_2$, $CH_2CH_2$, -O-, NHC(O)NH-, single bond

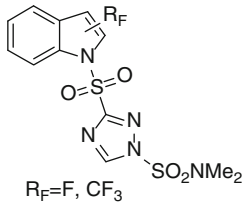
Antitumor activity [80]



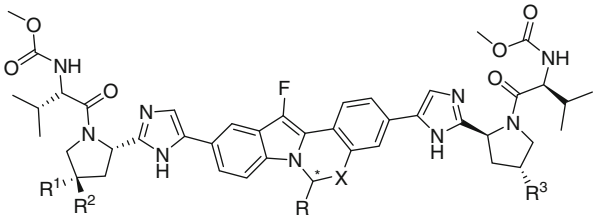

Antitumor activity [79c]



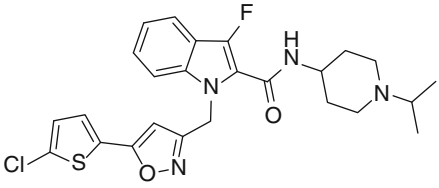
Herbicide [81]



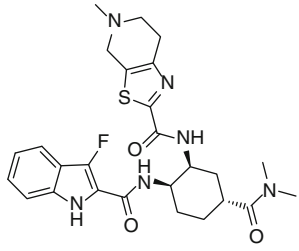

Agricultural and horticultural fungicide [82]




Antiviral against hepatitis C virus [83]



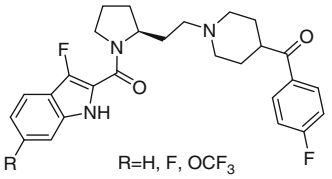
Factor Xa inhibitor [4]



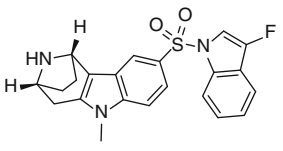
Inhibition of factor Xa, anticoagulant [84]

(continued)

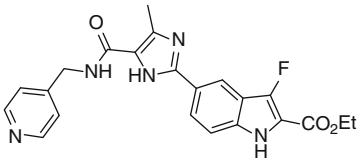
**Table 1** (continued)



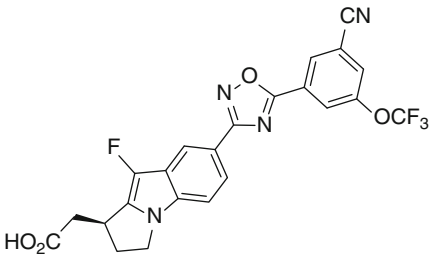

Inhibitors of dopamine D2L receptor, serotonin 5-HT2A receptor, serotonin 5-HT6 receptor, adrenaline α1D receptor [85]



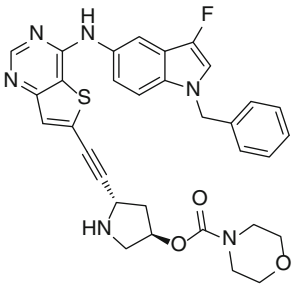

Human 5-HT6 receptor modulator [86]



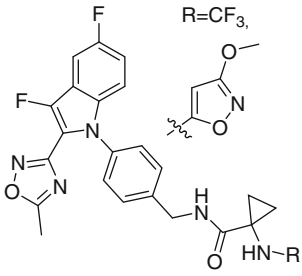

Inhibitor of matrix metalloprotease 13 (MMP13) [87]



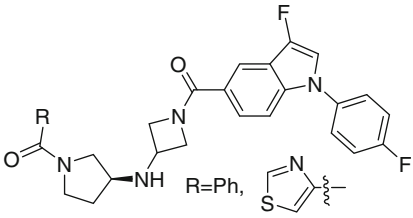

Agonist of the sphingosine-1-phosphate S1P1 receptor [88]



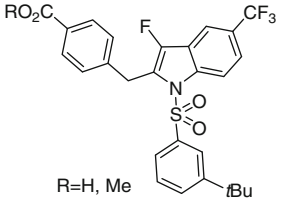

Inhibitor of EGFR and ErbB-2 kinases antiproliferative, cytotoxic for foreskin fibroblast of human [89]




Bradykinin B1 receptor antagonist [90]



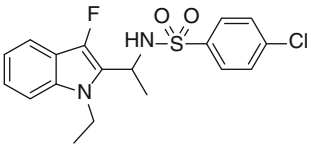
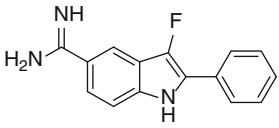
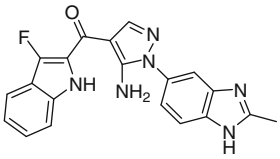
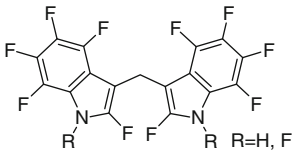

Monoacylglycerol lipase inhibitors [91]




Activators of NURR-1/RXRα and NURR-1/RXRγ heterodimers formation [92]

(continued)

**Table 1** (continued)

| | |
|---|---|
|  |  |
| Edg-1 receptor antagonist [93] | ASIC (acid-sensing ion channel) modulator [94] |
|  |  |
| Inhibitor of fibroblast growth factor receptor 1 (FGFR1) [95] | Antiproliferative activity, antiandrogen (R=F). Immune response activator (R=H) [96] |

## 7 Conclusions

Recent decades, fluorinated indoles and their analogues have enjoyed remarkable attention of chemists. However, one can definitely conclude that synthesis of these compounds is still challenging and attractive task.

**Acknowledgments** Financial support from the Russian Foundation for Basic Research (grants no. 12-03-00292-a and 13-03-01129) are gratefully acknowledged.

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