DOI: 10.1070/RCR4871

Organofluorine chemistry: promising growth areas and challenges

Larisa V. Politanskaya,[a] Galina A. Selivanova,[a] Elena V. Panteleeva,[a, b] Evgeny V. Tretyakov,[a, b*] Vyacheslav E. Platonov,[a*] Pavel V. Nikul'shin,[a] Andrey S. Vinogradov,[a] Yaroslav V. Zonov,[a] Victor M. Karpov,[a*] Tatyana V. Mezhenkova,[a] Aleksander V. Vasilyev,[c, d*] Andrei B. Koldobskii,[e*] Olga S. Shilova,[e] Sofia M. Morozova,[e] Yanina V. Burgart,[f, g] Evgeny V. Shchegolkov,[f, g] Victor I. Saloutin,[f, g*] Vladimir B. Sokolov,[h] Aleksey Yu. Aksinenko,[h*] Valentine G. Nenajdenko,[i*] Mikhail Yu. Moskalik,[j] Vera V. Astakhova,[j] Bagrat A. Shainyan,[j*] Andrey A. Tabolin,[k*] Sema L. Ioffe,[k] Vasiliy M. Muzalevskiy,[i*] Elizaveta S. Balenkova,[i] Alexey V. Shastin,[l] Andrey A. Tyutyunov,[e] Vladimir E. Boiko,[e] Sergei M. Igumnov,[e*] Alexander D. Dilman,[k*] Nicolay Yu. Adonin,[m *] Vadim V. Bardin,[a] Salekh M. Masoud,[e] Daria V. Vorobyeva,[e] Sergey N. Osipov,[e*] Emiliya V. Nosova,[f, g] Galina N. Lipunova,[f, g] Valery N. Charushin,[f, g*] Darya O. Prima,[a, n] Arkady G. Makarov,[a] Andrey V. Zibarev,[a, n*] Boris A. Trofimov,[j*] Lyubov N. Sobenina,[j] Kseniya V. Belyaeva,[j] Vyacheslav Ya. Sosnovskikh,[g*] Dmitrii L. Obydennov,[g] Sergey A. Usachev [g]

[a] N.N.Vorozhtsov Novosibirsk Institute of Organic Chemistry,
Siberian Branch of the Russian Academy of Sciences
prosp. Akademika Lavrentieva 9, 630090 Novosibirsk, Russian Federation
[b] Novosibirsk State University
ul. Pirogova 2, 630090 Novosibirsk, Russian Federation
[c] Saint Petersburg State Forest Technical University
Institutsky per. 5, 194021 Saint Petersburg, Russian Federation
[d] Saint Petersburg State University
Universitetskaya nab. 7 – 9, 199034 Saint Petersburg, Russian Federation
[e] A.N.Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences
ul. Vavilova 28, 119991 Moscow, Russian Federation
[f] Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences
ul. S.Kovalevskoi 22/ul. Akademicheskaya 20, 620990 Ekaterinburg, Russian Federation
[g] Ural Federal University named after the first President of Russia B.N.Yeltsin
ul. Mira 19, 620002 Ekaterinburg, Russian Federation
[h] Institute of Physiologically Active Compounds, Russian Academy of Sciences
Severnyi pr. 1, 142432 Chernogolovka, Moscow Region, Russian Federation
[i] Department of Chemistry, Lomonosov Moscow State University
Leninskie Gory 1, stroenie 3, 119992 Moscow, Russian Federation
[j] A.E.Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences
ul. Favorskogo 1, 664033 Irkutsk, Russian Federation
[k] N.D.Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences
Leninsky prosp. 47, 119991 Moscow, Russian Federation
[l] Institute of Problems of Chemical Physics, Russian Academy of Sciences
prosp. Akademika Semenova 1, 142432 Chernogolovka, Moscow Region, Russian Federation
[m] Boreskov Institute of Catalysis, Siberian Branch of the Russian Academy of Sciences
prosp. Akademika Lavrentieva 5, 630090 Novosibirsk, Russian Federation
[n] Department of Chemistry, National Research University — Tomsk State University
prosp. Lenina 36, 634050 Tomsk, Russian Federation

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Currently, the chemistry of organofluorine compounds is a leading and rapidly developing area of organic chemistry. Fluorine present in a molecule largely determines its specific chemical and biological properties. This thematic issue covers the trends of organofluorine chemistry that have been actively developed in Russia the last 15 – 20 years. The review describes nucleophilic substitution and heterocyclization reactions involving fluorinated arenes and quinones and skeletal cationoid rearrangements in the polyfluoroarene series. The transformations involving CF_3-substituted carbocations and radical cations are considered. Heterocyclization and oxidative addition reactions of trifluoroacetamide derivatives and transformations of the organic moiety in polyfluorinated organoboranes and borates with retention of the carbon – boron bond are discussed. Particular attention is devoted to catalytic olefination using freons as an efficient synthetic route to fluorinated compounds. The application of unsymmetrical fluorine-containing N-heterocyclic carbene ligands as catalysts for olefin metathesis is demonstrated. A variety of classes of organofluorine compounds are considered, in particular, polyfluorinated arenes and 1,2-diaminobenzenes, 1-halo-2-trifluoroacetylacetylenes, α-fluoronitro compounds, fluorinated heterocycles, 2-hydrazinylidene-1,3-dicarbonyl derivatives, imines and silanes. The potential practical applications of organofluorine compounds in fundamental organic chemistry, materials science and biomedicine are outlined.
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1. Introduction

The significance of organofluorine compounds for the progress of main areas of modern chemistry such as development of new functional materials and pharmaceuticals, synthesis of biologically active compounds and the use of spectroscopic approaches to investigate the docking mechanisms in biological systems has been widely recognized and reflected in a series of recently published books.[1 – 7] These achievements were supported by the development of synthetic routes to fluorinated compounds and fundamental studies of their physical properties and reactivity. While looking back to the information gained, one would pay attention to series of studies characterized, by analogy with a chess game, by a common opening and multi-move combinations during the game. The present review is focused on this type of studies.

Despite a more than 150-year history of organofluorine chemistry, intensive research in this area is still a key trend of modern organic synthesis. Although compounds containing carbon – fluorine bonds in the molecule are very rarely encountered in nature (only several dozens such molecules have been isolated by now), fluoro derivatives play an exceptionally important role in the development of new drugs and design of materials with unique properties. Indeed, about one-fourth of the currently manufactured agrochemical and pharmaceutical products contain at least one fluorine atom.[8] About 20% of these products appeared on the market in the first decade of the 21st century.[9] All this accounts for the interest in the development of efficient

and environmentally benign processes for the synthesis of organofluorine compounds of a definite structure.[10, 11]

Fluorine is a peculiar element, not just the first of the halogens. The properties of the element and its organic compounds have a vivid specificity.[12–15] The highest electronegativity of fluorine among chemical elements (4.0) makes the C–F bond highly polar (dipole moment of 1.4 D). Meanwhile, the van der Waals radius of fluorine (1.47 Å) is only 23% higher than that of hydrogen (1.20 Å). High strength of the C–F bond (116 kcal mol^{-1})[16, 17] combined with low polarizability makes organofluorine molecules highly unique. The set of these properties is extensively utilized in the modern drug design. As noted above, ~20%–25% of small-molecule pharmaceutical products contain at least one fluorine atom,[18] while 10 out of the 30 drugs most marketable in the US in 2008 were organofluorine molecules.[19] The introduction of a fluorine atom into the target molecule changes the lipophilicity and solubility of the compound and considerably affects the basicity and acidity of functional groups and tendency for hydrogen bonding.[12] This also changes the metabolism, membrane permeability, efficiency of binding to biological targets, bioavailability and other important parameters of such biologically active molecules. Furthermore, increased stability of organofluorine compounds makes them highly demanded also in the materials chemistry.

The demand for organofluorine compounds provides impetus for the development of synthetic strategies towards these compounds. However, selective introduction of a fluorine atom or a polyfluoroalkyl substituent into the desired structure is a synthetic challenge and, in each particular case, it is performed by a dedicated method. The currently existing methods for direct fluorination and fluoroalkylation of organic compounds[10–22] are by no means always suitable for introducing a fluorine-containing group (R_F) into the required position of the molecule; therefore, a flexible synthon-based approach involving the use of readily accessible organofluorine substrates with moderate molecular weights[23–28] is a good supplement to direct fluorination methods and has lately acquired increasing significance.

This review was written by a group of 49 co-authors and includes 19 chapters related to the chemistry of organofluorine compounds. Colleagues from 14 Russian institutes and universities made an attempt to describe the development of organofluorine chemistry over the last 15–20 years.

The following abbreviations are used in the review:

Ad — adamantyl,
AIBN — azobis(isobutyronitrile),
All — allyl,
Am — amyl (pentyl),
AOR — anomalous olefination reaction,
Ar_F (R_F) — perfluorinated aryl (alkyl) substituent,
Az — azolyl,
B — base,
BA — Brønsted acid,
BAC — biologically active compounds,
Boc — *tert*-butoxycarbonyl,
BODIPY — boron-dipyrromethane,
bpy — 4,4′-bipyridine,
Cat — catalyst,
Cbz — benzyloxycarbonyl,
CEYM/D-A — cross enyne metathesis/Diels–Alder reaction sequence,
CM — olefin cross-metathesis,
cod — cycloocta-1,5-diene,
CTAB — cetyltrimethylammonium bromide,
Cy — cyclohexyl,
dba — dibenzylideneacetone,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DC — dicarbonyl compounds,
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
DFT — density functional theory,
DIPP — 3,5-diisopropylphenyl,
DMAD — dimethyl acetylenedicarboxylate,
DMAP — 4-dimethylaminopyridine,
DME — 1,2-dimethoxyethane,
DMPU — *N*,*N*-dimethylpropyleneurea,
dppe — 1,2-bis(diphenylphosphino)ethane,
dr (*er*) — diastereomer (enantiomer) ratio,
EDC — 3-ethyl-1-(3-dimethylaminopropyl)carbodiimide,
ee — enantiomer excess,
EWG — electron-withdrawing group,
FNSM — fluoronitro(phenylsulfonyl)methane,
Fu — furyl,

* Contact information:
E.V.Tretyakov. Doctor of Chemical Sciences,
e-mail: tretyakov@nioch.nsc.ru;
V.E.Platonov. Doctor of Chemical Sciences, Professor,
e-mail: platonov@nioch.nsc.ru;
V.M.Karpov. Doctor of Chemical Sciences,
e-mail: karpov@nioch.nsc.ru;
A.V.Vasilyev. Doctor of Chemical Sciences, Professor,
e-mail: aleksvasil@mail.ru;
A.B.Koldobskii. Doctor of Chemical Sciences,
e-mail: andikkold@rambler.ru;
V.I.Saloutin. Corresponding Member of the RAS,
e-mail: saloutin@ios.uran.ru;
A.Yu.Aksinenko. PhD
e-mail: alaks@ipac.ac.ru;
V.G.Nenajdenko. Doctor of Chemical Sciences, Professor,
e-mail: nenajdenko@gmail.com;
B.A.Shainyan. Doctor of Chemical Sciences, Professor,
e-mail: bagrat@irioch.irk.ru;
A.A.Tabolin. PhD,
e-mail: tabolin87@mail.ru;
V.M.Muzalevskiy. PhD,
e-mail: muzvas@mail.ru;
S.M.Igumnov. Doctor of Chemical Sciences,
e-mail: igumnov@fluorine1.ru;
A.D.Dilman. Doctor of Chemical Sciences, Professor,
e-mail: dilman@ioc.ac.ru;
N.Yu.Adonin. Doctor of Chemical Sciences, Professor,
e-mail: adonin@catalysis.ru;
S.N.Osipov. Doctor of Chemical Sciences,
e-mail: osipov@ineos.ac.ru;
V.N.Charushin. Academician, Professor,
e-mail: Valery-Charushin-562@yandex.ru;
A.V.Zibarev. Doctor of Chemical Sciences, Professor,
e-mail: zibarev@nioch.nsc.ru;
B.A.Trofimov. Academician,
e-mail: boris_trofimov@irioch.irk.ru;
V.Ya.Sosnovskikh. Doctor of Chemical Sciences, Professor,
e-mail: vy.sosnovskikh@urfu.ru

Received 16 November 2018
Translation: Z.P.Svitanko

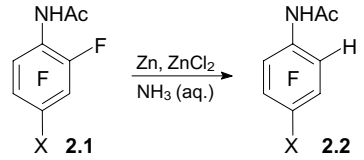
HFA — hexafluoroacetone
HMPA — hexamethylphosphoramide,
IC_{50} — half-maximal inhibitory concentration,
IL — ionic liquid,
IMHB — intramolecular hydrogen bond
LA — Lewis acid,
LC — liquid-crystalline,
LTMP — lithium 2,2,6,6-tetramethylpiperidide,
mCPBA — *m*-chloroperoxybenzoic acid,
MIC — minimal inhibitory concentration,
Mes — 2,4,6-trimethylphenyl (mesityl),
MS — molecular sieves,
MTFP — methyl trifluoropyruvate
MW — microwave radiation,
Naph — naphthyl,
NBS — *N*-bromosuccinimide,
mNBSA — *m*-nitrobenzenesulfonic acid,
NFSI — *N*-fluorobenzylsulfonimide,
NHC — N-heterocyclic carbene,
Ni-Ra — Raney nickel,
NMP — *N*-methylpyrrolidin-2-one,
Ns — *p*-nitrobenzenesulfonyl (nosyl),
PFB — 1,1,1,3,3-pentafluorobutane,
PG — protecting group,
phen — phenanthroline,
PPA — polyphosphoric acid,
ppy — 2-phenylpyridine,
RA — radical anion
RCM — ring-closing olefin metathesis,
RCEYM — ring-closing enyne metathesis,
RCEYM/cycloprop — ring-closing enyne metathesis/cyclopropanation sequence,
RCEYM/D-A — ring-closing enyne metathesis/Diels–Alder reaction sequence,
ROM/RCM — ring opening/ring closing metathesis,
rt — room temperature,
Selectfluor — 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate),
Solv — solvent,
SS — stainless steel,
TBDPS — *tert*-butyldiphenylsilyl,
TDAE — tetrakis(dimethylamino)ethylene,
TEMPO — 2,2,6,6-tetramethylpiperidin-1-yloxyl,
Tf — trifluoromethanesulfonyl (triflyl),
Th — thienyl,
THP — tetrahydropyran-2-yl,
TMS — trimethylsilyl,
Tol — tolyl,
Ts — *p*-toluenesulfonyl (tosyl),
Xantphos — 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene,

2. Nucleophilic substitution and heterocyclization reactions of fluorinated arenes and quinones

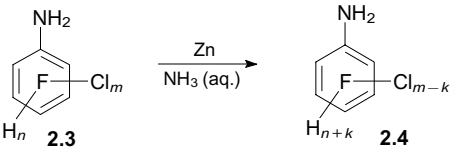
Aromatic substitution reactions result in the formation of a broad range of polyfunctional fluorinated arenes and hetarenes. The presence of several fluorine atoms in the aromatic ring facilitates displacement of halogen atoms by heteroatomic and carbon-centred (including paramagnetic) nucleophiles. Intramolecular reactions of the resulting compounds open up the way to the synthesis of heterocyclic products.

A unique reaction of polyfluoroaromatic derivatives is the reductive hydrodehalogenation of polyfluorinated acetanilides **2.1** (to give products **2.2**)[29–33] and chlorine-containing anilines **2.3** (to give compounds **2.4**)[34] on treatment with zinc in aqueous ammonia (Scheme 1; in this review, the first digit in the compound numbers indicates the number of the chapter; the letter F in the ring implies a fluorine atom in a random position). Like in a chess game, in which different lines of play become already possible after the standard opening, this reaction can be considered as the opening phase for numerous chemical transformations.

Scheme 1



X = F, CF_3, H



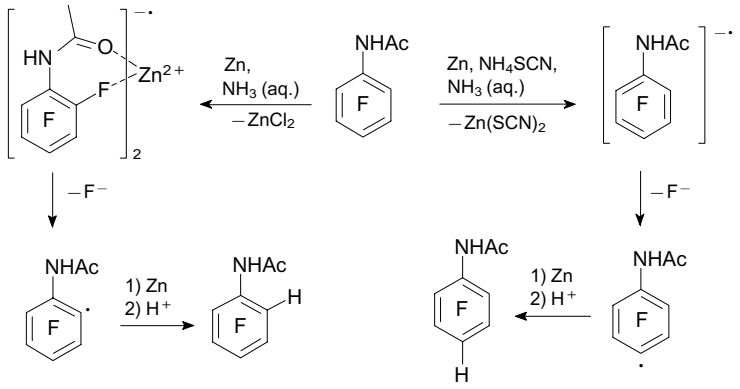
m = 1, 2; *n* = 0, 1; *k* = 1, 2

The extent of transformation and the ratio of *ortho*- to *para*-dehalogenation products are determined by both the nature of the reducing agent (either Zn or a Zn–Cu pair)[32] and the inorganic salts added; salt addition demonstrates the considerable effect of ion association on the system of equilibria involving Zn^{2+} ions, the acetanilide radical anion ($Ar^{-\bullet}$), F^- ion, ammonia and water. The addition of $ZnCl_2$ leads to increasing concentration of the Zn^{2+} complex with $Ar^{-\bullet}$, the geometry of which is favourable for F^- elimination from the *ortho*-position (Scheme 2). Conversely, the addition of anions that efficiently compete with $Ar^{-\bullet}$ for the Zn^{2+} coordination sphere, for example, SCN^- ion, mitigates the influence of Zn^{2+} on defluorination, and the structure of $Ar^{-\bullet}$ that should promote F^- elimination from the *para*-position becomes the crucial factor.[30,31]

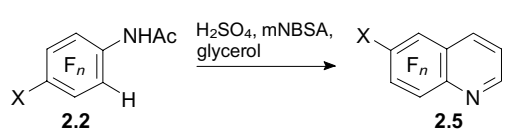
Like in chess, the position of key pieces — in this particular case, the presence of a hydrogen atom in the *ortho*-position to the functional group of the polyfluorinated substrate — opens up the way to effective lines of play. Examples are provided by the involvement of some polyfluorinated acetanilides **2.2** into the Skraup reaction to give the corresponding quinolines **2.5** and acid-catalyzed cyclization of cinnamic acid anilides **2.6** to quinolin-2-ones **2.7**, which are readily converted to 2-chloroquinolines **2.8** (Scheme 3).[30–33,35–39]

Going ahead with the chess analogy, *ortho*-iodination of fluorinated anilines **2.9** followed by iodine atom-for-acetylene group sacrifice can be considered as a gambit. The iodination occurs in systems with various hardness based on crystalline iodine: $I_2-NaHCO_3-H_2O$, $I_2-Ag_2SO_4-$EtOH, I_2-HIO_3-aqueous dioxane (Scheme 4; Solv is solvent).[40] The subsequent cross-coupling of polyfluorinated *o*-iodoanilines **2.10** with terminal alkynes gives rise to *o*-(2-R-alkynyl)anilines **2.11** in high yields. Anilines with

Scheme 2

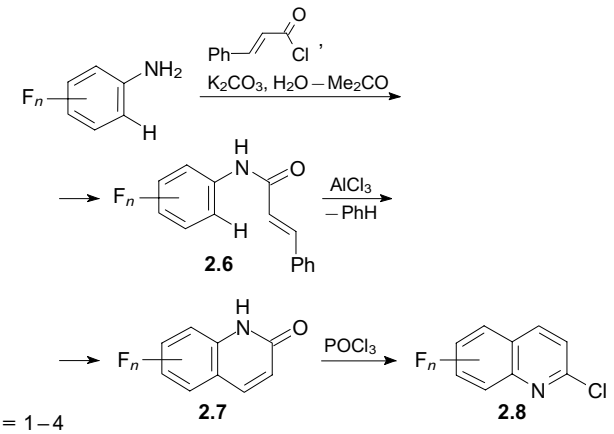


Scheme 3



2.2 **2.5**

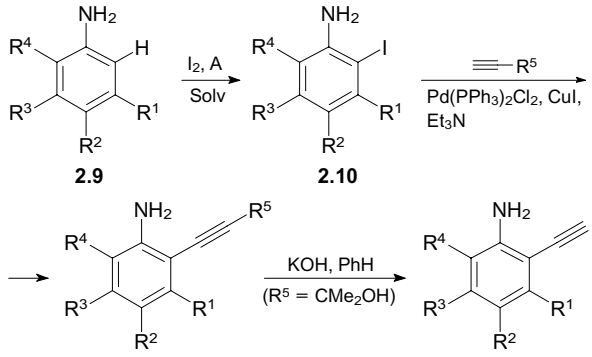
n = 2, 3; X = F, H, CF_3; mNBSA is *m*-nitrobenzenesulfonic acid



2.6 **2.7** **2.8**

n = 1 – 4

Scheme 4



2.9 **2.10** **2.11** **2.12** (~80%)

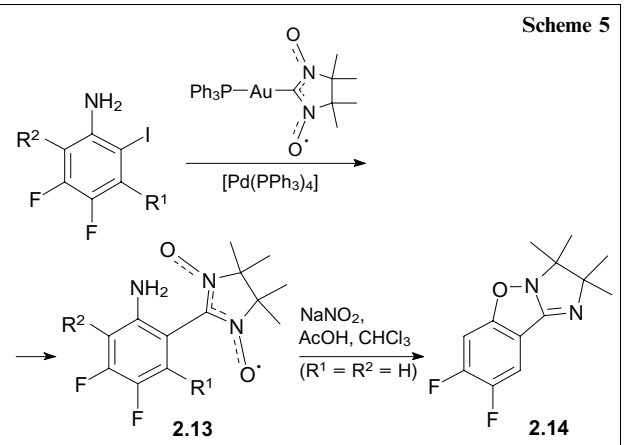
R^5 = CMe_2OH, Bu^n, Ph, CH_2OTHP, H; THP is tetrahydropyran-2-yl

R^1	R^2	R^3	R^4	A	Solvent	Yield (%)
F	CF_3	F	F	Ag_2SO_4	EtOH	93
F	CF_3	F	F	HIO_3	Dioxane (aq.)	97
F	F	F	F	HIO_3	Dioxane (aq.)	88
F	F	H	F	HIO_3	Dioxane (aq.)	97
H	F	H	F	HIO_3	Dioxane (aq.)	95
H	F	F	H	$NaHCO_3$	H_2O	97

the unsubstituted acetylene group (**2.12**) are formed *via* the retro-Favorskii reaction on refluxing the products with R^5 = CMe_2OH in benzene in the presence of KOH (see Scheme 4).[40, 41]

The scope of application of cross-coupling using iodoanilines was extended by involvement of 4,5-difluoro-2-iodoaniline and 4,5,6-trifluoro-2-iodoaniline in the reaction with the complex [$AuPPh_3NN$] (NN is 4,4,5,5-tetramethyl-2-imidazolin-2-ide-1-oxyl 3-oxide),[42] which allowed the synthesis of new nitroxides **2.13** (Scheme 5).[43] The performance of this approach is limited by the number of fluorine atoms and the presence of electron-withdrawing substituents in iodoaniline. The presence of four fluorine atoms or three fluorine atoms and a CF_3 group hampers the reaction of iodoaniline with [$AuPPh_3NN$]: 3,4,5,6-tetrafluoro-2-iodoaniline repeatedly gives low yields of cross-coupling products (~4%), whereas 3,5,6-trifluoro-2-iodo-4-trifluoromethylaniline does not react. When nitronyl nitroxide **2.13** with the aminodifluorophenyl substituent reacts with $NaNO_2$, 7,8-difluoro-2,2,3,3-tetramethyl-2,3-dihydrobenzo[*d*]imidazo[1,2-*b*]isoxazole **2.14** is formed.

Scheme 5

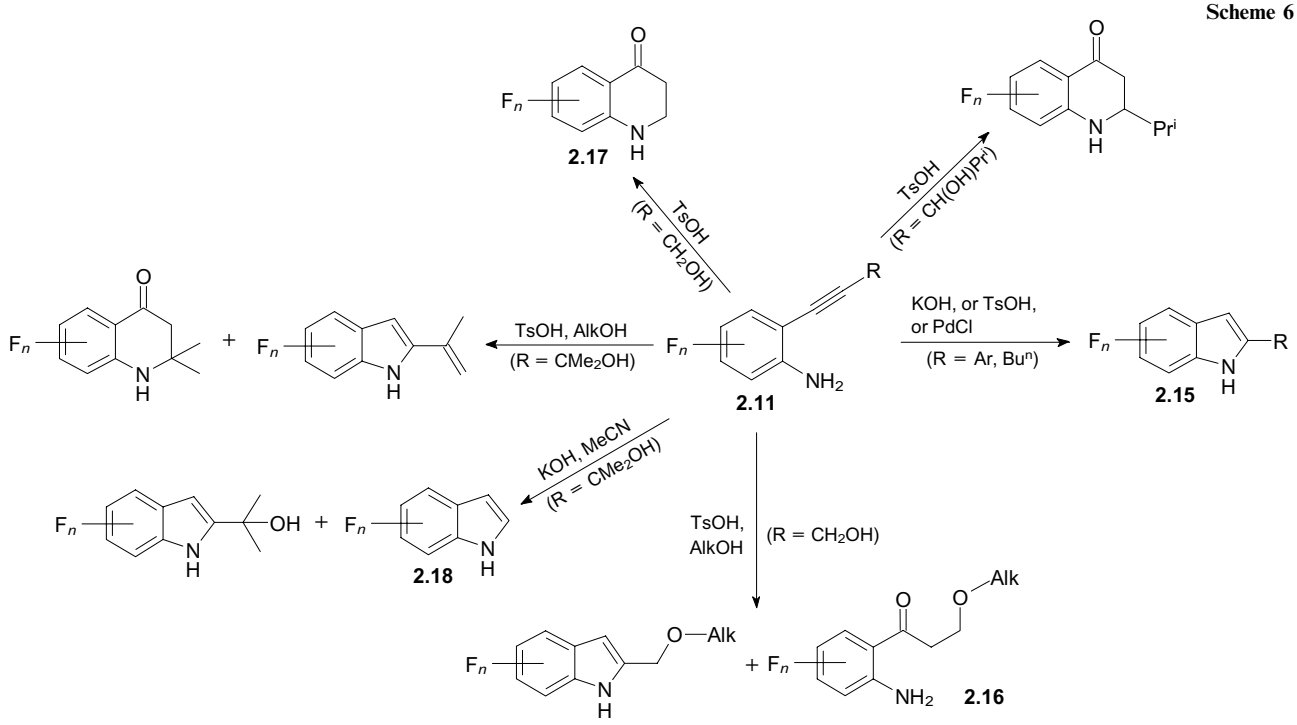


2.13 **2.14**

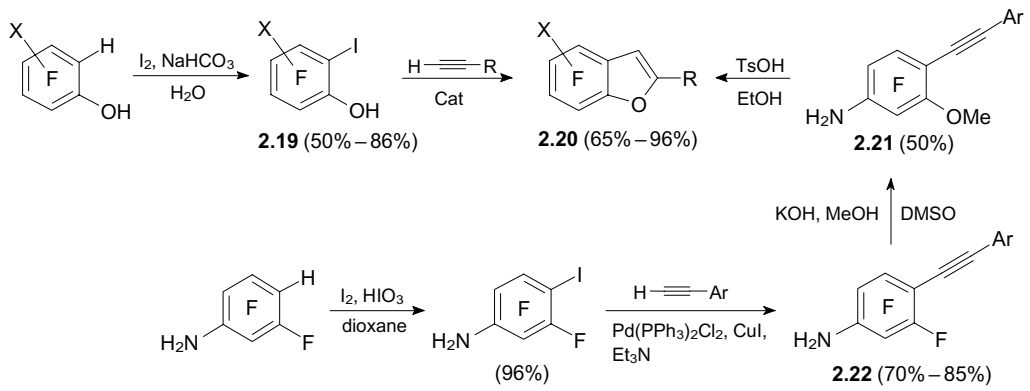
R^1 = R^2 = H, F; R^1 = H, R^2 = F

A broad range of heterocyclization products was obtained *via* transformations of fluorinated *o*-alkynylanilines **2.11** catalyzed by *p*-toluenesulfonic acid (TsOH). The reaction gives substituted indoles (**2.15**), 2-aminoaryl ketones (**2.16**) or 2,3-dihydroquinolinones (**2.17**) depending on the nature of the substituent at the triple bond and the solvent. It was shown that substrates with R = Ph, Bu^n

Scheme 6



Scheme 7



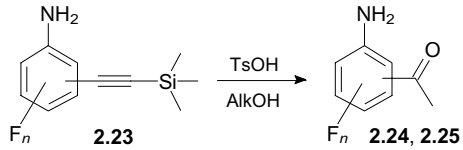
X = H, F, NH_2; R = Ar, Alk

cyclize in acetonitrile in the presence of $PdCl_2$ to give the corresponding indoles in high yields. Using KOH in acetonitrile, the one-pot transformation of tertiary carbinol to 2- and 3-unsubstituted indole **2.18** was carried out (Scheme 6).[44 – 47]

The involvement of fluorinated *o*-iodophenols **2.19** into cross-coupling with terminal acetylenes carried out as a one-pot procedure afforded benzofurans **2.20**. An alternative approach to the synthesis of these fluorinated O-heterocycles is heterocyclization of *o*-methoxyalkynylarenes **2.21** in the presence of TsOH (Scheme 7). The required methoxylated precursors are prepared by methoxide anion substitution for fluorine in fluorinated alkynylanilines **2.22** in a superbasic medium.

A study of the transformations of *o*-alkynylanilines **2.23** in the presence of TsOH identified a synthetically useful general one-pot process for transformation of the $Me_3Si-C\equiv C$ moiety into the acetyl group, which was used to prepare a broad range of fluorinated 2- (**2.24**) and

Scheme 8

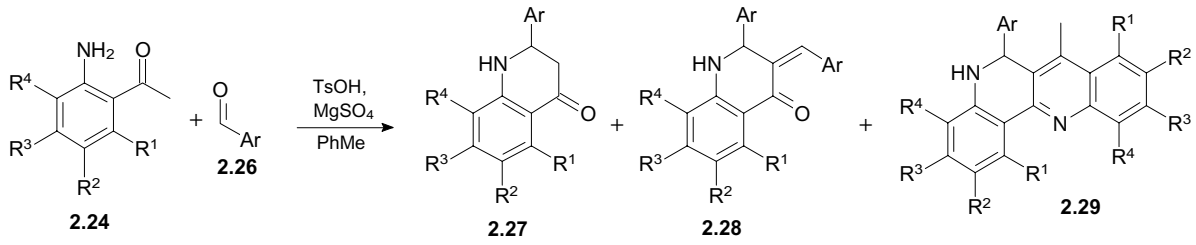


4-amino-substituted acetophenones (**2.25**) in high yields (Scheme 8).[48]

The 2-aminoacetophenones **2.24** prepared in this way were involved in the acid-catalyzed reaction with 3,4,5-trifluorobenzaldehyde (**2.26**), which gave polyfluorinated 2-phenyl-2,3-dihydroquinolin-4(1*H*)-ones **2.27** – **2.29** (Scheme 9).[49]

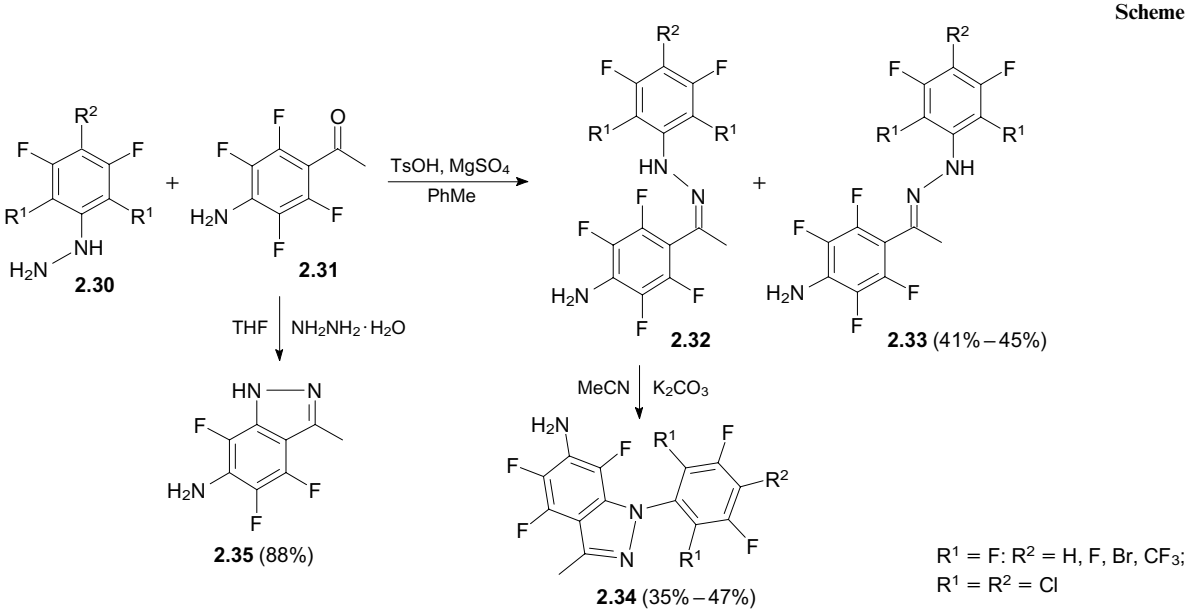
The efficient utilization of the $TsOH-MgSO_4$ system to prepare hydrazones from fluorinated phenylhydrazines **2.30** and 4-aminotetrafluoroacetophenone (**2.31**) and the subsequent cyclization of one of isomeric phenylhydrazones **2.32** in the presence of K_2CO_3 gives benzindazole **2.34**, easily

Scheme 9



$R^2 = R^3 = F$: $R^1 = R^4 = H, F$; $R^1 = H$, $R^4 = F$; $R^1 = R^3 = H$, $R^2 = R^4 = F$; $R^1 = R^2 = R^4 = F$, $R^3 = H$; $R^1 = R^3 = R^4 = F$, $R^2 = CF_3$;
Ar is 3,4,5-trifluorophenyl

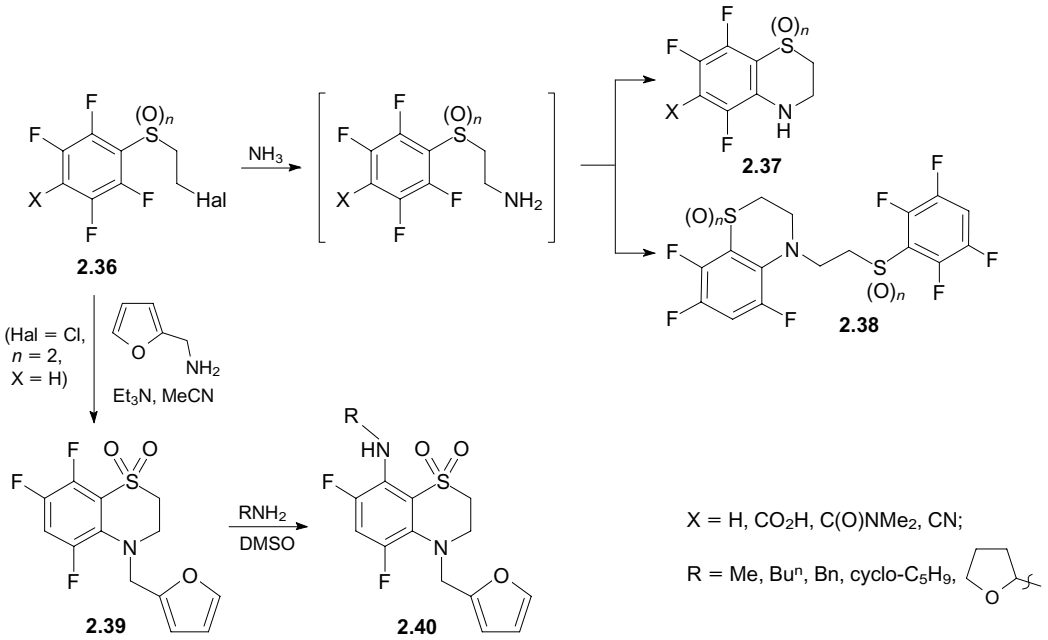
Scheme 10



$R^1 = F$: $R^2 = H, F, Br, CF_3$;
$R^1 = R^2 = Cl$

separable from hydrazone **2.33**, which does not undergo cyclization. The reaction of 4-aminotetrafluoroacetophenone (**2.31**) with hydrazine gives 6-amino-4,5,7-trifluoro-3-methylindazole (**2.35**) in high yield (Scheme 10).[50]

Scheme 11

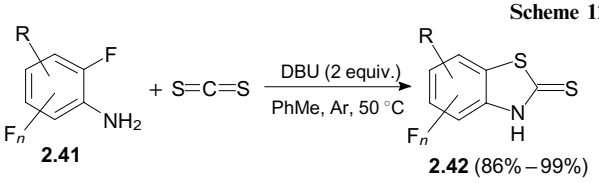


X = H, CO_2H, $C(O)NMe_2$, CN;

R = Me, Bu^n, Bn, cyclo-C_5H_9,

The above examples of benzindazole formation illustrate the key feature of the reactivity of functionalized polyfluoroarenes, in particular, the fact that a heteroatomic nucleophilic centre present in the substituent promotes the subsequent heterocyclization *via* nucleophilic substitution reaction involving the *ortho*-fluorine atom. This approach was successfully used to convert substrates **2.36** to a broad range of fluorinated polyfunctionalized benzothiazines **2.37** – **2.39** (Scheme 11). Actually, a domino reaction takes place, being triggered by nucleophilic substitution in which the halogen atom at the end of the alkyl chain is replaced by an amino group. In the next step, this group functions as a nucleophile substituting the fluorine atom in the arene. Fluorinated benzothiazines **2.39** thus formed are still reactive towards aromatic nucleophilic substitution, and react with amines yielding a number of polyfunctional derivatives **2.40**; examples of these products are shown in Scheme 11.[51, 52] Some representatives of the obtained benzothiazines have low toxicity and show mild hypertensive action (increase patients' blood pressure by 29% – 34% when used in a 5 mg kg^{-1} dose) and high antiarrhythmic activity in calcium chloride- and adrenaline-induced arrhythmia.[53, 54]

Scheme 12



2.41 **2.42** (86% – 99%)

R = H, F, I, CF_3, C≡CPh, C≡CBu^n; *n* = 2, 3;
DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene

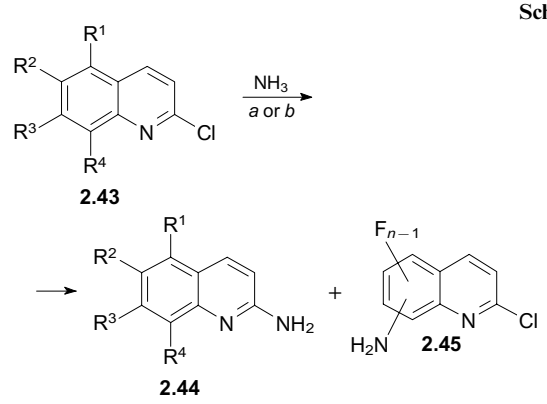
This approach is effective for the conversion of compounds **2.41** to fluorinated 2-benzothiazolethiones **2.42**. Heterocyclization proceeds under mild conditions and requires readily accessible reagents (Scheme 12).[55]

The development of theoretical views is very important for the targeted application of nucleophilic reactions of fluoroarenes. Reliable experimental data on the factors controlling the reactivity of fluoroaromatic substrates towards a broad range of nucleophilic reagents are needed. These factors have been investigated in a study of the direction of nucleophilic attack in the reactions of polyfluorinated quinolines with heteroatomic and carbon-centred nucleophiles such as ammonia, amines, Me_3MEMe_2 (M = Si, Sn; E = P, As), NaOMe, LiR (R = Me, Bu^n, Ph) and PhMgBr.[35] It was shows that soft heteroatom-centred nucleophiles displace the fluorine atom, while hard organometallic reagents add, for example, to the α-position of the pyridine moiety. The reactions involving nitrogen-centred nucleophiles that are most important for practical application are presented below.

In the reactions of 5,7-difluoro-, 5,7,8-trifluoro-, 5,6,8-trifluoro-, 5,7-difluoro-8-chloro-, 5,6,7,8-tetrafluoro- and 5,7,8-trifluoro-6-(trifluoromethyl)quinolines with aqueous or liquid ammonia, hydrazine hydrate or piperidine, the site of nucleophilic attack is determined by the number of fluorine atoms in the substrate. In the molecules containing three or four fluorine atoms, the overall effect of the halogen atoms prevails over the effect of heterocycle nitrogen and directs the substitution into the fluorinated moiety. The regioselectivity of reactions of 5,6,8-trifluoro- and 5,7,8-trifluoro-6-(trifluoromethyl)quinolines with piperidine was found to be temperature-dependent as a result of switching from the enthalpy to entropy control of the ratio of the reaction rates along competing pathways.[56]

In the reaction of 2-chloroquinolines **2.43** with liquid and aqueous ammonia, 2-chloro-5,7-difluoro-, -5,6,8-trifluoro- and -5,7,8-trifluoroquinolines were found to mainly form products devoid of chlorine atoms (**2.44**), while 2,6-dichloro-5,7-difluoroquinoline and 2-chloro-5,6,7,8-tetrafluoro- and -6,7-difluoroquinolines are converted to products (**2.45**) of fluorine atom displacement from various positions of the benzene ring (Scheme 13).[37]

Scheme 13



(*a*) NH_3 (liq.), 70 – 150 °C; (*b*) NH_3 (aq.), 100 – 150 °C; *n* = 2 – 4

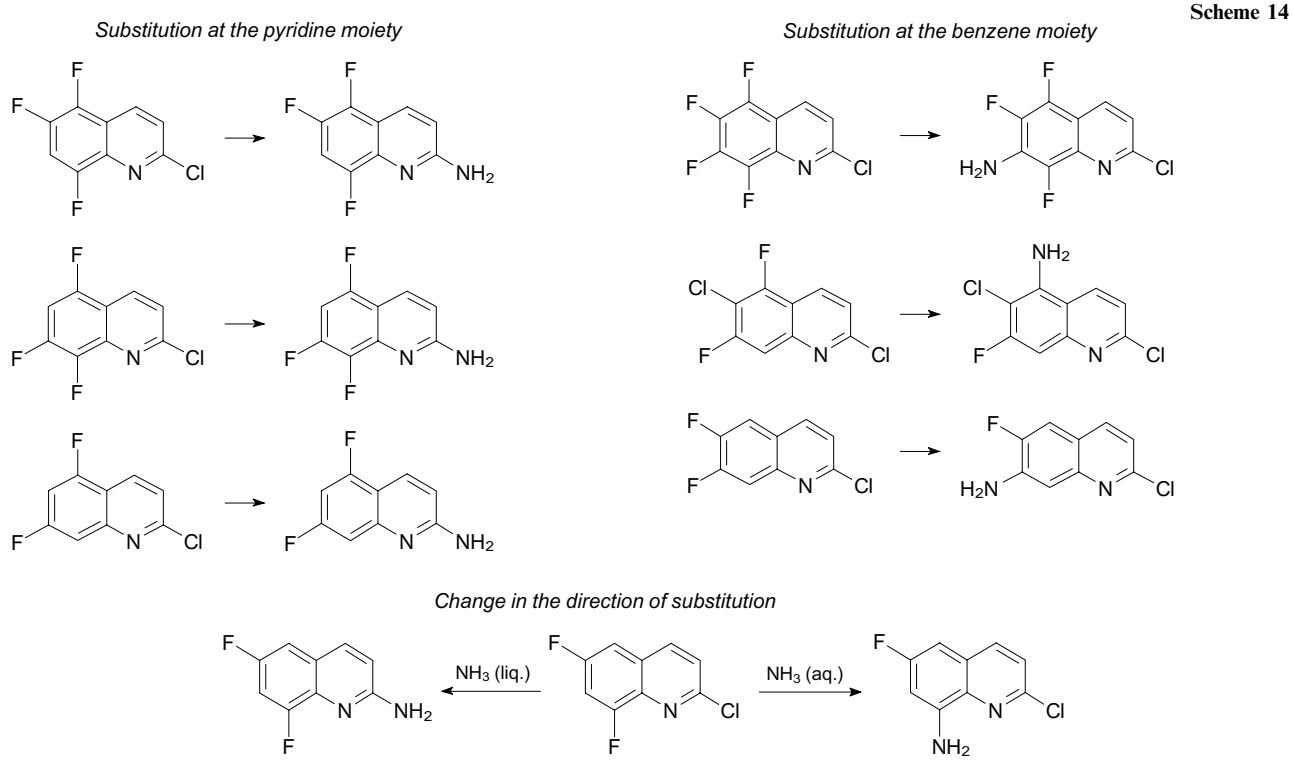
R^1	R^2	R^3	R^4	R^1	R^2	R^3	R^4
F	H	F	F	F	Cl	F	H
F	F	H	F	F	F	F	F
F	H	F	H	H	F	H	F
				H	F	F	H

On going from liquid to aqueous ammonia, the fraction of aminodechlorination products relative to the aminodefluorination products increases for all substrates. In the reaction of 2-chloro-6,8-difluoroquinoline (Scheme 14), the direction of dehalogenation changes with varying conditions of the use of ammonia as the nucleophile.[37]

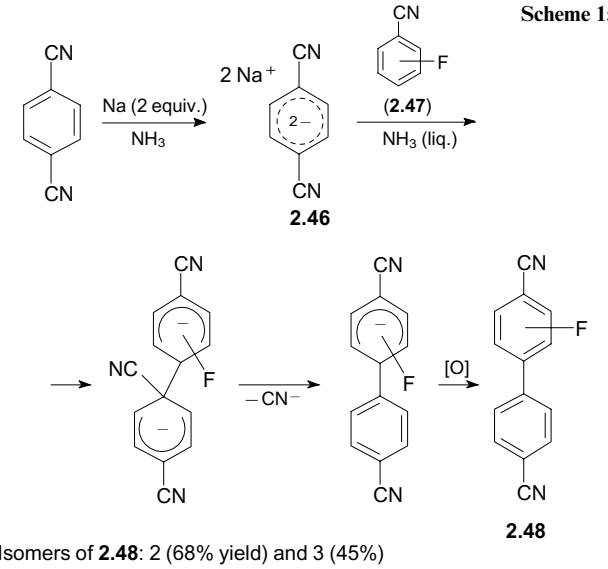
Quantum chemical calculations for the pathways of halogen atom displacement by an amino group in the substitution reaction between polyfluorinated 2-chloroquinolines and ammonia were carried out by B3LYP and CAM-B3LYP methods with the 6-31 + G(d) basis set. According to the results, this is a one-step reaction, with transition states being structurally similar to σ-complexes; the relative energies of the transition states are in line with the experimentally observed regioselectivity of the reactions.

The ease of generation of the terephthalonitrile dianion **2.46** (reduction with an alkali metal in liquid ammonia) and its high nucleophilic and electron-donating reactivity open up the way to numerous useful synthetic transformations. One type of such transformations is the reaction of this dianion with monofluorinated benzonitriles **2.47**. In all cases, the dianion performs cyanophenylation of the neutral substrate into the *para*-position to give either fluoro-substituted 4,4′-dicyanobiphenyls **2.48** (Scheme 15) or 4,4′-

Scheme 14

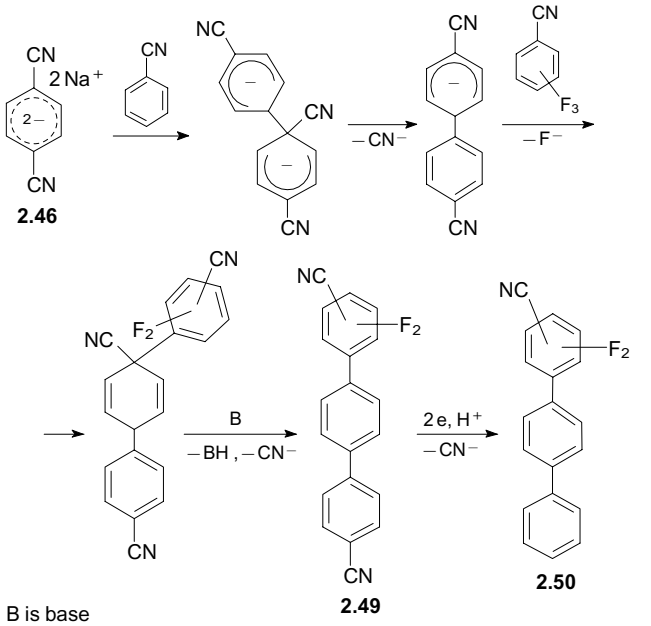


Scheme 15



Isomers of **2.48**: 2 (68% yield) and 3 (45%)

Scheme 16



B is base

dicyanobiphenyl *via* displacement of the F atom (40% yield).[57, 58] For description of the reaction pathway and interpretation of the observed trends, quantum chemical calculations [Möller – Plesset — MP2/6-31 + G(d)] were carried out for the structure and energies of the anionic intermediates in the gas phase and in a polar solvent (ammonia). The results of calculations are in qualitative agreement with experimental yields of cross-coupling products for 2-fluoro- and 3-fluorobenzonitriles.

Further studies demonstrated that the anionic intermediate formed upon cross-coupling of terephthalonitrile dianion **2.46** generated at low temperature (in liquid ammonia) with benzonitrile can be arylated by polyfluorinated substrates to give fluorinated *p*-terphenylcarbonitriles **2.49** and **2.50** (Scheme 16).[59]

Scheme 17

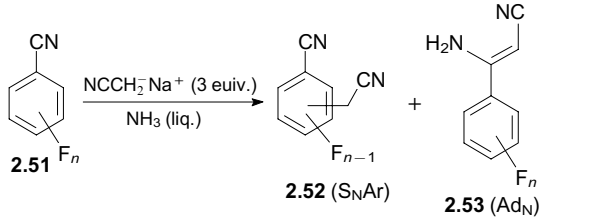
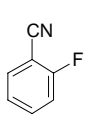
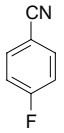
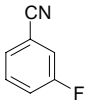
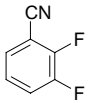
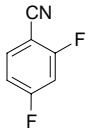
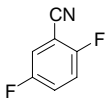
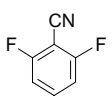
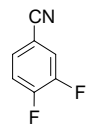
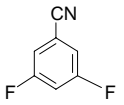
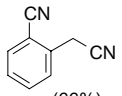
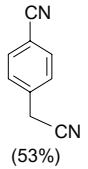
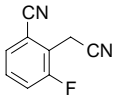
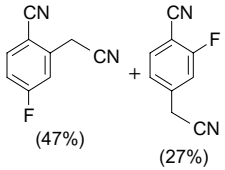
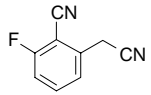
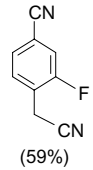
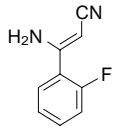
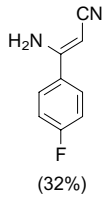
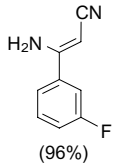
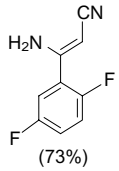
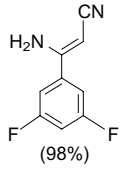
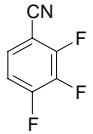
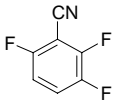
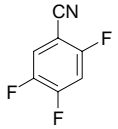
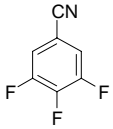
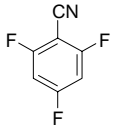
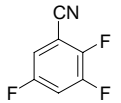
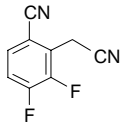
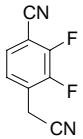
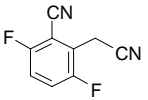
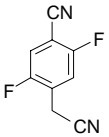
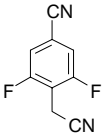
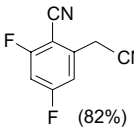
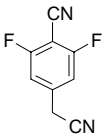
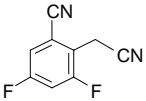
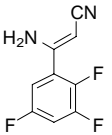
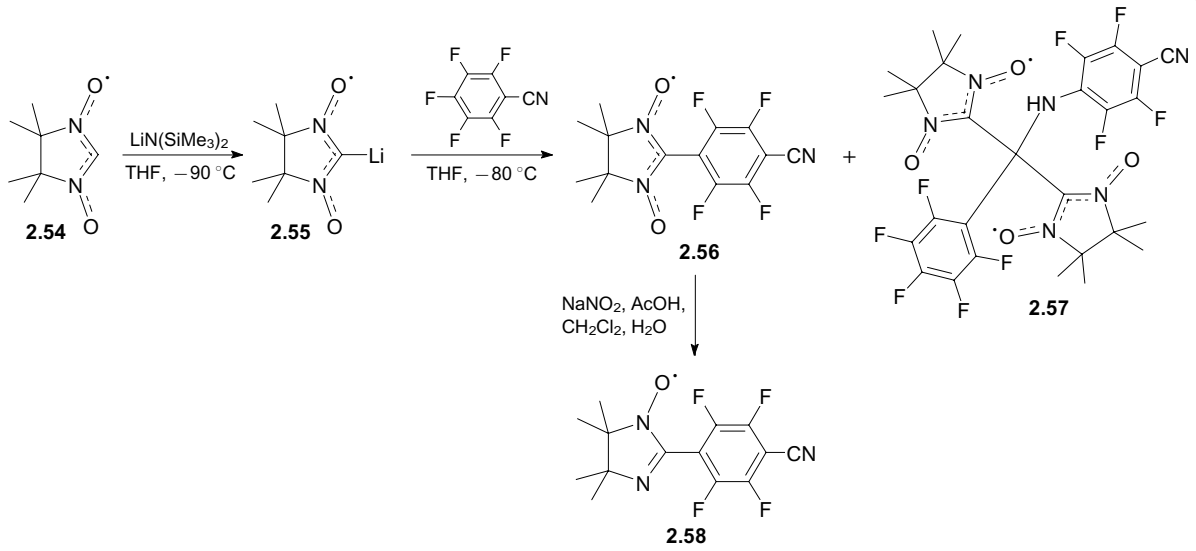


Table 1. Products of reaction of fluorobenzonitriles with the cyanomethyl anion (see Scheme 17).[60]

Substrate (**2.51**)										
S_NAr (**2.52**)	 (66%)	 (53%)	–	 (49%)	 (47%) (27%)		–	 (36%)	 (59%)	–
Ad_N (**2.53**)	 (34%)	 (32%)	 (96%)	–	–		 (73%)	–	–	 (98%)
Sub-strate (**2.51**)										
S_NAr (**2.52**)	 (62%) +  (38%)		 (95%)	 (96%)	 (96%)		 (82%) +  (18%)		 (61%)	
Ad_N (**2.53**)	–		–	–	–		–		 (19%)	

Scheme 18



These results are synthetically significant, as they expand the scope of bis-aryl cross-coupling owing to the use of the terephthalonitrile dianion for *para*-cyanophenylation of fluorinated arenes to afford new cyano-substituted biphenyls and terphenyls — potential practically valuable materials (monomers, liquid crystals, OLED components) and biologically active compounds. Owing to the fluorine atom and cyano group present in the product molecules, further targeted modification is possible.

In order to elucidate the factors controlling the direction of nucleophilic attack for the reaction of carbon-centred nucleophiles with fluorinated benzonitriles, reactions between series of mono-, di- and trifluorobenzonitriles **2.51** and the cyanomethyl anion in liquid ammonia were investigated. The formation of two structural types of products was ascertained, namely, cyanomethylbenzonitriles **2.52** (S_NAr mechanism) and β-aminocinnamonitriles **2.53** (Ad_N mechanism). The product ratio increases in favour of the former type of products with increasing number of fluorine atoms activated towards the substitution and with increasing amount of the cyanomethyl anion (Scheme 17, Table 1).[60]

The possibility of preparing nitronyl nitroxides with a fluorinated aromatic moiety was examined by converting 4,4,5,5-tetramethylimidazolin-1-oxyl 3-oxide (**2.54**) to lithium derivative **2.55**, which was then allowed to react with 3,4-difluoro-, 2,4,6-trifluoro- and pentafluorobenzonitriles. Only the reaction involving pentafluorobenzonitrile proved to be synthetically significant, resulting in the target 2-(4-cyanotetrafluorophenyl) derivative **2.56** in a moderate yield (26% – 34%). Apart from the major product, dimer **2.57**, the biradical product of addition to the substrate cyano group, was isolated from the reaction mixtures in a minor amount and characterized by X-ray diffraction (Scheme 18).[61] The reduction of nitroxide **2.56** in the $NaNO_2$ – AcOH system gave imino nitroxide **2.58**.

The experimental results were interpreted resorting to quantum chemical calculations [CAM-B3LYP/6-31 + G(d) method taking account of the solvent] of the potential energy surfaces along the reaction coordinates for competing nucleophilic substitution reactions involving *para*- and *ortho*-fluorine atoms in the aromatic ring and addition of radical **2.55** to the carbon atom of the pentafluorobenzonitrile cyano group (Fig. 1). Each of the reaction pathways was found to include one step. The lowest energy barrier (ΔE^a) is inherent in the addition of radical **2.55** to the cyano group to give imino anion **A**. However, this imino anion has the highest energy among the possible products and, unlike displacement of the fluorine atom (see Fig. 1, products **B** and **C**), this reaction pathway is reversible, which accounts for the predominance of the nucleophilic substitution product. In turn, the *para*-substitution is more favourable as regards both the activation energy and the reaction heat; this is in line with the formation of the *para*-substituted product. Of special note is the fact that, according to calculations, the fluorine atom is displaced *via* a concerted process without the formation of an anionic intermediate.

The presented results served as a fruitful impetus to the development of a new synthetic approach to polyfunctional nitronyl nitroxides. It is based on the use of radical **2.55** as a nucleophilic synthon, which efficiently substitutes the fluorine atom in arenes activated towards the nucleophilic substitution (Scheme 19).[62]

Phosphinodefluorination of fluoroarenes **2.59** with secondary phosphines (HPR_2) is widely used to prepare fluoroarylphosphines **2.60** and **2.61**. The phosphines HPR_2 as such react only with reactive substrates such as trifluorobenzonitrile, tetrafluorophthalonitrile and pentafluoropyridine.[63, 64] Less reactive fluorinated arenes require silylated phosphines or their anionic forms and, in some cases, specific reaction conditions.[65, 66] For example, relatively unreactive substrates — di- and trifluorobenzenes — react with silyl phosphine Me_2PSiMe_3 without a solvent or in benzene at rather high temperature (> 180 °C) in sealed tubes.[67 – 69] Rather drastic conditions (~150 °C) are also required for reactions of (trimethylsilyl)diphenylphosphine or methyl(trimethylsilyl)phenylphosphine with more fluorinated substrates. In these cases, it is better to use alkali metal phosphides and carry out phosphinodefluorination at room temperature (Scheme 20).[70]

Perfluorobenzoquinones and -naphthoquinones are formed upon the oxidation of the corresponding perfluoroarenes. Being highly polyelectrophilic, these compounds easily react with nucleophilic reagents *via* vinylic substitu-

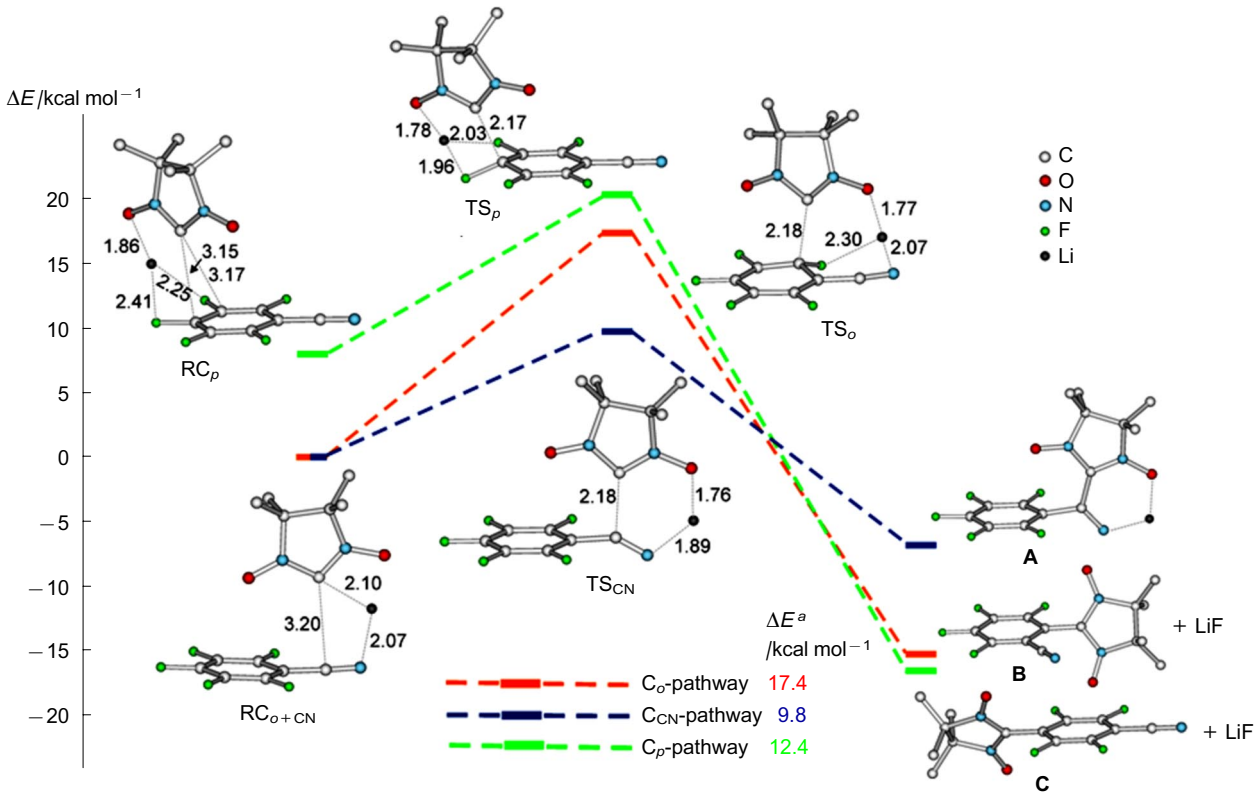
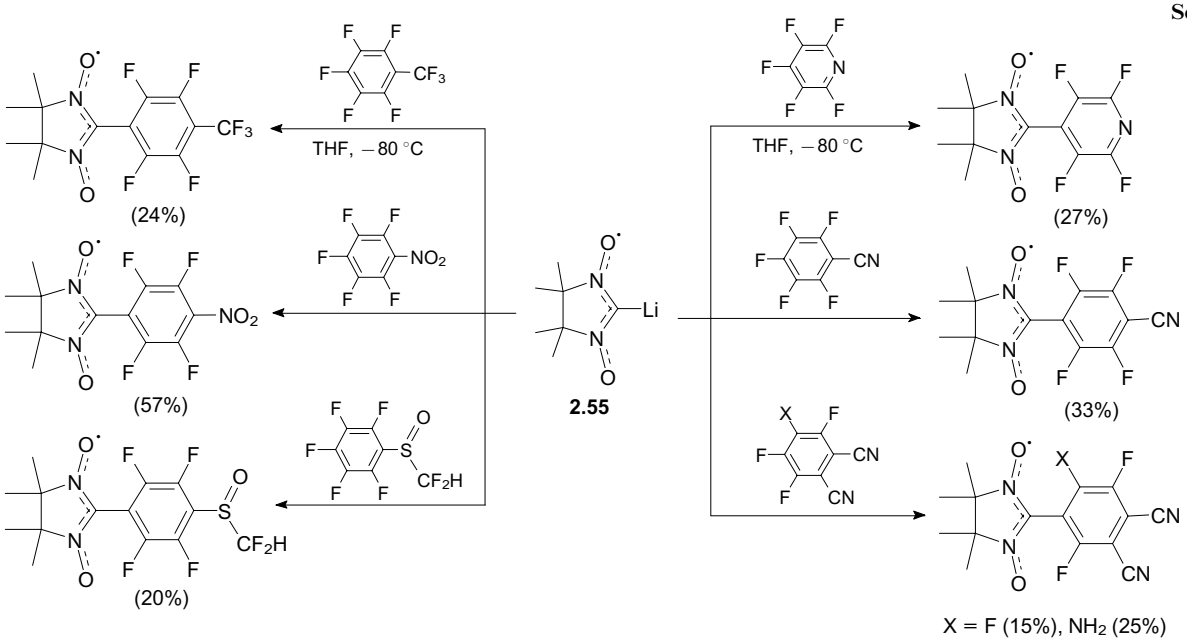


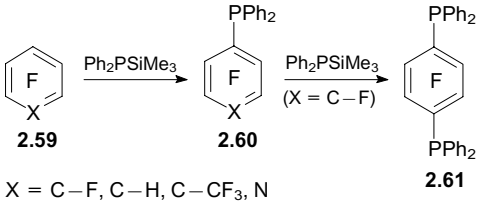
Figure 1. Possible pathways of reaction of NCC_6F_5 with lithium nitronyl nitroxide **2.55**.[61]
The H atoms are omitted; reaction complexes (RC) are depicted on the left, transition states (TS) are in the middle, and reaction products are on the right (**A**, **B**, **C**); the numbers near the structures are bond lengths (*AA*).

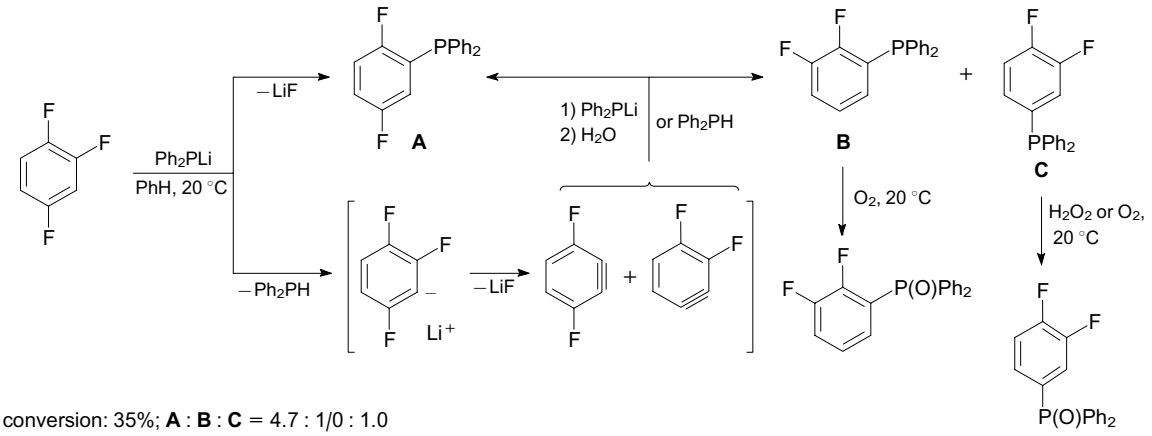
tion, which is commonly believed to occur by the Ad_N-E mechanism. It comprises *ipso*-addition of the reagent generating the σ-complex, which loses a halide anion to give the substitution product.[71] This mechanism typical of activated (in this case, by the π-electron-withdrawing effect of carbonyl groups) vinyl halides[72] resembles the S_NAr mechanism in its structural and electronic effects. Furthermore, quinones are well-known oxidants; this affects the course of their reactions with nucleophiles. The reaction of polyfluoro-1,4-naphthoquinones **2.62** with triarylphosphines proceeds as competition between phosphinodefluorination (giving products **2.63**–**2.65**) and reduction of the starting quinone. Variation of the solvent, in particular, replacement

Scheme 19



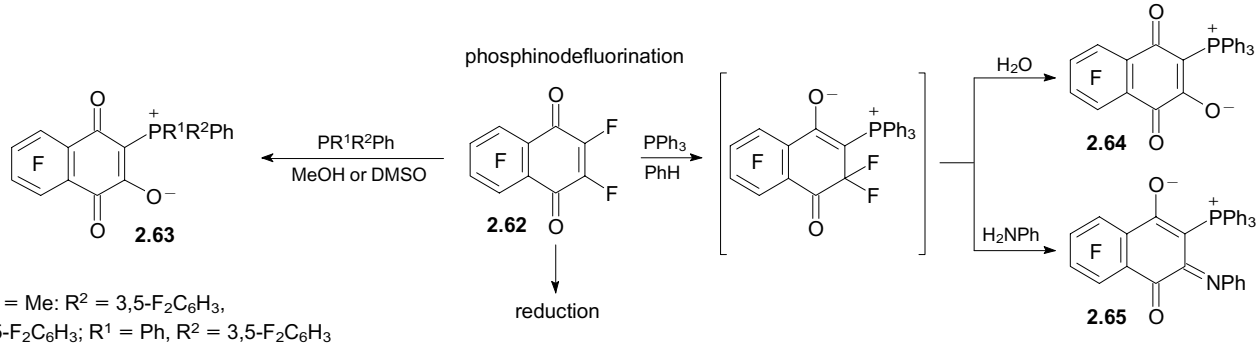
Scheme 20





Degree of conversion: 35%; **A** : **B** : **C** = 4.7 : 1/0 : 1.0

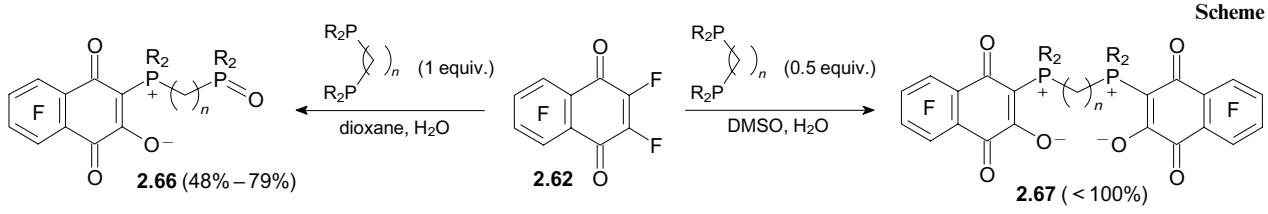
Scheme 21



of benzene by MeOH and then by DMSO, boosts the phosphinodefluorination pathway (Scheme 21).[73–75]

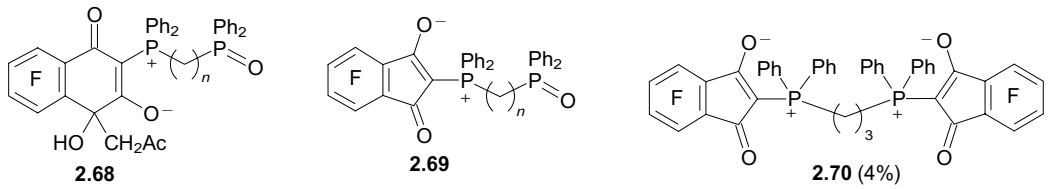
Thorough selection of the solvent, namely, the use of dioxane – H_2O (10 : 1) and DMSO – H_2O (20 : 1) mixtures allowed the researchers to synthesize several mono- (**2.66**) and bis-phosphonium betaines (**2.67**) in high preparative yields (Scheme 22). It was found that during silica gel chromatography acetone, which is used as the eluent, adds

Scheme 22



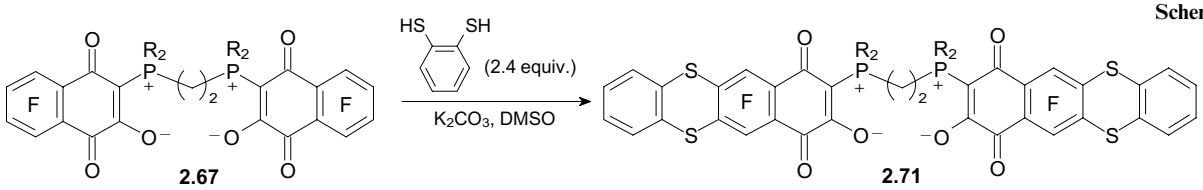
R = Ph, *n* = 1–5; R = Et, *n* = 2

Products of transformation on silica gel (R = Ph)



n = 1 (25%), 2 (15%)

Scheme 23



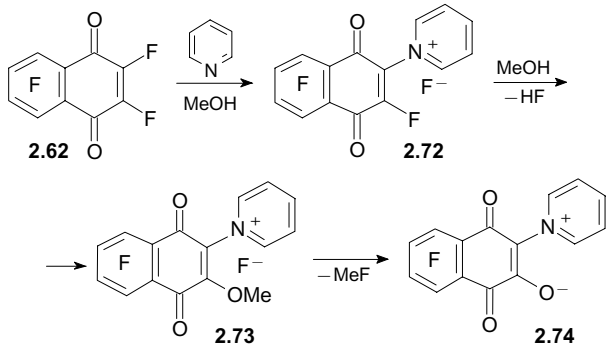
R = Ph, Et

to the carbonyl group of the betaine products yielding stable adducts **2.68**, while naphthoquinone phosphonium betaines with R = Ph undergo ring contraction to afford indenone type betaines **2.69** and **2.70**.[76]

The resulting fluorinated betaines **2.67** retain high reactivity towards nucleophilic substitution reactions involving fluorine atoms and react with benzene-1,2-dithiol with heterocyclization to give polyfunctional thianthrenedione type betaines **2.71** (Scheme 23).

The reactions of polyfluoroquinones with nitrogen- and oxygen-centred nucleophiles resemble the reactions with phosphorus-centred reagents and involve displacement of fluorine atoms. No reduction of quinones by N- or O-nucleophiles takes place. Thus, in the case of pentafluoro-2-methyl-, 2,5,6,7,8-pentafluoro- and hexafluoro-1,4-naphthoquinones, the fluorine atoms of the quinone ring are displaced on treatment with amines; this is followed by aminodefluorination of the benzene rings of the products with displacement of one or two fluorine atoms in different positions depending on the solvent nature.[77] In the reaction of hexafluoro-1,4-naphthoquinone **2.62** with pyridine in methanol, the initial pyridinodefluorination involving position 2 and giving salt **2.72** is accompanied by displacement of fluorine atoms from position 3 by a methoxy group (**2.73**), followed by introduction of an ionized oxy group to give pyridinium betaine **2.74** (Scheme 24).[78]

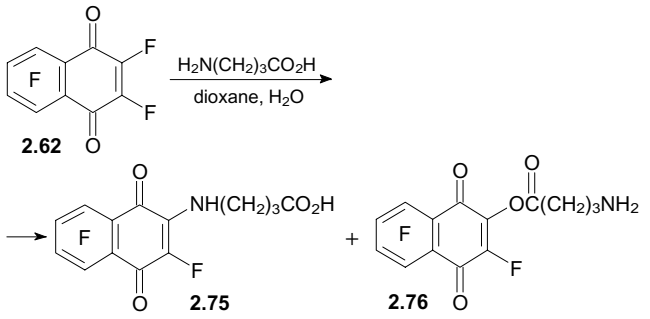
Scheme 24



The use of bifunctional nucleophiles leads to polyfluorinated 1,4-naphthoquinones containing ω-functionalized substituents in position 2 and quinones fused with the heterocycle at the benzene moiety. Aliphatic amino acids give products of aminodefluorination of the quinone ring. Hexafluoro-1,4-naphthoquinone reacts with 4-aminobutyric acid to form products of fluorine displacement by either the nitrogen (**2.75**) or oxygen centre of the dinucleophile (**2.76**) (Scheme 25).[79]

According to primary *in vitro* assays, among the numerous functionalized polyfluoronapthtalene-1,4-diones, compounds with high inhibitory activity against cancer cells and

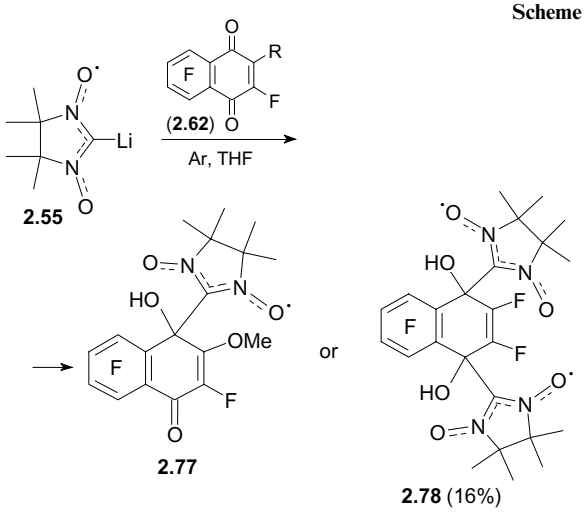
Scheme 25



with antioxidant and antimutagenic properties were identified.[80–82]

As opposed to heteoatomic nucleophiles, carbon-centred reagent **2.55** (like acetone, see Scheme 22) adds to the carbonyl group of the polyfluorinated naphthoquinone. 2,5,6,7,8-Pentafluoro-3-methoxy-1,4-naphthoquinone **2.62** (R = OMe) reacts with radical **2.55** to give the product of addition to the carbonyl group neighbouring to the methoxy group. A temperature rise considerably increases the yield of radical product **2.77** (the maximum yield of 84% was attained at 0 °C). The reaction of the same lithium derivative **2.55** (2 equiv.) with hexafluoro-1,4-naphthoquinone **2.62** (R = F) gives the addition product to both carbonyl groups (**2.78**) in a 16% yield (Scheme 26).[83] According to UV and EPR spectroscopy data, the obtained

Scheme 26



R = OMe, F

Conditions	Yield of **2.77** (%)
–90 °C, 2 h	31
–30 °C, 1 h	34
0 °C, 1 h	84

mono- (**2.77**) and dinitronyl nitroxides (**2.78**) tend to undergo spontaneous deoxygenation in a toluene solution, whereas in water these paramagnets are stable.

Thus, nucleophilic modification is still the mainstream in the polyfluoroarene and quinone chemistry. The central point of studies has lately been shifting towards the targeted use of the identified regularities of these reactions in the structure-directed synthesis of new compounds and materials with useful properties. Of particular value is the development of hydrodefluorination methods giving defluorinated products in the *ortho*-position relative to the functional group. Extending the range of transformations and products of this type opens up ways to prepare previously inaccessible fluorinated heterocyclic compounds.

3. Development of the chemistry of polyfluoroaromatic compounds

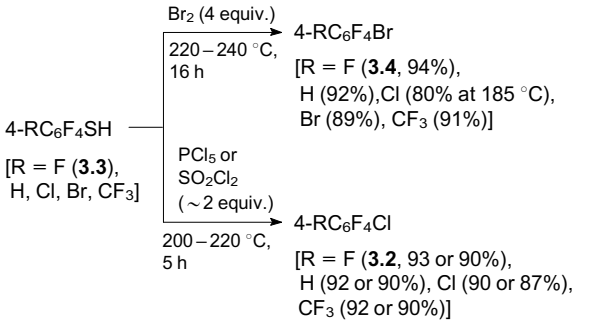
Polyfluoroaromatic compounds occupy a prominent place in the chemistry of arenes. The interest in this class of compounds is caused by not only their peculiar chemical properties, but also practical applications, which include medicine [6, 84–87] and agrochemistry.[88] These derivatives are used to produce polymers,[84, 89] liquid crystals [90] and semiconductors,[91] while fluorinated dendrimers are employed as new electron transporting materials for the manufacture of diodes.[92] Polyfluoroaromatic compounds are mainly synthesized by displacement of chlorine atoms in fully chlorinated aromatic compounds by fluorine on treatment with KF. In the 1960s, an industrial method was developed for the synthesis of key products, hexafluorobenzene (**3.1**) and chloropentafluorobenzene (**3.2**), by heating hexachlorobenzene with KF in an autoclave at ~450 °C.[93] Tetrafluorophthalic and -terephthalic acid difluorides were prepared in a similar way.[94] This method was extended to the synthesis of decafluorobiphenyl, octafluoronapthtalene, decafluoropyrene,[94] as well as perfluoroarenes containing CN groups [94] and polyfluorinated nitrogen-containing hetarenes.[95]

Thermal reactions of perfluoroarenes and their derivatives with tetrafluoroethylene and chlorodifluoromethane, serving as sources of difluorocarbene, conducted in flow reactors resulted in the synthesis of perfluoromethylarenes, perfluorobenzocycloalkenes (benzocyclobutene, indane and tetralin analogues) and polyfluorostyrenes.[96] Polyfluorinated chloroarenes formed in the reactions of perchloroarenes with KF are of interest for the synthesis of polyfluoroaromatic compounds with various functional groups.[95] However, the number of chloropolyfluoroarenes obtained in this way is limited. Therefore, chemists are developing new methods for the introduction of chlorine and bromine atoms into perfluoro- and polyfluoroarenes. One such method is high-temperature co-pyrolysis, of, for example, arene **3.1** with chlorine or bromine in a flow reactor. As a result, fluorine atoms of this compound are displaced by chlorine and bromine atoms.[97] One more method includes the displacement of hydrogen atoms of polyfluoroarenes by chlorine and bromine in a drastic medium such as SbF_5 (Ref. 98) or oleum.[94] However, these processes are unsuitable for the preparation of a broad range of chloropolyfluoro- and bromopolyfluoroarenes. In recent years, the authors of this chapter developed an alternative process for the synthesis of these compounds according to which a thiol group, which can be easily and rather selectively introduced into polyfluoroarenes *via* nucleophilic substitution reaction, is replaced by a chlorine or bromine atom.

3.1. Displacement of a thiol group in polyfluoroarenethiols by chlorine and bromine atoms

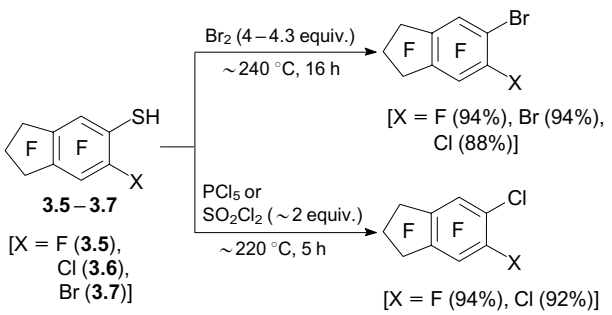
Polyfluoroarenethiols were synthesized by treatment of polyfluoroarenes with potassium hydrogen sulfide in DMF or ethanol.[99] The introduction of chlorine and bromine atoms into polyfluoroarenethiols instead of the thiol group was carried out in sealed tubes at a temperature of 200 – 240 °C under the action of PCl_5 or SO_2Cl_2 and Br_2 or PBr_5. This gave high yields of chloro- and bromopolyfluoroarenes. For example, the reactions of pentafluorobenzenethiol (**3.3**) and its *para*-substituted analogues with PCl_5 or SO_2Cl_2 at 200 – 220 °C or with Br_2 at 220 – 240 °C afford chloro and bromo derivatives in high yields (Scheme 27).[100–102] On heating of thiol **3.3** with PBr_5 (1 : 2 ratio) at ~220 °C for 8 h, the thiol group is also displaced by bromine to give bromopentafluorobenzene (**3.4**) in a good yield.[102]

Scheme 27



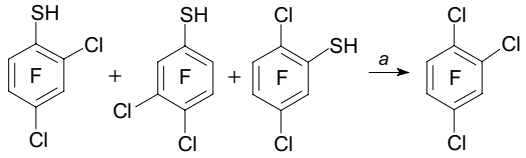
The reactions of nonafluoroindane-5-thiol (**3.5**) and 6-chlorooctafluoroindane-5-thiol (**3.6**) with PCl_5 or SO_2Cl_2 at ~220 °C afford 5-chlorononafluoro- and 5,6-dichlorooctafluoroindanes, respectively, in high yields (Scheme 28).[100, 101] Similarly, thiol **3.5** and 6-bromooctafluoroindane-5-thiol (**3.7**) were converted in high yields to 5-bromononafluoro- and 5,6-dibromooctafluoroindanes *via* reactions with Br_2; thiol **3.6** was converted to 5-bromo-6-chlorooctafluoroindane by long-term (82 h) heating with Br_2 at ~150 °C (see Scheme 28).[102]

Scheme 28



Hexachlorobenzene reacts with KF to afford a crude mixture of dichlorotetrafluorobenzenes, which was allowed to react with KSH to be converted to a mixture of 2,4-, 3,4- and 2,5-dichlorotrifluorobenzenethiols in a ~ 70 : 18 : 12

Scheme 29

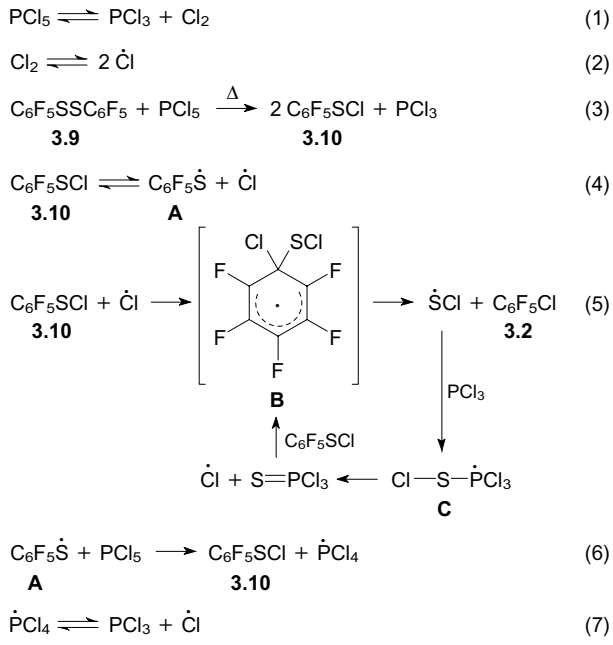


(*a*) PCl_5 or SO_2Cl_2 (~2.2 equiv.), ~200 °C, 5 h

ratio, according to ^{19}F NMR spectroscopy data. Heating of this mixture with PCl_5 or SO_2Cl_2 in a sealed tube at ~200 °C resulted in the synthesis of virtually pure 1,2,4-trichlorotrifluorobenzene (**3.8**), that is difficult to obtain by other methods (Scheme 29).[100, 101]

The displacement of the thiol group in polyfluoroarenethiols by chlorine apparently involves the intermediate formation of polyfluoroarenesulfenyl chlorides. They react with the chlorine atom to be converted to chloropolyfluoroarenes. The homolytic substitution of chlorine for the thiol group was studied in more detail in relation to the reaction of thiol **3.3** with PCl_5 or SO_2Cl_2. The mechanism of conversion of thiol **3.3** to arene **3.2** *via* the reaction with PCl_5 is shown in Scheme 30.[100] Phosphorus pentachloride gives off Cl_2, which can dissociate to chlorine atoms [reaction (2)]. Heating of decafluorodiphenyl disulfane (**3.9**) with PCl_5 leads to pentafluorobenzenesulfenyl chloride (**3.10**) [reaction (3)], which can decompose to give a chlorine atom and thiyl radical **A** [reaction (4)]. Compound **3.2** may be formed from sulfenyl chloride **3.10** *via* radical σ-complex **B** [reaction (5)].[100] The $^{\bullet}SCl$ radical, which is eliminated upon degradation of σ-complex **B**, reacts with PCl_3 to give phosphoranyl radical **C**. The latter undergoes β-scission, thus yielding thiophosphoryl chloride, which was detected by ^{31}P NMR spectroscopy and gas chromatography – mass spectrometry. It is known that phosphoranyl radicals, although relatively stable, can undergo β-scission, in particular, with S=P bond formation.[100] Also, radical **A** can detach a chlorine atom from PCl_5, being converted to

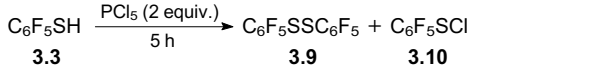
Scheme 30



sulfenyl chloride **3.10** and the $^{\bullet}PCl_4$ radical, which degrades to PCl_3 and a chlorine atom [reactions (6) and (7), respectively].

The intermediate formation of disulfane **3.9** and sulfenyl chloride **3.10** in the reaction of thiol **3.3** with PCl_5 is evidenced by the results of this reaction at ~20 and ~100 °C; according to ^{19}F NMR data, their ratios were ~100 : 0 and ~69 : 31 (Scheme 31).[100]

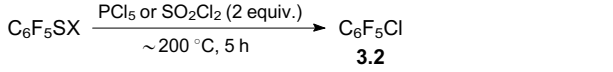
Scheme 31



Unlike the reaction of thiol **3.3** with PCl_5 at room temperature, which yields disulfane **3.9**, the reaction of thiol **3.3** with SO_2Cl_2 under the same conditions gives mainly sulfenyl chloride **3.10**, together with a minor amount of compound **3.9** (the ratio of **3.10** to **3.9** is ~95 : 5 according to ^{19}F NMR data).[101]

Perhaps, compound **3.9** reacts with SO_2Cl_2 to be converted to sulfenyl chloride **3.10**,[101] which is converted to arene **3.2** under the action of a chlorine atom generated from SO_2Cl_2, with intermediate formation of radical σ-complex **B** (see Scheme 30).[101] The participation of sulfenyl chloride **3.10** and disulfane **3.9** in the formation of arene **3.2** is confirmed by reactions of compounds **3.9** and **3.10** with PCl_5 or SO_2Cl_2 at ~200 °C (Scheme 32).[100, 101]

Scheme 32



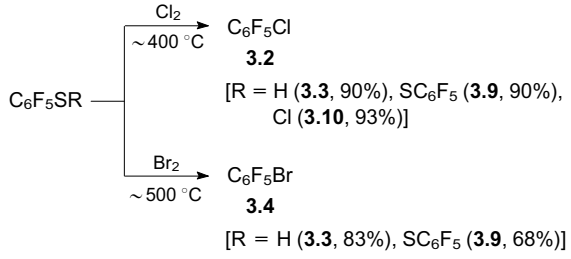
X = Cl (**3.10**, 85% or 89%), SC_6F_5 (**3.9**, 88% or 85%)

The displacement of the thiol group of polyfluoroarenethiols by a bromine atom on treatment with Br_2 and PBr_5 may follow a homolytic mechanism, similarly to the displacement by chlorine on treatment with PCl_5 or SO_2Cl_2. Apart from bis(polyfluoroaryl) disulfanes, polyfluoroarenesulfenyl bromides can be formed as intermediates. By analogy with the conversion of disulfane **3.9** to sulfenyl chloride **3.10**,[100, 101] the reaction of bis(polyfluoroaryl) disulfanes with bromine to give intermediate polyfluoroarenesulfenyl bromides and then bromopolyfluoroarenes cannot be ruled out either. Presumably, the reaction of pentafluorobenzenesulfenyl bromide (**3.11**) with a bromine atom with the intermediate formation of a radical σ-complex of type **B** (see Scheme 30) followed by elimination of the sulfur group affords compound **3.4**.[102] The formation of sulfenyl bromide **3.11** was postulated earlier.[103] The reaction of thiol **3.3** with PBr_5 can also give sulfenyl bromide **3.11** as an intermediate, which reacts with a bromine atom, generated upon PBr_5 degradation, to give arene **3.4** *via* a radical σ-complex of type **B** (see Scheme 30). The $^{\bullet}SBr$ radical eliminated upon decomposition of this σ-complex reacts with PBr_3 to afford phosphoranyl radical of type **C** (see Scheme 30). The β-scission of the radical yields thiophosphoryl bromide, which was detected by ^{31}P NMR spectroscopy and GC/MS.[102]

An alternative substitution pattern of polyfluoroarenethiols to displace the thiol group by chlorine and bromine

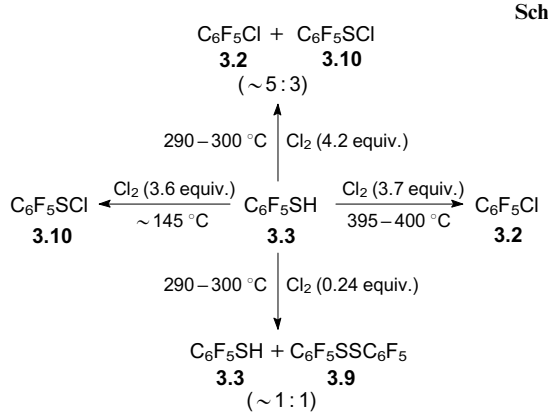
atoms is to carry out the reaction in a flow reactor. It was shown that during co-pyrolysis of polyfluoroarenethiols with Cl_2, SO_2Cl_2 or Br_2 in a flow reactor at ~400 – 500 °C, the thiol group is replaced by clorine or bromine atoms to give halogenated polyfluoroarenes.[104] The reaction is highly selective, the target product yields being from 68% to 95% and the purity being 96% – 99%. The co-pyrolysis of thiol **3.3**, disulfane **3.9** or sulfenyl chloride **3.10** with Cl_2 at ~ 400 °C gives arene **3.2** in a high yield.[104] Thiol **3.3** and disulfane **3.9** react with Br_2 at ~500 °C to afford arene **3.4** (Scheme 33).[104]

Scheme 33



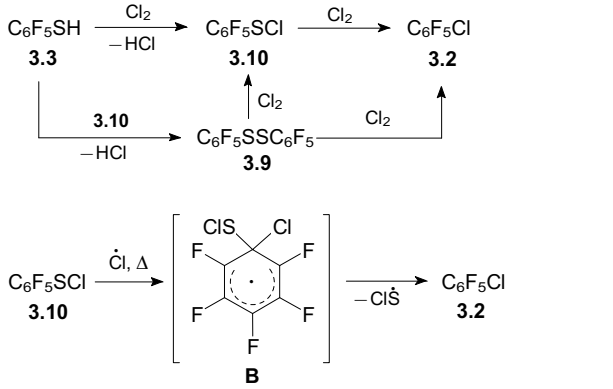
The reaction of thiol **3.3** with Cl_2 was studied in more detail under various conditions (Scheme 34).[104] As the reaction temperature decreases to 145 °C, sulfenyl chloride **3.10** is formed in a high yield, together with a minor amount of arene **3.2**. At similar molar amounts of reactants at ~ 300 °C, the reaction gives a mixture containing arene **3.2** as the major product, together with sulfenyl chloride **3.10**. When thiol **3.3** reacts with a deficient amount of Cl_2 (~4 : 1 molar ratio of the reactants) at ~300 °C, the reaction gives a mixture containing the starting thiol **3.3** and disulfane **3.9** in equimolar amounts. Disulfane **3.9** is formed, most likely, upon the reaction of the starting thiol **3.3** with intermediate sulfenyl chloride **3.10**.

Scheme 34



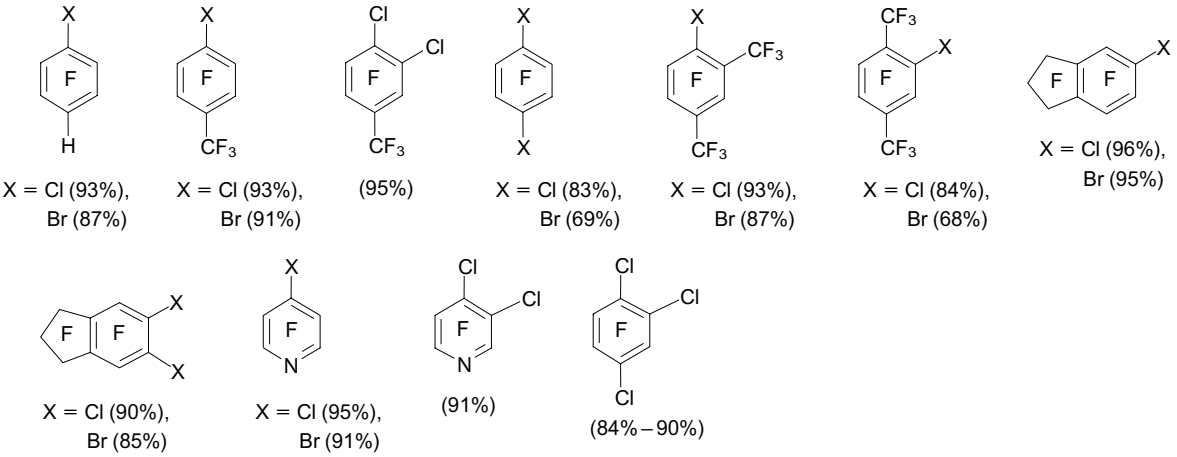
Relying on these data and data for the reaction of thiol **3.3** and disulfane **3.9** with Cl_2 at −10 and 20 °C, published previously by German chemists,[105] which resulted in the formation of sulfenyl chloride **3.10** in high yield (90%), it is possible to conceive the mechanism of chlorine substitution for the thiol group in thiol **3.3** and in other polyfluoroarenethiols. The mechanism includes the initial transformation of thiol **3.3** on treatment with Cl_2 to give sulfenyl chloride **3.10**, which then reacts with Cl_2 to afford arene **3.2**. In the presence of thiol **3.3**, sulfenyl chloride **3.10** can form disulfane **3.9**, which also reacts with Cl_2 to be converted to arene **3.2**. It could have been expected that the reaction of disulfane **3.9** with Cl_2 gives, first, sulfenyl chloride **3.10**. Thus, the latter can be an intermediate on the way to arene **3.2** from thiol **3.3** and disulfane **3.9**, which proceeds *via* radical σ-complex **B** (Scheme 35). A similar scheme may be proposed for bromine substitution for the thiol group in thiol **3.3** upon co-pyrolysis with Br_2.[104]

Scheme 35



The synthesis of arene **3.2** by co-pyrolysis of thiol **3.3** with SO_2Cl_2 in a flow reactor may also involve the intermediate formation of sulfenyl chloride **3.10**. The latter reacts with a chlorine atom to give radical σ-complex **B**

Structures of (di)halofluoroarenes



(see Scheme 35), similarly to the reaction of thiol **3.3** with SO_2Cl_2 in a sealed tube.

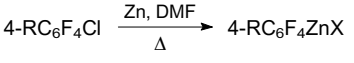
Similar schemes were proposed for displacement of a sulfur functional group by a chlorine or bromine atom in the reactions of other polyfluoroarenethiols with Cl_2 and Br_2 in flow reactors. Halopolyfluoroarenes obtained in this way, which were converted to dihalopolyfluoroarenes containing chlorine and bromine atoms in the *para*- and *ortho*-positions of the aromatic ring, are depicted below (the yields are given in parentheses).[104, 106 – 108]

Arene **3.8** was isolated in 90% yield as virtually the only product upon co-pyrolysis of Cl_2 with a dichlorotrifluorobenzenethiol mixture prepared from a crude mixture of dichlorotetrafluorobenzenes.[108] The chemistry of this product was little studied previously and its synthesis developed in our work is suitable for conducting the reaction with nucleophilic agents.[109]

3.2. Preparation and reactions of polyfluoroaryl organozinc derivatives

Perfluoroarenes and chloro- and bromopolyfluoroarenes were used for the synthesis of organozinc compounds for their subsequent functionalization. Previously, it was shown that the reactions of pentafluoroiodobenzene and arene **3.4** with Zn in various solvents yield pentafluorophenyl organozinc halides.[110] The reactions of **3.2** and its *para*-CF_3- and Me-substituted derivatives with Zn in DMF yield the corresponding organozinc compounds (according to ^{19}F NMR data) (Scheme 36).[111, 112]

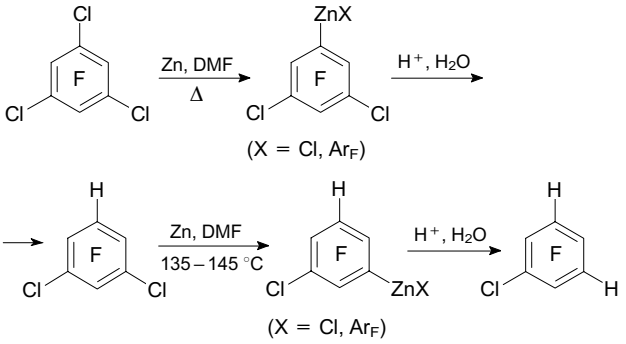
Scheme 36



R	*T*/°C	Yield (%)
F	135	98
CF_3	135	98
Me	185	61

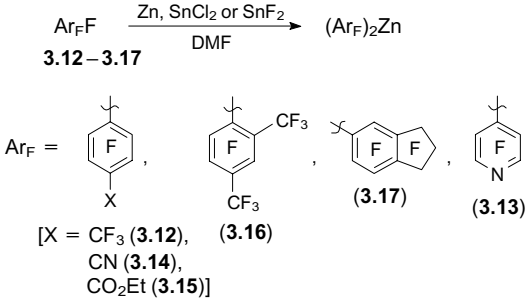
1,3,5-Trichlorotrifluorobenzene also reacts with Zn in DMF to give, after acid treatment of the organozinc compound, dichlorotrifluorobenzene, which also reacts with Zn to yield (after acid treatment) chlorotrifluorobenzene (Scheme 37).[113] Thus, zinc reacts with chloropolyfluoroarenes at the C – Cl bond.

Scheme 37



Perfluoroarenes react with Zn in the presence of $SnCl_2$ or SnF_2 giving rise to organozinc compounds. This reaction proceeds for perfluorinated benzene, indane and pyridine

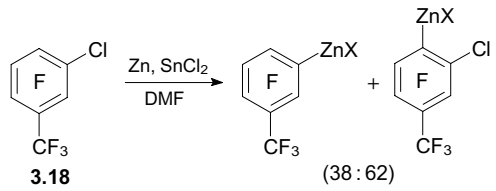
Scheme 38



derivatives (Scheme 38).[114] The importance of adding $SnCl_2$ and SnF_2 was demonstrated in relation to reactions of octafluorotoluene (**3.12**) and pentafluoropyridine (**3.13**). Thus in the presence of $SnCl_2$ or SnF_2, the expected organozinc compounds were obtained in nearly quantitative yields, as opposed to reactions with no tin salts.[115] Pentafluorobenzonitrile (**3.14**), ethyl pentafluorobenzoate (**3.15**), perfluoro-*m*-xylene (**3.16**) and perfluoroindane (**3.17**) react with zinc in a similar way.[112, 114]

The reaction of 3-chloroheptafluorotoluene (**3.18**) with Zn in the presence of $SnCl_2$ in DMF affords a mixture of organozinc compounds; the reaction largely involves the C – F bond in position 4 (Scheme 39).[115]

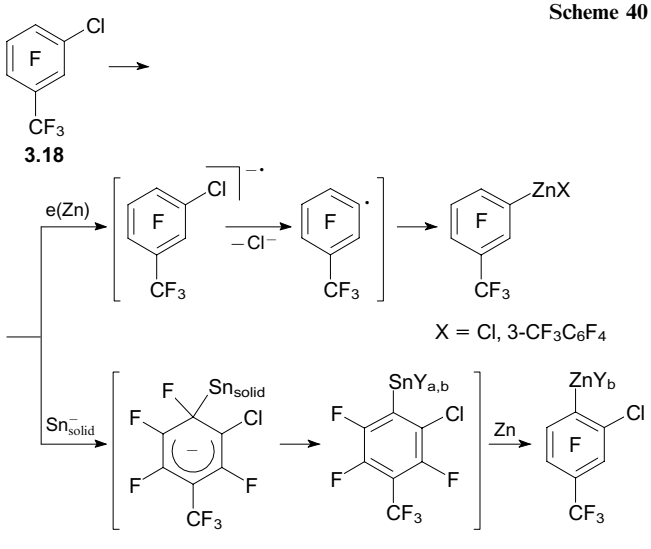
Scheme 39



X = Cl, 3-$CF_3C_6F_4$, 2-Cl-4-$CF_3C_6F_3$

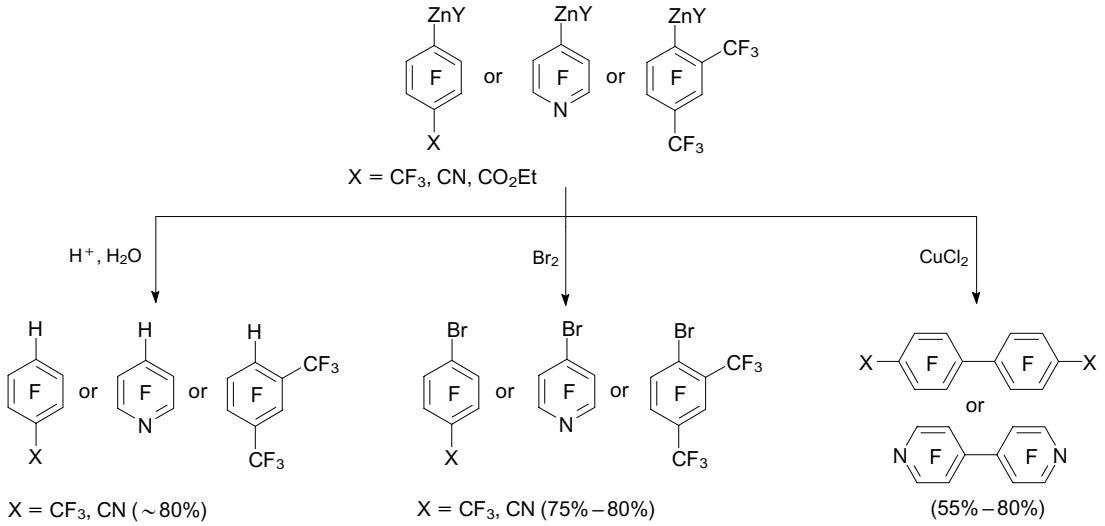
The formation of organozinc compounds from chloropolyfluoroarenes in the absence of tin salts, which involves the C – Cl bond, can be interpreted in terms of a radical anion mechanism (by analogy with the mechanism of

Scheme 40



Ya = Sn_{solid}, F; Yb = Cl, 3-$CF_3C_6F_4$, 2-Cl-4-$CF_3C_6F_3$

Scheme 41



formation of Grignard reagents and organozinc derivatives of hydrocarbons) (Scheme 40).[115] Meanwhile, the effect of $SnCl_2$ addition on the major reaction pathway, for example, for arene **3.18** may change the mechanism to the nucleophilic substitution. The negatively charged Sn intermediates (Sn^-_{solid}), which are formed under the action of Zn, can be considered as nucleophiles. They are expected to attack position 4 of arene **3.18** according to the orientation of the nucleophilic substitution in this compound in the reaction with dimethylamine.[115] This attack results in the formation of intermediate organotin compounds, which are then converted to organozinc derivatives (see Scheme 40).[115]

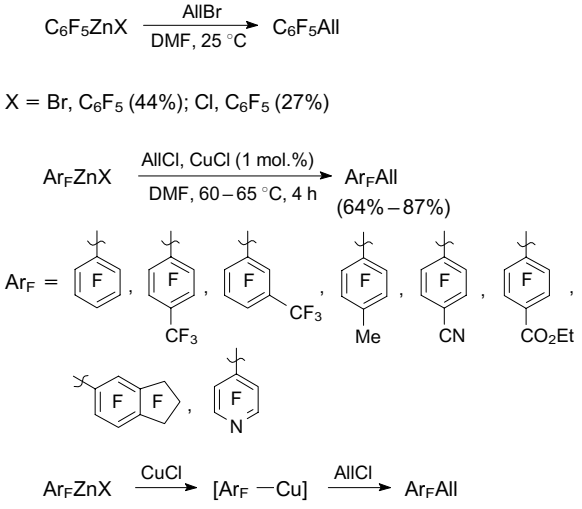
The reactions of organozinc reagents synthesized from arenes **3.12** – **3.16** with acids, bromine and $CuCl_2$ result in the formation of the corresponding H- and Br-derivatives and symmetrical perfluorinated biaryls (Scheme 41).[114, 116]

Organozinc compounds formed from arene **3.15** react with $CuCl_2$ being converted to diethyl octafluorobiphenyl-4,4′-dicarboxylate, which was then converted to octafluorobiphenyl-4,4′-dicarboxylic acid.[116] This acid was employed to prepare photoluminescent lanthanide complexes, which were of interest as materials for light emitting diodes and chemosensors.[116] This acid was also converted to metal-organic coordination polymers used as new porous materials.[117]

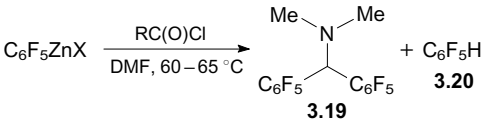
Organozinc reagents prepared from compounds **3.2** and **3.4** react with allyl bromide at room temperature to give allylpentafluorobenzene (Scheme 42).[112] Unlike allyl bromide, allyl chloride virtually does not react with polyfluoroaryl organozinc reagents. However, the addition of copper(I) chloride to the reaction mixture boosts these reactions, which now give products in satisfactory yields. The catalytic role of copper(I) salt consists apparently in its reaction with polyfluoroaryl organozinc reagents with intermediate formation of polyfluoroarylcopper, which reacts with allyl chloride yielding allylpolyfluoroarenes (see Scheme 42).[112]

Pentafluorophenyl organozinc reagents react with pivaloyl chloride or benzyl chloride in DMF to afford a mixture of *N*,*N*-dimethyl-1,1-bis(pentafluorophenyl)methylamine (**3.19**) and pentafluorobenzene (**3.20**) (Scheme 43).[118, 119]

Scheme 42



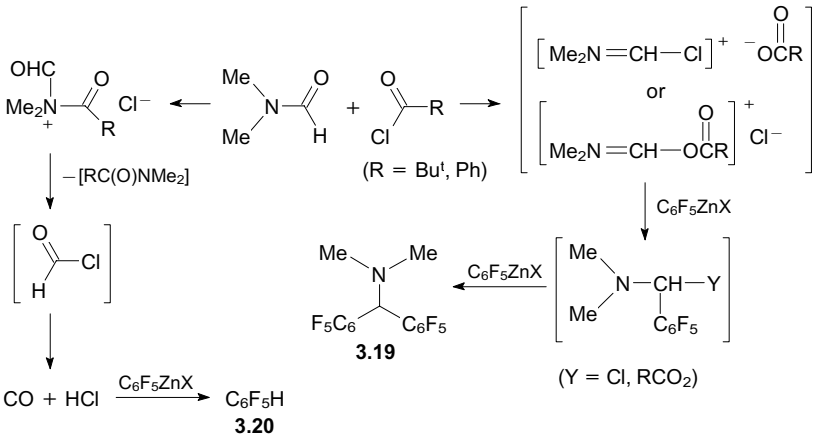
Scheme 43



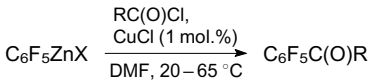
The mechanism of formation of these products can be described as transamidation giving intermediate ammonium cations, which are then converted to amides and unstable formyl chloride, decomposing to CO and HCl. The latter reacts with organozinc reagents leading to compound **3.20** (Scheme 44).[119] A different reaction pathway involving pivaloyl and benzoyl chlorides is, probably, interaction of the electrophilic centres of these acid chlorides with the DMF oxygen atom, thus yielding Vilsmeier – Haack reagents. These intermediates can further react with organozinc compounds, which finally furnishes amine **3.19** (see Scheme 44).[118, 119]

Amines of this type were prepared from benzoyl chloride and other polyfluoroaryl organozinc reagents containing the benzene, indane or pyridine core (the yields of amines

Scheme 44



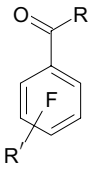
Scheme 45



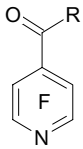
X = Cl, C_6F_5; R = Me (44% – 47%), Et (66 – 69%), Pr^i (65%), Bu^t (71%), Ph (75%)

were 36% – 46%).[119] The addition of CuCl changed the reaction pathway. Indeed, pentafluorophenyl organozinc compounds reacted with acetyl, propionyl, isobutyryl, pivaloyl and benzoyl chlorides in the presence of CuCl, yielding the corresponding ketones containing a pentafluorophenyl group (Scheme 45).[120]

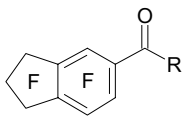
Structures of polyfluoroketones



R′ = 4-CF_3: R = Et (67%), Ph (75%);
R′ = 3-CF_3, R = Et (45%);
R′ = 4-CN: R = Et (43%), Ph (75%);
R′ = 4-CO_2Et: R = Et (43%), Ph (64%)



R = Et (68%), Ph (76%)



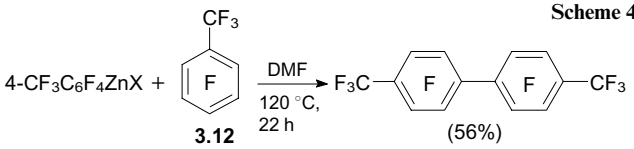
R = Et (50%), Ph (41%)

This method was extended to other polyfluoroaryl organozinc reagents; this resulted in the synthesis of polyfluoroaromatic ketones.[120]

The synthesis of ketones in the presence of CuCl added to the reaction mixture can be interpreted by transmetallation and intermediate formation of polyfluoroaryl organocopper compounds, which then react with acid chlorides,[120] by analogy with reactions of polyfluoroaryl organozinc reagents with allyl chloride in the presence of CuCl (see Scheme 42).

Polyfluoroaryl organozinc reagents react with perfluoroarenes yielding symmetrical and unsymmetrical perfluorinated biaryls. For example, symmetrical perfluorinated biaryls were synthesized from arenes **3.12**, **3.13** and organozinc compounds they form (Schemes 46 and 47).[121]

Scheme 46



X = Cl, Ar_F

Scheme 47

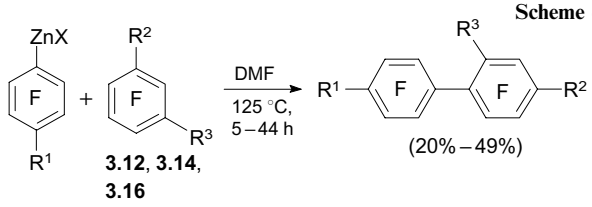


X = Cl, C_5F_4N

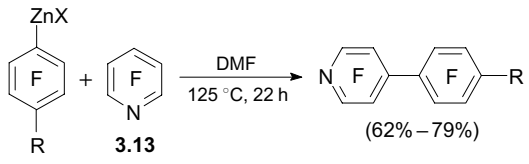
The reactions of pentafluorophenyl and heptafluorotolyl organozinc reagents with arenes **3.12** – **3.14** and **3.16** afford unsymmetrical perfluorobiaryls (Scheme 48).[121]

The substituent orientation in the reaction between perfluoroaryl organozinc reagents and perfluoroarenes is in line with that observed for nucleophilic substitution.[95, 122]

Scheme 48



R^1 = F, CF_3; X = Cl, Ar_F: R^2 = CF_3, R^3 = F (**3.12**); R^2 = CN, R^3 = F (**3.14**); R^2 = CF_3, R^3 = CF_3 (**3.16**)



R = F, CF_3; X = Cl, Ar_F

Thus, these reactions should be considered as nucleophilic aromatic substitution.

Perfluoroarenes and chloropolyfluoro- and bromopolyfluoroarenes are important key products in the chemistry of polyfluoroaromatic compounds. The new method for introducing chlorine and bromine atoms into the molecule by displacing the thiol group of polyfluoroarenethiols was recognized as a promising approach suitable for the synthesis of poorly accessible polyfluoroaromatic compounds containing one or several chlorine and/or bromine atoms. These polyhaloarenes are of considerable interest for the preparation of organometallic compounds with selective involvement of C—Cl or C—Br bonds. Quite a number of functional derivatives of polyfluoroaromatic compounds can be prepared *via* Grignard reagents and organolithium and organozinc reagents with the participation of C—Cl and C—Br bonds. Generally, the synthesis of organometallic compounds from various chloro- and bromopolyfluoroarenes opens up new prospects of polyfluoroarene chemistry. One more important type of reactions are $SnCl_2$- or SnF_2-catalyzed reactions of perfluoroarenes with zinc, which involve the C—F bond and give rise to polyfluoroaryl organozinc reagents. In view of the importance of fluorinated organozinc compounds [123] and increasing role of the chemistry of polyfluoroaromatic derivatives, one may hope that further research along this line would facilitate the development of efficient synthetic routes to polyfluoroarenes and disclosure of new aspects of their reactivity.

4. Skeletal and other cationoid transformations of polyfluoroarenes

Fluorinated aromatic compounds are of considerable interest for fundamental organic chemistry [124, 125] and for practical applications, especially those related to materials science, biomedicine and agriculture.[124–129] Among reactions of polyorganofluorine compounds, a considerable place is occupied by transformations involving carbocations.[130, 131]

A large number of studies in the carbocation chemistry are available in the literature. It is noteworthy that cationoid skeletal rearrangements are frequently encountered for hydrocarbons, whereas in the case of polyfluorinated compounds, they are quite rare [130, 131] and mainly occur in reactions of polyfluorinated benzocycloalkenes with antimony(V) fluoride. The presence of an aromatic ring in the reactants contributes to stabilization of the intermediate cations, which facilitates the reactions.

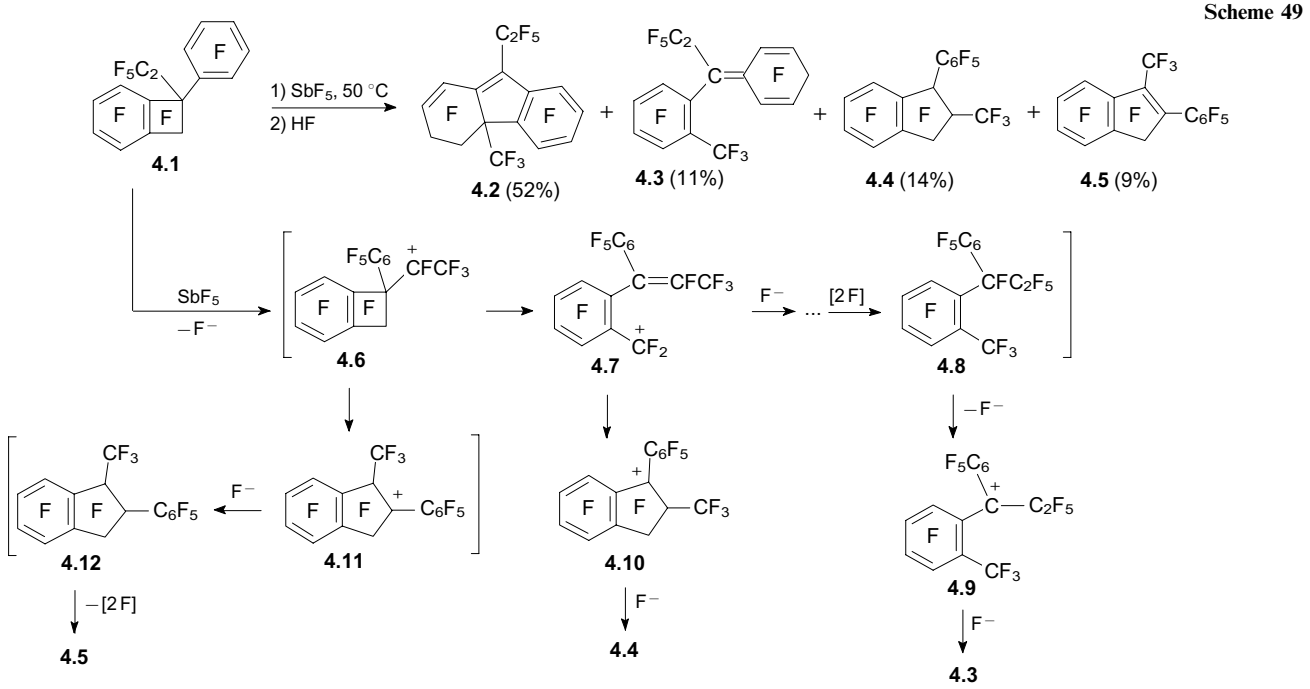
4.1. Perfluoro-1-arylbenzocyclobutenes

Perfluoro-1-phenylbenzocyclobutene, which exists in SbF_5 as the perfluoro-1-phenylbenzocyclobuten-1-yl cation, does not undergo changes of the carbon skeleton when heated with antimony(V) fluoride at 170 °C.[132] However, the introduction of a perfluoroalkyl group into the *ortho*- or *para*-position of the pentafluorobenzene ring or into the four-membered ring of benzocyclobutene enables skeletal rearrangements. Thus perfluoro-1-ethyl-1-phenylbenzocyclobutene (**4.1**) kept with SbF_5 at 50 °C for 1 month is converted to dihydrofluorene **4.2**, compound **4.3**, indane **4.4** and indene **4.5** (Scheme 49).[133]

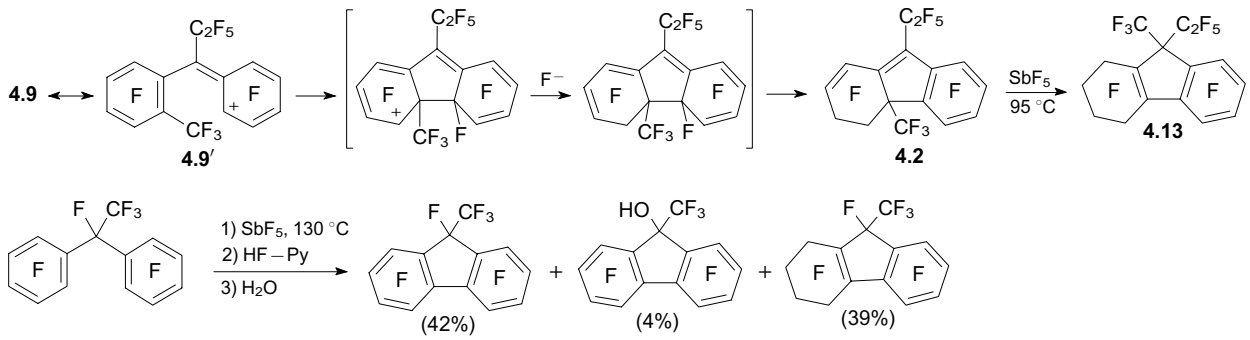
Opening of the four-membered ring in benzocyclobutene **4.1** proceeds apparently *via* alkyl cation **4.6**, which isomerizes to benzyl ion **4.7**. The attachment of F^- and double bond fluorination yield diarylalkane **4.8**, which generates diarylpropyl cation **4.9** in the SbF_5 medium. The intramolecular cyclization of cation **4.7** affords phenylindanyl cation **4.10**. The addition of the fluoride ion to cations **4.9** and **4.10** upon quenching with anhydrous HF leads to compounds **4.3** and **4.4** (see Scheme 49).[133]

The formation of indene **4.5** follows a different pathway. Presumably, the intramolecular attack by the cationic centre on the tetrafluorobenzene ring of ion **4.6** generates cation **4.11**, which is converted to indane **4.12** upon addition of the fluoride anion; the last-mentioned product is

Scheme 49



Scheme 50



defluorinated to be converted to indene **4.5** (Scheme 49). Dihydrofluorene **4.2** is likely to result from cyclization of cation **4.9′** (Scheme 50),[133] which agrees with the formation of fluorene derivatives in the reaction of perfluoro-1,1-diphenylalkanes with antimony(V) fluoride (see Scheme 50).[134] On treatment with SbF_5 at 95 °C, dihydrofluorene **4.2** is converted to perfluoro-9-ethyl-9-methyl-1,2,3,4-tetrahydrofluorene (**4.13**) *via* several 1,2-shifts of the CF_3 group and fluorination.[133]

Unlike isomer **4.1**, perfluoro-2-ethyl-1-phenylbenzocyclobutene reacts with SbF_5 only at 170 °C, giving perfluoro-9-ethylfluorene, compound **4.13** and the product of four-membered ring opening in the substrate.[135]

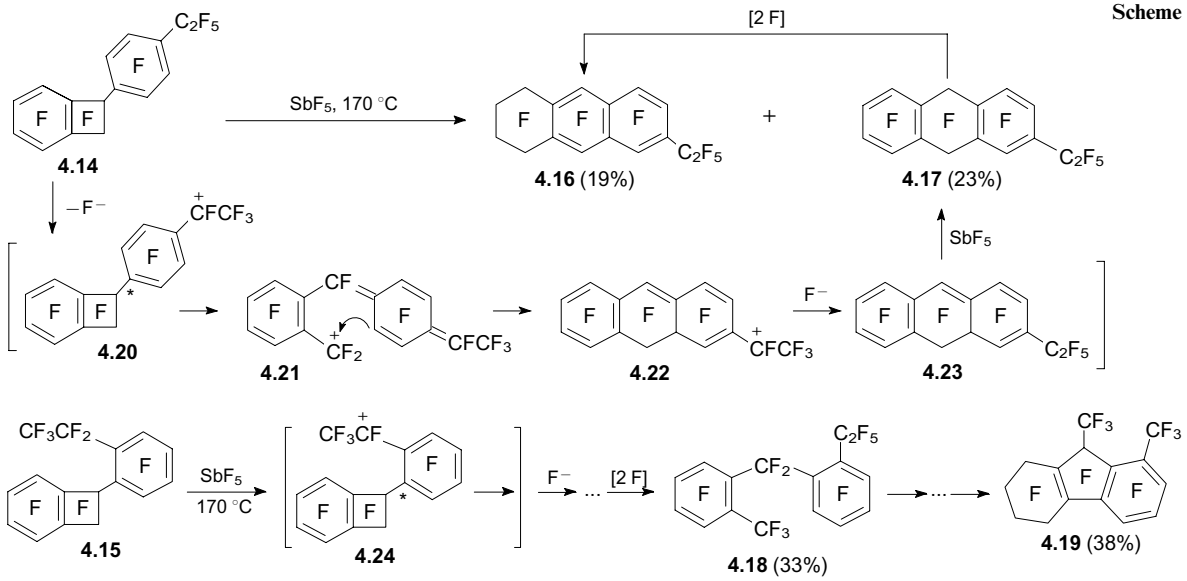
Perfluorinated 1-(4-ethylphenyl)- (**4.14**) and 1-(2-ethylphenyl)benzocyclobutenes (**4.15**) also undergo skeletal transformations under similar conditions. Compound **4.14** is converted to tetrahydroanthracene **4.16** and dihydroanthracene **4.17**, while isomer **4.15** is converted to diarylmethane **4.18**, which is transformed to dimethyltetrahydrofluorene **4.19** (Scheme 51).[132]

In the case of compound **4.14**, treatment with SbF_5 probably results in the generation of benzyl cation **4.20** in which some of the charge is located on the *ipso*-carbon atom linked to the benzocyclobutenyl moiety (marked by an asterisk). In this cation, as in similar cations formed from perfluoro-1-alkylbenzocyclobutenes, the four-membered ring is opened, thus yielding cation **4.21**. Cyclization followed by F^- addition to the resulting cation **4.22** and the subsequent isomerization of compound **4.23** afford dihydroanthracene **4.17**, which is fluorinated to give tetrahydroanthracene **4.16**. In the case of arylbenzocyclobutene **4.15**, fluorination occurs for the opening product of cation **4.24** and results in the formation of diarylmethane **4.18**, which undergoes a sequence of transformations ending with tetrahydrofluorene **4.19**.[132]

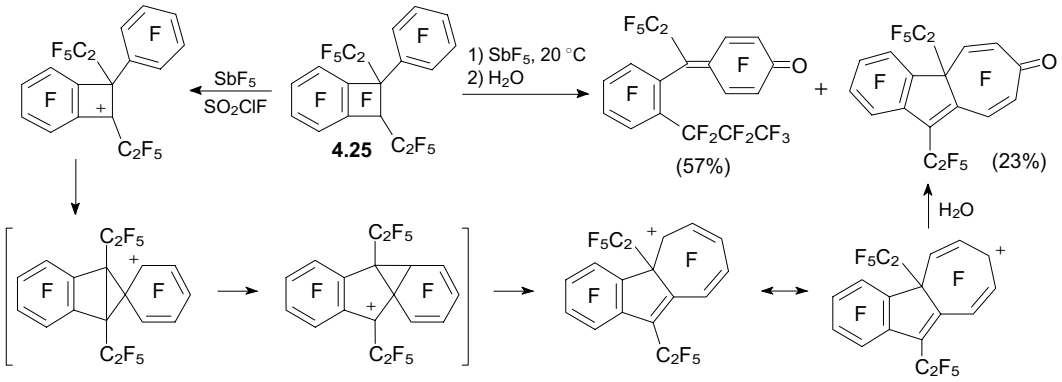
When perfluoro-1,2-diethyl-1-phenylbenzocyclobutene (**4.25**) reacts with excess SbF_5, opening of the four-membered ring typical of perfluoroalkylbenzocyclobutenes is accompanied by an unusual rearrangement of the carbon skeleton of the substrate including expansion of the pentafluorobenzene ring to a seven-membered ring (Scheme 52).[136, 137] On treatment with SbF_5, perfluoro-1,2-dialkyl-1-phenylbenzocyclobutenes with various alkyl groups undergo four-membered ring opening and expansion to a five-membered ring without involvement of the pentafluorophenyl group.[138]

1,1,2-Triphenylbenzocyclobutene **4.26** formed in the reaction of compound **4.27** with an excess of C_6F_5H in a SbF_5 medium isomerizes on long-term treatment with the HF – Py system to be converted to perfluoro-9,10-diphenyl-*n*,*m*-dihydroanthracenes (*n*, *m* = 1, 4; 1, 10; 2, 9; 9, 10), which react with SbF_5 to give anthracene **4.28** (Scheme 53).[139]

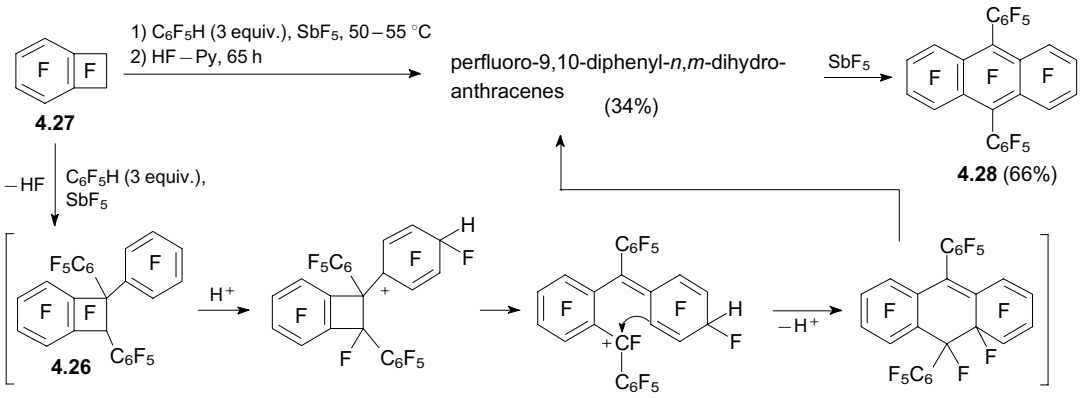
Scheme 51



Scheme 52



Scheme 53



4.2. Perfluoro-1-phenylindane and perfluoro-1-phenyltetralin

Perfluoro-1-phenylindane (**4.29**) reacts with antimony(V) fluoride to give fluorene **4.30**, octahydroanthracene **4.31** and compound **4.32**, which results from six-membered ring contraction in **4.31** to a five-membered ring (Scheme 54).[140]

In SbF_5, indane **4.29** generates cation **4.33**, which undergoes opening of the five-membered ring; the subsequent formation of fluorene **4.30** is described by analogy with Scheme 50, and compound **4.31** is formed similarly to Scheme 51.

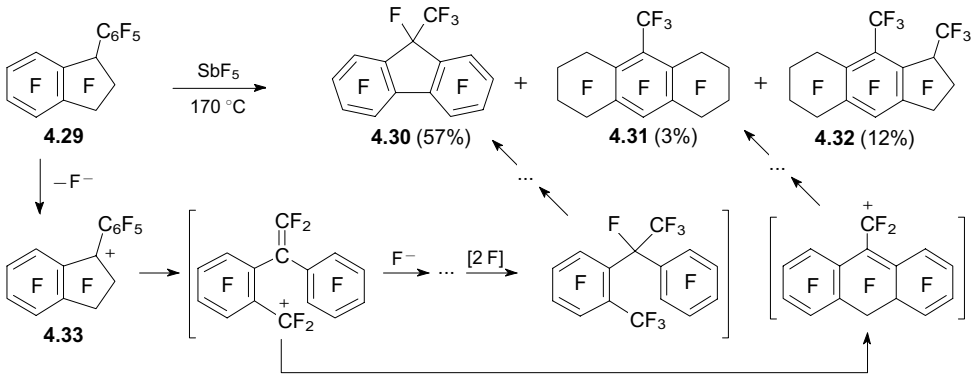
Treatment of perfluoro-1-phenyltetralin (**4.34**) with SbF_5 induces contraction of the alicyclic moiety yielding indene **4.5** and methylphenylindane **4.35**, which later gives rise to compounds **4.31** and **4.32** (Scheme 55).[141]

Tetralin **4.34** isomerization to indane **4.35** apparently involves cation **4.36**; the 1,2-shift of the perfluoroalkyl moiety towards the cationic centre yields cation **4.37**, and the addition of F^- gives indane **4.35**. A similar six-membered to five-membered ring contraction in cation **4.38** and a sequence of subsequent transformations furnish indene **4.5** (see Scheme 55).[141]

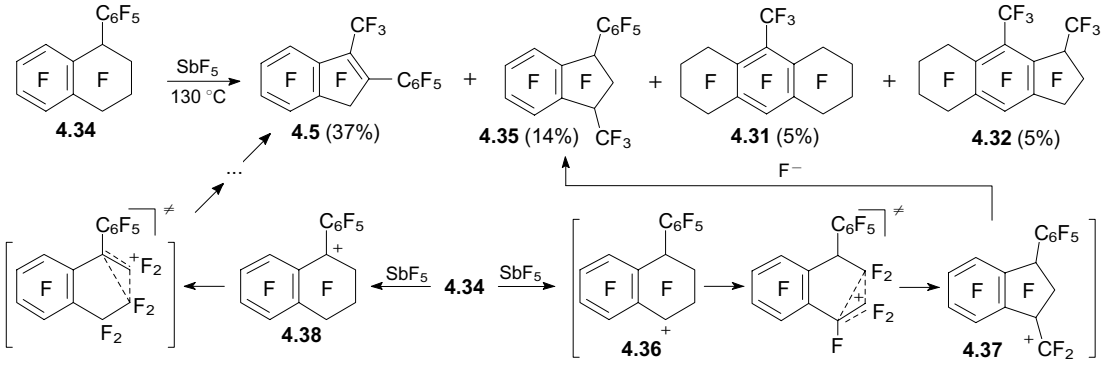
4.3. Carbonyl derivatives of perfluorobenzocycloalkenes

Monocarbonyl perfluorobenzocycloalkene derivatives disproportionate on heating with SbF_5 to give benzocycloalkenes and diketones. In SbF_5, both mono- and diketones can undergo skeletal transformations giving mixtures of five- and six-membered oxygen-containing heterocycles and/or products of alicyclic moiety cleavage in the substrate.[142, 143] For instance, under the action of SbF_5, perfluoroindan-1-one is converted to perfluoro-2-ethylbenzoic

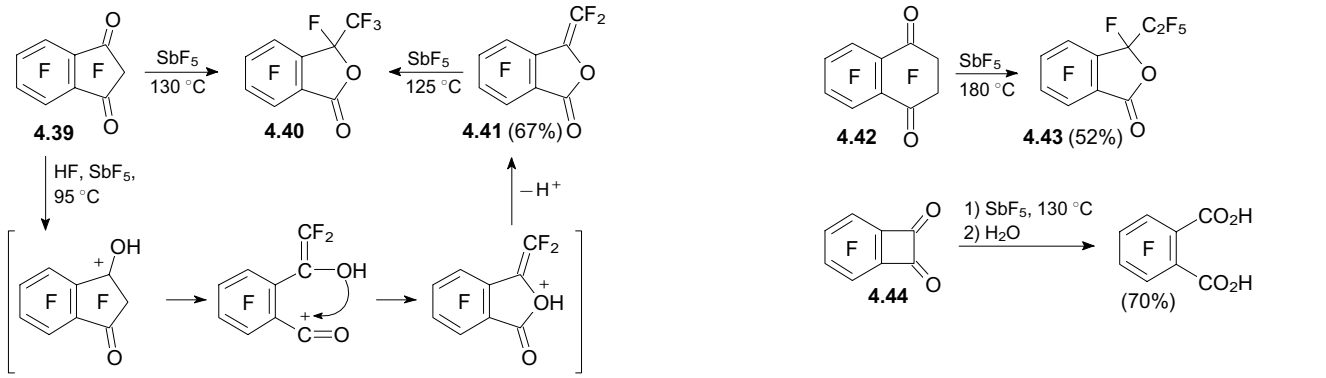
Scheme 54



Scheme 55



Scheme 56



acid and disproportionates to give perfluoroindane and indanedione **4.39**, which is converted in SbF_5 to methylphthalide **4.40** (72% yield).[143] Indanedione **4.39** reacts with HF in SbF_5 giving rise to methylenephthalide **4.41**, which is fluorinated on heating with SbF_5 to afford methylphthalide **4.40** in 69% yield (Scheme 56).[144]

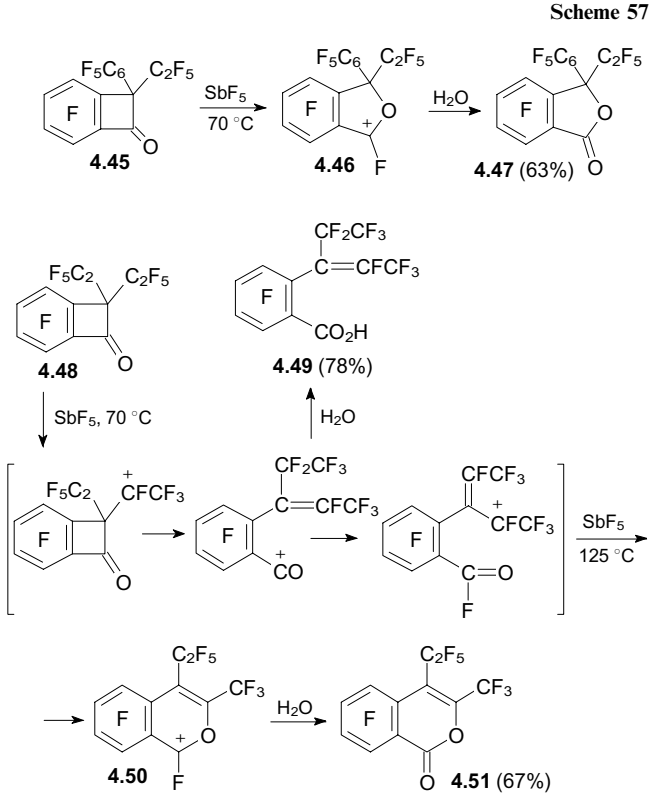
In the reaction of tetralindione **4.42** with antimony(V) fluoride, the major product is ethylphthalide **4.43**, while perfluorobenzocyclobutenedione **4.44** undergoes C(O) – C(O) bond cleavage under the action of SbF_5, thus giving tetrafluorophthalic acid (see Scheme 56).[142]

On heating with SbF_5 at 75 and 120 °C, perfluorinated 2-methyl- and 2-ethylbenzocyclobutenones isomerize to perfluoroindanone and perfluoro-2-methylindanone, respectively.[145] Heating of perfluoro-2-ethyl-2-phenylbenzocyclobutenone (**4.45**) with antimony(V) fluoride (70 °C) produces a solution of a salt of cation **4.46**, which is hydrolyzed to phthalide **4.47** (Scheme 57).[146]

The four-membered ring of diethylbenzocyclobutenone **4.48** is opened on treatment with SbF_5 at 70 °C, giving acid **4.49**. At 125 °C, a salt of cation **4.50** is formed, hydrolysis of which leads to isochromenone **4.51** (see Scheme 57).[146] Perfluoro-2-ethyl-2-methylbenzocyclobutenone behaves in SbF_5 in a similar way [145] and forms the same products as perfluoro-3-ethylindanone (**4.52**) (Scheme 58).[147]

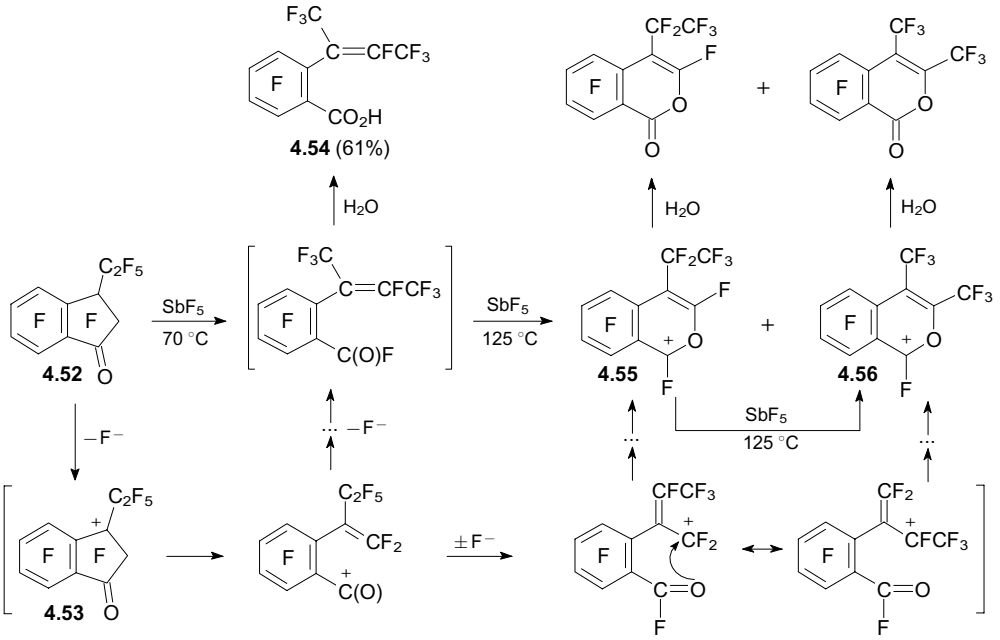
The reaction of ethylindanone **4.52** with SbF_5 at 70 °C is also accompanied by five-membered ring opening in cation **4.53**, resulting in the formation of acid **4.54**. Under more drastic conditions, a solution of salts of isochromenyl cations **4.55** and **4.56** is formed; these products are hydrolyzed to give a mixture of isochromen-1-ones in 61% yield (see Scheme 58).[147] Perfluoro-3-methylindan-1-one behaves in a similar way.[148]

Scheme 57

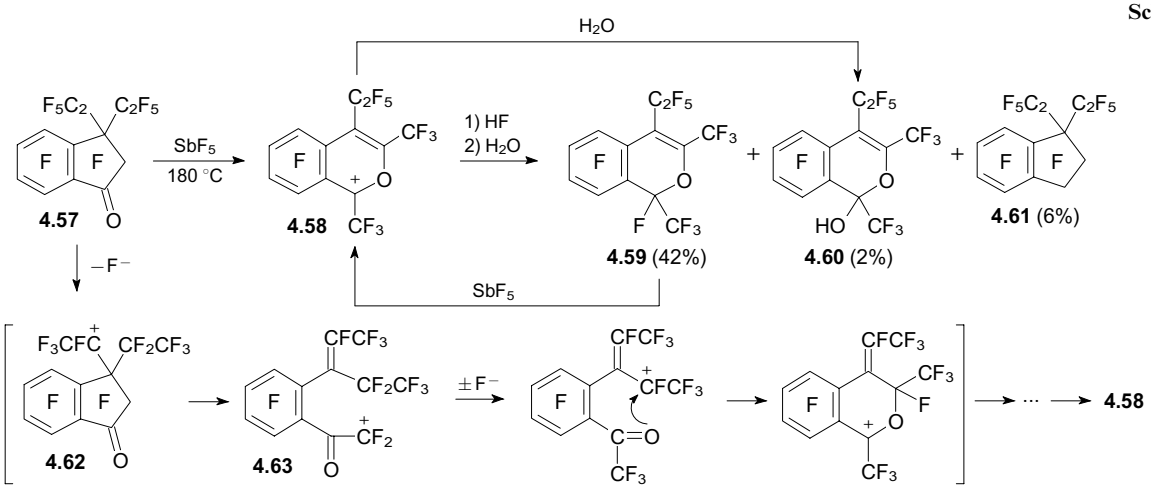


Unlike compound **4.52**, perfluoro-3,3-diethylindan-1-one (**4.57**) does not undergo skeletal transformations under the action of SbF_5 at 130 °C; meanwhile, at 180 °C,

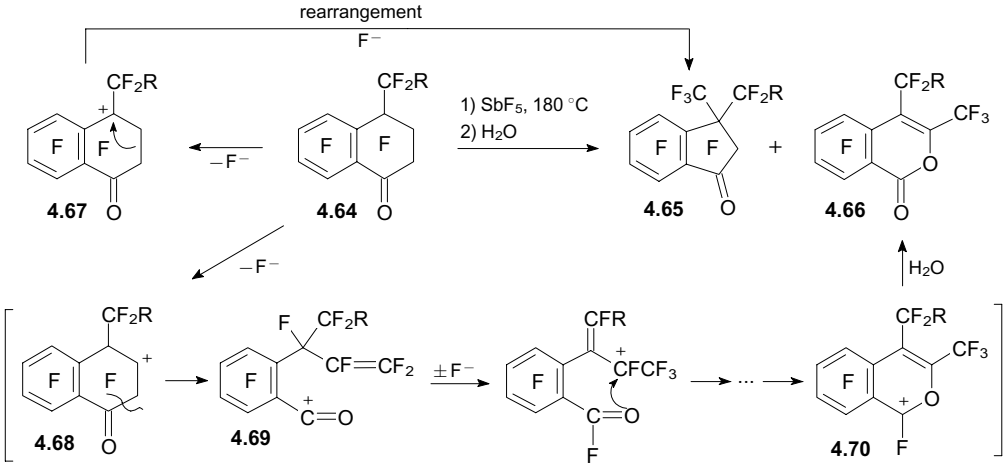
Scheme 58



Scheme 59



Scheme 60



R	Yield of **4.65** (%)	Yield of **4.66** (%)
F	22	56
CF_3	34	34

the reaction gives a mixture containing a salt of isochromenyl cation **4.58** (Scheme 59).[149] Treatment of this mixture with anhydrous HF and then with water yields isochromene **4.59**, together with the starting ketone **4.57** and a minor amount of compounds **4.60** and **4.61**. Apparently, on treatment with SbF_5, compound **4.57** generates cation **4.62** in which the five-membered ring is opened, generating ion **4.63**, which is converted to cation **4.58** *via* a sequence of steps.

The mechanism of opening of the five-membered ring of diethylindanone **4.57** is similar to that for the four-membered ring of diethylbenzocyclobutenone **4.48** (see Scheme 57)[146] and differs from the mechanism of ring opening in ethylindanone **4.52**. In the case of diethylindanone **4.57**, the C – C bond cleavage occurs in ion **4.62** with the cationic centre in the side chain (see Scheme 59),[149] while in the case of ethylindanone **4.52**, it takes place in ion **4.53** with the cationic centre in the benzylic position (see. Scheme 58).[147]

Perfluoro-4-alkyltetralin-1-ones **4.64** also undergo skeletal rearrangements when treated with SbF_5. Heating of methyl- (R = F) and ethyltetralones (R = CF_3) with SbF_5 at 180 °C followed by treatment of the reaction mixture with water gives the corresponding 3,3-dialkylindanones **4.65** and 3,4-dialkylisochromen-1-ones **4.66** as the major products (Scheme 60).[150] The isomerization of tetralones **4.64** to indanones **4.65** apparently involves cations **4.67**, in which the perfluoroalkyl group undergoes 1,2-shift to the cationic centre, and after attachment of the fluoride anion, indanones **4.65** are produced.

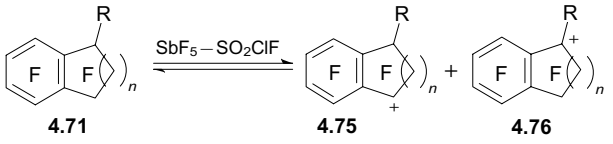
The formation of isochromenones **4.66** apparently proceeds *via* opening of the aliphatic ring in cations **4.68**. The benzoyl cations **4.69** thus formed isomerize to isochromenyl cations **4.70** *via* a sequence of transformations; hydrolysis of the latter yields isochromenones **4.66** (see Scheme 60).[150]

4.4. Polyfluorobenzocycloalkenyl cations and some of their reactions

On dissolution of perfluorobenzocycloalkenes **4.71** in the $SbF_5 - SO_2Cl_2$ system, 1-chloroperfluorobenzocycloalken-1-yl cations **4.72** are formed, while in SbF_5, perfluorinated cations **4.73** are generated in only a low concentration.[151] Compounds **4.71** react with C_6F_5H in SbF_5 to give solutions of salts of perfluoro-1-phenylbenzocycloalkenyl cations **4.74** (Scheme 61).[152] The relative stability of cations **4.72** – **4.74** decreases with increasing size of the alicyclic moiety.

A series of long-lived perfluorinated alkylbenzocyclobutenyl ($n = 0$) and indanyl ($n = 1$) cations were generated, including those with a perfluoroisopropyl group attached to the carbocationic centre (Scheme 62).[153] This fact proved to be unexpected, as it is well known that the perfluoroalkyl groups located at the cationic centre or in charge positions reduce the stability of cations relative to those with a fluorine atom.[124, 125, 131] The B3LYP/6-31G(d) calculations of the relative stability of isomeric cations **4.75** and **4.76** with the fluorine atom or perfluoroalkyl group at the

Scheme 62

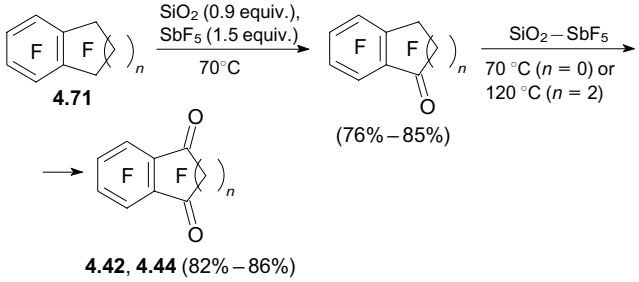


R	Substrate **4.71**		Cation **4.75**		Cation **4.76**	
	$n = 0$	$n = 1$	$n = 0$	$n = 1$	$n = 0$	$n = 1$
CF_3	80	95	20	5	0	0
CF_2CF_3	48	87	48	5	4	8
$CF(CF_3)_2$	0	0	9	0	91	100

cationic centre are consistent with the experimental data, namely, with the ratio of ^{19}F NMR signals (in %) (see Scheme 62).[153]

In the hydrolysis of SbF_5 solutions of compounds **4.71**, carbonyl derivatives are formed only as mixtures with large amounts of the starting compounds, because the concentration of cations **4.73** is moderate. The reaction with the $SiO_2 - SbF_5$ system can serve for the synthesis of either mono- or dicarbonyl perfluorinated benzocycloalkene derivatives, in particular, from benzocycloalkenes that do not generate cations in noticeable concentrations (Scheme 63).[142, 143]

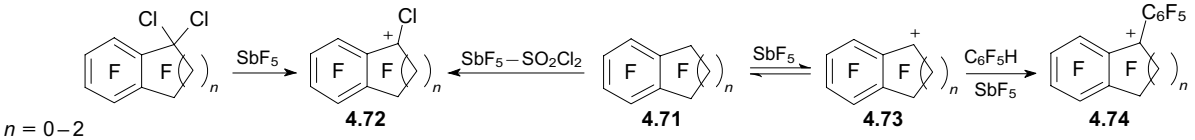
Scheme 63



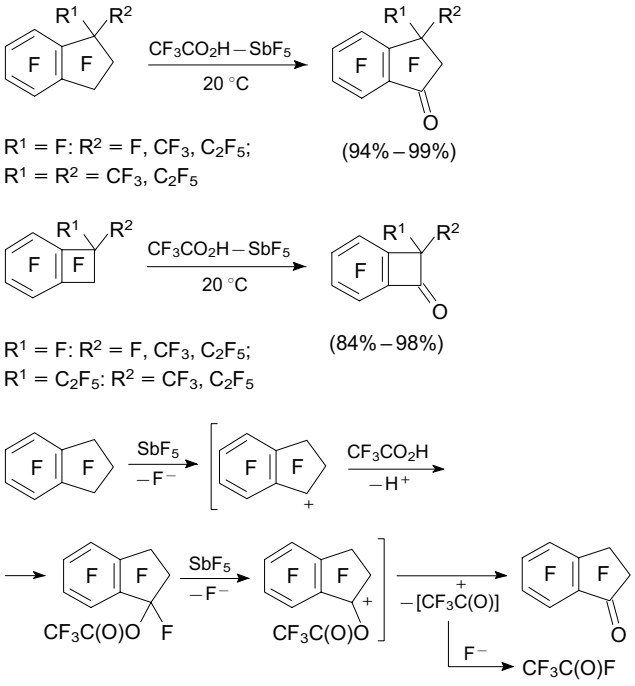
The reactions of perfluoro-1-methylindane and -1-ethylindane with $SiO_2 - SbF_5$ give the corresponding 3-alkylindanones in moderate yields as mixtures with other compounds.[147, 148] The replacement of SiO_2 by trifluoroacetic acid as a source of nucleophilic oxygen atom allows the reaction to be conducted under milder conditions to give carbonyl perfluoroalkylbenzocycloalkene derivatives in high yields (Scheme 64).[154]

Zonov *et al.*[155, 156] performed the first carbonylation of perfluorinated organic compounds with carbon(II) oxide in SbF_5 using perfluorobenzocyclobutene and its perfluoroalkyl and pentafluorophenyl derivatives. In these reactions, the irreversible transformations of the four-membered ring in the product of CO addition to the benzocyclobutenyl

Scheme 61



Scheme 64



cation promote the reaction, which affords fluorinated 2-arylalkenoic acids derived from isochromene and indan-2-one (Scheme 65).[155, 156]

Polyfluorinated indanes and tetralins are also carbonylated with the $CO-SbF_5$ system.[157] Perfluoroindane and its 4-CF_3-, 5-CF_3-, 5-Me- and 1,1-dihydro derivatives add two CO molecules to give, after water treatment, 1-hydropolyfluoroindane-1-carboxylic acids. 1-R-Perfluoroindanes (R = CF_3, C_2F_5, C_6F_5, H) and 1-R-perfluorotetralins (R = C_2F_5, C_6F_5) add one CO molecule yielding 1-R-1-carbonyl fluorides. They are hydrolyzed with decarboxylation of the resulting acids or react with methanol to give the methyl esters of the acids (45% – 84% yields). Perfluoro-2,3-dihydrobenzofuran is converted to both mono- and dicarbonylated products in the $CO-SbF_5$ system.[157]

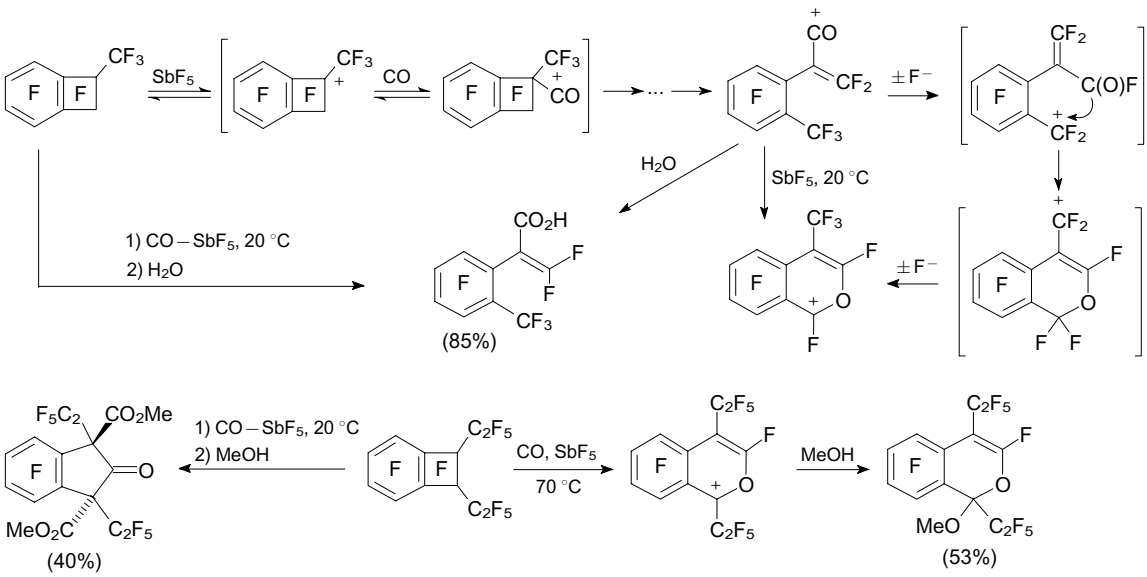
Thus, studies of electrophilic reactions, including cationoid skeletal transformations of polyfluorinated benzocycloalkenes and their derivatives, have been fruitful and have resulted in new knowledge on the effect of fluorine atoms on the behaviour of polyfluoroarenes in electrophilic reactions. The considered reactions, which are new for fluorocarbon chemistry, proved to be synthetically promising. They were employed to prepare poorly accessible perfluorinated alkylphthalides, isochromenones and fluorene and anthracene derivatives. For instance, isochromenones are fluorine-containing analogues of compounds possessing various types of biological activity; and polynuclear perfluoroarenes are employed in microelectronics. One may hope that further investigation of the cationoid reactions of polyfluoroarenes would provide more in-depth understanding of their reactivity, which, in turn, would boost the development of new efficient synthetic routes to diverse polyfluoroaromatic compounds.

5. Reactions of carbocations and radical cations generated from CF_3-substituted alkynes, alkenes, alcohols and ketones. Fluorination of organic compounds in HF

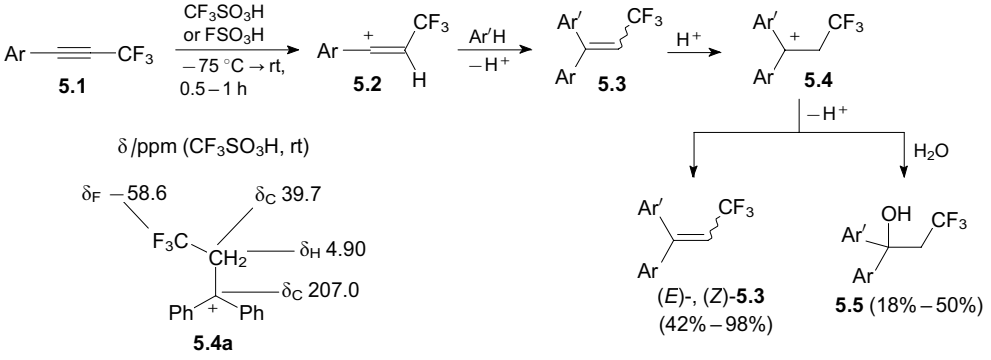
The electrophilic activation (protonation in Brønsted acids or coordination to Lewis acids) of CF_3-substituted alkynes, alkenes, alcohols or ketones using Brønsted superacids (CF_3SO_3H, FSO_3H, HF), strong Lewis acids ($AlCl_3$, $AlBr_3$) or conjugated Brønsted – Lewis acids ($CF_3SO_3H-SbF_5$, FSO_3H-SbF_5, $HF-SbF_5$, $HBr-AlBr_3$, $HCl-AlCl_3$) leads to generation of CF_3-carbocations. These species are highly electrophilic and highly reactive because of the electron-withdrawing properties of the CF_3 group and can react with various nucleophiles (arenes and so on) with high regio- and stereoselectivity.

The protonation of CF_3-alkynes **5.1** with CF_3SO_3H or FSO_3H affords vinyl cations **5.2**, which alkenylate arenes to give alkenes **5.3** (Scheme 66).[158, 159] However, compounds **5.3** are, in turn, protonated in superacids to give tertiary carbocations **5.4**. These species are stable in CF_3SO_3H even at room temperature; they were characterized in detail by

Scheme 65



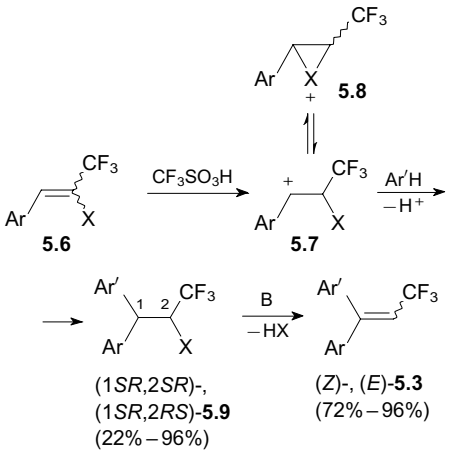
Scheme 66



NMR spectroscopy (the NMR chemical shifts for cation **5.4a** are given in Scheme 66). Depending on the workup procedure employed for superacid reaction solutions, cations **5.4** are subjected to either deprotonation or hydration yielding *E*- and *Z*-alkenes **5.3** or alcohols **5.5**, respectively. Quenching of reaction solutions with anhydrous MeCN or the MeOH – MeONa system gives only compound **5.3**. Treatment with water or aqueous mineral acids or alkalis leads to mixtures of compounds **5.3** and **5.5** (see Scheme 66).

On protonation of (*E*)- and (*Z*)-2-halo-2-CF_3-styrenes **5.6** (X = F, Cl, Br) in Brønsted superacids, benzyl cations **5.7** are generated.[160 – 162] The structures and electrophilic properties of these cations were studied by NMR spectroscopy and computations. According to the obtained data, bromo-substituted cations (X = Br) exist as cyclic bromonium ions **5.8**. However, chloro- and fluoro-substituted cations tend to exist as open forms **5.7**. The subsequent reactions of these cations with arenes afford compounds **5.9** as mixtures of two diastereomers with (1*SR*,2*SR*) and (1*SR*,2*RS*) configurations. By dehydrohalogenation induced by a base (KOH or Bu^{t}OK), compounds **5.9** are converted to mixtures of *E*- and *Z*-isomeric CF_3-alkenes **5.3** (Scheme 67). This dehydrohalogenation is stereoselective, with the product (*Z*)-**5.3** being formed from (1*SR*,2*SR*)-**5.9** and product (*E*)-**5.3** being formed from (1*SR*,2*RS*)-**5.9**, which made it possible to determine the exact structure of each diastereomer of **5.9**.

Scheme 67

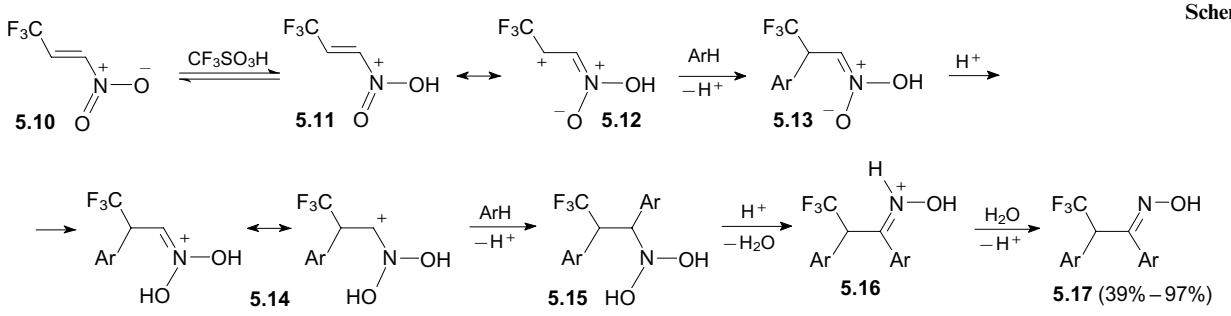


3,3,3-Trifluoro-1-nitropropene **5.10** reacts with arenes in CF_3SO_3H to give the diaryl-substituted CF_3-ketoximes (Scheme 68).[163] This transformation proceeds *via* a series of cationic intermediates **5.11** – **5.16** and affords products **5.17**. Some intermediates (*e.g.*, cation **5.11**) were characterized by NMR spectroscopy (see Scheme 68).

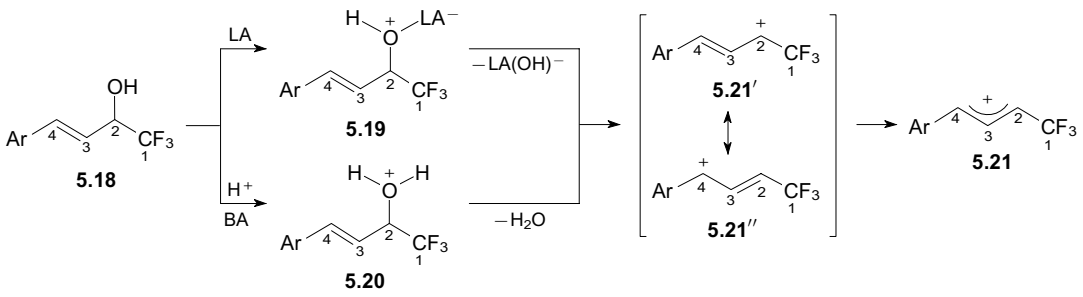
The reactions of CF_3-allylic alcohols **5.18** with Brønsted or Lewis acids involve the intermediate generation of electrophilic species. Oxygen atom coordination to a Lewis acid or protonation by a Brønsted acid gives species **5.19** or **5.20**. Finally, dehydroxylation of alcohols **5.18** results in the formation of CF_3-allylic cations **5.21**, which can be depicted as two resonance structures, **5.21′** and **5.21″**, with the cationic centres at C(2) and C(4) atoms, respectively. Due to the electron-withdrawing nature of the CF_3 group, these allylic cations react with arenes at the C(4) atom (resonance sructure **5.21″**). Intermediates **5.19** and **5.20** possess also high electrophilicity and can react with strong π-donor arenes (Scheme 69).[164, 165]

The reactions of CF_3-alcohols **5.18** with benzene, anisole, veratrole or *o*-xylele in the presence of $FeCl_3$ (room temperature) or FSO_3H (−75 °C) afford exclusively *E*-configured CF_3-alkenes **5.22**. This reaction involves only the C(4) atom of alcohols **5.18** (Scheme 70).[164, 165]

Scheme 68

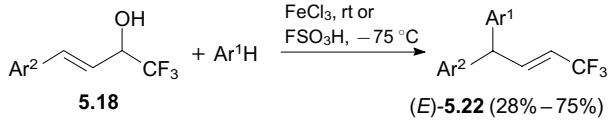


Scheme 69



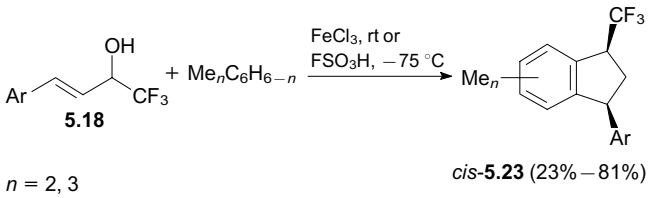
LA is Lewis acid, BA is Brønsted acid

Scheme 70



Stronger π-donor polymethylated arenes (pseudocumene, mesitylene) react with alcohols **5.18** giving only CF_3-indanes **5.23** with predominant *cis*-orientation of substituents in positions 1 and 3 of the indane ring (Scheme 71).[165] *Meta*- and *para*-substituted xylenes show intermediate behaviour, being converted to both CF_3-alkenes **5.22** and CF_3-indanes **5.23**.

Scheme 71

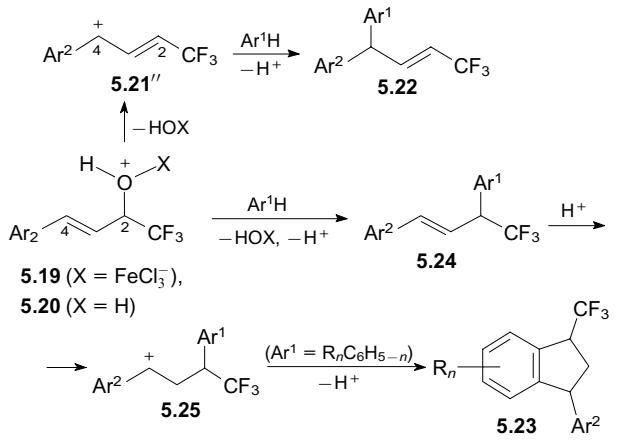


A possible mechanism of these reactions consists of the following steps. Cations **5.19** or **5.20** with C(2) as the electrophilic centre react with donor arenes such as xylenes, pseudocumene or mesitylene to yield compounds **5.24**. The latter are protonated being converted to cations **5.25**, which cyclize to indanes **5.23** (Scheme 72). It is noteworthy that alkenes **5.22** do not undergo cyclization to indanes **5.23** in $FeCl_3$- or FSO_3H-promoted reactions, since the double bond of compounds **5.22** deactivated by the CF_3 group cannot be protonated in superacids. The transformation pathway of alcohols **5.18** to compounds **5.22** or **5.23** depends on the electrophilicity of species **5.19**, **5.20** and **5.21** and nucleophilicity of arenes. In some cases, the reaction follows a mixed mechanism, which gives rise to both types of products, **5.22** and **5.23** (see Scheme 72).[165]

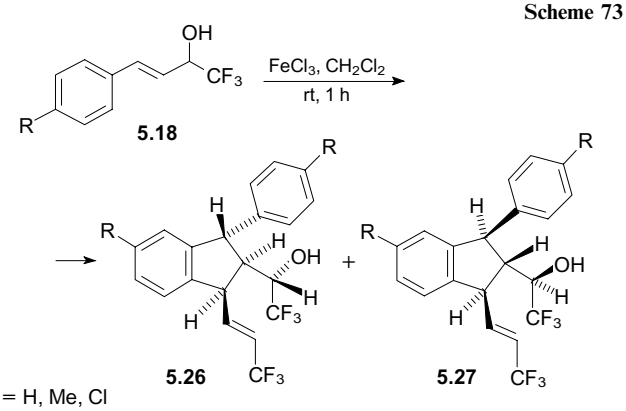
In the absence of arenes as external π-nucleophiles, compounds **5.18** undergo electrophilic 'dimerization' to give diastereomeric indanes **5.26** and **5.27** in 40% – 94% yields (Scheme 73).[164]

The first step of this reaction is the generation of cations **5.21″**. Then the C(4) electrophilic centre of this species attacks the double bond of the initial alcohol **5.18**; this results in generation of benzyl cations **5.28** and **5.29**, which cyclize at the aryl ring giving indanes **5.26** and **5.27**.

Scheme 72



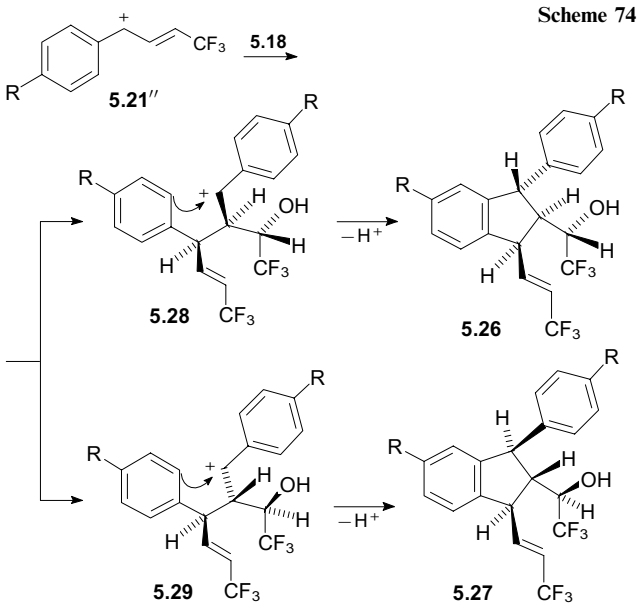
Scheme 73



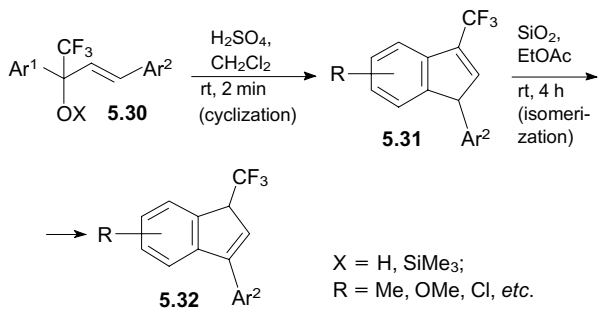
Altogether, this reaction gives rise to two new C – C bonds and four stereocentres. The reaction is relatively stereoselective, as only two of the eight possible diastereomers are formed. The stereochemical configuration of the C(4) atom (the atom numbering is the same as in the starting alcohol **5.18**) is identical for both diastereomers, **5.26** and **5.27**. This implies that the reaction between cation **5.21″** and alcohol **5.18** is completely stereoselective (Scheme 74).[164]

In the presence of H_2SO_4 at room temperature, 2,4-diaryl-substituted CF_3-allylic alcohols **5.30** or their trimethylsilyl ethers quantitatively cyclize to give CF_3-indenes **5.31** as fast as in 2 minutes.[166] The reaction involves the intermediate generation of CF_3-allylic cations, which cyclize with the involvement of the aromatic ring ($Ar^1 = RC_6H_4$) and the allyl triad carbon atom most remote from the CF_3 group. In the presence of silica gel in ethyl acetate, compounds **5.31**

Scheme 74



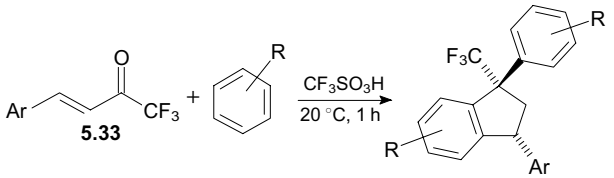
Scheme 75



quantitatively isomerize at room temperature within 4 h to give CF_3-indenes **5.32** *via* a double bond shift (Scheme 75).

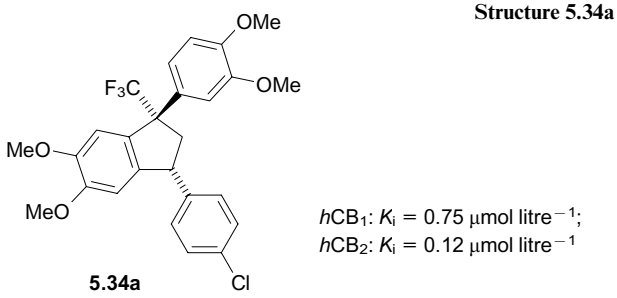
The reaction of CF_3-enones **5.33** with arenes in Brønsted superacids (CF_3SO_3H, FSO_3H) stereoselectively gives only *trans*-1,3-diaryl-1-trifluoromethylindanes **5.34** (Scheme 76).[167, 168] These compounds were investigated as potential ligands for CB_1 and CB_2 cannabinoid receptors. The most promising compound **5.34a** exhibited affinity to both types of receptors with a sixfold selectivity towards the CB_2 receptor without noticeable cytotoxicity in the submicromolar concentration range (K_i is the inhibition constant).

Scheme 76



R = H, Me, OMe; Ar = Ph, 4-ClC_6H_4 *trans*-**5.34** (35% – 85%)

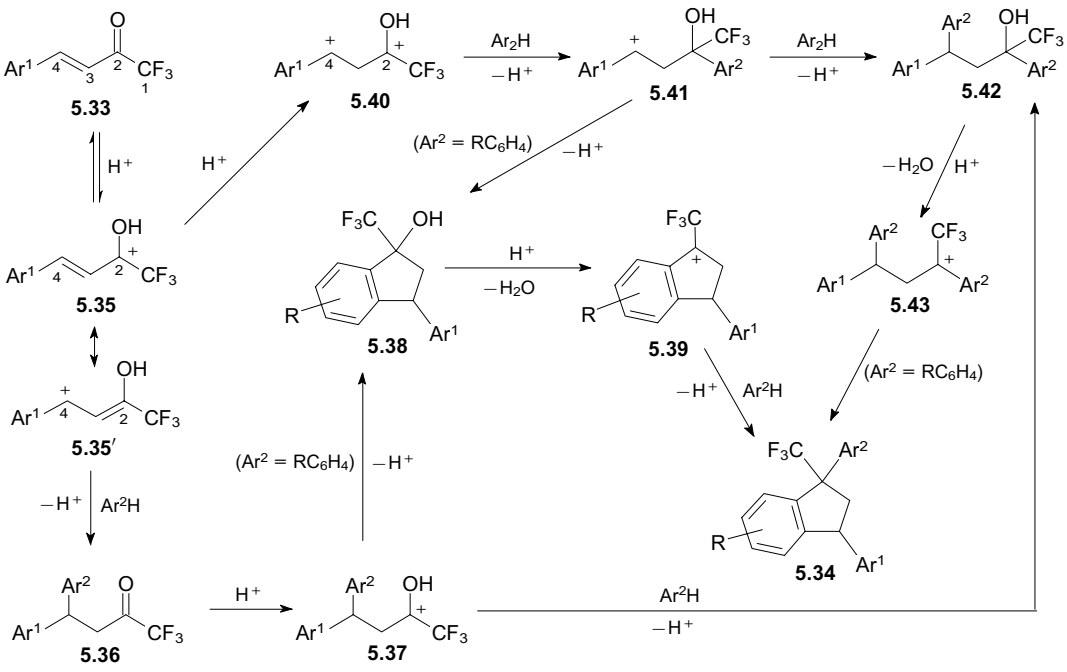
Structure 5.34a



hCB_1: K_i = 0.75 μmol litre^{-1};
hCB_2: K_i = 0.12 μmol litre^{-1}

The most probable pathways of this reaction are those involving either cation **5.35** leading to structures **5.36** – **5.39** and **5.34** or cation **5.40** leading to structures **5.41**, **5.38**, **5.39** and **5.34** (Scheme 77).[168] The formation of indanes **5.34** indicates that both the C(2) carbonyl and C(4) double bond

Scheme 77

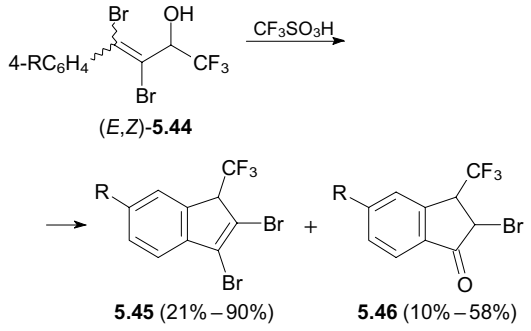


carbon atoms of substrates **5.33** participate in the reaction. The following transformation pathways of CF_3-enones **5.33** to indanes **5.34** were proposed. The reaction of arenes with cation **5.35′** at the C(4) atom affords compound **5.36**, which is protonated to give cation **5.37**. This cation is converted along two alternative pathways, namely, the intermolecular reaction with the arene giving compound **5.42** and intramolecular cyclization to indanol **5.38**. Compounds **5.42** and **5.38** can also arise upon the reaction of dication **5.40** with arene *via* the formation of cation **5.41**. The subsequent transformations of compounds **5.42** and **5.38** can involve the intermediate formation of cations **5.43** and **5.39**, respectively, giving finally indanes **5.34** (see Scheme 77).

Cation **5.39** is a key intermediate for both pathways of this reaction. The reaction of this species with an arene molecule affords indanes **5.34** with *trans*-orientation of bulky aromatic groups. Other intermediates of this reaction, O-protonated forms of **5.35**, were obtained in FSO_3H at -60 to -20 °C and characterized by NMR spectroscopy.

Brominated CF_3-allylic alcohols **5.44** are precursors of multicentre electrophiles under superelectrophilic activation. The reactions of alcohols **5.44** in CF_3SO_3H afford indenes **5.45** and indanones **5.46** as a result of intramolecular cyclization (Scheme 78).[169] The **5.45** : **5.46** product ratio depends on the conditions: a longer reaction time and higher temperature lead to a greater amount, or even exclusive formation, of indanones **5.46**.

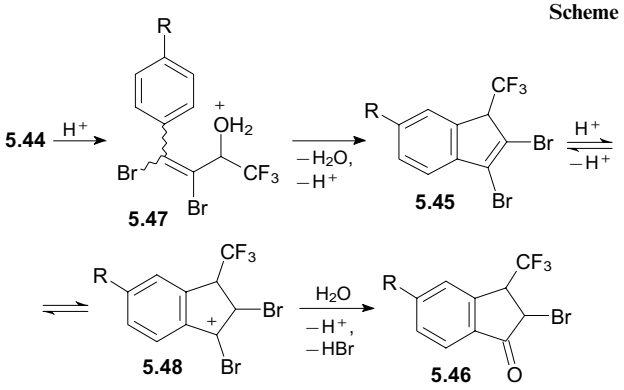
Scheme 78



R = H, Me, OMe, Cl

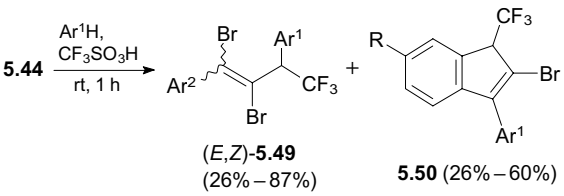
The probable mechanism of this reaction includes the formation of O-protonated species **5.47**, which cyclize to indenes **5.45**; protonation of **5.45** leads to cations **5.48**, which were detected by NMR spectroscopy. Hydrolysis of the reaction mixture is accompanied by deprotonation of cations **5.48** to give indenes **5.45**. Alternatively, the addition of a water molecule to the positively charged atom of **5.48** followed by deprotonation and dehydrobromination affords indanones **5.46** (Scheme 79).

Scheme 79



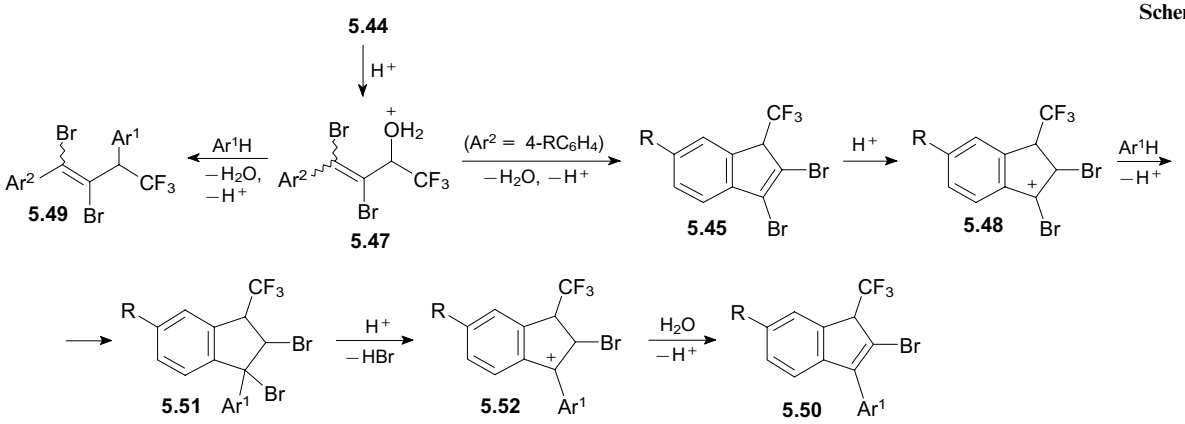
The reaction of alcohols **5.44** with arenes in CF_3SO_3H ends in the formation of dibromoalkenes **5.49** as the major products *via* arylation of the starting alcohols **5.44** at the C(2) atom. This indicates that the process involves O-protonated species **5.47** rather than pristine allylic cations. The reaction is stereoselective, giving most often only *Z*-isomers **5.49**, in which bromine atoms are located on one side of the double bond, although the starting **5.44** are mixtures of *E*- and *Z*-isomers. In some cases, indenes **5.50** are additionally formed (Scheme 80).[169]

Scheme 80



A probable mechanism of formation of compounds **5.49** and **5.50** includes the following steps. Cations **5.47** can react along two pathways. The first one is the reaction with arene, resulting in the formation of alkenes **5.49**. The second, multistep pathway includes (i) cyclization to indenes **5.45**;

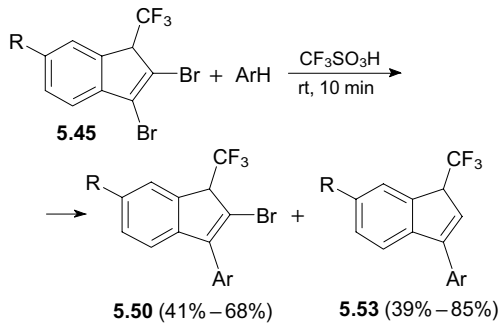
Scheme 81



(ii) protonation of indenes to cations **5.48**; (iii) reaction of the cations with arenes giving compounds **5.51**; (iv) protonation of bromine in the benzylic position of intermediates **5.51** followed by dehydrobromination to stable cations **5.52**, which were characterized by NMR data; (v) deprotonation of cations **5.52** upon hydrolysis of superacid reaction solutions, resulting in indenes **5.50** (Scheme 81).

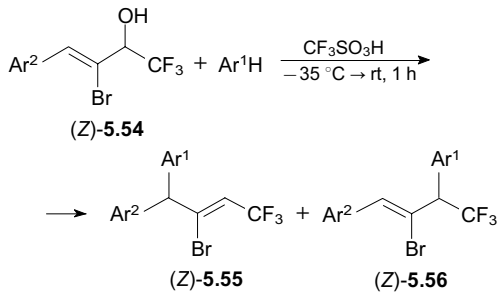
Evidence that indenes **5.50** are formed from compounds **5.45** was gained from investigation of reactions of the latter with arenes in CF_3SO_3H (Scheme 82).[169] Indeed, indenes **5.50** were isolated in good yields when the reaction was conducted at room temperature for 10 min. However, non-brominated indenes **5.53** were formed almost in all cases as side products. The highest yields of **5.53** were attained with π-donor arenes such as *m*-xylene and pseudocumene. This outcome can be attributed to an alternative pathway of transformation of cations **5.52** *via* elimination of Br^+. The steric repulsion between the bromine atom and the cumbersome *ortho*-methyl-substituted aryl moiety at the carbocation centre may serve as an additional driving force of debromination of cations **5.52**; this results in the predominant or exclusive formation of compounds **5.53** (see Scheme 82).

Scheme 82



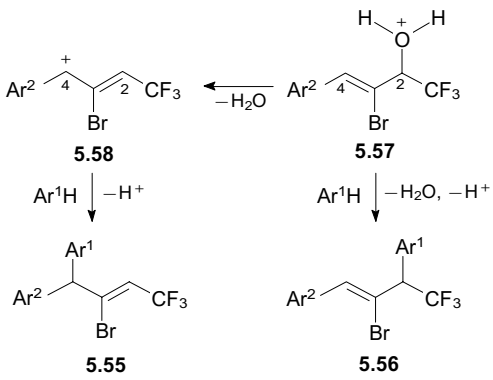
Monobrominated CF_3-allylic alcohols **5.54** react with arenes in CF_3SO_3H to give regioisomer mixtures of brominated CF_3-alkenes **5.55** and **5.56** with *Z*-configuration in an overall yield of 37% – 95% (Scheme 83).[169]

Scheme 83



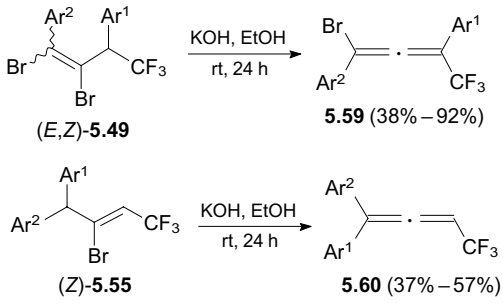
The arylation of alcohols **5.54** mainly involves the C(4) atom and predominantly gives alkenes **5.55**. The formation of two regioisomeric products can be attributed to formation of two types of electrophilic intermediates. On the one hand, cation **5.57**, resulting from O-protonation of alcohol **5.54**, reacts predominantly with arenes at the C(2) atom. On the other hand, the reaction of allylic cation **5.58** involves the C(4) atom (Scheme 84).

Scheme 84



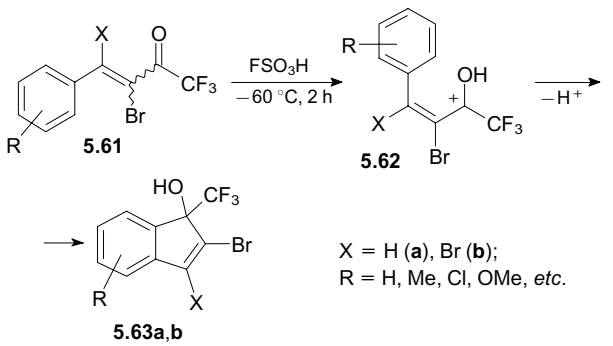
Treatment of bromoalkenes **5.49** and **5.55** with potassium hydroxide in ethanol at room temperature for 24 h affords CF_3-allenes **5.59** and **5.60** (Scheme 85).[169]

Scheme 85



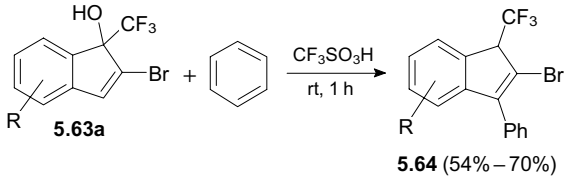
Monobromo- and dibromo-CF_3-enones **5.61** are converted, in FSO_3H at −60 °C, to O-protonated species **5.62** with the protonated carbonyl carbon atom as the electrophilic centre; these species cyclize to indenols **5.63a**,**b** (Scheme 86).[170]

Scheme 86

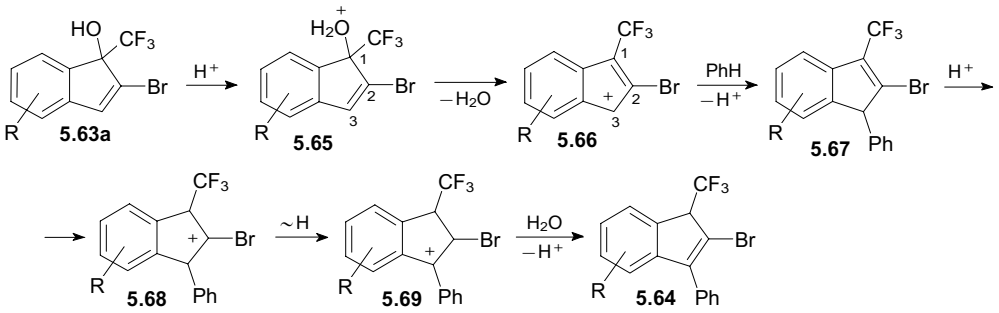


In turn, monobrominated indenols **5.63a** react with benzene in CF_3SO_3H to yield CF_3-indenes **5.64** (Scheme 87).

Scheme 87



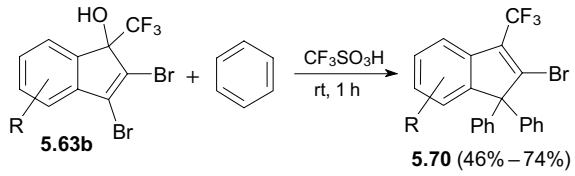
Scheme 88



A possible reaction mechanism includes the protonation of indenols **5.63** with intermediate generation of species **5.65** and then indenyl cations **5.66**, which react with benzene, being converted to compounds **5.67**. The latter are protonated giving cations **5.68**, which rearrange to more stable species **5.69**, and deprotonation of the latter gives the target indenes **5.64** (Scheme 88).

As opposed to monobrominated derivatives **5.63a** (X = H), dibromoindenols **5.63b** (X = Br) react with benzene in CF_3SO_3H to give a different type of CF_3-indenes **5.70** (Scheme 89).

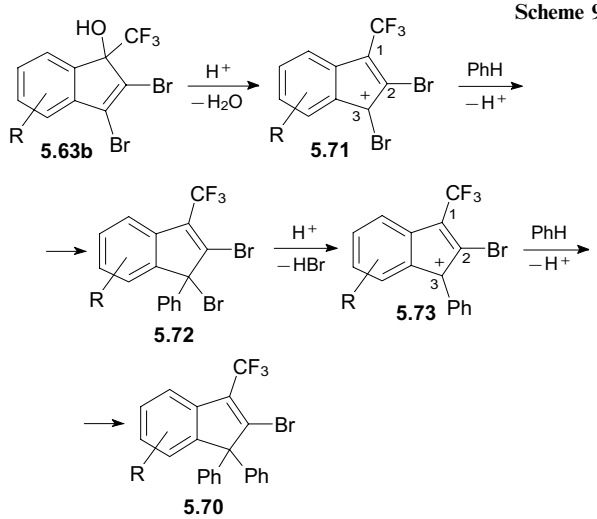
Scheme 89



R = H, Me, Cl, *etc.*

The reaction mechanism is as follows. In the first step, indenyl cations **5.71** with the positively charged C(3) atom are formed. They react with benzene to afford indenes **5.72**. The subsequent elimination of an HBr molecule under superacid conditions gives cations **5.73**. Finally, the reaction of these species with a second benzene molecule involves again the C(3) atom and gives indenes **5.70** (Scheme 90).

Scheme 90



Trimethylsilyl ethers of 1,5-diaryl-3-trifluoromethylpent-1-en-4-yn-3-ols **5.74** are converted in CF_3SO_3H to conjugated propargyl-allyl CF_3-carbocations, which can contain several electrophilic centres (resonance structures **5.75**, **5.75′** and **5.75″**) and react along different pathways. The reactions of these cations with arenes involve the C(1) atom (resonance structure **5.75′**), yielding intially conjugated (*Z*)-CF_3-enynes **5.76**.[171] This is followed by generation of intermediate cations **5.77**, which are converted to CF_3-benzocycloheptadienes **5.78**. The latter are protonated to give cations **5.79**, which finally cyclize to bicyclic compounds **5.80** (Scheme 91). The unusual structures such as **5.80** have been called helicopter-like molecules, in which the CF_3 group is the propeller and the bridgehead aryl ring is the tail. By varying the reaction conditions (the amount of superacid, temperature and time), one can selectively (step-by-step) obtain compounds **5.76**, **5.78** and **5.80**.

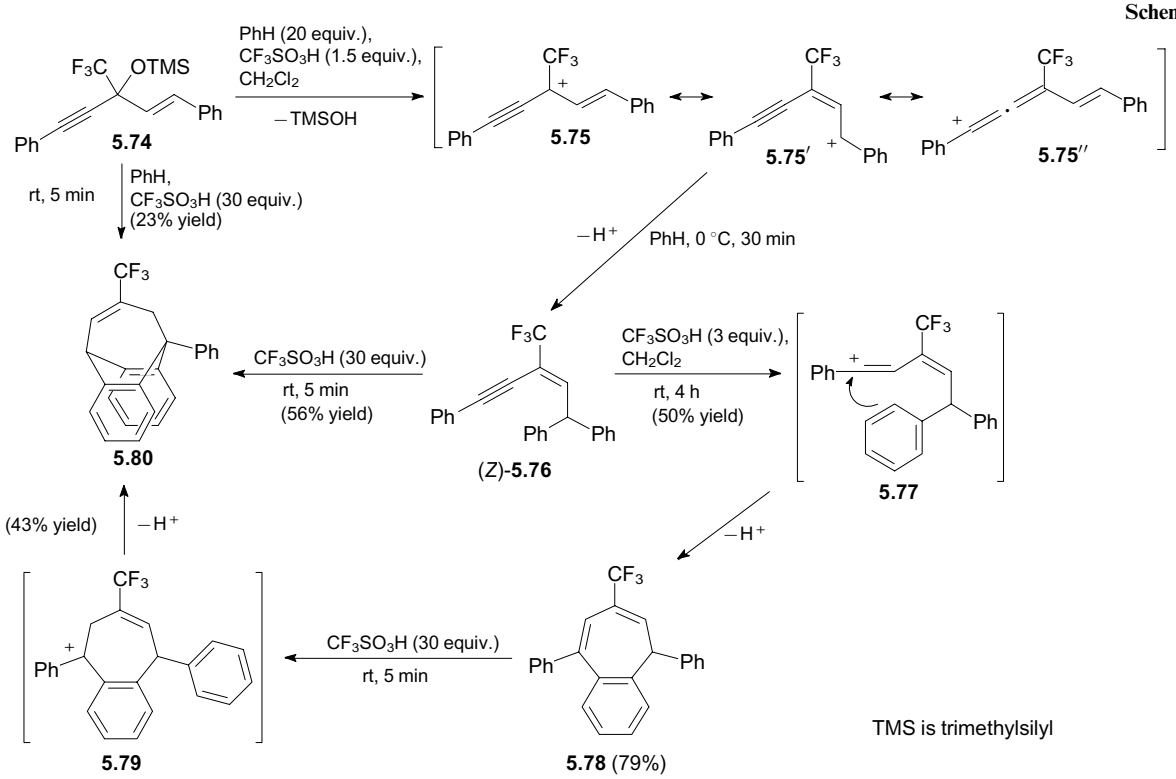
Yet another type of electrophilic, highly reactive intermediates, CF_3-radical cations, can be generated from CF_3-substituted alkynes and alkenes by single-electron oxidation in strong acids. Indeed, oxidation of 3,3,3-trifluoro-1-(4-methoxyphenyl)propyne (**5.1**) in the $PbO_2-CF_3CO_2H-CH_2Cl_2$ system, which proceeds *via* the intermediate generation of radical cation **5.81**, affords diketone **5.82** as the oxidative dimerization product (Scheme 92).[172] Note that the new C–C bond of compounds **5.82** is formed regioselectively involving the acetylenic carbon atoms adjacent to the CF_3 group. Ketone **5.83**, resulting from addition of a CF_3CO_2H molecule to the triple bond giving vinyl trifluoroacetate **5.84** and its subsequent hydrolysis during the workup of the reaction mixture, was isolated as a competitive reaction product.

Similarly, arylacetylenes **5.85** with the $C(O)CF_3$ electron-withdrawing group are converted to radical cations **5.86**. The reaction results in regioselective formation of a new C–C bond, giving rise to CF_3-furans **5.87** (Scheme 93).[173, 174] The so high regioselectivity of C–C bond formation in the reactions of radical cations **5.81** and **5.86** is a consequence of their electronic structure. The spin density (free-radical centre) is localized in these species on the acetylenic carbon atom adjoining the electron-withdrawing substituent [CF_3 or $C(O)CF_3$]; therefore, dimerization of two radical cations involves exactly these carbon atoms.[175]

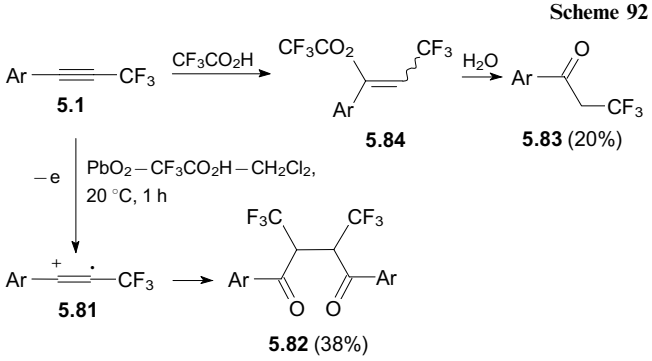
The oxidation of CF_3-arylalkene **5.88** with the $PbO_2-CF_3SO_3H$ system *via* radical cation **5.89** is regio- and stereoselective, giving rise to biaryl **5.90** with *Z*-configurations of both double bonds (Scheme 94).[176]

Using the PbO_2-HF oxidative system, one can introduce fluorine atoms into complex organic molecules. For example, diarylacetylenes **5.91** containing electron-with-

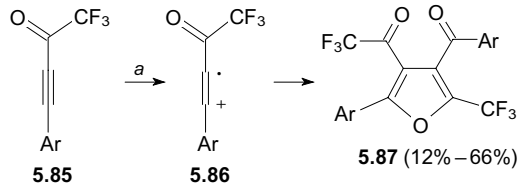
Scheme 91



Scheme 92

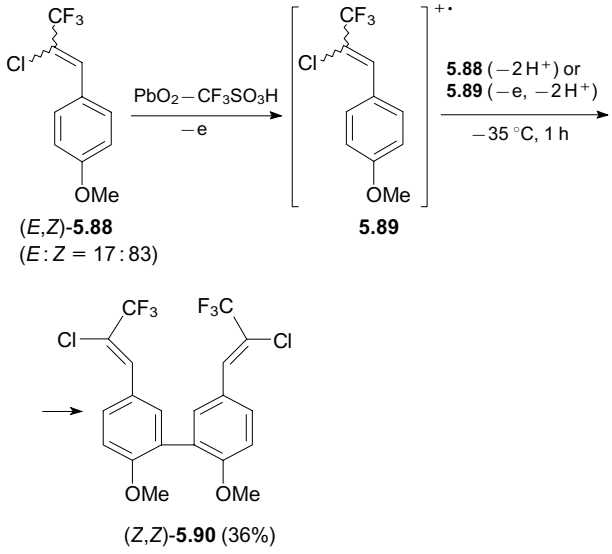


Scheme 93

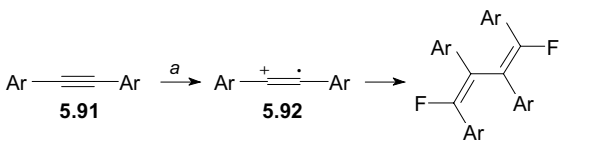


(*a*) $PbO_2 - CF_3CO_2H - CH_2Cl_2$, 0 °C → rt, 1 – 5 h

Scheme 94



Scheme 95

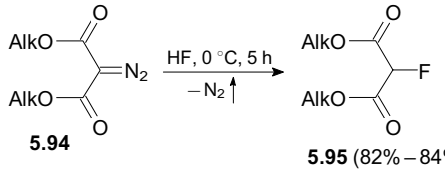


(*a*) $PbO_2 - HF$, – 10 °C, 0.5 – 3 h

drawing substituents can be oxidized in this system (Scheme 95).[177] This reaction follows the radical cation **5.92** dimerization pathway, with cationic intermediates reacting with fluoride anions to give difluorobutadienes **5.93**.

One more example of direct fluorination of organic compounds is displacement of the diazo group of diazo malonates **5.94** in HF to give monofluoromalonates **5.95** (Scheme 96).[178]

Scheme 96



5.94 **5.95** (82% – 84%)

6. 1-Halo-2-trifluoroacetylacetylenes and their cycloadducts: new versatile reagents in organic synthesis

Cycloaddition reactions are among the most versatile methods for the construction of carbo- and heterocyclic fluorine-containing systems ranging from small molecules to complex fused polycycles.[179] Often, this method is not only the simplest, but also the only possible one for the design of an organic structure.

Of particular interest are reactions involving highly electrophilic acetylenes activated with the trifluoroacetyl group, which is a potent mesomeric acceptor.[180, 181] Methods for the synthesis of such compounds have long remained scarce and their known cycloaddition reactions have been mainly limited to Diels – Alder reactions.[182 – 185] Alkynes containing a trifluoroacetyl group and a halogen atom as substituents at the C≡C bond were unknown until recently. It was assumed that these compounds not only should possess very high reactivity towards known transformations, but may also exhibit some properties not inherent in alkynes. It is also noteworthy that the presence of a reactive halogen atom in the β-position of the C=C bond relative to the trifluoroacetyl group in the cycloadducts provides access to a broad range of new systems, in particular, fused fluorine-containing heterocycles.

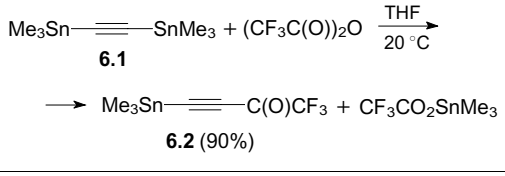
6.1. Synthesis of 1-halo-2-trifluoroacetylacetylenes

Several methods for the introduction of a trifluoroacetyl group into the acetylene molecule are currently known.[180] The most popular approach is the reaction of acetylene-based organolithium or -magnesium compounds with trifluoroacetic acid derivatives.[186 – 188] One more general method for the synthesis of alkynyl trifluoromethyl ketones is oxidation of trifluoromethyl-substituted propargyl alcohols, although preparation of the latter, most often, also includes a step of addition of metallated acetylenes to fluoral.[188, 189]

1-Halo-2-trifluoroacetylacetylenes occupy a special place among alkynes. Analysis of their structures demonstrated that these compounds are expected to behave as exceptionally reactive electrophiles and to have relatively low boiling points, which imposes heavy limitations on the suitable processes for their synthesis and isolation.[190] For the synthesis of alkynes of this type, bis(trimethylstannyl)-acetylene (**6.1**) was proposed as a versatile substrate; this compound is readily formed from lithium acetylide and trimethyltin chloride.[191] This process has been optimized,[192, 193] which allowed isolation of up to 150 – 200 g of the desired product per batch.

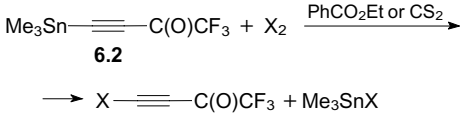
Trifluoroacetic anhydride, which has enhanced electrophilic activity, undergoes an exothermic reaction with acetylene **6.1** in THF even at 20 °C to give 1-trimethylstannyl-2-trifluoroacetylacetylene (**6.2**), which can be isolated from the reaction mixture in high yield by vacuum distillation (Scheme 97).[185, 192, 193]

Scheme 97



Despite the presence of both nucleophilic and electrophilic centres in the molecule, compound **6.2** is stable on storage and starts to decompose only above 85 – 90 °C. Chlorine or bromine react with alkyne **6.2** even at −25 °C, while iodine reacts much more slowly in the temperature range of 0 – 5 °C; this gives the target 1-halo-2-trifluoroacetylacetylenes **6.3a – c** in high yields (Scheme 98).[192, 193]

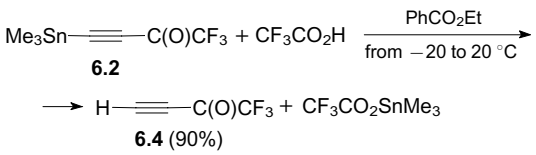
Scheme 98



X = Cl (**a**), Br (**b**), I (**c**)

Monosubstituted trifluoroacetylacetylene (**6.4**) was previously synthesized in a minor amount in a low yield as a mixture with isomeric trifluorotetrolaldehyde.[194] It was shown[195] that alkyne **6.4** is formed in a high yield upon acidification of stannylated acetylene **6.2** with trifluoroacetic acid (Scheme 99). With high-boiling ethyl benzoate as the solvent, the target product can be isolated from the reaction mixture by mere distillation.

Scheme 99



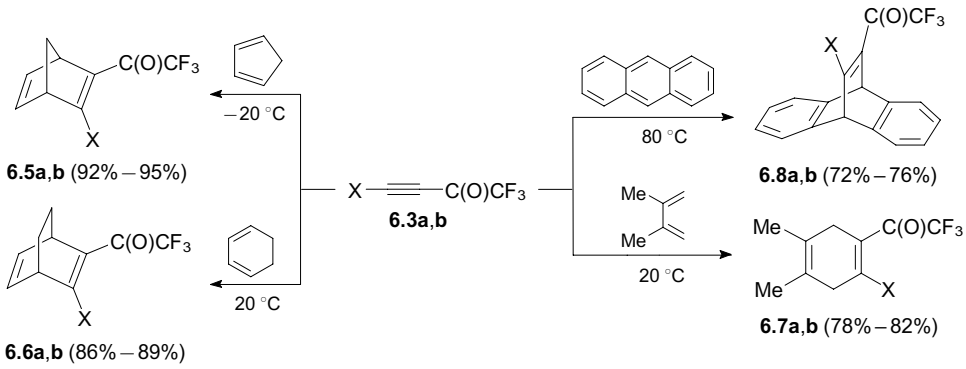
Thus, compound **6.2** can be regarded as a versatile precursor in the synthesis of some electrophilic alkynes, which cannot be synthesized by traditional methods.

6.2. Diels – Alder reactions involving 1-halo-2-trifluoroacetylacetylenes

Halogenated acetylenes **6.3a – c** are probably most reactive of the known acetylenic dienophiles, as they rapidly add many carbodienes even at reduced temperatures.[185, 192, 196] They react with dienes to give cycloadducts **6.5a**,**b** – **6.7a**,**b** in high yields. The reaction with the least reactive diene, anthracene, proceeds on refluxing of the components in benzene and gives adducts **6.8a**,**b** (Scheme 100).

Promising types of Diels – Alder reactions are the reactions involving heterocyclic dienes; of these, furans and *N*-acylpyrroles are used most often. It was found[196] that chloride **6.3a** undergoes an exothermic reaction with furan and *N*-methoxycarbonylpyrrole, which affords relatively unstable 7-oxa- and 7-azanorbornadienes **6.9a,b**, whereas

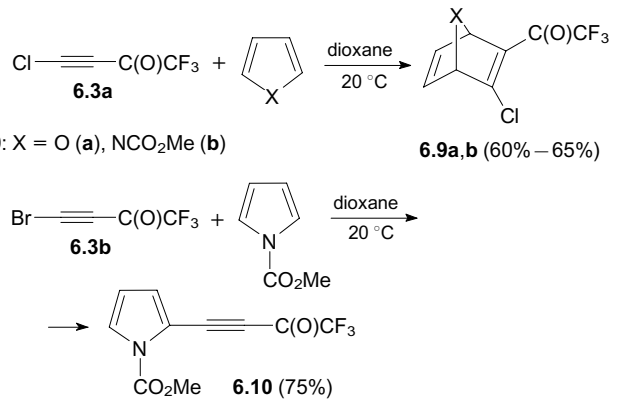
Scheme 100



X = Cl (**a**), Br (**b**)

bromide **6.3b** reacts with *N*-methoxycarbonylpyrrole according to an unusual electrophilic alkynylation pathway leading to adduct **6.10** (Scheme 101).

Scheme 101



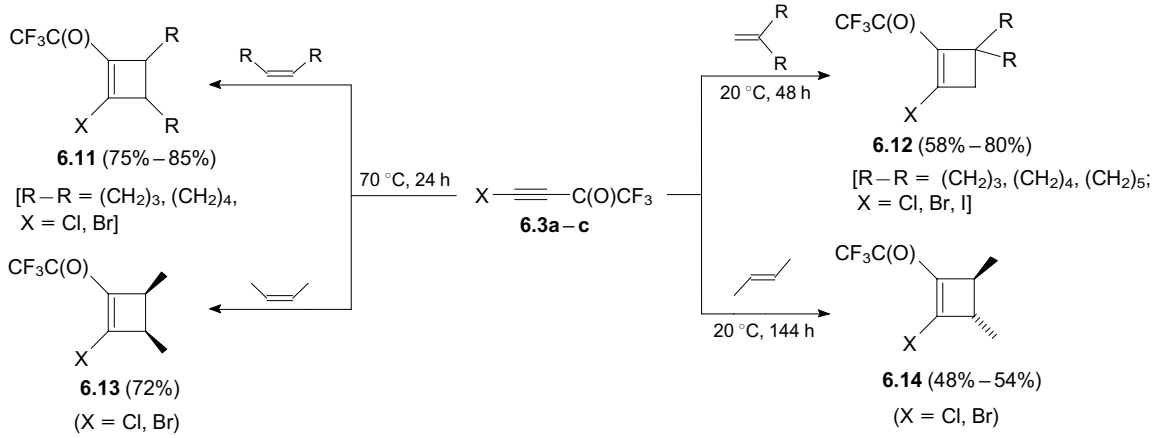
6.3. [2 + 2]-Cycloaddition reactions of trifluoroacetylacetylenes

In a study of the reaction of bromide **6.3b** with isoprene by ^{1}H NMR spectroscopy, the complex product mixture was found to contain compounds that did not result from the Diels – Alder reaction.[192, 193] This observation suggested that acetylenes **6.3a** – **c** are also able to react with simple alkenes. The first experiments not only confirmed this assumption, but also provided quite unusual results: it was shown that halides **6.3a** – **c** react with alkenes to give [2 + 2]-cycloaddition products **6.11** – **6.14** in the dark without a catalyst, with excess alkene serving as the solvent (Scheme 102). The reactions also give minor amounts of isomeric ene addition products, the amount of which depends on the natures of the alkene and haloacetylene.[193] In the case of 1,1-disubstituted alkenes, the reaction proceeds even at 20 °C, while the addition of 1,2-disubstituted alkenes requires heating to 70 °C; virtually no resinification products are formed.

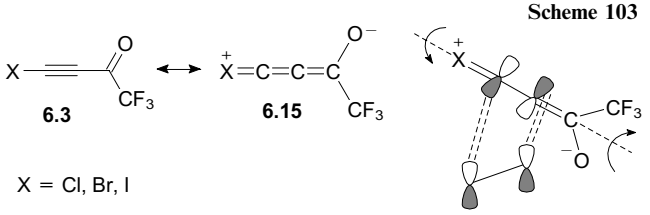
A peculiarity of this transformation is that it belongs to the type of orbital symmetry-forbidden reactions and takes place under exceptionally mild conditions, requiring no irradiation or catalyst. To eliminate the orbital symmetry prohibition imposed by the Woodward – Hoffmann rule on the found [2 + 2]-cycloaddition reactions, it was hypothesized that because of the strong negative mesomeric effect of the trifluoroacetyl group in molecules **6.3a** – **c**, the degree of double bonding between the terminal carbon atom and the halogen atom sharply increases and the C≡C bond order decreases. The resonance structure **6.15** describing this electron density redistribution is a cumulene, which enables the concerted antarafacial [$_\pi$2s – $_\pi$2a]-cycloaddition of acetylenes **6.3a** – **c** to alkenes (Scheme 103).

The proposed mechanism was experimentally verified by investigating the reactions of some alkenes with acetylene **6.4**, in which the C≡C bond is also activated by the

Scheme 102

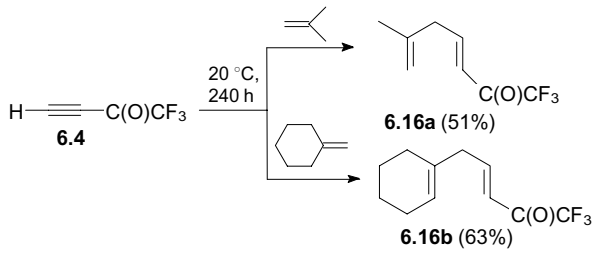


Scheme 103



trifluoroacetyl group; however, the second substituent does not have a mesomeric effect, which precludes the formation of the cumulene resonance structure similar to **6.15**.[193] Indeed, it was shown that compound **6.4** is less reactive than halides **6.3a**–**c**. However, it slowly reacts with isobutylene and methylenecyclohexane at 20 °C to give ene adducts **6.16a**,**b** as the only products, whereas not even traces of [2 + 2]-cycloadducts are detected (Scheme 104). These results support the assumption that the cumulene resonance structure is necessary for the concerted [2 + 2]-cycloaddition of acetylenes to alkenes to occur.

Scheme 104

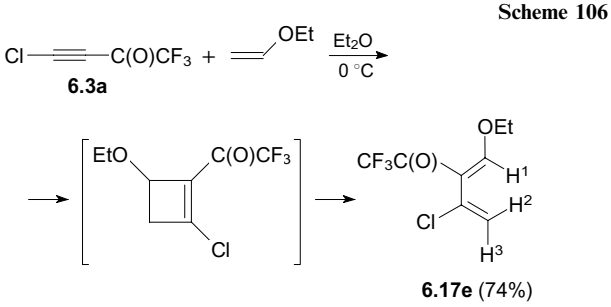


Due to abnormally high electrophilicity of the C≡C bond, alkyne **6.3a** very readily adds to alkyl vinyl ethers.[197] The reaction proceeds even at 0 °C in dilute solutions in diethyl ether and gives [2 + 2]-cycloadducts **6.17a**–**d** in good yields (Scheme 105).

The reaction of the simplest vinyl ether derivative, ethyl vinyl ether, with acetylene **6.3a** rapidly proceeds even at 0 °C; however, cyclobutene thus formed undergoes spontaneous rearrangement to substituted buta-1,3-diene **6.17e**, which is formed as a single stereoisomer (Scheme 106).[197]

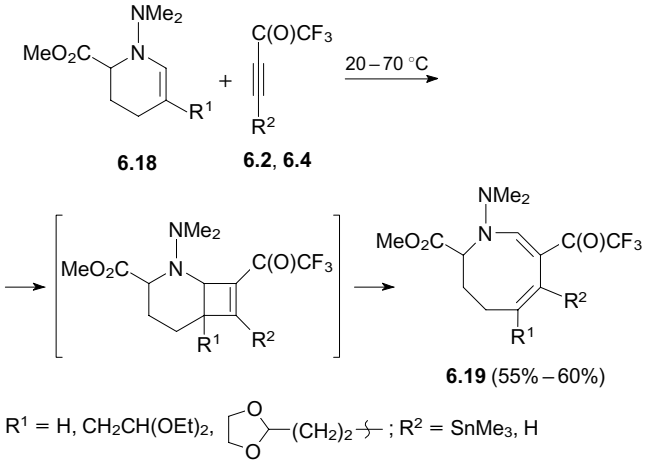
It is important that acetylenes **6.2** and **6.4** without a halogen atom at the C≡C bond do not react with simple alkenes and alkyl vinyl ethers, but they readily add polysubstituted tetrahydropyridines **6.18**, which exist as cyclic enamines.[198] The [2 + 2]-cycloaddition products formed at 20 °C spontaneously rearrange to polysubstituted trifluoroacylated tetrahydroazocines **6.19**. The ease of this rearrangement can be attributed to the fact that formation

Scheme 106



of the long chain of conjugation of the potent electron-withdrawing trifluoroacetyl group with the π-electron system of dienamine in compounds **6.19** is energetically favourable (Scheme 107).

Scheme 107

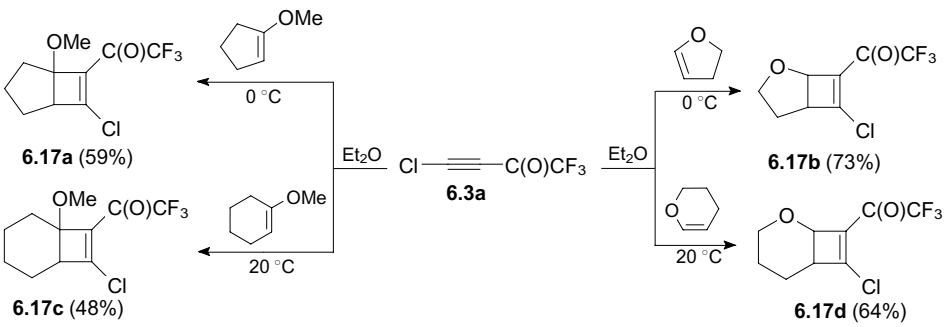


Probably, this method opens up broad opportunities for the synthesis of trifluoroacylated polysubstituted tetrahydroazocines **6.19** from cycloadducts derived not only from acrylic acid derivatives, but also from maleic or fumaric acid and other dienophiles. There are also good prospects for hydrogenolysis of the N–N bond and cross-coupling reactions involving the C–$SnMe_3$ bond in heterocycles **6.19**.

6.4. Reactions of 1-halo-2-trifluoroacetylacetylene cycloadducts

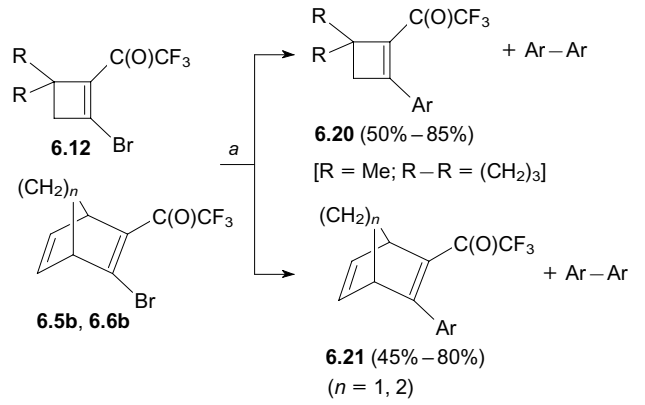
The [4 + 2]- and [2 + 2]-cycloaddition reactions of trifluoroacetylacetylenes **6.3a**–**c** can be used for the synthesis of new compounds with a skeleton structure varying over broad

Scheme 105



limits and corresponding to β-halovinyl ketones. The expected high mobility of the halogen atom and the presence of several reactive functional groups in the resulting cycloadducts suggested that these compounds can serve as versatile reagents in numerous functionalization and heterocyclization reactions. Koldobskii *et al.*[196,199] studied some transformations accompanied by displacement of the halogen atom. It was shown that in the presence of tetrakis(triphenylphosphino)palladium, bromides **6.5b**, **6.6b** and **6.12** readily undergo the Negishi reaction with various hetaryl and aryl organozinc compounds to give cross-coupling products **6.20** and **6.21** containing no trifluoromethylcarbinol impurities (Scheme 108).

Scheme 108

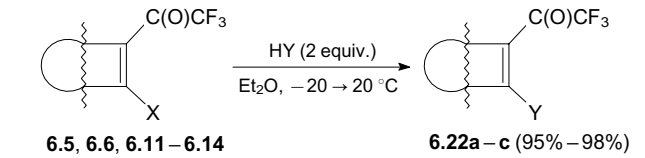


(*a*) $ArZnBr$, $Pd(PPh_3)_4$ (5 mol.%), THF, 20 °C;
Ar = 2-Th, 2-Fu, Ph, 4-FC_6H_4; Th is thienyl, Fu is furyl

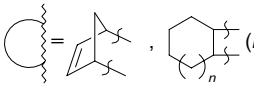
The key drawback of this method is contamination of the target products **6.20** and **6.21** by a biaryl impurity difficult to separate, which stimulated the search for alternative methods for cycloadduct functionalization. It was found that compounds **6.5**, **6.6** and **6.11**–**6.14** (chlorides and bromides are equally reactive) react with dimethylamine, diethylamine or pyrrolidine (2 equiv.) in a cooled diethyl ether solution to give enamino ketones **6.22a**–**c** in a nearly quantitative yield.

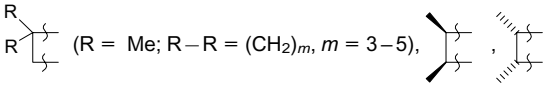
In reactions with organolithium reagents, compounds **6.22** behave as ambident electrophiles, *i.e.*, they add nucleophiles not only to the β-position of the conjugated C=C bond (1,4-addition), but also to the carbonyl group

Scheme 109



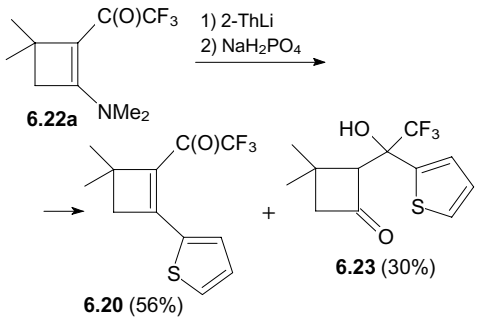
X = Cl, Br; Y = NMe_2 (**a**), NEt_2 (**b**), $N(CH_2)_4$ (**c**);

here and in Schemes 112–116:  (*n* = 0, 1),

 (R = Me; R–R = $(CH_2)_m$, *m* = 3–5),

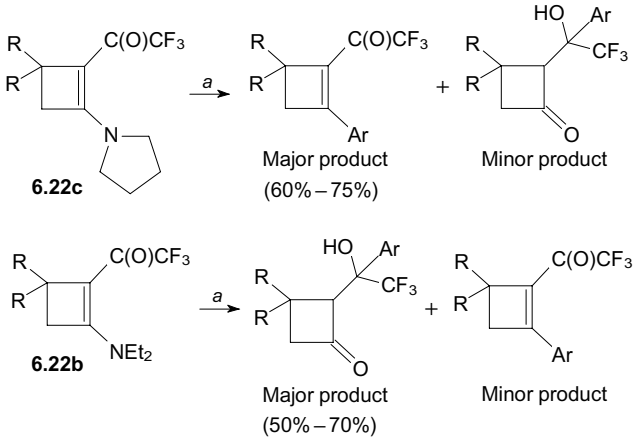
(1,2-addition); this proved to be a new transformation among β-enamino ketones.[200] The subsequent acid hydrolysis of the reaction products leads to an easily separable mixture of, for example, β-arylvinyl ketone **6.20** and polysubstituted cyclobutanone **6.23** as a single diastereomer (Scheme 110).

Scheme 110



It was found that the nucleophile addition pathway strongly depends on the nature of the dialkylamino group in compounds **6.22**.[200] In the case of pyrrolidine derivatives, β-arylvinyl ketones **6.20** and **6.21** are the major reaction products, whereas β-diethyl enamino ketones are mainly converted to polysubstituted cyclobutanones **6.23** (Scheme 111); the product ratio changes in some cases by more than an order of magnitude! Probably, this pronounced difference between addition pathways is caused by not only higher shielding of the vinylogous β-carbon centre of the enamine C=C bond by the bulky diethylamino group, but also disruption of the planarity and, hence, a decrease in the conjugation of the nitrogen lone pair with C=C bond and the carbonyl group in diethylamine derivatives in comparison with that in pyrrolidines.

Scheme 111

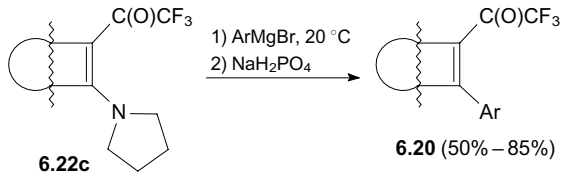


(*a*) 1) ArLi; 2) NaH_2PO_4; R = Me; R–R = $(CH_2)_3$, $(CH_2)_5$;
Ar = 2-Fu, 2-Th, 2-thiazolyl

Despite the fact that the reaction of pyrrolidine enamino ketones **6.22** with relatively weakly basic 2-thienyllithium, 2-furyllithium or 2-thiazolyllithium gives high yields of β-arylvinyl ketones (see Scheme 111), more strongly basic 4-fluorophenyllithium and phenyllithium react with any

compound **6.22** forming only trace amounts of β-arylvinyl ketones, with enolization of enamino ketones and, to some extent, 1,2-addition being the predominant processes. In order to suppress enolization and modify the addition regioselectivity, enamino ketones **6.22a – c** were allowed to react with organomagnesium compounds.[200] It was found that Grignard reagents of different nature (even markedly differing in the thermodynamic basicity) react with pyrroldine enamino ketones **6.22c** to give exclusively β-arylvinyl ketones **6.20** in high yields, while the 1,2-addition and enolization reactions are completely suppressed (Scheme 112).[200]

Scheme 112

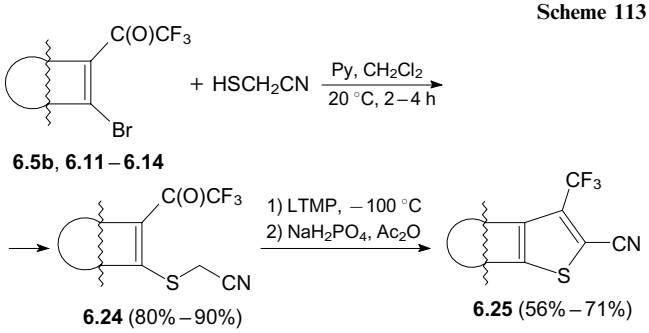


The results indicate that this method is preferable over the Negishi synthesis of compounds **6.20**, because it has better reproducibility, does not produce hard-to-separate impurities and allows more diverse functionalization of substrates, for example, the synthesis of alkyl and thiazolyl derivatives. Unlike organolithium compounds, Grignard reagents show no dependence of the regioselectivity of addition to enamino ketones on the thermodynamic basicity, the reactions always giving only 1,4-adducts.

Since the [4 + 2]- and [2 + 2]-cycloadducts of acetylenes **6.3a – c** have a β-halovinyl ketone structure, they can serve as convenient substrates in the synthesis of various classes of trifluoromethylated heterocyclic compounds in which the fused carbocyclic skeleton can also be varied over wide limits. It is worthy of special note that aromatic and heteroaromatic compounds fused to the cyclobutane moiety are representatives of a new class of compounds, cyclobutarenes; and no general methods for the synthesis of such structures were available for a long time. A series of studies[201 – 205] demonstrate the scope of application of cycloadducts **6.5**, **6.11 – 6.14** as versatile heterocyclization reagents.

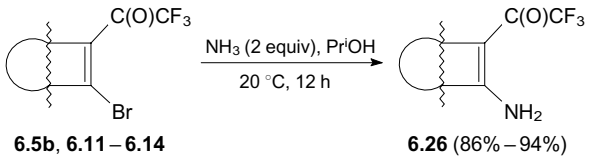
For example, these compounds readily react with thiogycolic acid nitrile in the presence of pyridine to give ketonitriles **6.24** in high yields. Treatment of these products with lithium 2,2,6,6-tetramethylpiperidide (LTMP) at low temperature and then with acetic anhydride leads to fused trifluoromethylated nitriles **6.25** with an annulated thiophene ring in high yield (Scheme 113).[201]

Scheme 113



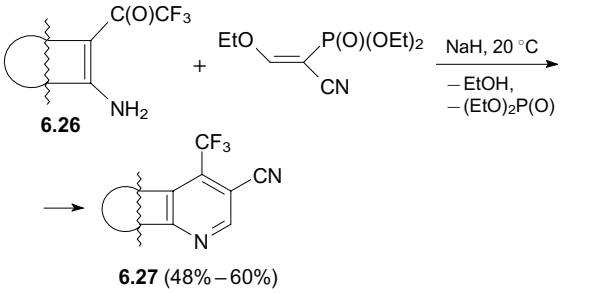
Trifluoromethylated pyridines belong to one of the most interesting and pharmacologically promising classes of fluorinated heterocycles. The amination of cycloadducts **6.5**, **6.11 – 6.14** was investigated as the first step of the synthesis of pyridines from these cycloadducts. It was ascertained that upon the reaction with a solution of ammonia in isopropyl alcohol, they are converted to trifluoromethyl enamino ketones **6.26** with a free amino group and a strained carbocyclic skeleton in high yield (Scheme 114).[202]

Scheme 114



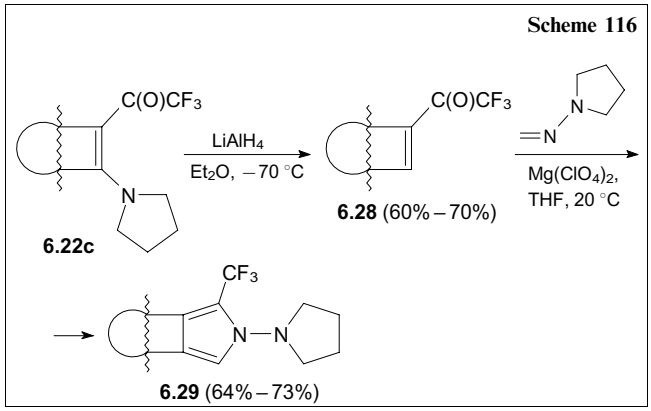
The reaction of compounds **6.26** with diethyl (1-cyano-2-ethoxyvinyl)phosphonate in the presence of sodium hydride proceeds as a complex cascade process (Scheme 115) including the steps of amino group deprotonation, Michael addition and intramolecular Wittig – Horner – Emmons reaction. This gives various trifluoromethylated pyridines **6.27** fused to strained carbocycles in preparative yields.[202]

Scheme 115



An interesting synthesis of complex trifluoromethylated pyrroles has been proposed.[203] The reduction of pyrrolidine enamino ketones **6.22c** led to the synthesis of α,β-unsaturated ketones **6.28**, which add 1-methyleneaminopyrrolidine as a C-nucleophile in the presence of magnesium perchlo-

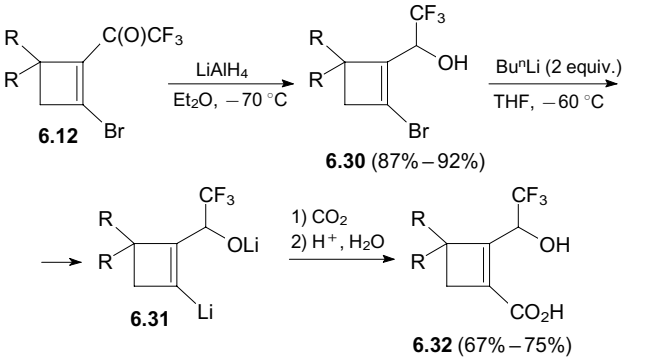
Scheme 116



rate. The subsequent dehydration of the intermediates affords the target products **6.29** in good yields (Scheme 116).

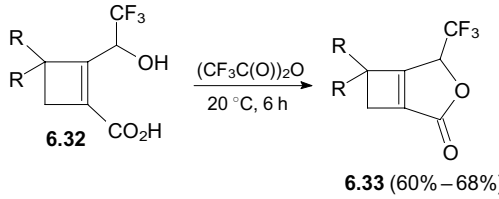
The above-described methods for functionalization and heterocyclization of adducts **6.5**, **6.11** – **6.14** include a nucleophilic substitution step in which the labile halogen atom in the β-position of the C=C bond is displaced. A fundamentally different approach has also been reported,[204, 205] namely, anionic heterocyclization using new organolithium trifluoromethylated cyclobutenes. It was shown that bromides **6.12** are reduced by lithium aluminium hydride to give high yields of carbinols **6.30**, in which the bromine atom and the C=C bond are retained. At low temperature, these compounds react with butyllithium (2 equiv.) yielding organolithium compounds **6.31**, which can be carboxylated to give hydroxy acids **6.32** (Scheme 117).

Scheme 117



Although hydroxy acids **6.32** proved to be stable to lactonization, on dissolution in excess trifluoroacetic anhydride, they are converted to lactones **6.33** in preparative yields (Scheme 118).

Scheme 118



R = Me; R – R = $(CH_2)_3$, $(CH_2)_5$

The structure of lactones **6.33** opens up broad opportunities for further transformations, both addition to the activated C=C bond and transformations of the reactive carboxyl group.

Thus, on the basis of the above data, it can be concluded that 1-halo-2-trifluoroacetylacetylenes and their cycloadducts are versatile and multi-purpose reagents. Their transformations constitute quite a new trend of organic synthesis, which appeared not more than a decade ago and has good prospects for further development. A considerable part of the prospects is related to the general nature and substrate diversity of the anomalous thermal [2 + 2]-cycloaddition reaction of electron-withdrawing haloacetylenes, which is evidently a new facile route to complex polysubstituted cyclobutenes. However, the question of how strong electron-withdrawing properties are required for the second substituent in haloacetylene for [2 + 2]-cycloaddition with alkenes to proceed is still open. For example, difluoroacetyl derivatives of haloacetylenes are unknown, and, although they are expected to be somewhat less electrophilic than compounds **6.3a** – **c**, they probably could also serve as versatile building blocks for the assembly of new strained carbocycles and heterocycles containing difluoroacetyl and difluoromethyl groups. Haloacetylenes activated by strong heteroatomic acceptors such as sulfonyl, phosphoryl or nitro groups are also virtually unexplored. One more relevant task is to develop catalyzed [2 + 2]-cycloaddition, which could be able to sharply increase the regioselectivity of reactions involving monosubstituted alkenes or, in the presence of a chiral catalyst, to provide enantioselective synthesis of fluorinated cyclobutarenes. It is worthy of special note that reactions of haloacetylenes **6.3a** – **c** with simple nucleophiles are still unknown.

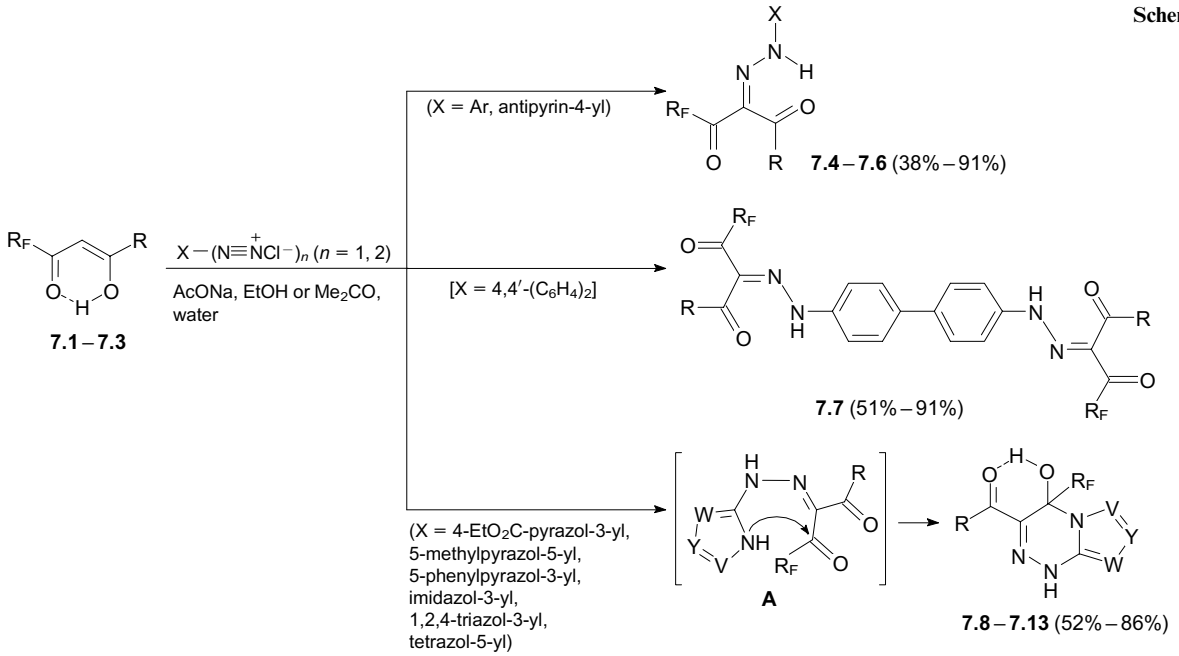
Further study of the chemistry of cycloadducts and their derivatives obtained from acetylenes **6.3a** – **c** seems important. Indeed, deprotonation of the free amino group of enamino ketones **6.26** is likely to give new anionic nucleophilic trifluoromethylated 1-azadienes reactive towards the Diels – Alder reactions and numerous cascade transformations including the Michael addition and intramolecular aldol crotonic condensation, which yield complex polysubstituted heterocyclic systems fused to strained carbocyclic skeletons. Enamino ketones **6.26** could also serve as exceptionally useful substrates of the Friedlander reaction, which opens up the way to polysubstituted fluorinated heterocyclic compounds.

7. Chemistry of polyfluorinated 2-(het)arylhydrazinylidene-1,3-dicarbonyl compounds

1,3-Dicarbonyl compounds (1,3-DC), in particular, fluorine-containing ones, are among the most demanded building blocks suitable for solving a variety of synthetic tasks, in particular, the targeted preparation of practically valuable molecules.[206 – 210] A modern trend is the use of 1,3-DC in stereoselective domino and multicomponent reactions[211 – 216] and in metal-catalyzed reactions of C – C bond formation.[217] Considerable attention is paid to the synthetic potential of functionalized 1,3-DC,[218, 219] for example, vinyl triflates[220] or 2-ethoxymethylidene derivatives.[221, 222]

High potential is inherent in the molecules combining 1,3-dicarbonyl and (het)arylhydrazone reaction centres.[223] The introduction of such a substituent into organic molecules modulates their biological,[224] coordination,[225] liquid crystalline[226] and dyeing[227] properties. Furthermore, 2-(het)arylhydrazinylidene 1,3-dicarbonyl compounds are convenient objects for investigation of theoretical aspects related to interconversions of tautomers and isomers, intramolecular hydrogen bonding, regioselective reactions involving competing reaction centres and so on. High interest in this class of compounds is indicated by the fact that, according to the Scifinder database, 966 studies on this subject, mainly devoted to the synthesis of biologically active derivatives, have been published all over the world since 2000. However, development of the chemistry of fluorine-containing representatives has received much less attention; only 109 references are available over the same period, with more than one-third of the papers being

Scheme 119



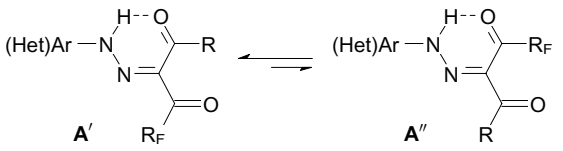
7.1: R = Me, Bu^n, Bu^t, Ph, 1-Naph, 1-Fu, CF_3; R_F = HCF_2, CF_3, $H(CF_2)_2$, C_3F_7, C_4F_9; **7.2**: R = OAlk: R_F = HCF_2, CF_3, $H(CF_2)_2$, C_3F_7, C_4F_9, $H(CF_2)_4$, C_6F_5, C_6F_{13}; **7.3**: R = CO_2Alk: R_F = CF_3, $H(CF_2)_2$, C_3F_7, C_6F_5; **7.4**: R = Me, Bu^t, Bu^n, Ph, CF_3; R_F = HCF_2, CF_3, $H(CF_2)_2$, C_3F_7, $H(CF_2)_4$, C_4F_9; X = Ph, 4-MeC_6H_4, 4-MeOC_6H_4, antipyrin-4-yl; **7.5**: R = OAlk: R_F = HCF_2, CF_3, $H(CF_2)_2$, C_3F_7, $H(CF_2)_4$, C_4F_9, C_6F_5, C_6F_{13}; X = Ph, 4-MeC_6H_4, 4-MeOC_6H_4, antipyrin-4-yl; **7.6**: R = CO_2Alk: R_F = CF_3, $H(CF_2)_2$, C_3F_7, C_6F_5; X = Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 2-MeC_6H_4, 4-$NO_2C_6H_4$, 4-BrC_6H_4; **7.7**: R = Me, Bu^t, Bu^n, Ph, OAlk; R_F = CF_3, $H(CF_2)_2$, C_3F_7, C_4F_9; **7.8**: W = C – CO_2Et, Y = CH, V = N: R_F = CF_3, C_3F_7; R = Me, Ph, CF_3, OAlk; **7.9**: W = CH, Y = C – Me, V = N: R_F = CF_3, $H(CF_2)_2$, C_3F_7, C_4F_9; R = Me, Ph, OAlk; **7.10**: W = CH, Y = C – Ph, V = N: R_F = CF_3, C_4F_9; R = OEt; **7.11**: W = C – CO_2Et, Y = N, V = CH: R_F = CF_3, $H(CF_2)_2$, C_3F_7; R = Me, Bu^t, Ph, 1-Naph, 1-Fu, OAlk; **7.12**: W = V = N, Y = CH: R_F = HCF_2, CF_3, $H(CF_2)_2$, C_3F_7, C_4F_9; R = Ph, OAlk; **7.13**: W = Y = V = N: R_F = CF_3, $H(CF_2)_2$, C_3F_7, C_4F_9; R = Me, Ph, OAlk; Naph is naphthyl

reported by our research team. Meanwhile, it is generally known that the presence of electronegative fluorine atoms or a polyfluoroalkyl group changes the physical, chemical and biological properties of organic molecules.[15, 18, 19, 125, 228, 229] The present chapter is devoted to analysis of the synthesis, structures and chemical reactivity of polyfluorinated 2-(het)arylhydrazinylidene-1,3-DC. Potential uses of these compounds in organic synthesis and possible practical applications are considered.

A universal method for the synthesis of 2-(het)arylhydrazinylidene-1,3-DC is the Japp – Klingemann reaction — azo coupling of (het)aryldiazonium salts with dicarbonyl reagents. If various polyfluorine-containing 1,3-diketones **7.1**, 3-oxo esters **7.2** and 2,4-dioxo esters **7.3** are used as reagents, the reactions give fluoro derivatives **7.4** – **7.6** (Scheme 119).[230 – 232] The introduction of bis(diazonio)-4,4′-biphenyl dichloride into azo coupling with polyfluoroalkyl-containing 1,3-DC resulted in the synthesis of bis(1,3-dicarbonyl) compounds **7.7**, diketone derivatives of which are able to bind transition metal ions.[233]

2-Arylhydrazinylidene-1,3-DC are characterized by isomerism caused by different positions of the (het)arylamine substituent relative to the C=N bond. According to X-ray diffraction and ^{1}H, ^{13}C and ^{19}F NMR spectroscopy data, a characteristic feature of polyfluorine-containing compounds is that they exist in crystals as isomers **A′** stabilized by an intramolecular hydrogen bond (IMHB) between hydrogen of the arylhydrazone group and the carbonyl group of the non-fluorinated substituent. In solutions, they may exist as mixtures of geometric isomers with a minor content of the second isomer **A″** and with IMHB formed with the participation of the polyfluoroacyl substituent (Scheme 120).[234, 235] According to quantum chemical calculations by the B3LYP/6-31G(d,p) method, isomer **A′** is more favourable. X-Ray diffraction analysis revealed specific features of the crystal packing of fluorinated derivatives with respect to non-fluorinated analogues caused by the presence of the intermolecular H···F contacts.[236]

Scheme 120



Recently, polyfluoroalkyl-2-arylhydrazinylidene-3-oxo esters (in the nanomolar concentration range) were found to selectively inhibit carboxylesterase — the enzyme of first-phase metabolism of xenobiotics with an ester, amide or carbamate function. This activity enables the application of these compounds as co-drugs increasing the bioavailability of drugs that are hydrolyzed by carboxylesterase.[237, 238] In addition, trifluoroacetylacetate 2-arylhydrazones can be used as insecticides to fight mosquitoes,[239, 240] and compounds with substantial antitumour,[241] anti-inflammatory,[242, 243] antifungal[244] and fungicidal[245] activities were

detected among CF_3-substituted 2-arylhydrazinylidene-3-aryl-1,3-diketones. One more practically important feature of 2-(het)arylhydrazinylidene-1,3-d iketones is the complexing ability,[246, 247] which makes them applicable for determination of Cu^{II} (Ref. 248) and Eu^{III} (Ref. 249) ions. In this connection, derivatives containing additional chelating groups in the arylhydrazone moiety are especially promising. For example supramolecular clusters were obtained from 3-[(2-carboxyphenyl)hydrazono]-1,1,1-trifluoropentane-2,4-dione, sodium ions and alcohols.[250]

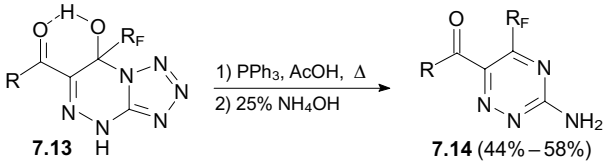
There are examples of azo coupling reactions between non-fluorinated 1,3-DC and hetaryldiazonium salts, resulting in azolotriazines *via* spontaneous cyclization of the intermediate arylhydrazones.[223] A specific feature of the azo coupling of polyfluoroalkyl-1,3-DC **7.1** or **7.2** with hetaryldiazonium salts containing an α-NH group is the formation of (4)7-polyfluoroalkyl-(4)7-hydroxy-(1,4)4,7-dihydroazolo[5,1-*c*]triazines **7.8**–**7.13** *via* intramolecular addition of the hetaryl NH group to the polyfluoroacyl substituent (see Scheme 119).[251] This method was used to prepare dihydroazolotriazines fused to 4-ethoxycarbonylpyrazole (**7.8**),[251, 252] 5-methylpyrazole (**7.9**),[253] 5-phenylpyrazole (**7.10**),[253] imidazole (**7.11**),[252, 254] triazole (**7.12**)[251 – 253] and tetrazole (**7.13**)[253, 255] rings.

Open-chain 2-hetarylhydrazinylidene-1,3-DC **7.4**–**7.6** (for X = azolyl) and dihydroazolotriazines **7.8**–**7.13** are structural isomers; their structures in the solid state were confirmed by X-ray diffraction. The structures in solutions can be determined using the NMR chemical shifts of not only the sp^3- or sp^2-carbon atom (depending on the particular compound) at the polyfluorinated substituent, but also the α-CF_3 and α-CF_2 groups at the bridgehead carbon atom.[252] It was shown by NMR spectroscopy that in solutions, dihydroazolo[5,1-*c*]-1,2,4-triazines **7.8**–**7.13** undergo ring – chain isomerization *via* triazine ring opening at the C(4)—N(5) bond to give the open-chain hetarylhydrazone form **A** (see Scheme 119); the use of deuteropyridine as the solvent results in appearance of the open isomer virtually in all cases.

The attempts to subject tetrazolo[5,1-*c*]-1,2,4-triazines **7.13** to dehydration were unsuccessful, but on refluxing in acetic acid in the presence of Ph_3P, they underwent tetrazole ring opening accompanied by nitrogen elimination giving 3-amino-1,2,4-triazines **7.14** (Scheme 121).[256]

However, microwave-assisted azo coupling of 4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione with azolyldiazonium salts in pyridine resulted in the formation of dehydrogenated pyrazolo[5,1-*c*]-, benzimidazo[5,1-*c*]- and triazolo[3,4-*c*]-1,2,4-triazines.[257]

Scheme 121



7.13 **7.14** (44% – 58%)

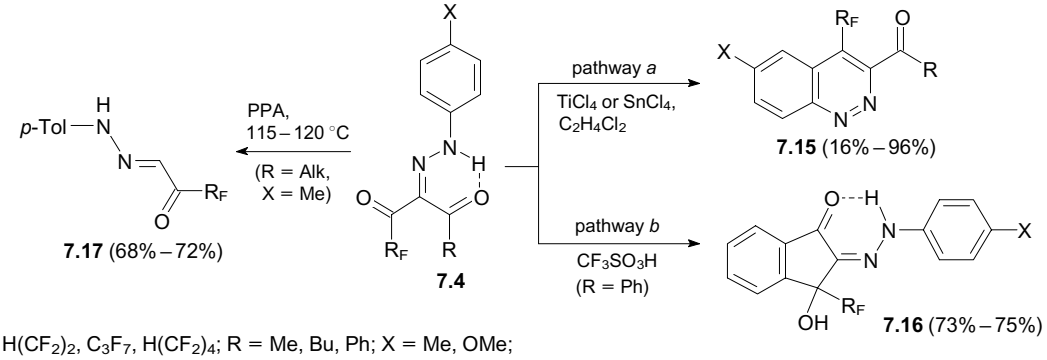
R_F = CF_3, C_3F_7, C_4F_9; R = OEt, OMe, Me, Ph

Polyfluoroalkyl-containing dihydroazolotriazines show the ability to inhibit carboxylesterase when present at concentrations of 10^{-5} – 10^{-7} mol litre^{-1}, while dihydrotetrazolotriazines and 7-phenylpyrazolotriazines also possess high antioxidant activities.[253] Furthermore, compounds with moderate to high tuberculostatic activities were found among dihydroazolotriazines.[256]

Whereas polyfluoroalkyl-2-hetarylhydrazinylidene-1,3-DC tend to undergo spontaneous cyclization during the formation, in the case of 2-arylhydrazinylidene-1,3-diketones **7.4**, the intramolecular cyclization requires acidic conditions and the transformation pathway depends on the substrate and the reaction conditions (Scheme 122). For example, compounds **7.4** selectively cyclize to 3-acyl(benzoyl)cinnolines **7.15** under the action of $TiCl_4$ *via* intramolecular Friedel – Crafts reaction involving polyfluoroacyl and arylhydrazone substituents. For 2-arylhydrazinylidene-1-polyfluoroalkyl-3-phenylpropane-1,3-diones, an alternative cyclization pathway involving the benzoyl group was found, leading to 2-arylhydrazinylidene-3-hydroxy-3-polyfluoroalkylindan-1-ones **7.16**, as a result of activation of the polyfluoroacyl substituent with CF_3SO_3H.[258] Cinnoline (**7.15**) and indanone (**7.16**) derivatives showed tuberculostatic activity at the pyrazinamide or higher level. In addition, indanones **7.16** exhibited good antioxidant activity.

Heating of polyfluoroalkyl-2-tolylhydrazinylidene-1,3-diketones **7.4** in polyphosphoric acid up to 115 – 120 °C affords thermal decomposition products — 1-polyfluoroalkyl-2-(2-tolylhydrazinylidene)ethan-1-ones **7.17** (see Scheme 122), as opposed to non-fluorinated analogues, which cyclize under these conditions to cinnolines.[259, 260] Note that previously, 2-arylhydrazinylidene-4,4,4-trifluoro-1-(2-thienyl)butane-1,3-diones were reported to undergo regioselective C—C bond cleavage on heating (80 °C) in aqueous methanol, with the trifluoroacyl group being elim-

Scheme 122



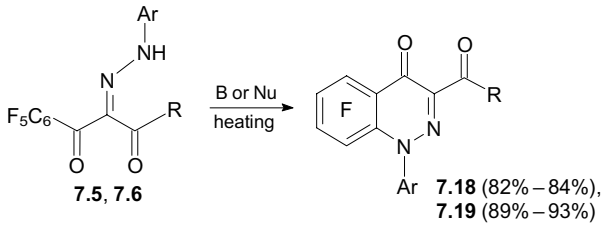
7.17 (68% – 72%) **7.4** **7.15** (16% – 96%) **7.16** (73% – 75%)

R_F = CF_3, $H(CF_2)_2$, C_3F_7, $H(CF_2)_4$; R = Me, Bu, Ph; X = Me, OMe;
PPa is polyphosphoric acid, Tol is tolyl (methylphenyl)

inated to give 2-arylhydrazinylidene-1-(2-thienyl)ethanones.[261]

Under the action of a base, both 3-oxobutanoates **7.5** and their pyruvate analogues **7.6** undergo cyclization to cinnolin-4-ones **7.18** [262] and **7.19**,[230] respectively, as a result of intramolecular displacement of the *ortho*-fluorine atom by the hydrazone amino group (Scheme 123).

Scheme 123



7.5, **7.6**

7.18 (82% – 84%),
7.19 (89% – 93%)

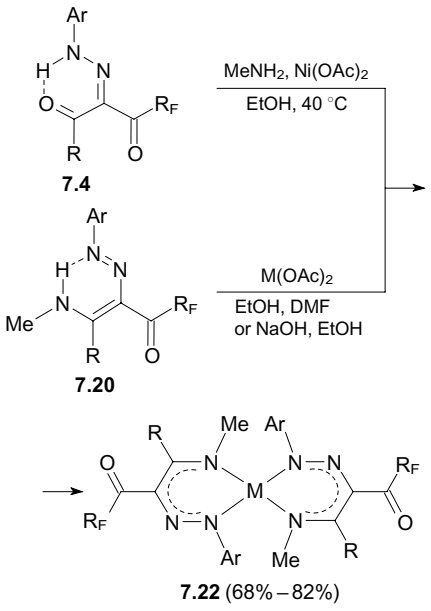
R = OEt (**7.5**, **7.18**), CO_2Et (**7.6**, **7.19**);
Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-MeC_6H_4, 4-BrC_6H_4;
Nu is nucleophile

The molecules of polyfluoroalkylated 2-arylhydrazinylidene-1,3-DC **7.4** and **7.5** have two non-equivalent electrophilic centres (carbonyl groups at the polyfluoroalkyl and non-fluorinated substituents), which can participate in reactions with nucleophilic reagents. The scope of applicability of these compounds as electrophilic reagents were investigated in the reaction with methylamine. 2-Arylhydrazinylidene-1,3-diketones **7.4** with a short polyfluoroalkyl substituent ($\leqslant$ 2 carbon atoms) are converted to 2-arylazo-1,3-enamino ketones **7.20**, resulting from monocondensation at the carbonyl group in the non-fluorinated substituent (pathway *a*) (Scheme 124).[263]

However, the transformations of arylhydrazones of Me-containing diketones **7.4** with a longer polyfluorinated substituent ($\geqslant$ 3 carbon atoms) are not selective. In this case, apart from enamino ketones **7.20**, *N*-methyl-2-arylhydrazinylidene-3-oxobutanamides **7.21**, resulting from haloform reaction of the intermediates *via* elimination of polyfluoroalkane, were isolated from reaction mixtures (pathway *b*). In the case of similar reactions of arylhydrazones **7.4** with a polyfluoroalkyl ($\geqslant$ 3 carbon atoms) and a bulky *tert*-butyl or phenyl substituent, only amides **7.21** were isolated. It is evident that 2-arylhydrazinylidene-1,3-diketones **7.4** can add methylamine to either of the carbonyl carbon atoms with intermediate formation of hemiaminals **B** or **C**, the stabilization pathway of which is determined by the nature of the polyfluoroalkyl and non-fluorinated substituents.[264]

In the template condensation with methylamine with Ni^{II} ions, 2-arylhydrazinylidene-1,3-diketones **7.4** form metal chelates **7.22**. An advantage of the template process is the possibility to obtain metal chelates from ligands with a long polyfluoroalkyl ($\geqslant$ 3 carbon atoms) and a bulky hydrocarbon substituent (Scheme 125). An alternative synthetic route to chelates **7.22** is to treat 2-arylazo-3-methylamino-1-polyfluoroalkylket-2-en-1-ones **7.20** with metal salts; this method is also suitable for the preparation of complexes with other metals. According to X-ray diffrac-

Scheme 125



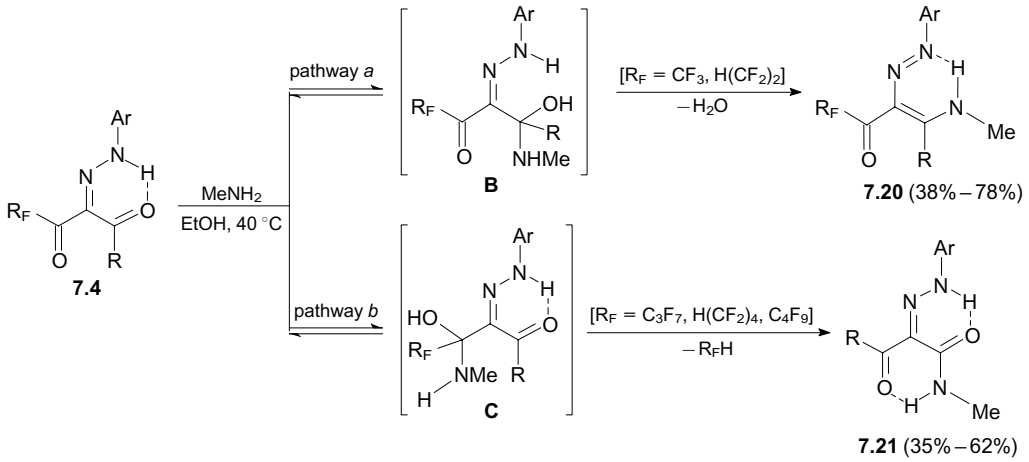
7.4

7.20

7.22 (68% – 82%)

R_F = CF_3, $H(CF_2)_2$, C_3F_7; R = Me, Ph; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; M = Ni, Cu

Scheme 124



7.4

B

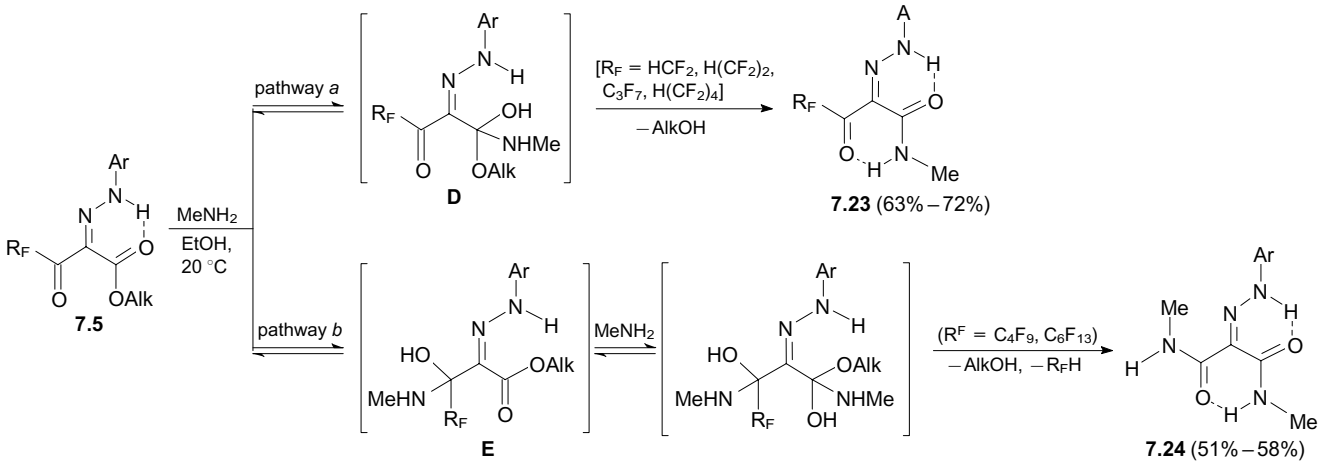
C

7.20 (38% – 78%)

7.21 (35% – 62%)

R_F = CF_3, $H(CF_2)_2$, C_3F_7, $H(CF_2)_4$, C_4F_9; R = Me, Bu^n, Bu^t, Ph; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 126



Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$

tion data, the metal ion is coordinated to two donor nitrogen atoms, the arylhydrazone and methylamine ones, whereas the polyfluoroacyl substituent remains free.

The key step of the reaction of 2-arylhydrazinylidene-3-oxo esters **7.5** with methylamine is amine condensation with the ester group yielding amides **7.23** (Scheme 126). However, in the case of esters **7.5** with a long polyfluoroalkyl substituent, this reaction pathway is accompanied by addition of amine to the polyfluoroacyl moiety followed by the haloform reaction to give diamide **7.24**. The initial attack by the amine may involve either of the carbonyl groups of oxo ester **7.5**, like in 2-arylhydrazinylidene-1,3-diketones **7.4**. Stabilization of intermediate **D** rapidly proceeds as a result of alcohol elimination to give amide **7.23** (pathway *a*), which is typical of esters **7.5** containing a relatively small polyfluoroalkyl substituent ($\leqslant 8$ fluorine atoms). The attachment of amine to the polyfluoroacyl substituent leads to more stable hemiaminal **E** able to add a second amine molecule to the ester group. Elimination of an alcohol and a polyfluoroalkane molecule affords diamide **7.24** (pathway *b*).

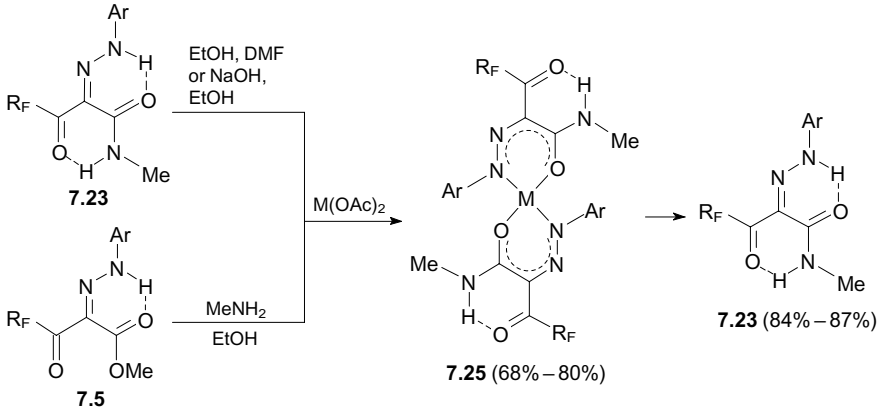
2-Arylhydrazinylidene-3-oxo amides **7.23** possess complexing properties towards transition metal ions forming complexes **7.25** (Scheme 127). Nickel complexes **7.25** were prepared by three-component condensation from oxo ester **7.5**, amine and nickel(II) salt. The template reaction can be applied to prepare oxo amides **7.23** with a long fluorinated substituent from unstable amide metal complexes.

Polyfluorinated 2-(het)arylhydrazinylidene-1,3-DC **7.4**–**7.6** and their cyclic analogues, dihydroazolotriazines **7.8** and **7.12**, were used as the starting compounds to synthesize new heterocyclic systems. Among these heterocycles, pyrazoles are of the most interest as structural analogues of the pyrazole-derived anti-inflammatory agents. The reactions of 2-(het)arylhydrazinylidene-1,3-DC **7.4** and **7.5** with hydrazines involve the 1,3-dicarbonyl moiety and regiospecifically give pyrazoles **7.26**[265] and pyrazolones **7.27** (Scheme 128)[223, 230, 231] of the same regioisomeric series. Dihydroazolo[5,1-*c*]triazines **7.8** and **7.12** are capable of ring transformation reactions under the action of hydrazines to give substituted pyrazoles **7.26** also of the same series.[251]

Good prospects for the synthesis of pyrazole structures based on 2-(antipyrin-4-ylhydrazinylidene)-1,3-diketones were opened by detection of compounds possessing a high analgesic activity in combination with low toxicity among them.[266] In addition, some CF_3-4-arylazapyrazoles show antitumour[241] and anti-inflammatory[242] action, while metal complexes of 4-isoxazolylpyrazoles were patented as optically active materials.[267]

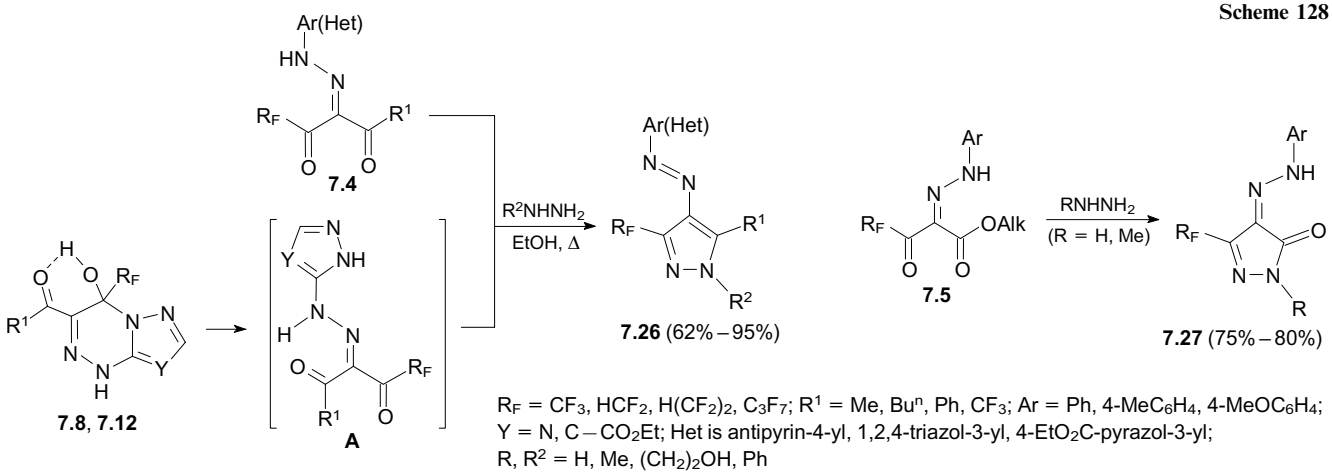
Unlike hydrazines, hydrazides and thiosemicarbazide react with polyfluoroalkylated 2-arylhydrazinylidene-

Scheme 127



R_F = HCF_2, $H(CF_2)_2$, C_3F_7, C_4F_9; Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$; M = Ni, Cu

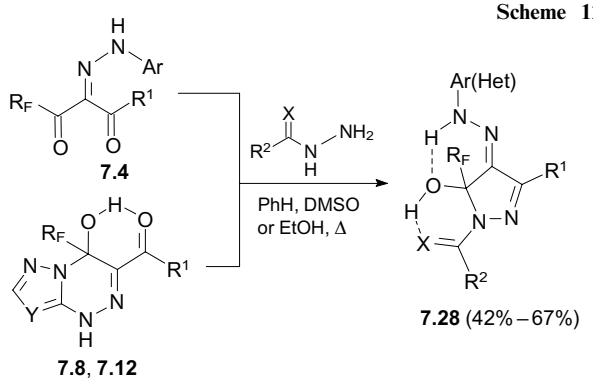
Scheme 128



R_F = CF_3, HCF_2, $H(CF_2)_2$, C_3F_7; R^1 = Me, Bu^n, Ph, CF_3; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; Y = N, C – CO_2Et; Het is antipyrin-4-yl, 1,2,4-triazol-3-yl, 4-EtO_2C-pyrazol-3-yl; R, R^2 = H, Me, $(CH_2)_2OH$, Ph

1,3-diketones **7.4** and their analogues, dihydroazolotriazines **7.8** and **7.12** yielding 5-R_F-5-hydroxypyrazolines **7.28** (Scheme 129).[268] It is important that in the reaction of dihydroazolotriazines **7.8** and **7.12** and arylhydrazone **7.4** with hydrazides, the site of initial attack by the nucleophile changes compared with similar transformations involving hydrazines, since pyrazoles of the different regioisomeric series are formed. Apparently, this corresponds to the Pearson concept, according to which the attack by a weak nucleophile (hydrazide) is initially directed to a softer electrophilic site (acyl group), while for hydrazines the situation is opposite. However in reactions of non-fluorinated 2-arylhydrazinylidene-1,3-diketones with hydrazines and hydrazides, the cyclocondensation pathway changes.

Scheme 129

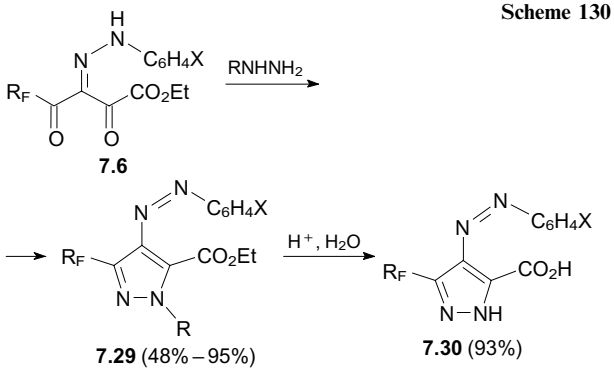


X = O: R^2 = Ph, 4-Py; X = S, R^2 = NH_2; R^1 = Me, Ph; Het is 1,2,4-triazol-3-yl, 4-EtO_2C-pyrazol-3-yl; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$

Polyfluoroalkyl-3-arylhydrazinylidene-2,4-dioxo esters **7.6** react with hydrazines at the 1,3-dicarbonyl moiety to give 5-ethoxycarbonylpyrazoles **7.29**, which are hydrolyzed giving pyrazole-5-carboxylic acids **7.30** (Scheme 130).[230, 232]

The replacement of the polyfluoroalkyl group in 3-arylhydrazinylidene-2,4-dioxo esters **7.6** by a pentafluorophenyl substituent considerably changes the pathway of the reaction with hydrazines, since the major isolable products in this case are pyridazines **7.31**, which are formed upon the addition of dinucleophile to the γ-dicarbonyl system (Scheme 131). The regioisomeric structure of phenyl-substituted pyridazines **7.32** was confirmed by the fact that they cannot undergo intramolecular cyclization to pyridazocinnolines **7.33**, which were obtained in the reaction with phenylhydrazine in refluxing ethanol. Apparently, under these conditions, cyclization to cinnolinone takes place initially and is followed by the formation of the pyridazine system.[269, 270]

Scheme 130



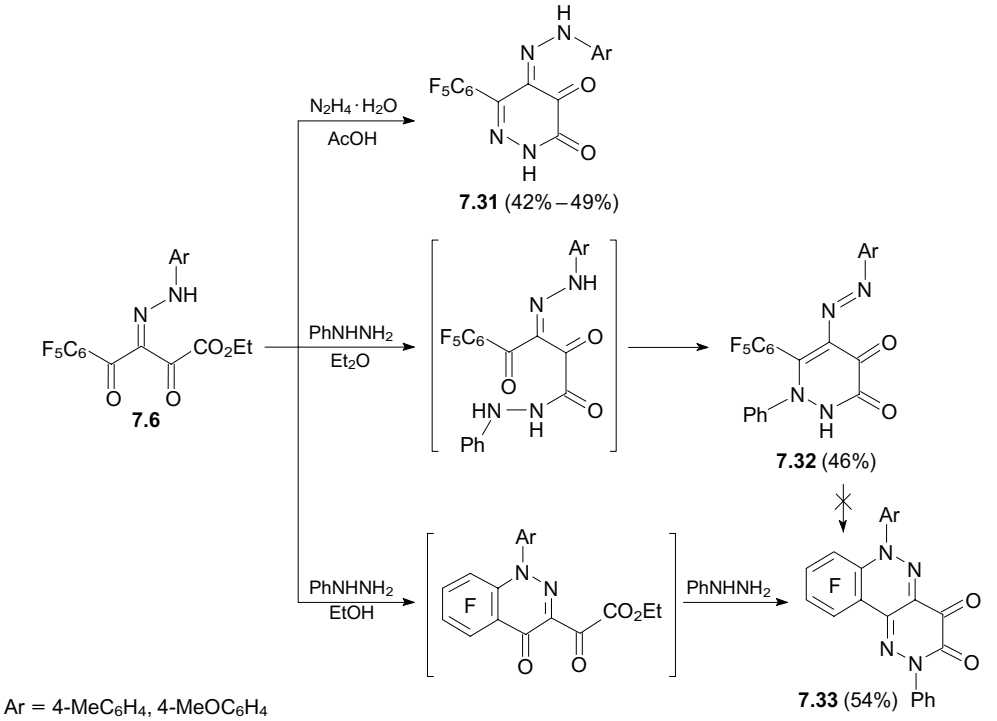
R_F = CF_3, $H(CF_2)_2$; X = H, 4-MeO, 2-Me; R = H, Me, Ph

A large series of patents[271 – 274] is devoted to the synthesis of 1-aryl-3-alkoxycarbonyl-4-trifluoromethylpyridazin-3-ones **7.34** *via* cyclization of 2-arylhydrazinylidene-3-oxo esters **7.5** with malonic acid derivatives or triphenylphosphoranylideneacetates. The enhanced interest in these compounds is related to their application as herbicides (Scheme 132).

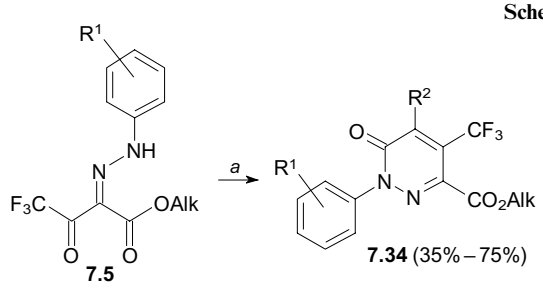
2-Arylhydrazinylidene-substituted trifluoroacetylacetate **7.5a** cyclizes with hydroxylamide hydrochloride yielding 4-(arylhydrazinylidene)-3-trifluoromethylisoxazol-5-one **7.35**, whereas 2-arylhydrazinylidene-1,3-diketones **7.4** tend to cyclize with this dinucleophile being converted to 4-arylhydrazinylidene-5-hydroxy-5-polyfluoroalkylisoxazolines **7.36**. Dehydration of the latter furnishes 4-arylazoisoxazoles **7.37** (Scheme 133).[230, 275, 276] Most of these isoxazoles showed antibacterial and fungicidal activities.

An approach was proposed to the synthesis of 4-ethoxycarbonyl-2-phenyl-5-trifluoromethyl-1,2,3-triazole (**7.38**) from ethyl 4,4,4-trifluoro-2-phenylhydrazonobutanoate (**7.5b**) by Cu^{II}-catalyzed oxidation induced by ammonium

Scheme 131

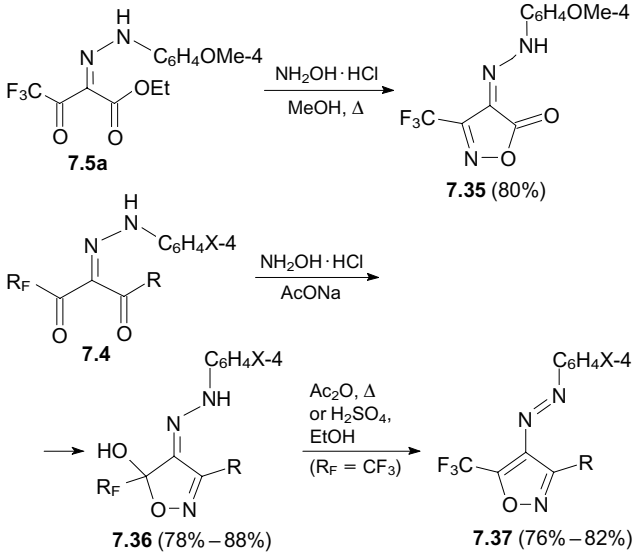


Scheme 132



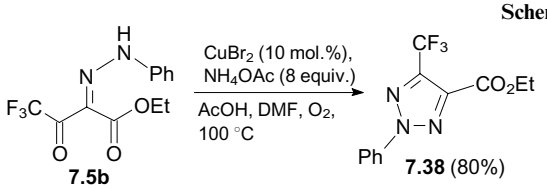
(*a*) $HO_2CCHR^2CO_2X$ or $Ph_3P{=}CHCO_2Me$, DBU;
R^1 = H, OH, Hal, Alk, OAlk, CO_2Alk, CO_2H; R^2, X = H, Alk

Scheme 133



R_F = CF_3, $H(CF_2)_2$; X = H, Me, F, Cl, Br, NO_2, OMe;
R = Me, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2-Th

Scheme 134



acetate (Scheme 134). This reaction makes use of the synthetic potential of the hydrazone substituent.[277]

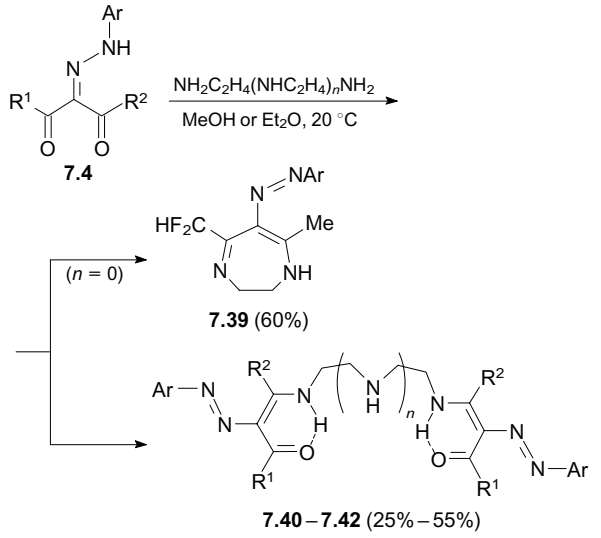
The reaction of 2-arylhydrazinylidene-1,3-diketones **7.4** with ethylenediamine is the only example of formation of a heterocyclic product, difluoromethyl-substituted diazepine **7.39** (Scheme 135). The other arylhydrazones react with ethylenediamine to afford open-chain *N*,*N*′-ethylenebis(aminovinyl ketones) **7.40**.[278]

Analogous penta- (**7.41**) and hexadentate (**7.42**) podands were prepared by reactions with diethylenetriamine and triethylenetetramine, respectively (see Scheme 135). These reactions are regioselective, as the nucleophile adds to the carbonyl carbon atom at the nonfluorinated substituent.[279]

On treatment with nickel and copper acetates, the synthesized podands **7.40** give the corresponding metal chelates **7.43** (Scheme 136). Nickel chelates **7.43** were obtained by the template method directly from 2-arylhydrazinylidene-1,3-diketones **7.4**.

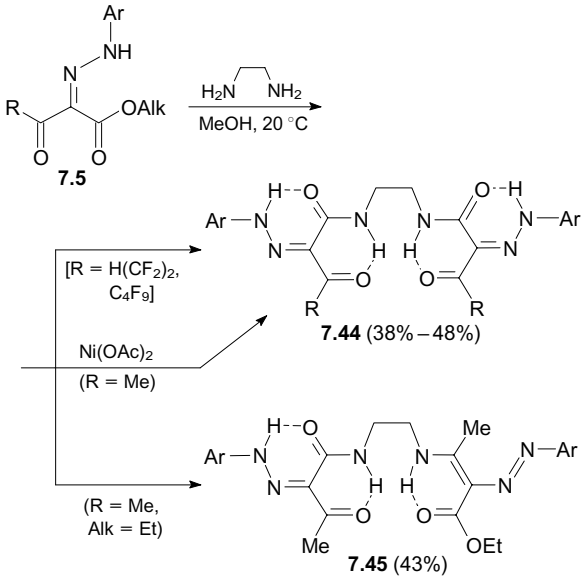
Polyfluoroalkylated 2-arylhydrazinylidene-3-oxo esters **7.5** react with ethylenediamine at the alkoxycarbonyl group,

Scheme 135



R^1 = Me, CF_3, $H(CF_2)_2$, $H(CF_2)_4$; R^2 = Me, Ph;
Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$; *n* = 0 (**7.40**), 1 (**7.41**), 2 (**7.42**)

Scheme 137



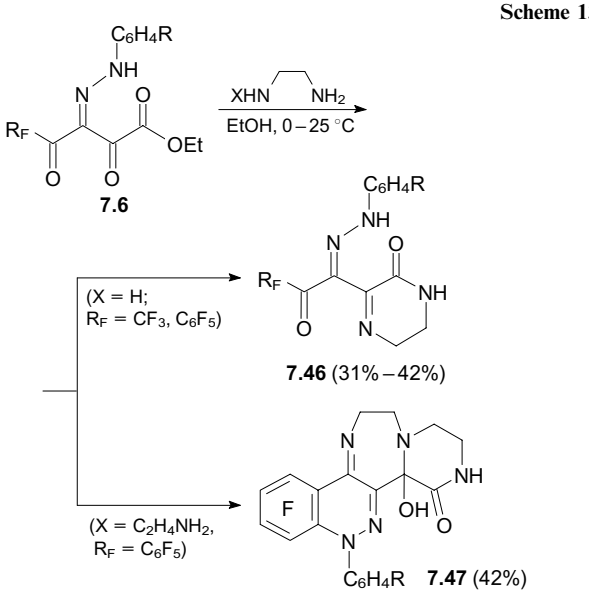
Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$

thus giving *N*,*N*′-ethylenediamides **7.44** (Scheme 137). Meanwhile, 2-arylhydrazinylidene-substituted acetoacetate is converted to mixed type addition product **7.45** under the same conditions, since ethylenediamine adds to the ester group of one dioxo ester molecule and to the oxo group of the second dioxo ester molecule. The template reaction of the same reactants led to symmetrical diamide **7.44** instead of the expected chelate.[278, 279]

Fluorine-containing 3-arylhydrazinylidene-2,4-dioxo esters **7.6** react with ethylenediamine through their 1,2-dicarbonyl moiety yielding tetrahydropiperazinones **7.46** (Scheme 138). The reaction with diethylenetriamine results in the isolation of only tetracyclic piperazodiazepinocinnoline **7.47**, formed upon exhaustive equimolar reaction of diethylenetriamine with the starting ester accompanied by simultaneous displacement of the *ortho*-fluorine atom of the pentafluorophenyl moiety.[270]

Unlike the reactions of 2-unsubstituted 1,3-diketones with *o*-phenylenediamine, which predominantly yield benzodiazepine derivatives, analogous transformations involving 2-arylhydrazinylidene 1,3-diketones **7.4** afford 2-substituted benzimidazoles, with their structure being dependent on the nature of the non-fluorinated substituent in the diketone moiety (Scheme 139). For example, the reactions of alkyl-substituted 1,3-diketones mainly result in the formation of (2-acylarylhydrazinylidene)benzimidazoles **7.48**, whereas the phenyl-containing analogue gives 2-phenylbenzimidazole **7.49** and fluorinated hydrazone **7.50**.

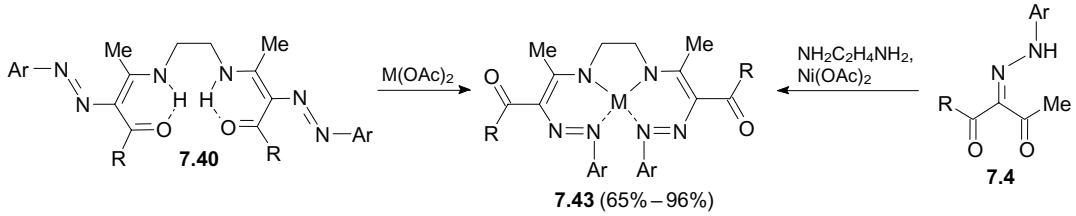
Scheme 138



X = H, $C_2H_4NH_2$; R = H, 4-MeO

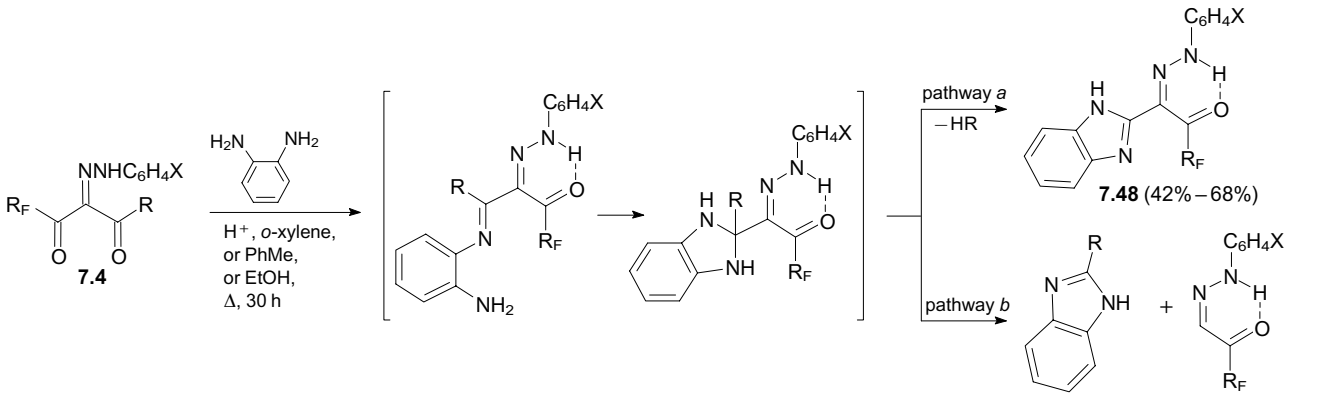
Apparently, both types of benzimidazoles are formed *via* two alternative aromatization pathways of the intermediate *gem*-substituted benzimidazoline. The acid cleavage giving phenylbenzimidazoles is a known process typical of 1,3-diketones and their 2-substituted analogues, but the

Scheme 136



R = Me, $H(CF_2)_4$, C_4F_9; M = Ni, Cu; Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 139



R_F = CF_3, HCF_2, $H(CF_2)_2$, $H(CF_2)_4$, C_4F_9; R = Me, Bu^n, Bu^t, Ph, CF_3; X = 4-Me, 4-OMe

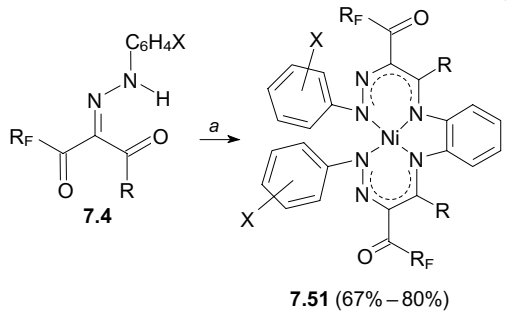
second aromatization pathway implemented *via* elimination of non-fluorinated saturated hydrocarbon is unexpected. The particular aromatization pathway is apparently determined by the thermodynamic stability of the final products.[262, 280]

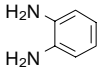
Conduction of the reactions between 2-arylhydrazinylidene 1,3-diketones **7.4** and *o*-phenylenediamine as template synthesis with nickel(II) affords chelates — nickel *N*,*N*′-phenylenebis(2-arylazo-3-oxopropane-1-iminates) **7.51** (Scheme 140).[281]

2-Arylhydrazinylidene 3-oxo esters **7.5** react with *o*-phenylenediamine with the involvement of the alkoxycarbonyl moiety, which leads to *o*-aminoanilides of 2-arylhydrazinylidene 3-oxo acids **7.52**. These products can further cyclize to 3-arylhydrazinylidene-4-fluoroalkyl-1*H*-1,5-benzodiazepin-2-ones **7.53** (Scheme 141). However, this reaction pathway is not the only one; this is evidenced by the isolation, in some cases, of 2-substituted benzimidazoles **7.54**, resulting from the addition of the diamine to the polyfluoroacyl moiety and the subsequent elimination of fluorohydrocarbon.[282]

Heterocyclization of arylhydrazones of pentafluorobenzoylpyruvate **7.6** with aromatic dinucleophiles involves the

Scheme 140



(*a*) 

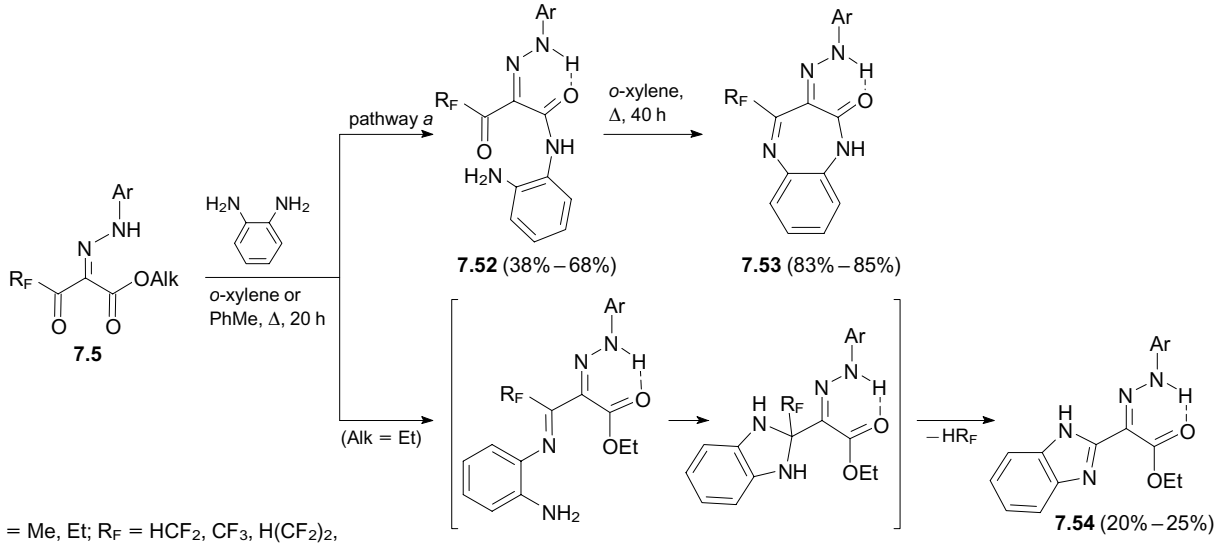
, $Ni(OAc)_2 \cdot 4H_2O$, EtOH, Δ;

R_F = CF_3, $H(CF_2)_2$, $H(CF_2)_4$; R = Me, Bu^n, Ph; X = 4-Me, 4-OMe

1,2-dicarbonyl moiety and gives substituted quinoxalones **7.55** and benzoxazinones **7.56** (Scheme 142).[270]

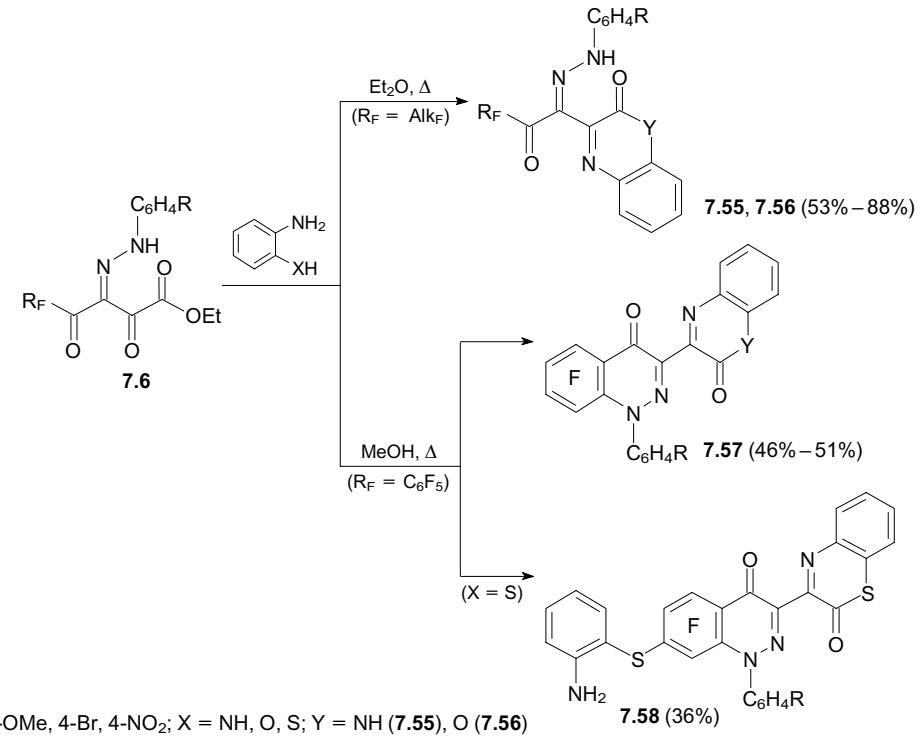
In the case of pentafluorophenyl-containing esters, products of further intramolecular cyclization — hetarylcinnolinones **7.57** — can also be obtained. When *o*-amino-

Scheme 141



Alk = Me, Et; R_F = HCF_2, CF_3, $H(CF_2)_2$, C_4F_9, C_6F_{13}; Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 142



R = H, 4-Me, 4-OMe, 4-Br, 4-NO_2; X = NH, O, S; Y = NH (**7.55**), O (**7.56**)

benzenethiol is used, the fluorine atom in position 7 of cinnolinne is additionally displaced (**7.58**), which is caused by higher nucleophilicity of the sulfur atom.

The above-presented data attest to good prospects of using polyfluorinated 2-(het)arylhydrazinylidene-1,3-dicarbonyl compounds as reagents for coordination, heterocyclic and medicinal chemistry. This is due to their synthetic accessibility, broad variability of substituents in the (het)arylhydrazone moiety and also the ability to undergo a variety of chemical transformations, the most popular of which are reactions with nucleophilic agents at the carbonyl groups. In addition, these compounds tend to undergo cyclizations involving their (het)arylhydrazone moiety and various unusual C – C bond cleavage reactions. They proved to be convenient substrates for the synthesis of diverse compounds: metal complexes, functionalized aminoene ketones, indanes, pyrazoles, isoxazoles, triazoles, pyridazines, piperazines, triazines, diazepines, cinnolines, benzimidazoles, benzodiazepines, azolotriazines, quinoxalines, benzoxazines, benzothiazines and pyridazocinnolines. The regiochemistry of reactions is determined by the nature of the dicarbonyl moiety. The intensive development of research in this area is induced by the broad spectrum of biological activities exhibited by these fluoro derivatives.

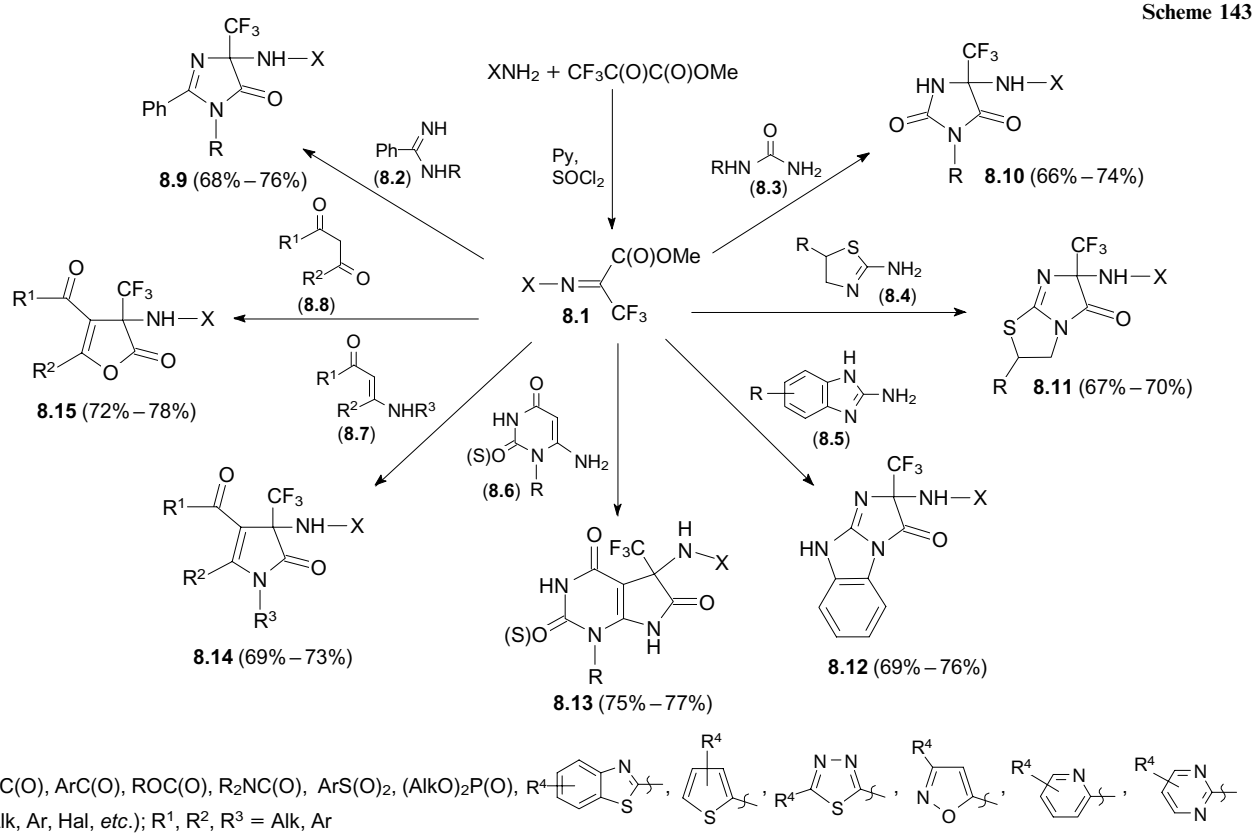
8. Methyl trifluoropyruvate and hexafluoroacetone imines: reagents for modification of biologically active amides and amines with fluorinated heterocycles

The development of new original approaches to the rational design of biologically active compounds (BAC) is a highly fruitful line of research in organic chemistry. Functionalization of BAC with fluorinated, in particular, heterocyclic substituents is especially attractive in this respect. Most often, the introduction of fluorine-containing substituents into the molecule does not decrease the biological activity, but endows the compound with unique physicochemical properties, which, in turn, improve and, in some cases, change, in a controlled manner, pharmacological characteristics.[283] This chapter presents data on the modification of various biologically active amides and amines with trifluoromethyl-containing five- and six-membered heterocycles *via* cyclocondensation reactions of N-substituted imines of methyl trifluoropyruvate (MTFP) and hexafluoroacetone (HFA) with 1,3-C,N-, C,O- and N,N-dinucleophiles. The synthetic potential of MTFP and HFA hetarylimines is considered in relation to defluorocyclization reactions to prepare fluorinated heterocyclic precursors of modified biologically active compounds. Data on the behaviour of MTFP and HFA imines in heterocyclization are documented in reviews in considerable detail.[284 – 287]

8.1. Cyclocondensation of methyl trifluoropyruvate and hexafluoroacetone imines

In the cyclocondensation with 1,3-dinucleophiles, MTFP imines behave as 1,2-dielectrophiles and give five-membered heterocycles. The transformations proceed by a two-step route including C-alkylation of dinucleophile and the subsequent cyclization with elimination of methanol. These reactions were carried out for the MTFP acyl-,[288 – 298] sulfonyl-,[298 – 301] carbamoyl-,[302] dialkoxyphosphoryl-,[303] thiazol-2-yl-,[304] benzothiazol-2-yl-,[305] thiophen-2-yl-,[306] thiadiazol-2-yl-,[307] isoxazol-2-yl-,[308] pyridin-2-yl-[309] and pyrimidin-2-ylimines[310] (compounds **8.1**), which were allowed to react with benzamidines **8.2**, ureas **8.3**, 2-aminothiazolines **8.4**, benzimidazoles **8.5**, 6-aminouracils **8.6**, enamines **8.7** and 1,3-dicarbonyl compounds **8.8** to afford imidazolones **8.9**, imidazolidinediones **8.10**, dihydroimidazothiazolones **8.11**, benzoimidazoimidazolones **8.12**, pyrrolopyrimidinetriones **8.13**, pyrrolones **8.14** and furanones **8.15**, respectively (Scheme 143).

Scheme 143



Experimental data on the reactions of N-substituted MTFP imines with 1,3-dinucleophilic reagents revealed some regularities of these processes regarding the natures of both dielectrophile and dinucleophile. The reactions are rate-limited by addition of the dinucleophile to the C=N bond, the electrophilicity of which is determined, first of all, by the electron-withdrawing properties of N-substituents. Sulfonylimines proved to be the most reactive, while pyridin-2-yl- and thiophen-2-ylimines are the least reactive. The nature of the dinucleophile usually affects the second step (condensation) in which the highest reactivity was found for 1,3-C,N-dinucleophiles and the lowest reactivity was inherent in 1,3-N,N- and 1,3-C,O-dinucleophiles.

Hexafluoroacetone acylimines **8.16** are convenient synthons for the preparation of various heterocyclic compounds with geminal trifluoromethyl groups. These compounds are used as azadienes, dienophiles or 1,3-dielectrophiles in cycloadditions and cyclocondensations resulting in the formation of five- and six-membered azaheterocycles. The greatest synthetic potential is inherent in the cyclocondensation of imines **8.16** with diverse 1,3-dinucleophiles, *e.g.*, with 2-aminopyridines **8.17**,[311] enamines **8.7**,[312, 313] 6-aminouracils **8.6**,[289, 314 – 316] benzamidines **8.2**,[288, 313] 2-aminothiazolines **8.4**,[290, 313] 2-aminobenzimidazoles **8.5** [296] and carboxamides **8.18**; [314] this gives dihydropyrimidines **8.19**, **8.20**, dihydrotriazines **8.21** – **8.24** and oxadiazines **8.25** (Scheme 144).

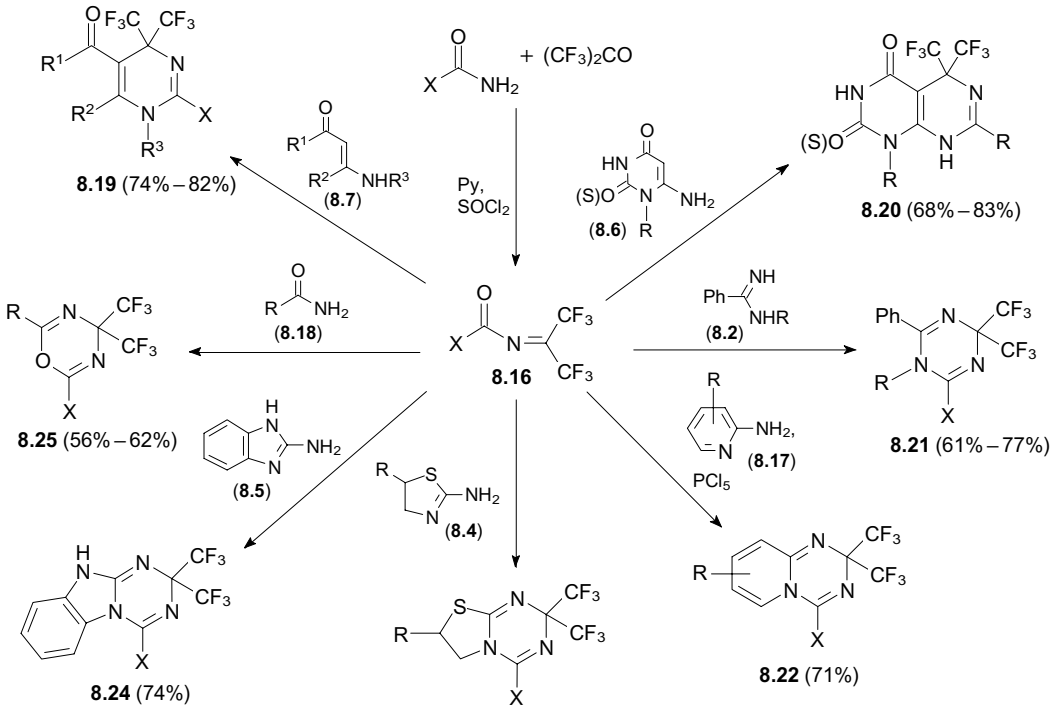
Like in the case of MTFP imines, this reaction includes two stages; the second one is dehydration followed by cyclization usually proceeding on heating in DMF in the presence of bases, while in the case of 2-aminopyridines and amides, it is necessary to employ a dehydrating agent (PCl_5 or a Py – $SOCl_2$ mixture).

Cyclocondensation of HFA ethoxycarbonylimine (**8.26**) with 1,3-dinucleophiles, namely, enamines **8.7**,[317] 6-aminouracils **8.6**,[288, 317] benzamidines **8.2**,[318] 2-aminothiazolines **8.4** (in the presence of bases), 2-aminothiazoles **8.27**,[318] 2-aminothiadiazoles **8.28**,[318] 2-aminobenzothiazoles **8.29** and 2-aminopyridines **8.17** (in the presence of TsOH) [318] proceeds with elimination of ethanol to give the corresponding dihydropyrimidinones **8.30** and **8.31** and dihydrotriazinones **8.32** – **8.37** (Scheme 145).

Kutovaya *et al.* [319 – 321] proposed an original approach to the synthesis of trifluoromethyl-containing five-membered aza-heterocycles, exemplified by intramolecular cyclocondensation of transformation products of nitromethane-alkylated trifluoroacetophenone alkoxycarbonylimines (compounds **8.38**). For example, carbamates **8.38** undergo the Nef reaction and are thus converted to imidazolidine-2,4-diones **8.39** (Ref. 321) *via* the formation of hydroxylamide **8.40**. The reduction of carbamates **8.38** with sodium borohydride affords amines **8.41**, which are converted to imidazolin-1-ones **8.42** upon refluxing in toluene with DBU (Ref. 319) (Scheme 146).

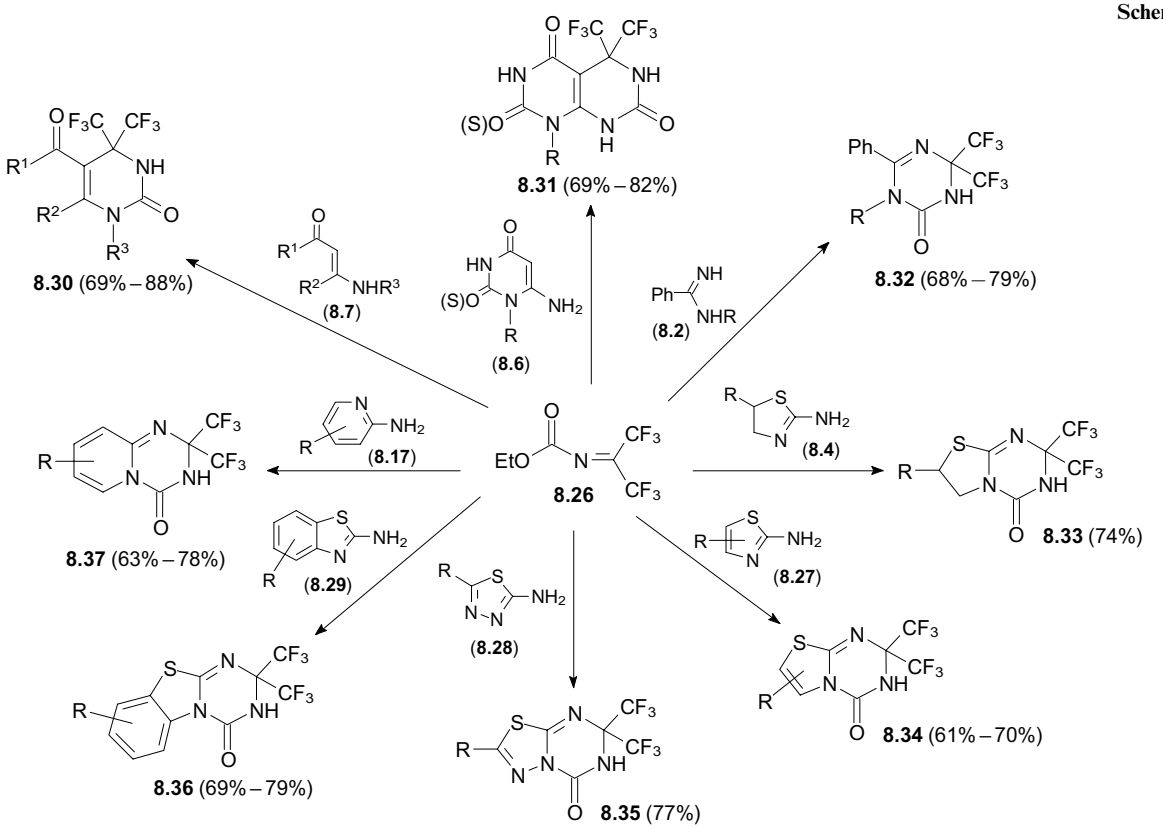
Apart from the participation in cyclocondensation reactions, HFA and MTFP heterylimines **8.43** obtained by one-pot synthesis proved to be convenient precursors for modification of biologically active compounds — annulated 3-fluoroimidazoles. For example, MTFP and HFA pyridin-2-yl-,[322 – 324] pyrimidin-2-yl-[325 – 327] and thiazol-2-ylimines [327] react exothermically with equimolar amounts of trimethyl phosphite giving the corresponding 3-fluoroimidazo[1,2-*a*]pyridines, -pyrimidines and -thiazolines **8.44**, in which the fluorine atom is displaced almost quantitatively by an amino group (compounds **8.45**) (Scheme 147).

Scheme 144



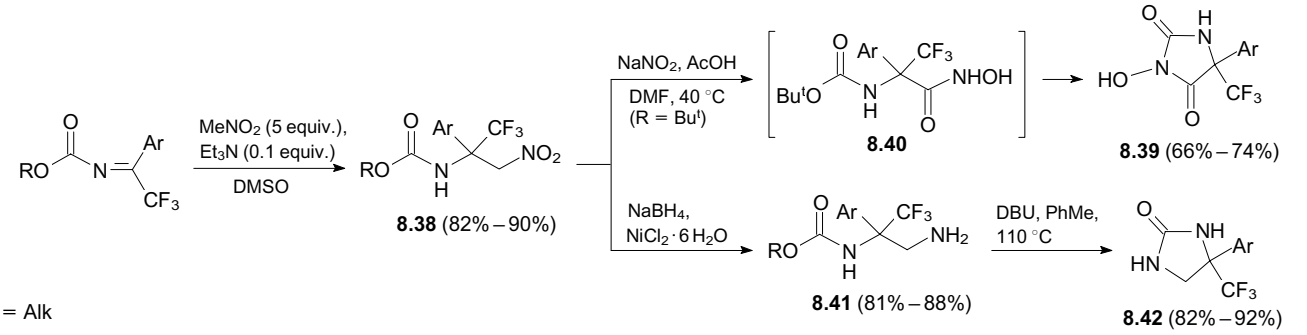
X = Alk, Ar, AlkO; R, R^1, R^2, R^3 = Alk, Ar, *etc*.

Scheme 145

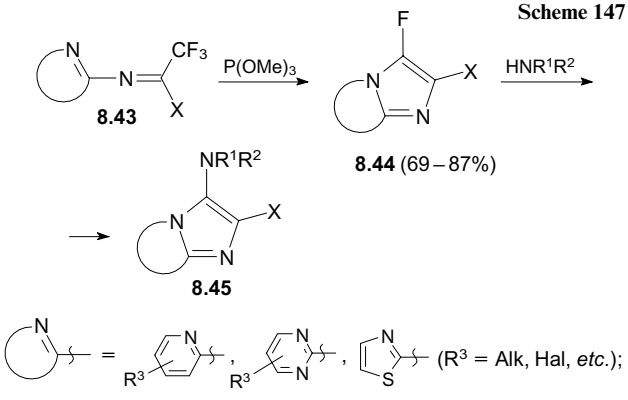


R, R^3 = Alk, Ar, *etc*.; R^1 = Alk, AlkO; R^2 = Alk

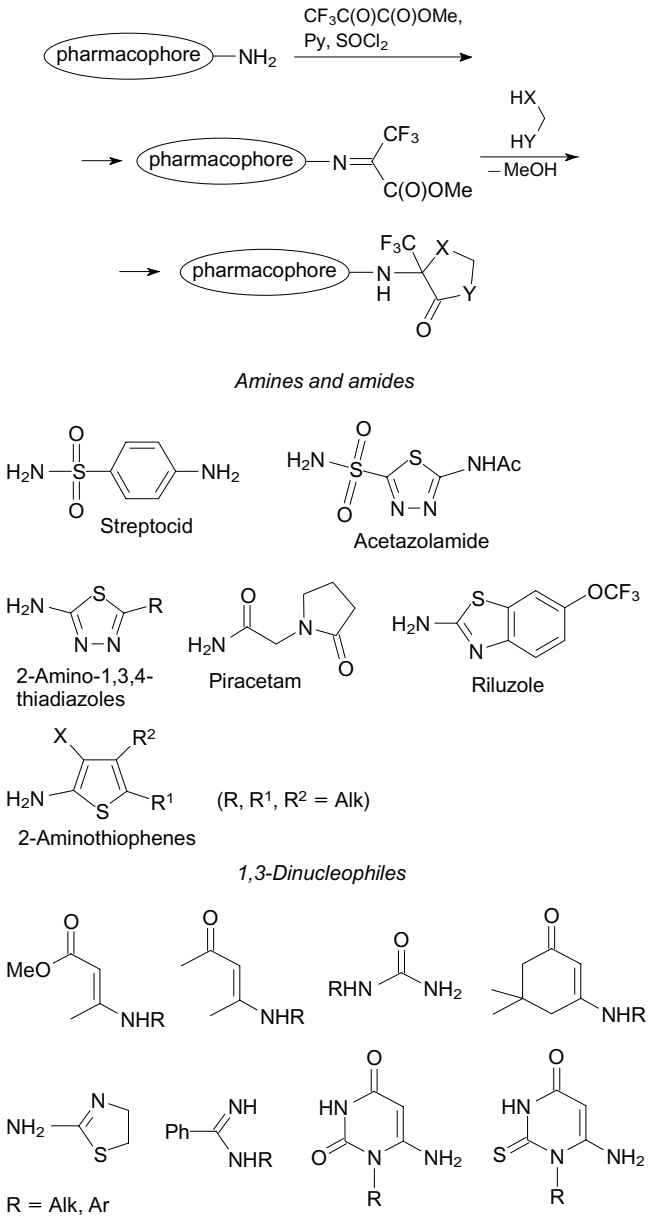
Scheme 146



Scheme 147



Scheme 148



Thus, the above cyclocondensation and defluorocyclization reactions of MTFP and HFA imines represent a fruitful synthetic tool for modification of BAC.

8.2. Modification of biologically active amides and amines with fluorinated heterocycles

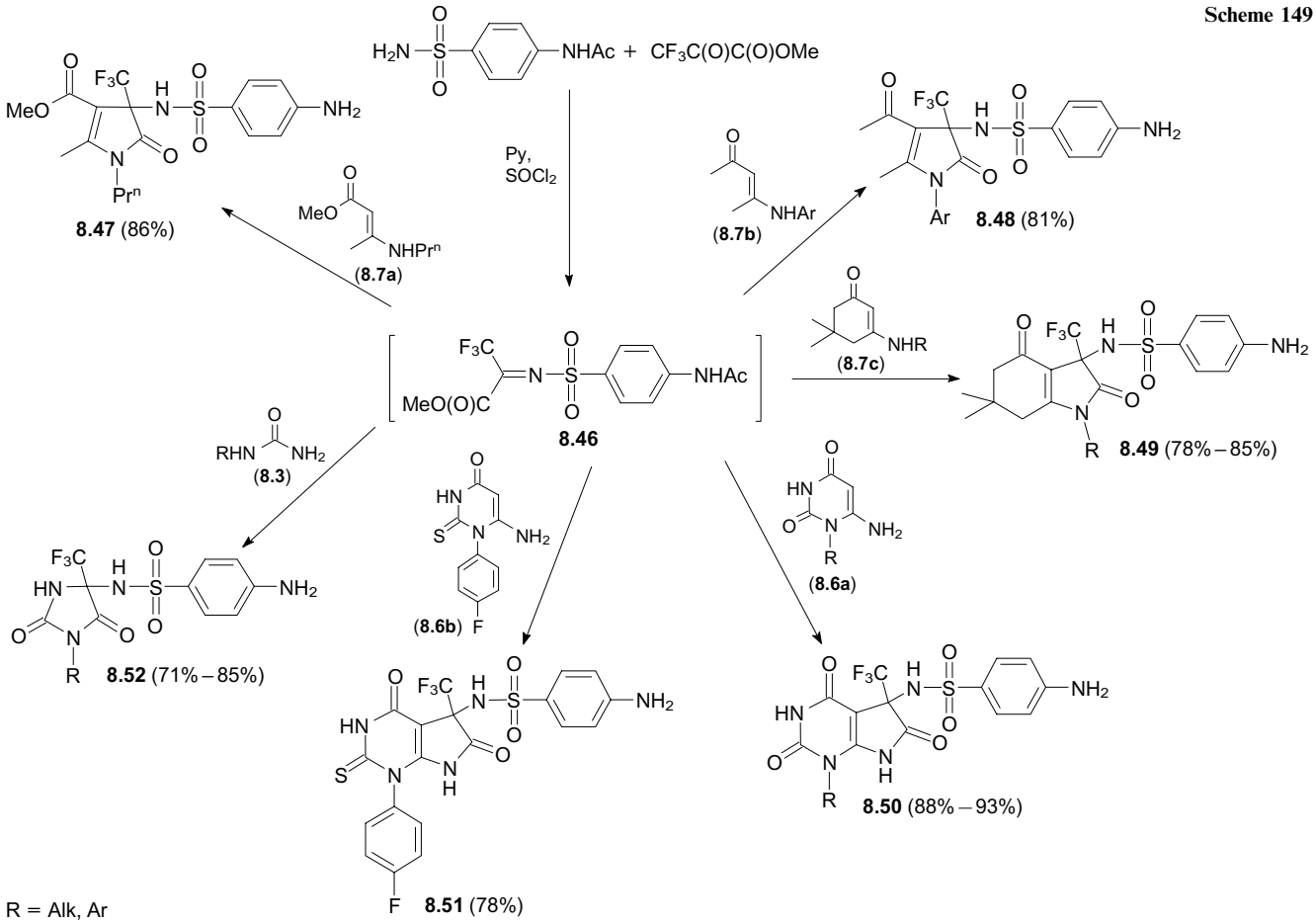
Biologically active amides and amines, for example, sulfonamide drugs, acetazolamide, piracetam, 2-amino-1,3,4-thiadiazoles, riluzole and 2-aminothiophenes, are successfully used for the treatment of various diseases; the variation of substituents at the amino group has been and apparently will be the major trend of modification of these compounds. From this standpoint, we consider approaches to the rational design of the pharmacophore amine function using diverse fluorine-containing five- and six-membered heterocycles. The approaches are based on a multicomponent reaction involving biologically active amides or amines, MTFP or HFA, and 1,3-dinucleophiles (Scheme 148).

Below we present examples of modification of known drugs including streptocid (antibacterial agent),[300] acetazolamide (effective carbonic anhydrase inhibitor),[301] riluzole (non-specific NMDA receptor modulator)[305] with trifluoromethyl heterocycles using cyclocondensation and the biological activity data for modified agents. These transformations are conducted as one-pot procedures by successive addition of reagents — MTFP, pyridine, $SOCl_2$ and dinucleophile — to a DMF solution of the amide (Schemes 149 – 151).

The modified streptocid analogues (**8.46** – **8.52**), especially compound **8.48**, exhibited considerably higher activity, compared with the parent structure, towards the bacteria *Staphylococcus aureus*, *Salmonella enteritidis*, *Bacillus anthracis* and *Escherichia coli*.[300]

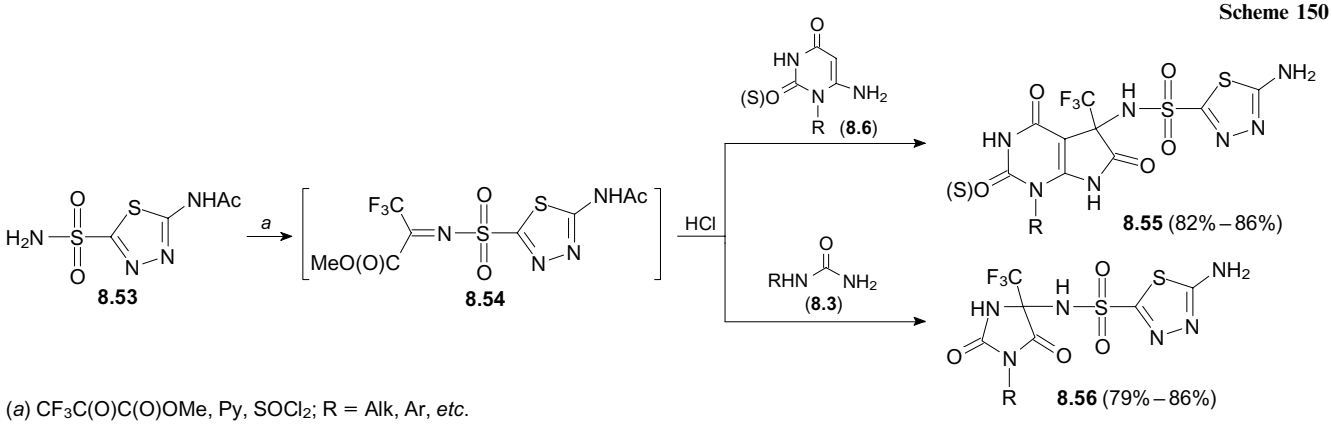
A similar modification was performed for acetazolamide **8.53**; the subsequent hydrolysis of cyclocondensation prod-

Scheme 149



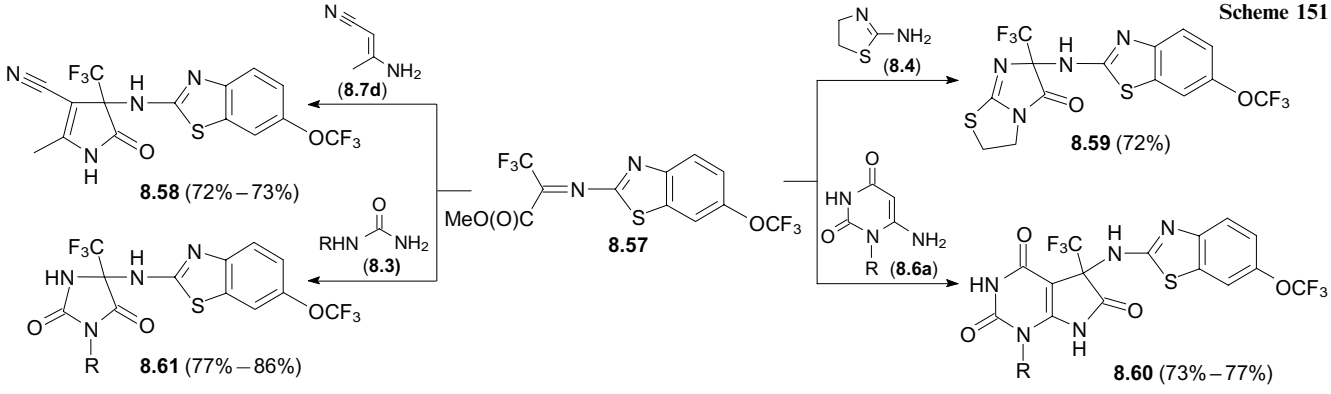
R = Alk, Ar

Scheme 150



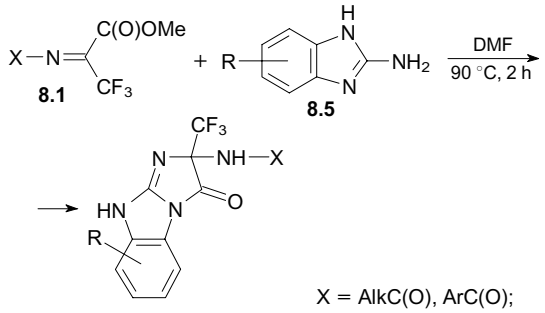
(*a*) $CF_3C(O)C(O)OMe$, Py, $SOCl_2$; R = Alk, Ar, *etc*.

Scheme 151



R = Alk, Ar, *etc*.

Scheme 152



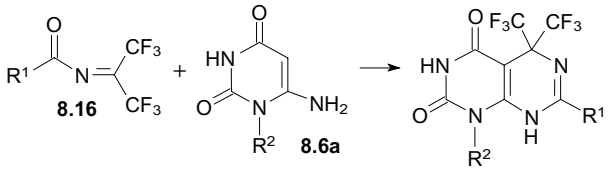
8.12 (69% – 76%)

ucts **8.54** gave rise to fluorine-containing heterocyclic 5-amino-1,3,4-thiadiazole-2-sulfonic acid derivatives **8.55** and **8.56**, which exhibit antibacterial activity.[301]

The cyclocondensation of MTFP benzothiazol-2-ylimine **8.57** with aminocrotonitrile (**8.7d**), 2-aminothiazoline (**8.4**), substituted ureas **8.3** and 6-aminouracils **8.6a** yielded modified analogues of the riluzole drug **8.58** – **8.61**. These compounds were found to affect the release and reuptake of labelled [^{3}H]glutamate by synaptosome preparations and, hence, affect the glutamate transport, the disruption of which is a key cause of the amyotrophic lateral sclerosis (Charcot disease).[305]

The products of cyclocondensation of N-substituted MTFP imines **8.1** and 2-aminobenzimidazoles **8.5** — benzoimidazoimidazolones **8.12** (Refs 296, 297) — proved to be promising agents for the treatment of cancer, autoimmune disorders, inflammatory and neurodegenerative diseases as S100 calcium binding protein inhibitors (Scheme 152).[297]

Scheme 153



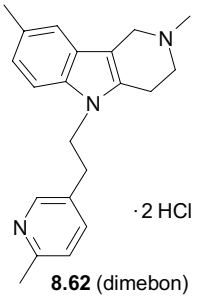
R^1, R^2 = Alk, Ar

8.20 (70% – 93%)

Another type of derivatives promising for further research are dihydropyrimido[4,5-*d*]pyrimidinediones **8.20** obtained by cyclocondensation of 6-aminouracils **8.6a** and HFA acylimines **8.16**. These compounds possess antibacterial[315] and anticonvulsant activities (Scheme 153).[316]

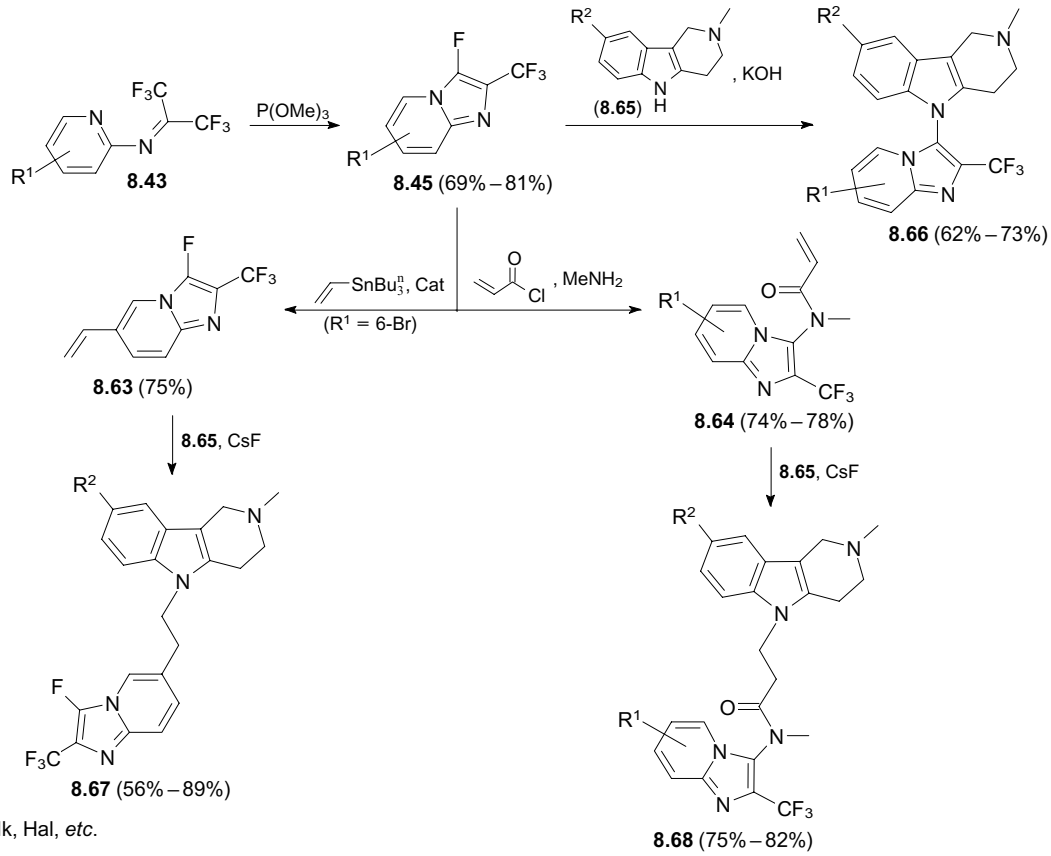
The products of defluorocyclization of HFA pyridin-2-ylimines **8.43** (X = CF_3) — 2-trifluoromethylimidazo-[1,2-*a*]pyridines **8.45** — proved to be useful synthons for decoration of tetrahydro-γ-carboline, the pharmacophore moiety of dimebon (**8.62**), an antihistaminic and neuro-

Structure 8.62



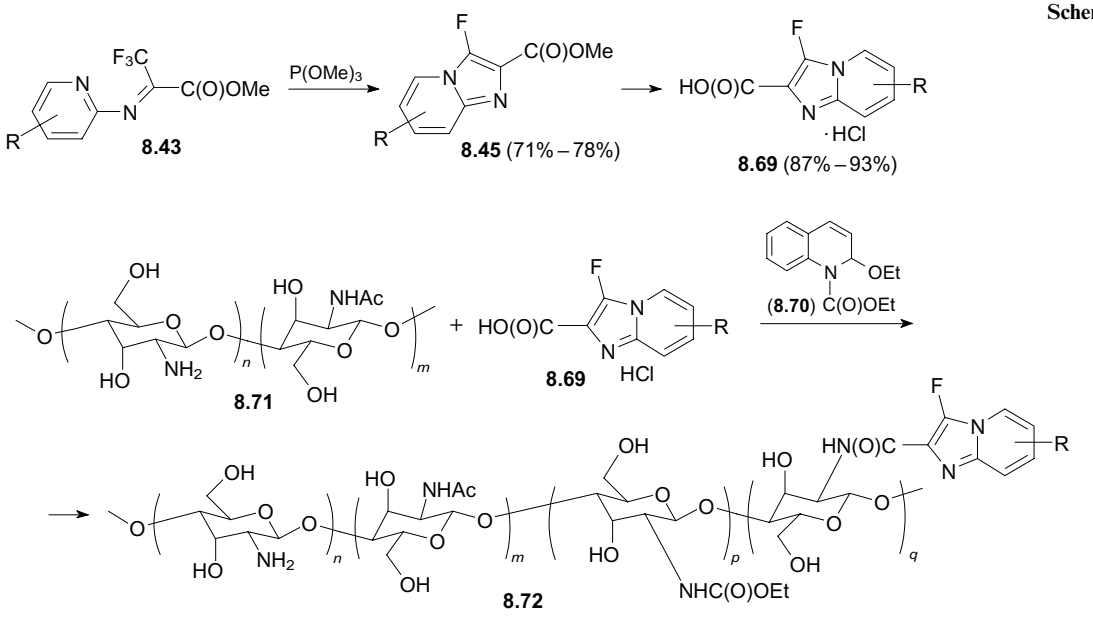
8.62 (dimebon)

Scheme 154



R^1, R^2 = Alk, Hal, *etc.*

Scheme 155



R = Alk, Hal, *etc.*

protective agent.[328] Tetrahydro-γ-carbolines **8.65** are hetarylated with trifluoromethylimidazo[1,2-*a*]pyridines **8.45** in the superbasic medium[329] and are catalytically alkylated with vinyl derivatives **8.63** and **8.64**;[330, 331] these reactions generate the corresponding conjugates **8.66** – **8.68** (Scheme 154).

The replacement of the 3-pyridylethyl substituent at the indole atom of dimebon by the 2-trifluoromethylimidazo[1,2-*a*]pyridine moiety in various combinations induces a substantial increase in the effect of these compounds on neuronal NMDA receptors, a principal type of ionotropic glutamate receptors of the central nervous system, which play a key role in the neuroprotection and neurotoxicity mechanisms.[329 – 331] Effects of the same type are observed upon similar modification of carbazoles[332] and tetrahydrocarbazoles.[332]

3-Fluoroimidazo[1,2-*a*]pyridine-2-carboxylic acid hydrochlorides **8.69**, synthesized by the hydrolysis of defluorocyclization products of MTFP pyridin-2-ylimines **8.45**, acylate, in the presence of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (**8.70**), the glucosamine unit of the natural biopolymer chitosan **8.71** to give modified polymer **8.72** which altered its physicochemical properties (Scheme 155).[324]

The considered data on the behaviour of N-substituted MTFP and HFA imines towards cyclocondensation and defluorocyclization reactions demonstrate the extensive synthetic potential of these compounds in the rational design of biologically active products. Apparently, the future use of these highly electrophilic reagents in the medicinal chemistry would be directed, on the one hand, towards further expansion of the range of pharmacophores containing an activated azomethine group, and, on the other hand, towards introduction of various pharmacophoric 1,3-dinucleophiles in these reactions. Combinations of pharmacophore-containing MTFP or HFA imines and dinucleophiles in the cyclocondensation would allow researchers to develop a synthetic approach to the conjugation of pharmacophore moieties linked by trifluoromethylated heterocyclic spacers. One should also expect a considerable expansion of the range of annulated 3-fluoroimidazoles, including phosphorus-containing ones, for hetarylation of biologically active amines.

9. Perfluoroalkylated cyclic imines: new fluorine-containing building blocks

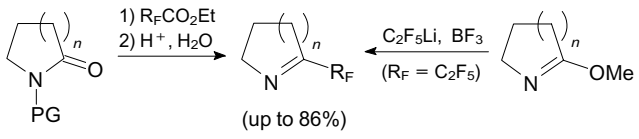
Cyclic amines constitute an important class of compounds. Many natural compounds contain this structural moiety, for example, alkaloids: nicotine, anabasine and hygrine. A special role in the formation of the secondary structure of a protein is played by cyclic amino acids (proline, hydroxyproline and pipecolic acid). A cyclic amine moiety is present in the molecules of >200 modern pharmaceutical products.[333, 334]

The use of cyclic ketimines opens up the route to molecules incorporating an α-substituted cyclic amine moiety or an aminoalkyl moiety. A series of earlier publications[335 – 340] demonstrate a high synthetic potential of cyclic ketimines.

The perfluoroalkyl-substituted cyclic imines, the synthesis of which was developed quite recently, are of particular interest. Two approaches were proposed for the preparation of these compounds, one being based on the Claisen condensation of N-protected lactams with trifluoroacetic and pentafluoropropionic acid esters followed by hydrolysis and decarboxylation in hydrochloric acid and the other being based on the addition of pentafluoroethyllithium to methoxyimines, giving rise to pentafluoroethylated esters (Scheme 156).[341]

It was found that perfluoroalkyl-substituted cyclic ketimines possess much higher electrophilicity than non-fluo-

Scheme 156

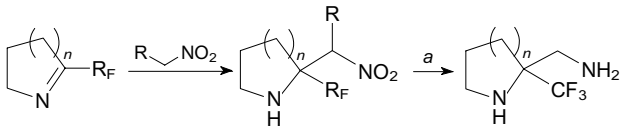


PG = $(EtO)_2CH$, $CH_2{=}CH$; $R_F = CF_3$, C_2F_5; $n = 1-3$;
PG is protecting group

rinated analogues. For this reason, they can act as efficient electrophiles, providing the route to molecules containing a five- or seven-membered cyclic amine moiety and a trifluoromethyl or perfluoroethyl group.

Perfluoroalkyl-substituted cyclic ketimines undergo the aza-Henry reaction with aliphatic nitro compounds in the presence of the activating $ZnCl_2-DBU$ system. The nitroamines **9.1** thus formed can be easily converted to 1,2-diamines **9.2** containing two amino groups markedly differing in the nucleophilicity because of the electron-withdrawing influence of the R_F group (Scheme 157).[342]

Scheme 157

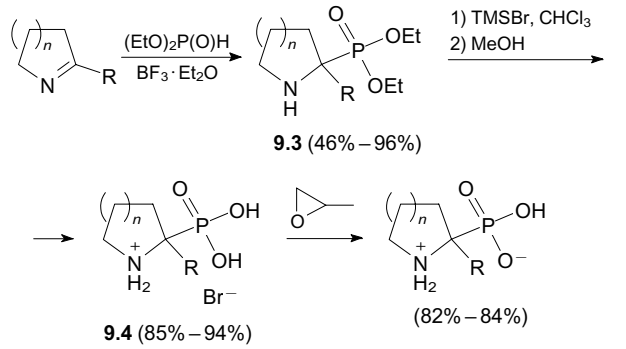


9.1 (up to 95%) **9.2** (up to 95%)

(*a*) H_2, Pd (R = H, $R_F = CF_3$); $R_F = CF_3$, C_2F_5; $n = 1-3$; R = H, Et

The reaction of perfluoroalkylated cyclic imines with diethyl phosphite proceeds in the presence of boron trifluoride etherate and affords cyclic α-perfluoroalkylaminophosphonates **9.3** in high yields. They are hydrolyzed to give phosphonic acids **9.4**, which exist as zwitter-ions (Scheme 158). This transformation is also realizable for non-fluorinated derivatives.[343, 344]

Scheme 158



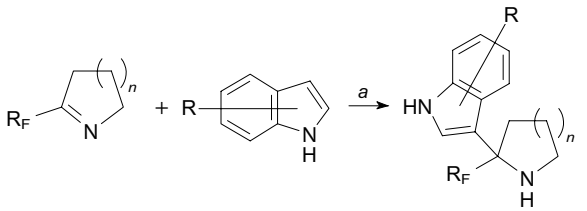
9.3 (46% – 96%)

9.4 (85% – 94%) (82% – 84%)

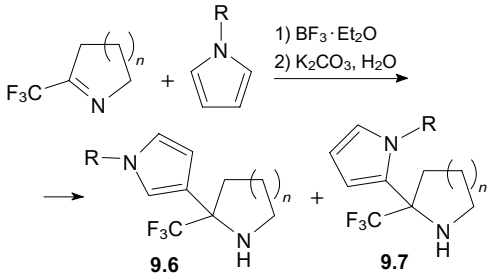
R = CF_3, Ar, Alk; $n = 1-3$

Perfluoroalkyl-substituted cyclic imines can alkylate indoles and pyrroles. They react with indoles in the presence of boron trifluoride etherate as an activating agent under mild conditions to give alkaloid-like structures **9.5** containing a perfluoroalkyl moiety (Scheme 159). A method has been developed for the synthesis of 3-substituted indoles containing a cyclic amine moiety and a fluorinated group.[345] The aminoalkylation of pyrroles with cyclic imines has been studied. This reaction proceeds only for imines containing perfluorinated substituents. An unusual regioselectivity, that is, formation of the β-isomer as the major product, was found for the reaction. The reactivity of perfluoroalkyl-substituted cyclic imines is substantially affected by the steric factor, that is, the size of the perfluoroalkyl group. Indeed, 2-C_2F_5 derivatives are markedly less

Scheme 159



(*a*) 1) $BF_3 \cdot Et_2O$; 2) K_2CO_3, H_2O; **9.5** (26 examples)
$R_F = CF_3$, C_2F_5; R = H, 1-Me, 2-Me, 4-Me, 4-OMe, 2-Ar; $n = 1$ (61% – 85%), 2 (47% – 79%), 3 (59% – 79%)



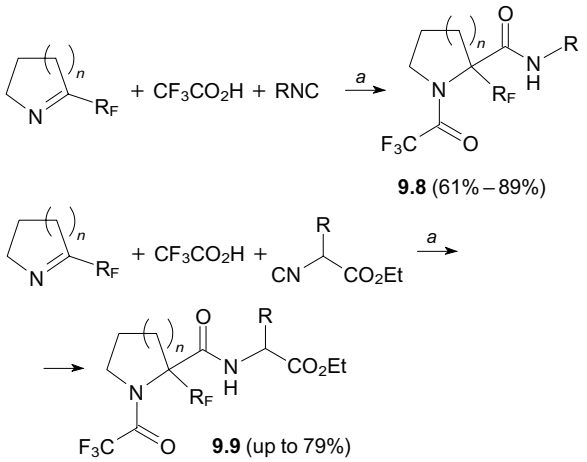
9.6 **9.7**

R = H, Me, CHR′CO_2Et, CH_2CH_2OH, $CHMeCO_2H$ (R′ = H, Me)

reactive, while CF_3 imines form compounds **9.6** as the major products when reacting with N-substituted pyrroles and isomeric compounds **9.7** as the major products when reacting with unsubstituted pyrrole (22 examples, up to 82% yields).[346, 347]

The Ugi reaction involving trifluoromethyl-substituted aldehydes and ketones is promising for the synthesis of fluorine-modified molecules, especially amino acid derivatives. In the case of perfluoroalkylated cyclic imines, this reaction provides a route to polyfluoro-substituted proline derivatives and their homologues **9.8** (Scheme 160). This approach is applicable for the preparation of dipeptides **9.9** containing a polyfluorinated cyclic amino acid residue (proline, pipecolic acid or azepanecarboxylic acid). It is note-

Scheme 160



9.8 (61% – 89%)

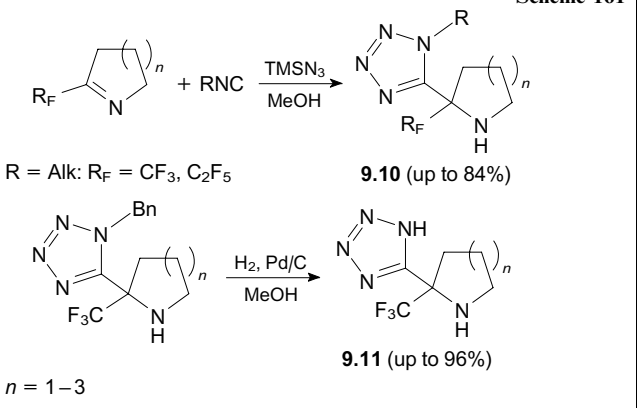
9.9 (up to 79%)

(*a*) CH_2Cl_2 – 20 °C; $R_F = CF_3$, C_2F_5; R = Et, Bu^t, Bn, 4-EtC_6H_4; $n = 1-3$

worthy that this method is also applicable for the synthesis of C_2F_5 derivatives.[348]

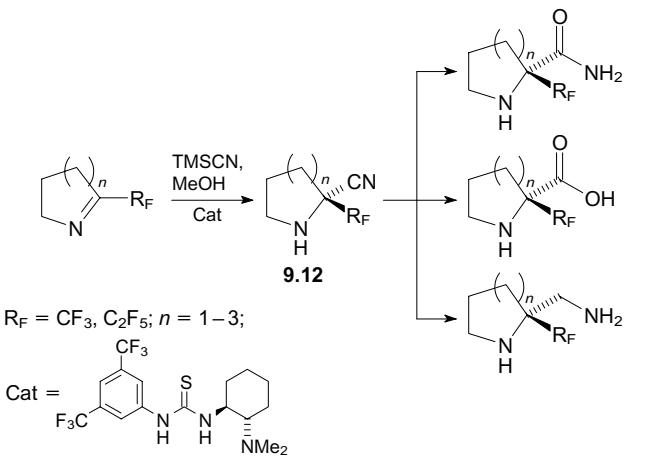
Perfluoroalkylated cyclic imines can be used as substrates for the azido-Ugi reaction. Study of the influence of the imine and isocyanide natures shows the versatility of this approach and a lower reactivity for C_2F_5-substituted imines. The reaction is suitable for the preparation of tetrazoles **9.10** connected to a pyrrolidine, piperidine or azepane ring with a perfluoroalkyl substituent, generally in good yields. New 1*H*-5-cyclic aminotetrazoles **9.11** with a CF_3 group were synthesized by the azido-Ugi reaction followed by debenzylation (Scheme 161).[349]

Scheme 161



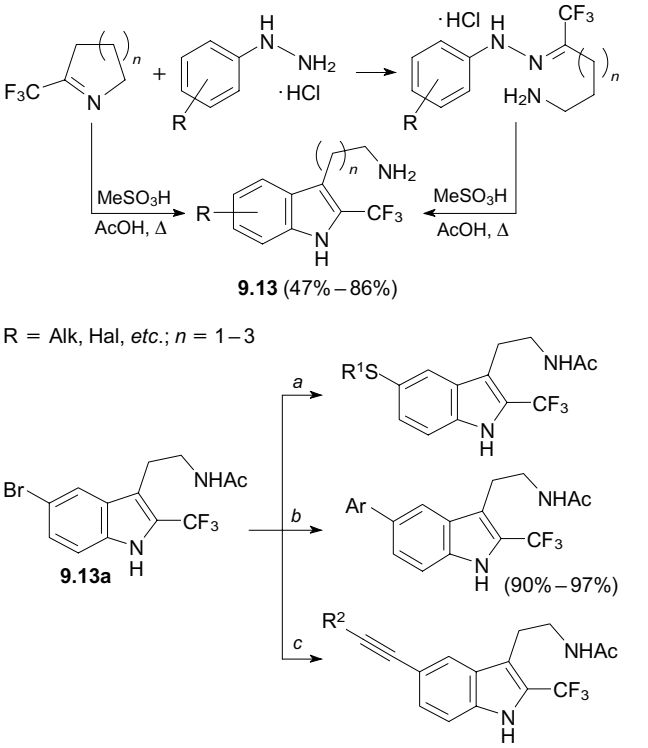
The organocatalytic Strecker reaction with five- to seven-membered cyclic fluorinated ketimines underlay the development of an efficient enantioselective synthesis of α-perfluoroalkylated cyclic amino acids and their derivatives. In this case, aminonitriles **9.12**, resulting from the Strecker reaction, are the key compounds (Scheme 162). They can be transformed into chiral R_F-prolines and their six(seven)-membered homologues and into analogous amides and diamines [the product yields are up to 99% and the enantiomeric excess (*ee*) is up to 99%].[350]

Scheme 162



The Fischer reaction with trifluoromethyl-substituted cyclic imines has formed the basis of the one-step synthesis of 2-trifluoromethyltryptamines and their homologues, compounds **9.13**. Unlike non-fluorinated ketimines, 2-perfluoroalkylated cyclic imines form stable hydrazones, which undergo the Fischer rearrangement in acid medium. The subsequent modification of the products is possible, *e.g.*, nucleophilic displacement of bromine in position 5 of the indole system (Scheme 163).[351]

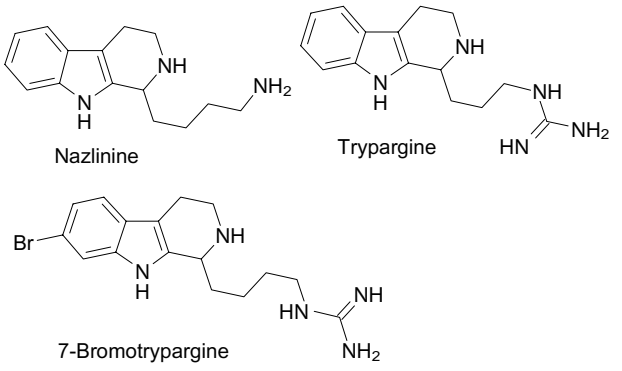
Scheme 163



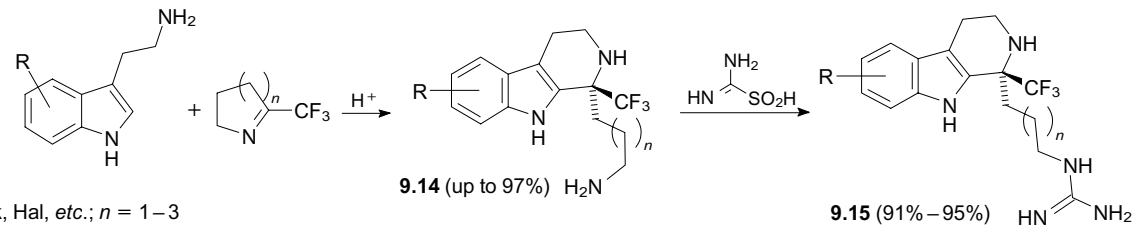
(*a*) R^1SH, $Pd(dba)_2$, Pr^iNEt_2, Xantphos, 130 °C;
(*b*) PBu^t_3, Na_2CO_3, $ArB(OH)_2$, dioxane, H_2O, 100 °C;
(*c*) $\equiv R^2$, CuI, $Pd(PPh_3)_2Cl_2$, PBu^t_3, Et_3N, 100 °C;
R^1, R^2 = Alk, Ar; dba is di(benzylidene)acetonate,
Xantphos is 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

It was shown that CF_3-substituted cyclic imines can be used as masked carbonyl compounds in the Pictet – Spengler reaction with tryptamines. As a result, an approach was developed suitable for the synthesis of trifluoromethyl derivatives of natural alkaloids such as nazlinine, trypargine and homotrypargine and their analogues **9.14** containing a trifluoromethyl group in position 1 of tetrahydrocarboline (Scheme 164).[352] The reaction effectively proceeds in the

Structures of alkaloids



Scheme 164



R = Alk, Hal, *etc.*; $n = 1-3$

presence of protic acids. The resulting primary amines **9.14** can be smoothly converted to the target guanidines **9.15**, trifluoromethylated derivatives of natural compounds.

10. Heterocyclization and oxidative addition of trifluoroacetamide derivatives

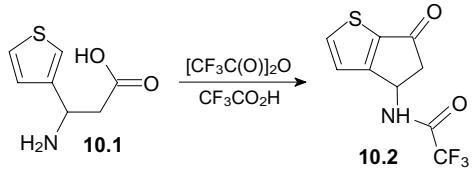
Fluorinated amides [12] often exhibit reactivity differing from that of non-fluorinated analogues [353] and various types of biological activity. Trifluoroacetamide is one of the most convenient reagents used for amine synthesis. Trifluoroacetamide derivatives are versatile synthons, equivalents of ammonia, owing to their high reactivity and easy removal of the trifluoroacetyl protecting group by treatment with KOH or $NaBH_4$.[354, 355] Note also relatively high electrophilicity of the trifluoroacetamide carbonyl group towards reactions with reducing agents and organometallic reagents, which yield trifluoromethylated amines.[356] Trifluoroacetamide is a precursor of *N*,*O*-bis(trimethylsilyl)trifluoroacetamide, a commercially available silylating agent, which readily reacts with alcohols or amino acids and is employed in chromatography to protect hydroxy groups in the analysis of natural products.[357]

There are two approach to the formation of the trifluoroacetamide group. The first one, acylation of amines with trifluoroacetic anhydride,[358, 359] requires the presence of an amino group in the substrate molecule and is used to protect the amino group. The second approach is the reaction of trifluoroacetamide with organic substrates, which allows simultaneous introduction of amino and trifluoroacetyl groups into the molecule. This chapter is mainly devoted to reactions of the latter type and includes analysis of reactions of trifluoroacetamide derivatives, namely, intramolecular heterocyclization and cycloaddition to alkenes and dienes. The amidation reactions giving N-aryl- and N-hetaryltrifluoroacetamides as well as unsaturated trifluoroacetamide derivatives are considered. Finally, we describe reactions of trifluoroacetamide with alkenes and dienes in the $Bu^tOCl-NaI$ system, which reveals most clearly the differences between trifluoroacetamide and its non-fluorinated analogues. Trifluoroacetamide derivatives obtained in different ways serve as precursors for the synthesis of some N-heterocycles and acyclic products. Furthermore, trifluoroacetamidation of various substrates opens the way to C – N bond formation, which is of particular interest for pharmaceutical chemistry in view of the presence of an amino group in many drugs and biologically active compounds.

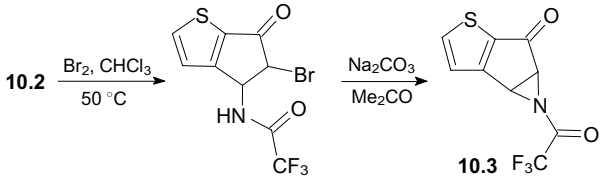
10.1. Cyclizations involving trifluoroacetamide derivatives

Treatment of 3-amino-3-(3-thienyl)propionic acid (**10.1**) with a mixture of trifluoroacetic acid and anhydride induces an intramolecular dehydration and N-acylation to 4-trifluoroacetamide 4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one derivative **10.2** (Scheme 165).[360]

Scheme 165



Scheme 166



Product **10.2** is further halogenated at the active methylene group and dehydrohalogenated to give aziridine **10.3** (Scheme 166).[361, 362]

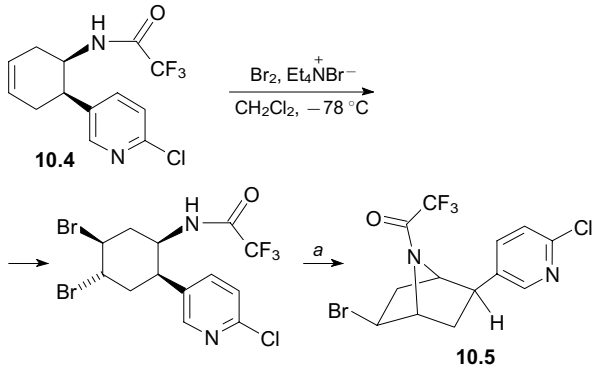
Similar transformations were accomplished for *N*-(1,3-dibromo-6-oxo-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-yl)trifluoroacetamide containing [*c*]-fused thiophene and cyclopentanone moieties.[363] This method was used to prepare the corresponding aziridine from 2-aminocyclohexanol; the selective trifluoroacetylation of the amino group was followed by mesylation of the hydroxy group and aziridine ring closure by the reaction of the trifluoroacetamide derivative with lithium bis(trimethylsilyl)amide.[364]

Dehydrobromination of trifluoroacetamide derivatives produces not only aziridine rings. Indeed, in one of the syntheses of the natural analgesic epibatidine, the 7-azabicyclo[2.2.1]heptane skeleton was constructed by amide **10.4** bromination and dehydrobromination with *trans*-elimination of the bromine atom from position 4 relative to the trifluoroacetamide group; this gave product **10.5** in 75% yield (Scheme 167).[365]

The preference of *trans*-elimination in the formation of bicyclic structures was demonstrated in relation to dehydrobromination of isomeric *N*-(3,4-dibromocyclohex-1-yl)trifluoroacetamides **10.6**: only the bromine atom in the *trans*-position relative to the trifluoroacetamide moiety is displaced, with the product yield being ~80% (Scheme 168).

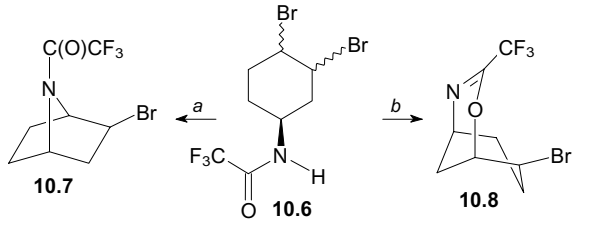
Depending on the position of the bromine atom that is displaced, the nucleophilic centre in the $CF_3C(O)NH$ moiety is located on either the nitrogen atom (when bicyclic product **10.7** is formed) or the oxygen atom, to avoid the formation of a sterically strained four-membered ring upon the displacement of the 3-*trans*-bromine atom.[366] A bicyclic

Scheme 167



(*a*) Bu^{t}OK, THF, −78 → 4 °C, 18 h

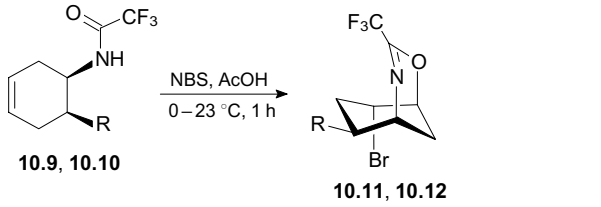
Scheme 168



(*a*) NaH, DMF (3-*cis*,4-*trans*); (*b*) NaH, DMF (3-*trans*,4-*cis*)

product similar to system **10.8** was also obtained by the intramolecular oxidative cyclization of *N*-[(1*R*,6*S*)-6-*R*-cyclohex-3-en-1-yl]trifluoroacetamide **10.9** or **10.10** with *N*-bromosuccinimide (NBS) in acetic acid. As a result, products **10.11** and **10.12** containing the dihydro-1,3-oxazine ring are formed in high yields (Scheme 169).[367] The steric control determines the structure of products depicted in Schemes 168 and 169.

Scheme 169

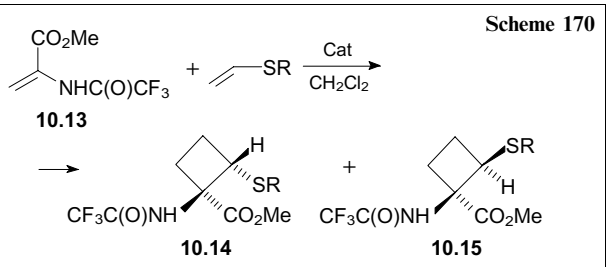


R = H (**10.9**, **10.11**), 6-chloropyridin-3-yl (**10.10**, **10.12**)

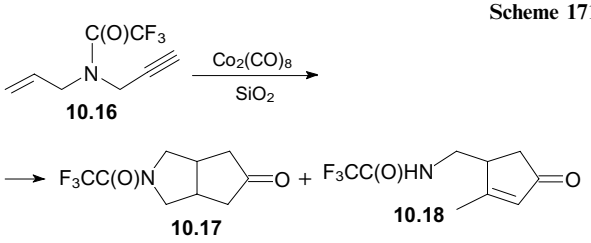
The preparation of strained four-membered rings in the reaction of methyl 2-(trifluoroacetylamino)acrylate **10.13** with vinyl sulfides has been reported.[368] For R = Et, the ratio of isomers **10.14** and **10.15** depends on the nature of the Lewis acid used as the catalyst; in the case of R = Ph, only isomer **10.15** is formed (Scheme 170).

N-Allyl-*N*-propargyltrifluoroacetamide (**10.16**) cyclizes on treatment with $Co_2(CO)_8$, resulting in the formation of hexahydrocyclopenta[*c*]pyrrol-5(1*H*)-one (**10.17**).[369] For selective formation of compound **10.17**, the complete absence of oxygen is required; otherwise, the reaction also gives side product **10.18**, the amount of which increases with increasing concentration of oxygen (Scheme 171).

Scheme 170

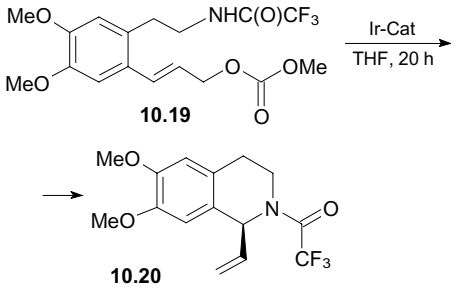


Scheme 171



Under the action of chiral iridium catalysts, the trifluoroacetamide carbonic acid ester derivative **10.19** enantioselectively cyclizes to 1-ethenyl-6,7-dimethoxy-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (**10.20**) in high yield. This reaction was extended to other 1,2,3,4-tetrahydroisoquinolines, which serve as building blocks for the synthesis of biologically active products (Scheme 172).[370]

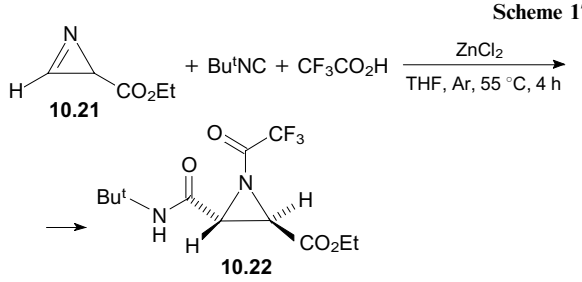
Scheme 172



To our knowledge, there are no published examples of formation of *N*-trifluoroacetylaziridines by methods normally used to prepare *N*-sulfonylaziridines from sulfonamides such as reaction of amides with alkenes under oxidative conditions. Furthermore, trifluoroacetamide derivatives substantially differ in the reactivity from benzamide derivatives. For example, the oxidative cyclization of amino(phenyl)malonates $PhCH(NHC(O)R)CH(CO_2Et)_2$ induced by PhI=O, which leads to *N*-benzoylaziridine in 88% yield when R = Ph, does not proceed for the trifluoroacetamide analogue (R = CF_3).[371] *N*-Trifluoroacetylaziridines are prepared by alternative routes. For example, in the presence of $ZnCl_2$, 2-carbethoxy-2*H*-azirine **10.21** diastereoselectively reacts with trifluoroacetic acid and *tert*-butyl isocyanide to give *N*-trifluoroacetylaziridine **10.22** in 54% yield (Scheme 173). N-Unsubstituted aziridine with retention of the configuration was prepared in 92% yield from compound **10.22** by the reaction with $NaBH_4$.[372] This is the first case of removal of the trifluoroacetyl protection in aziridines in this way.

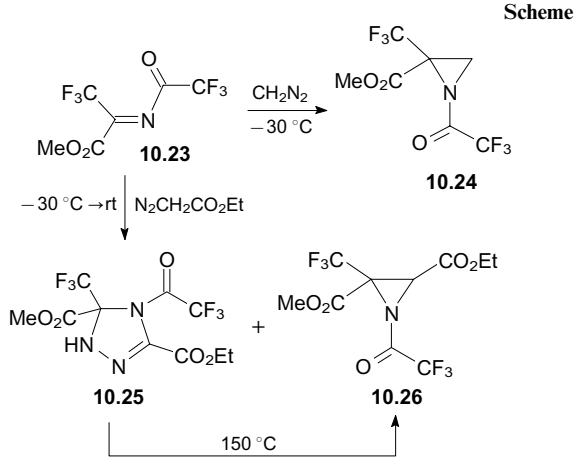
An alternative pathway to *N*-trifluoroacetylaziridines is the reaction of methyl 2-(*N*-trifluoroacetylimino)trifluoro-

Scheme 173



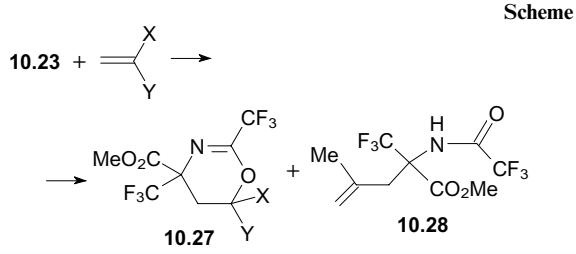
propionate (**10.23**) with diazomethane or ethyl diazoacetate.[373] In the former case, the reaction proceeds at −30 °C and the yield of product **10.24** is 60%, while the latter reaction gives triazoline **10.25** and aziridine **10.26** in 2 : 1 ratio. Thermolysis of triazoline **10.25** at 150 °C affords aziridine **10.26** in 70% yield (Scheme 174).

Scheme 174



The reactions of ester **10.23** with several linear and cyclic alkenes have been studied (Scheme 175). The reactions with vinyl ethers and 2-methylpropene give dihydrooxazines **10.27**. In the former case, isomers with different positions of substituents X and Y with respect to the ring are formed, while in the latter case, adduct **10.28** is formed as a minor product *via* addition to the C=N bond of ester **10.23** involving the methyl group of 2-methylpropene.[373]

Scheme 175

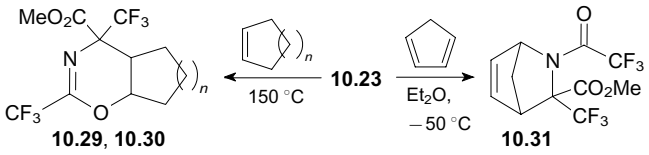


X = H: Y = OBu^n, CO_2Me; X = Y = Me

The reaction of ester **10.23** with cycloalkenes and cyclopentadienes affords bicyclic products **10.29** – **10.31** (50% – 70% yields); compound **10.31** was formed as a 1 : 1 mixture of *endo*- and *exo*-isomers (Scheme 176).[373]

Trifluoroacetamide reacts with 3-amino-2*H*-azirines **10.32** with azirine ring opening to give 4,4-disubstituted

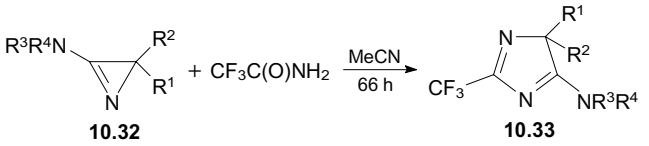
Scheme 176



n = 1 (**10.29**), 2 (**10.30**)

4*H*-imidazoles **10.33**. The maximum product yield in the BF_3-catalyzed reaction on refluxing in MeCN was attained for $R^1 = R^2 = R^3 = R^4 = Me$ and reached 80% (Scheme 177).[374]

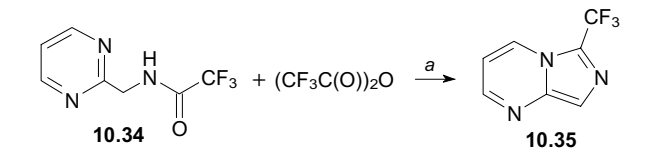
Scheme 177



R^1, R^2, R^3, R^4 = Me, Et, Pr^i, Ph

Recently a method has been developed for the synthesis of trifluoromethylated imidazo-annulated N-heterocycles from benzyl type trifluoroacetamide derivatives, as shown below. Amide **10.34** and its analogues are prepared by either trifluoroacetylation of the corresponding benzylamines with trifluoroacetic anhydride or by the substitution reaction of the corresponding benzyl halides or tosylates by the reaction with trifluoroacetamide. The reaction proceeds as intramolecular cyclization accompanied by dehydration; the yield of pyrimidine **10.35** is 67% (Scheme 178).[375]

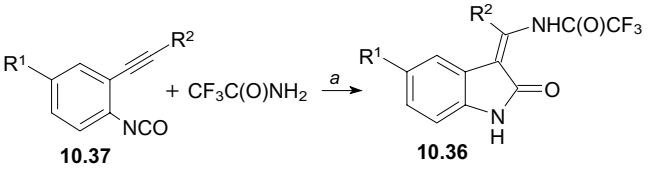
Scheme 178



(*a*) Et_3N (1 equiv.), THF, 0 °C → rt, 12 h

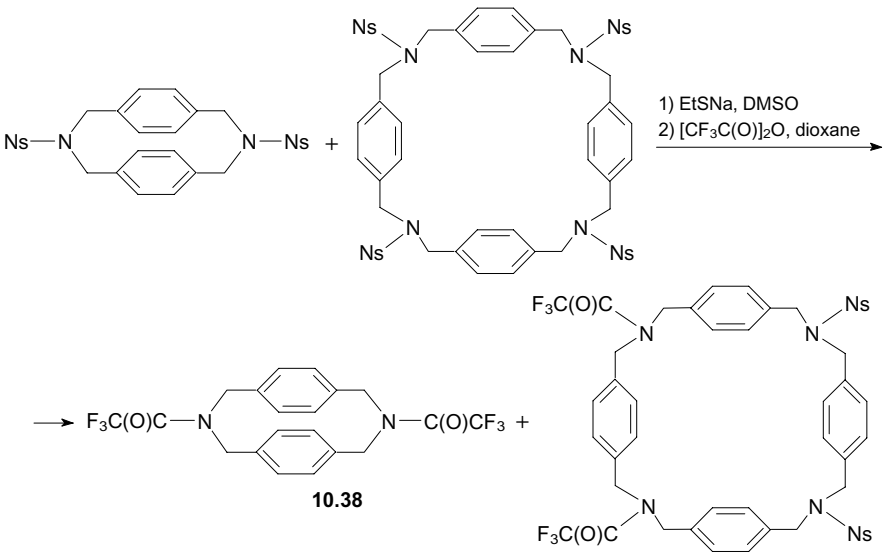
A stereoselective process was developed for the synthesis of 3-(amidoalkylidene)oxindoles **10.36** by cyclization of 2-(alkynyl)aryl isocyanates **10.37** with trifluoroacetamide in the presence of Pd^0 diphosphine catalyst, with product yields ranging from high to quantitative (Scheme 179).[376]

Scheme 179



(*a*) Pd^0 – P*, PhMe, 100 °C, 3 h; R^1 = H, Br, Cl, OMe, CO_2Et, CN; R^2 = Pr^n, Pr^i, Bu^t, Bu^n, Ph, CH_2=CH, Cy, *p*-Tol, *o*-Tol, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$; Cy is cyclohexyl; P* is phosphorus-containing ligand

Scheme 180



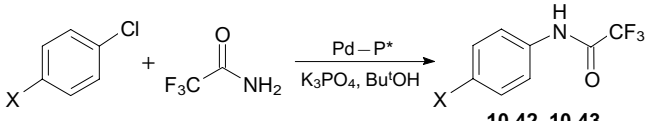
Ns is *p*-nitrobenzenesulfonyl (nosyl)

Finally, consider the synthesis of N-trifluoroacetyl derivatives of diaza[3_2]cyclophane **10.38**, triaza[3_3]cyclophane (not indicated in the Scheme) and tetraaza[3_4]-cyclophane **10.39**. They are synthesized from the corresponding *p*-nitrobenzenesulfonyl derivatives by removal of the *p*-nitrobenzenesulfonyl (nosyl) protecting group *via* the reaction with ethanethiolate and reprotection of the nitrogen atom by the trifluoroacetyl group (Scheme 180).[377]

10.2. Transition metal-catalyzed fluoroacetamidation of aromatic and linear unsaturated substrates

The reaction of aryl chlorides **10.40** and **10.41** with trifluoroacetamide in the presence of K_3PO_4 as a base and a palladium – phosphine catalyst in Bu^{t}OH leads to trifluoroacetamidation products **10.42** and **10.43** in 82% and 90% yields, respectively (Scheme 181).[378]

Scheme 181



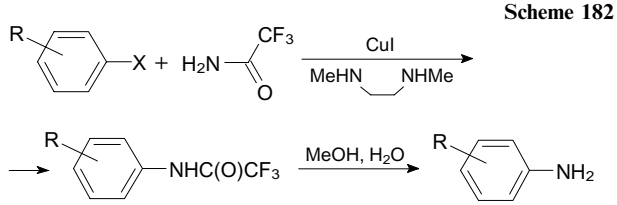
10.40, **10.41** **10.42**, **10.43**

X = Me (**10.40**, **10.42**), CN (**10.41**, **10.43**)

The cross-coupling of aryl bromides and aryl iodides with trifluoroacetamide catalyzed by CuI was studied with various ligands; the best results were obtained with *N*,*N*′-dimethylethylenediamine, which provided product yields of up to nearly quantitative under mild conditions.[379] The trifluoroacetyl protecting group was shown to be removed in the case of the one-pot process with methanol and water being added to the reaction mixture after trifluoroacetamidation. The yields of anilines substituted in various positions reach 100% (Scheme 182).

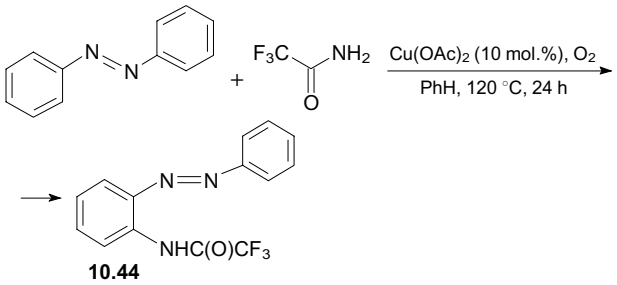
The aerobic oxidative amidation of azobenzene with trifluoroacetamide under the action of $Cu(OAc)_2$ is directed

Scheme 182



R = H, Me, Ph, MeO, Ac, EtO_2C, O_2N, Br, Me_2N, NC, H_2N; X = I, Br

Scheme 183

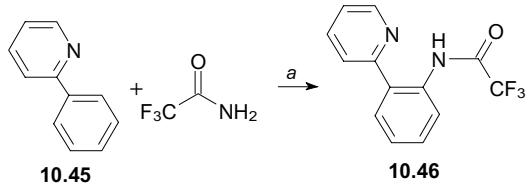


10.44

to the *ortho*-position to the diazo group and gives product **10.44** in 86% yield (Scheme 183).[380]

Trifluoroacetamidation of aromatic substrates containing linked or fused aromatic and heteroaromatic moieties in one molecule is directed to the aromatic ring. An exception is the reaction with *N*-methylbenzimidazole catalyzed by $Cu(OAc)_2$, which involves the C(2) atom of the imidazole ring.[381] The reaction of 2-phenylpyridine (**10.45**) with trifluoroacetamide in the presence of $Cu(OAc)_2$ and O_2 gives the product trifluoroacetamidated into the *ortho*-position relative to the pyridine ring (**10.46**) in 66% yield (Scheme 184).[382] Note that this is the highest yield among those obtained for other amides and sulfonamides studied in this work. However, previously it was shown that in the presence of $Pd(OAc)_2$ and potassium persulfate, the yield of product **10.46** is much higher (92%).[383]

Scheme 184

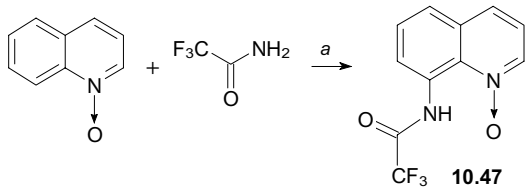


10.45 **10.46**

(*a*) $Cu(OAc)_2$ (20 mol.%), O_2, DMSO, anisole, 160 °C, 48 h

Trifluoroacetamidation of quinoline *N*-oxides containing fused benzene and oxidized pyridine rings was studied using various oxidants, catalysts and bases. The $PhI(OAc)_2 - AgOTf - Li_2CO_3$ system was most efficient, providing up to 94% yield of compound **10.47**, resulting from selective amination of position 8 (Scheme 185).[384]

Scheme 185



10.47

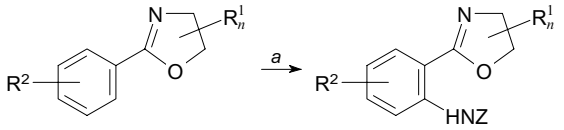
(*a*) AgOTf, $PhI(OAc)_2$, Li_2CO_3, CH_2Cl_2, rt, 1 h;
TfO is trifluoromethanesulfonate (triflate)

2-Aryloxazolines undergo selective amidation of the *ortho*-position relative to the oxazoline substituent; a comparison showed that trifluoroacetamide is more reactive than tosylamide (Scheme 186).[385]

The trifluoroacetamidation products are convenient precursors for the synthesis of quinazolines after trifluoroacetyl deprotection and ring transformation on treatment with formamidine with oxazole ring opening (Scheme 187).[386]

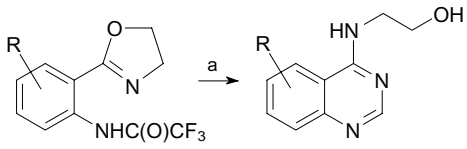
The trifluoroacetamidation of 2-, 3- and 4-oxazolylpyridines has been studied under the same conditions

Scheme 186



(*a*) ZNH_2, $PhI(OAc)_2$, $AgSbF_6$, [Rh]; Z = $CF_3C(O)$ > $ArSO_2$;
R^1_n = H, Me_2; R^2 = 4-Me, 4-OMe, *etc.*

Scheme 187



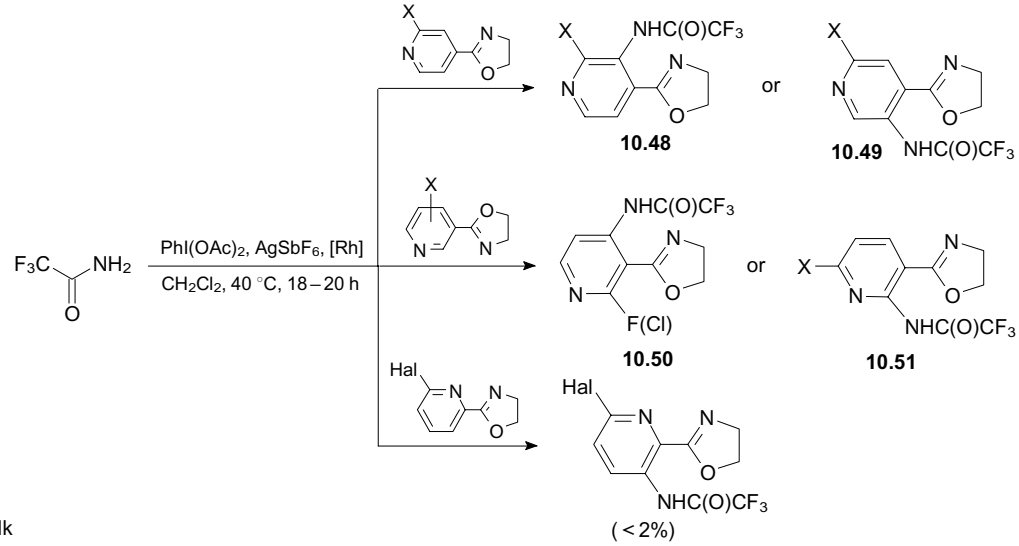
(*a*) 1) NaOH (20 equiv.), EtOH, rt; 2) $HN{=}CHNH_2 \cdot AcOH$ (3 equiv.), EtOH, 78 °C, 1 h; R = 5-Me, 6-Me, 7-Me, 7-OMe, 7-CF_3, *etc.*
(substituent positions in the product are indicated)

(Scheme 188).[387] The reaction of 4-substituted substrates is directed to position 3 or 5 and gives products **10.48** or **10.49**, depending on the nature of the substituent X. 3-Substituted substrates with the group X in position 2 are amidated into position 4 (products **10.50**), while 6-substituted substrates are amidated into position 2 (products **10.51**). 2-Halo-6-(2-oxazolyl)pyridines are inactive: the degree of conversion of the substrate is < 2% and amidation is directed to position 5.[387] The easy trifluoroacetyl deprotection by treatment with a solution of alkali in ethanol giving amines provides opportunities for further functionalization.

The reactions catalyzed by metal complexes were also used for allylic amidation of various substrates. Thus the reaction of unsaturated carbonates **10.52** catalyzed by iridium complexes with optically active ligands (L*) affords amides **10.53** in ~70% yield with almost quantitative enantioselectivity (Scheme 189).[388]

More recently, product **10.54**, an enantiomer of compound **10.53** (R = Ph), was obtained in 80% yield and 98%

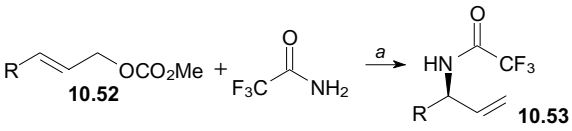
Scheme 188



X = Hal, Alk

(< 2%)

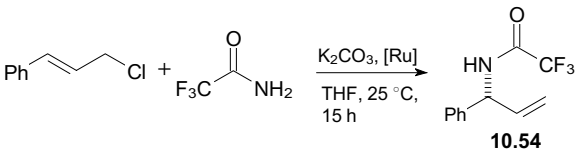
Scheme 189



(*a*) $[(cod)IrCl]_2$, L*, THF, rt, 15 h; R = Ph, *p*-Tol, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, n-C_7H_{15}, Cy;
cod is cycloocta-1,5-diene

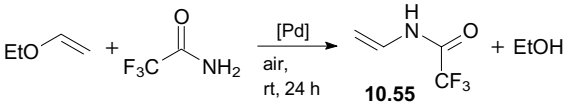
enantioselectivity by allylic amidation of cinnamoyl chloride with trifluoroacetamide catalyzed by a chiral Ru complex.[389] It is notable that with benzamide taken instead of trifluoroacetamide the amidation does not proceed (Scheme 190).

Scheme 190



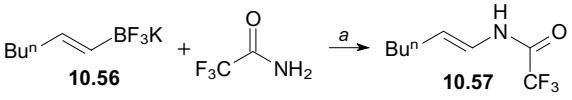
Transition metal catalysis was used not only for allylic, but also for vinylic amidation. For example, ethyl vinyl ether reacts with trifluoroacetamide in the presence of a Pd^{II} phenanthroline complex catalyst under mild conditions to give enamide **10.55** in 76% yield (Scheme 191).[390]

Scheme 191



The reaction of potassium hexenyltrifluoroborate **10.56** with trifluoroacetamide in the presence of the $Cu(OAc)_2$ catalyst is stereospecific, proceeding with retention of the configuration of enamide **10.57** (the yield is 86%, which is higher than the yields obtained with acetamide or benzamide) (Scheme 192).[391]

Scheme 192

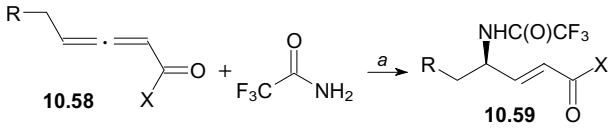


(*a*) $Cu(OAc)_2$ (10 mol.%), O_2, DMSO – CH_2Cl_2 (1 : 1), 40 °C, 20 h

The enantioselective synthesis of products of γ-addition of trifluoroacetamide to allenoates **10.58** in the presence of optically active spirophosphine catalysts was reported; the products are formed in high yields with high enantiomeric excess.[392] The replacement of the catalyst by its enantiomer leads to the reversal of stereoselectivity and formation of the enantiomer of product **10.59** (Scheme 193).

Owing to easy trifluoroacetyl deprotection, the trifluoroacetamidation of mono- and diiodocarboranes using

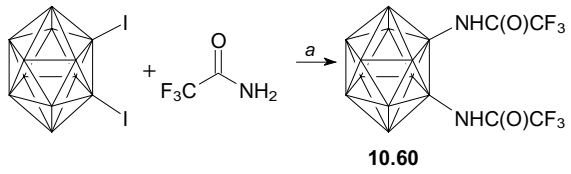
Scheme 193



(*a*) (*S*)-Cat, Bu^{t}OMe, 10 °C; R = Alk: X = OAlk, NMe_2

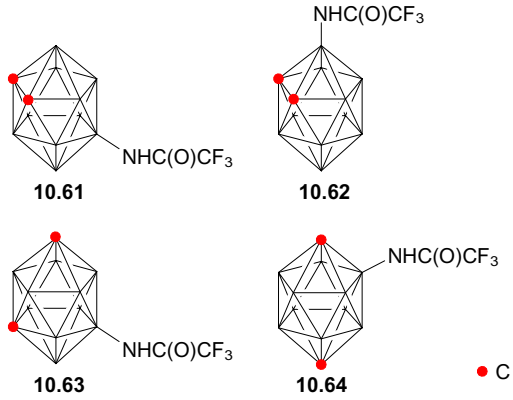
a Pd – phosphine catalyst and a base (K_3PO_4) is a very convenient method for the synthesis of aminocarboranes.[393] This method was employed to prepare a series of trifluoroacetylamino-substituted carboranes **10.60** – **10.64** (Scheme 194).

Scheme 194



(*a*) Pd – phosphine, K_3PO_4, PhMe, 100 °C, 2 h

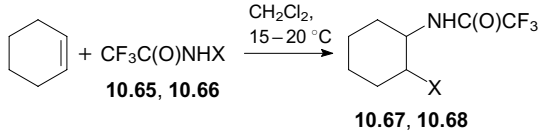
Structures 10.61 – 10.64



10.3. Oxidative addition and cyclization involving N-halogenated trifluoroacetamide derivatives

N-Halo derivatives of trifluoroacetamide are active reagents for cyclization and addition. For example, the reactions of *N*-chloro- (**10.65**) and *N*-bromotrifluoroacetamides (**10.66**) with cyclohexene afford adducts **10.67** and **10.68** in 97% and 36% yields, respectively; the *cis*- to *trans*-isomer ratio is 7.3 : 0.7 (Scheme 195).[394]

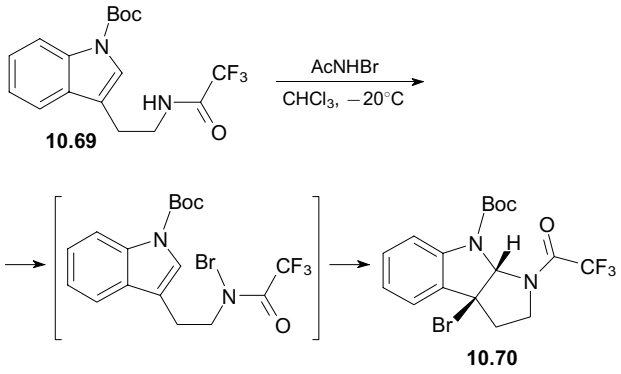
Scheme 195



X = Cl (**10.65**, **10.67**), Br (**10.66**, **10.68**)

The intramolecular cyclization of N-trifluoroacetyl derivative **10.69** involving the double bond of the indole ring is carried out with *N*-bromoacetamide as the brominating agent and camphorsulfonic acid and hydroquinone phthalazine-1,4-diyl ether as the catalyst (Scheme 196).[395] This gives tryptamine derivatives **10.70**.

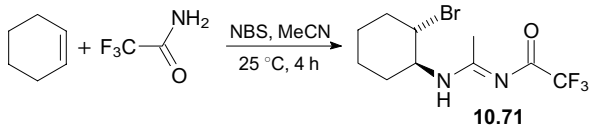
Scheme 196



Boc is *tert*-butoxycarbonyl

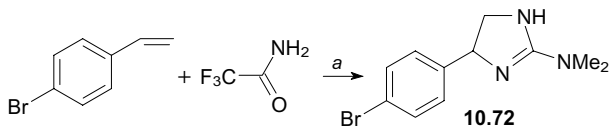
In the presence of *N*-bromosuccinimide, cyclohexene adds trifluoroacetamide to give amidine **10.71** in 90% yield.[396] Note that the corresponding amidine is formed from trichloroacetamide in approximately the same yield (Scheme 197).

Scheme 197



When *p*-bromostyrene reacts with trifluoroacetamide under similar conditions, but in the presence of cyanamide instead of MeCN, the corresponding imidazoline **10.72** is obtained in 90% yield. However, with trichloroacetamide the expected product is formed only in trace amounts (Scheme 198).[397]

Scheme 198

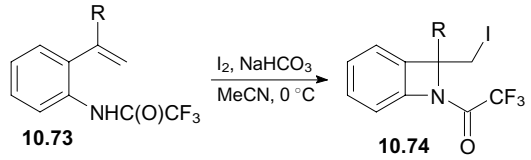


(*a*) NBS, Me_2NCN, 25 °C, 4 h

The cyclization can also be performed for N – I derivatives of trifluoroacetamide. It was found that on treatment with molecular iodine in the presence of $NaHCO_3$, trifluoroacetamides **10.73** cyclize under mild conditions to give benzazetidines **10.74** in good yields (Scheme 199).[398]

If the double bond and the benzene ring are separated by a bridging methylene group, the electrophilic cyclization (intramolecular iodotrifluoroacetamidation) gives rise to

Scheme 199

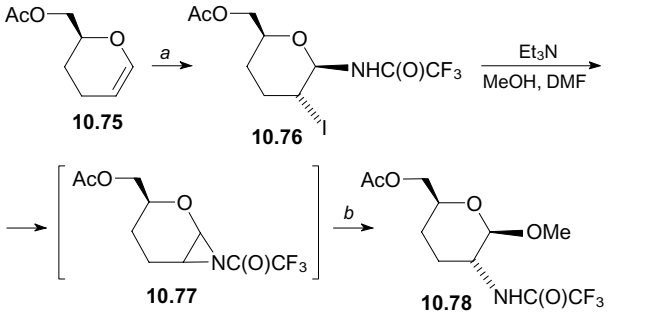


R = Alk

less strained five-membered rings — 1-trifluoroacetyl-2,3-dihydro-1*H*-indoles.[399]

N-Iodosuccinimide (NIS) initiates the oxidative addition of trifluoroacetamide to 3,4-dihydro-2*H*-pyran-2-ylmethyl acetate **10.75** to give adduct **10.76**, which eliminates HI to afford the intermediate *N*-trifluoroacetylaziridine **10.77**. The latter undergoes aziridine ring opening on treatment with methanol, thus yielding racemic *trans*-adduct **10.78** with a minor amount of the *cis*-isomer.[400] The racemate was separated by the biocatalytic method using enzymes (Scheme 200).

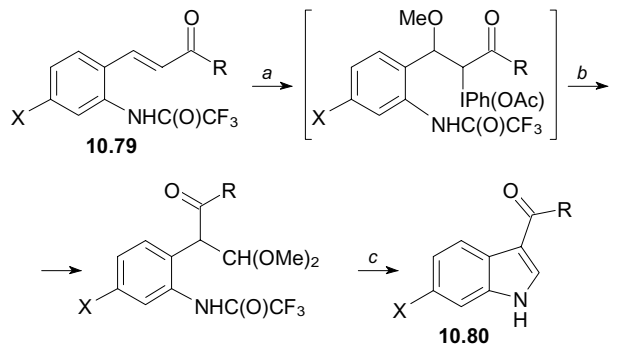
Scheme 200



(*a*) $CF_3C(O)NH_2$, NIS, MeCN, 0 °C, 1.5 h; (*b*) MeOH

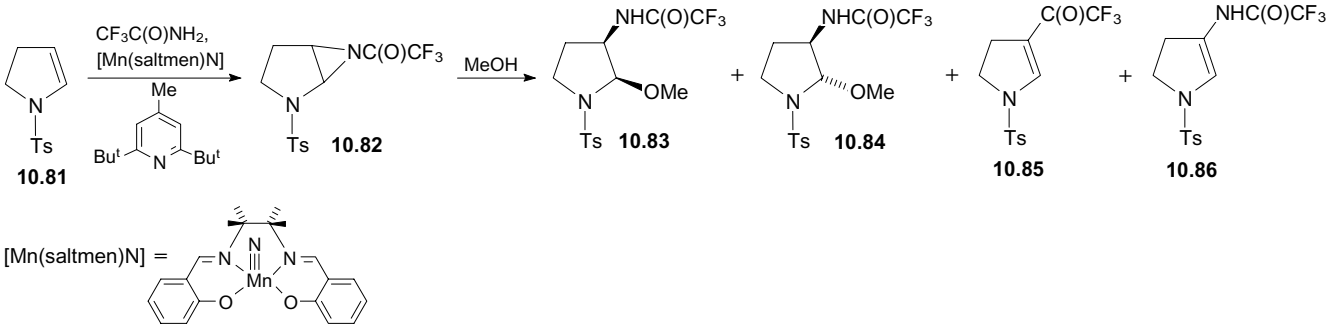
The easy trifluoroacetyl deprotection promoted the development of the one-pot synthesis of 3-acylindoles *via* the oxidative rearrangement of 2-aminochalcones **10.79** followed by intramolecular cyclization. The yields of indoles **10.80** depend on the nature of substituents R and X and vary from moderate to quantitative (Scheme 201).[401]

Scheme 201



(*a*) $PhI(OAc)_2$, $BF_3 \cdot Et_2O$, $CH(OMe)_3$, rt; (*b*) MeOH (−PhI, −AcOH); (*c*) K_2CO_3, THF, H_2O (−MeOH, $-CF_3CO_2Me$); R = 4-$MeOC_6H_4$: X = Alk, Hal, *etc.*

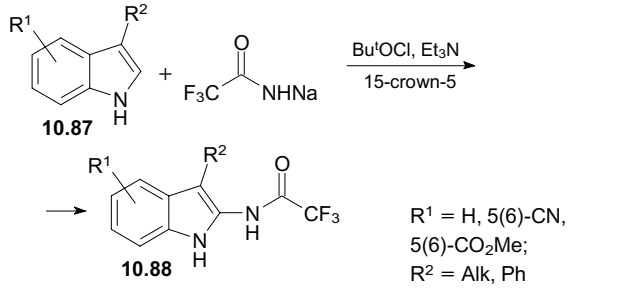
Scheme 202



Treatment of *N*-tosyl-2,3-dihydro-1*H*-pyrrole **10.81** with trifluoroacetamide results in the formation of *N*-trifluoroacetylaziridine **10.82**.[402] The reaction is induced by a nonnucleophilic base, 2,6-di(*tert*-butyl)-4-methylpyridine, and the complex [Mn(saltmen)N] [saltmen is *N*,*N*′-(1,1,2,2-tetramethylethylene)bis(salicylideneiminate)], which was earlier successfully used in oxidative trifluoroacetamidation reaction.[403 – 406] Opening of the three-membered ring affords 3-amino-2-methoxypyrrolidines **10.83**, **10.84** and 4-trifluoroacetoxy-2,3-dihydropyrrole (**10.85**) in 8%, 39% and 10% yields, respectively. The attempt to suppress the formation of product **10.85** by ageing the aziridinating agent (increasing the time of reaction between the complex [Mn(saltmen)N] and trifluoroacetamide) were unsuccessful, but provided some interesting results. Products **10.83** and **10.84** were formed in trace amounts, the yield of product **10.85** did not change, but 4-trifluoroacetamido-2,3-dihydropyrrole (**10.86**) was the major product (40%) (Scheme 202).[402]

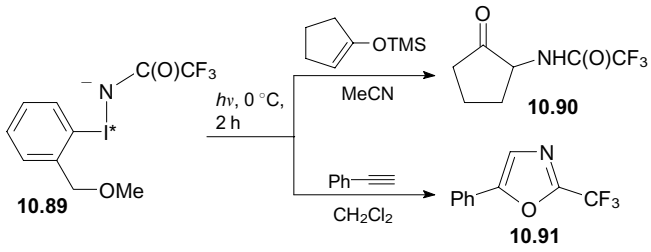
The reactions of an extensive series of indoles **10.87** with the salt $CF_3C(O)NHNa$ proceed selectively at the C(2) atom and give oxidative trifluoroacetamidation products **10.88** (51% – 97% yield).[407] The absence of saturated adducts similar to compounds **10.83** and **10.84** in Scheme 202 is evidently attributable to easy elimination of HCl, resulting in aromatization of the molecule (Scheme 203).

Scheme 203



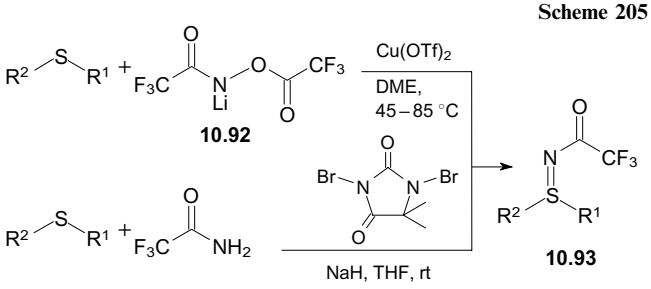
N-Acyliminoiodanes, sulfenyl analogues of which serve as precursors of sulfonylnitrenes, may be potential sources of the N-acylamino groups to be introduced into organic molecule.[408] However, they are unstable: for example, $PhI-NC(O)CF_3$, obtained at -40 °C as a solid, decomposes with explosion at about 100 °C,[409] which hampers its use in synthetic practice. Recently it was shown that the introduction of the *ortho*-methoxymethyl substituent (CH_2OMe) into the aryl moiety substantially stabilizes the molecule owing to the intramolecular MeO···I coordination; this made it possible to study the reactions of this reagent with some unsaturated substrates.[410] Unlike the reactions of N-sulfonyliminoiodanes, reactions of N-acyliminoiodanes are induced by UV radiation rather than transition metal-based catalysts. For instance, *N*-trifluoroacetyliminoiodane (**10.89**) reacts with trimethylsilyl ether of cyclopentene to give *N*-(2-oxocyclopentyl)trifluoroacetamide (**10.90**) (77% yield).[410] The reaction of iodane **10.89** with phenylacetylene affords 5-phenyl-2-(trifluoromethyl)-1,3-oxazole (**10.91**) in 87% yield; it is noteworthy that the formation of oxazoles is highly unusual for iminoiodane reactions (Scheme 204).

Scheme 204



The electrophilic trifluoroacetamidation can be utilized for the formation of not only the C – N bond, but also the S = N bond. Twenty years ago it was shown that the lithium salt of *N*,*O*-bis(trifluoroacetyl)hydroxylamine (**10.92**) reacts with sulfides in the presence of the $Cu(OTf)_2$ catalyst to give N-(trifluoroacetyl)sulfylimines **10.93** in 65% to 95% yields (Scheme 205).[411]

Scheme 205



R1, R2 = Alk; DME is 1,2-dimethoxyethane

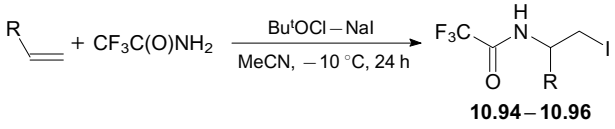
An alternative non-catalytic one-pot method has been developed for the preparation of imines **10.93** from sulfides and trifluoroacetamide under mild conditions using 1,3-dibromo-5,5-dimethylhydantoin as the oxidant.[412] The reaction pathway depends on the solvent: in methanol, *N*-(trifluoroacetyl)sulfylimine is formed as a 1 : 1 mixture with sulfoxide as a result of hydrolysis, which can be suppressed by conducting the reaction in CH_2Cl_2 or THF.[412]

10.4. Oxidative trifluoroacetamidation of alkenes and dienes in the Bu^{t}OCl – NaI system

This subchapter is devoted to the results of studies of the reactions between trifluoroacetamide and alkenes or dienes in the Bu^{t}OCl – NaI system. These transformations are analyzed separately due to the diversity of products, dependence of their composition on the substrate structure and the most vivid differences between the reactivities of trifluoroacetamide and non-fluorinated analogues. This oxidative system was used to study the reactions of amides with alkenes, which gave oxazolines as the only products, with their isomeric composition depending on the substrate structure.[413] A reaction mechanism was proposed, including the formation of the *N*,*N*-diiodoamide $RC(O)NI_2$, alkene iodination to give the cyclic iodonium cation and ring opening in the cation upon the reaction with the $RCONI^-$ anion.[413]

We showed that, unlike the reactions of non-fluorinated amides with alkenes in the (Bu^{t}OCl – NaI) system,[413] the reactions of trifluoroacetamide with vinylcyclohexane or styrenes under the same conditions give, instead of oxazolines, the amidoiodination products **10.94** – **10.96** in 80% yield.[414] The structures of products **10.94** and **10.95** were determined by X-ray diffraction (Scheme 206).[415]

Scheme 206



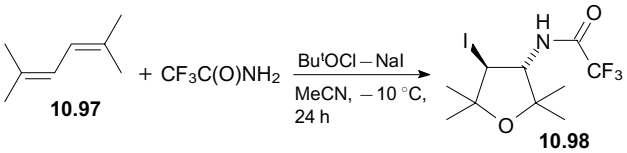
10.94 – **10.96**

R = Cy (**10.94**), Ph (**10.95**), 4-ClC_6H_4 (**10.96**)

It is worth noting that the distinction of alkene reactions with trifluoroacetamide is not only in the formation of linear adducts instead of oxazolines, like with other amides,[62] but in the opposite regioselectivity. The preferable or exclusive formation of 5- rather than 4-substituted oxazolines[62] implies that the precursor of the cyclization product has the structure of $RC(O)N(I)CH_2CH(I)R'$. Meanwhile, adducts **10.94** – **10.96** can be described by the general formula $CF_3C(O)NHCH(R)CH_2I$. In our opinion, this is attributable to the decrease in the degree of conjugation in the amide group under the action of the strong electron-withdrawing group (CF_3); this was confirmed by IR spectroscopy and quantum chemical calculations.[415] As a result, the nitrogen atom becomes more, and the oxygen atom becomes less nucleophilic, which accounts for the observed regioselectivity.

The reaction of trifluoroacetamide with 2,5-dimethylhexa-2,4-diene (**10.97**) generates the cyclization product, *trans*-*N*-(4-iodo-2,2,5,5-tetramethyltetrahydrofuran-3-yl)trifluoroacetamide (**10.98**) in 76% yield, which was also studied by X-ray diffraction (Scheme 207).[414, 415]

Scheme 207

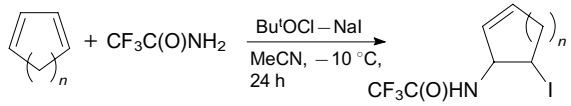


10.97 **10.98**

Considering the data obtained for the reactions of substrate **10.97** with triflamide $TfNH_2$,[416] the formation of heterocycle **10.98** is interpreted within the framework of the following mechanism (Scheme 208). Intermediate $CF_3C(O)NHI$ iodinates 2,5-dimethylhexa-2,4-diene at one double bond to give a stable tertiary cation, which is attacked by the Bu^{t}OOH molecule with elimination of Bu^{t}OH and $CF_3C(O)NHI$ and cyclization to a dihydrofuran intermediate. Further iodoamidation of the intermediate with a second $CF_3C(O)NHI$ molecule yields the *trans*-isomer of product **10.98**.

The same authors[414] studied the reactions of trifluoroacetamide with cyclopentadiene and cyclohexa-1,3-diene (Scheme 209). This gives only monoadducts **10.99** and **10.100**, with the second double bond remaining intact. The structures of products **10.99** and **10.100** were established by X-ray diffraction.[414, 415]

Scheme 209

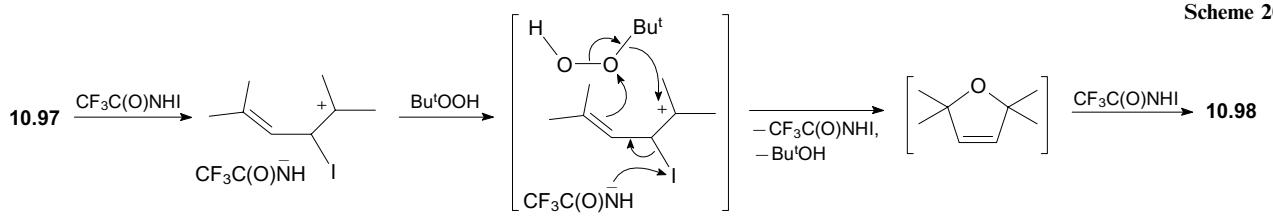


10.99, **10.100**

n = 1 (**10.99**, 71%), 2 (**10.100**, 85%)

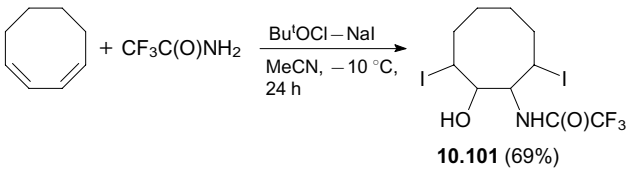
While comparing the results of reactions of cyclopentadiene or cyclohexa-1,3-diene with trifluoroacetamide or triflamide,[417] one should note that cyclopentadiene gives iodoamidation products with both $TfNH_2$ and trifluoroacetamide, whereas cyclohexa-1,3-diene is iodoamidated only in the case of trifluoroacetamide, while in the case of $TfNH_2$, the bis(triflamidation) product is formed.

Scheme 208



Unlike the cyclopentadiene and cyclohexa-1,3-diene, which react through only one double bond, the reaction of cycloocta-1,3-diene with trifluoroacetamide affords bis-adduct **10.101**, containing two iodine atoms and hydroxy and trifluoroacetamide groups in the ring (Scheme 210).[414]

Scheme 210

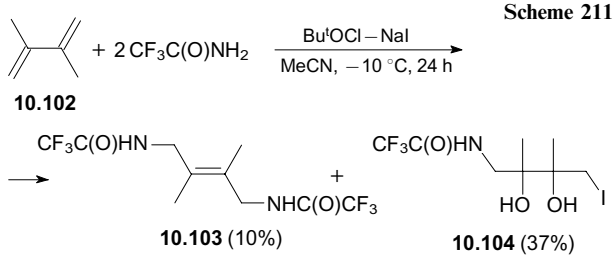


10.101 (69%)

In this case, the substrate also showed different behaviours towards trifluoroacetamide and triflamide; in the latter case, the reaction of cycloocta-1,3-diene is accompanied by a rearrangement and eight-membered ring contraction to a seven-membered ring.[418]

In view of the repeatedly demonstrated unusual behaviour of fluorinated amides, we studied the reaction of trifluoroacetamide with 2,3-dimethylbuta-1,3-diene (**10.102**) under the same conditions[419] hoping to prepare heterocyclic products, like in the reaction with $TfNH_2$ (Scheme 211).[416] Due to strong resinification of the reaction mixture, only acyclic adducts were isolated, namely, *N*,*N*′-[(2*E*)-2,3-dimethylbut-2-ene-1,4-diyl]bis(trifluoroacetamide) (**10.103**) and *N*-(2,3-dihydroxy-4-iodo-2,3-dimethylbutyl)trifluoroacetamide (**10.104**).[419] The structures of both adducts were established by X-ray crystallography.

Scheme 211



10.102

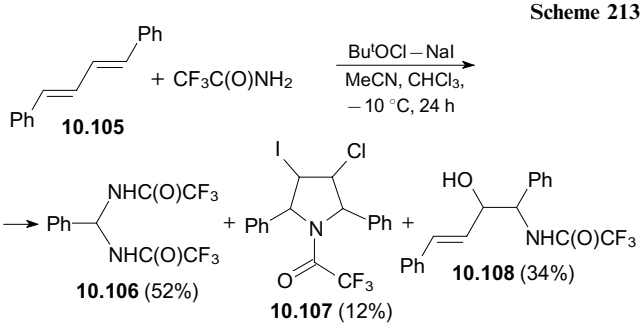
10.103 (10%) **10.104** (37%)

The possible reaction mechanism accounts for the observed stereoselectivity (Scheme 212). The reactive intermediate $CF_3C(O)NHI$ reacts with diene **10.102** giving rise to 1,4-adduct **A**. The latter reacts with a second $CF_3C(O)NHI$ molecule according to the halophilic mechanism *via* a four-membered transition state with elimination of iodine to give product **10.103**. Alternatively, adduct **A** reacts with $CF_3C(O)NHI$, thus generating iodonium cation **B**, which is hydrolyzed to intermediate **C** with (2*S*,3*R*)-configuration of chiral centres. Hydrolysis of **C** *via* the S_N2 mechanism with inversion of the C(2) configuration affords adduct **10.104** with the (2*R*,3*S*)-configuration, according to X-ray diffraction data. The formation of adduct **10.104** during long-term (80 h) column chromatography is in line with the possibility of hydrolysis by water adsorbed on silica gel.

For the new trifluoroacetamide derivatives, the molecular and crystal structures were studied by spectroscopic and theoretical methods; the structures of conformers and hydrogen-bonded associates in solutions were investigated using X-ray diffraction, solution and gas phase IR spectroscopy and quantum chemical calculations.[415, 420]

In the reactions of trifluoroacetamide with 1,4-diphenylbuta-1,3-diene (**10.105**), three products (**10.106** – **10.108**) were obtained in a nearly quantitative total yield (Scheme 213).[421, 422]

Scheme 213

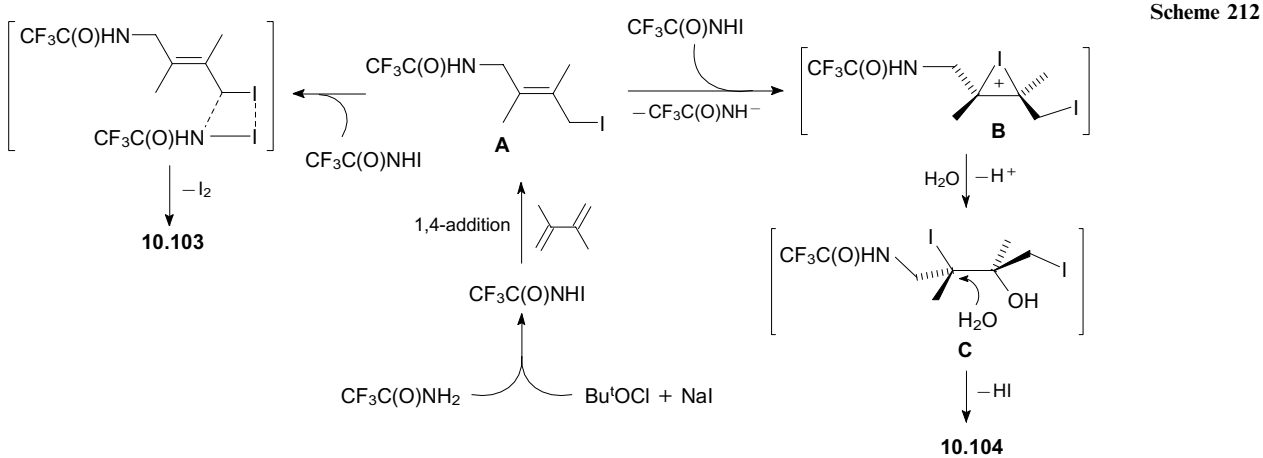


10.105

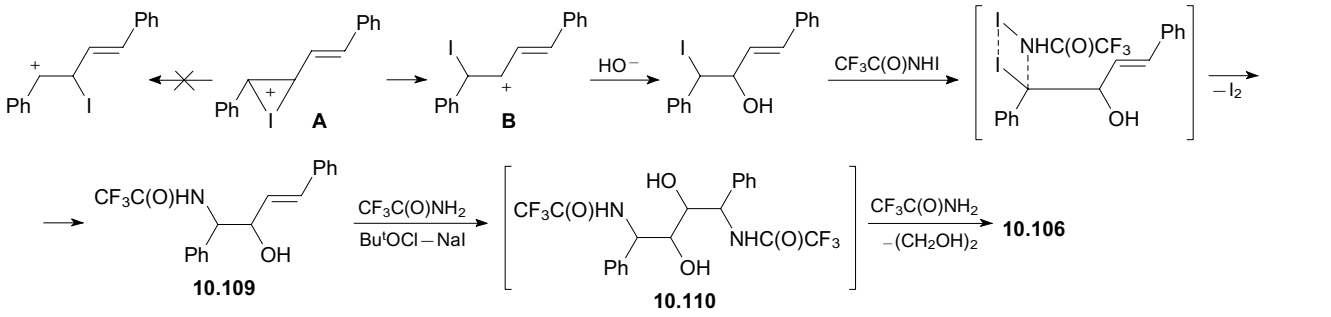
10.106 (52%) **10.107** (12%) **10.108** (34%)

An unexpected outcome is the cleavage of one of the two double bonds in diene **10.105** to give *gem*-disubstituted toluene **10.106**, the structure of which was proved by X-ray diffraction. An important feature of the structure of product **10.106** is the geminal positions of two trifluoroacetamide groups attached to the α-carbon atom. The formation of this type of products was not observed previously in reactions of this type. This is obviously due to the fact that instead of being cleaved at the C(1) – I bond to give the benzyl cation, the iodonium cation **A** is pref-

Scheme 212



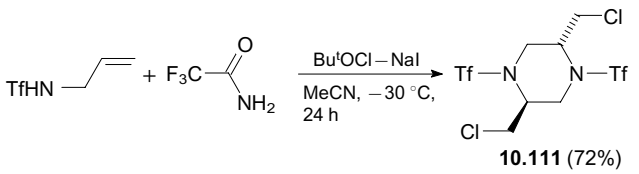
Scheme 214



erably cleaved at the C(2)—I bond giving the more stable phenylallenyl cation **B** with a longer conjugation chain (Scheme 214). The subsequent capture of the hydroxyl anion and exchange of the iodine atom for the trifluoroacetamide residue gives product **10.109**. A similar transformation of the second styryl moiety of compound **10.109** produces bis(trifluoroacetamide) **10.110** with weakened C(1)—C(2) and C(3)—C(4) bonds; on treatment with trifluoroacetamide under oxidative conditions, this compound is converted to **10.106** and glycol oxidation products up to CO_2 and water. 1,1,4,4-Tetraphenylbuta-1,3-diene does not react with trifluoroacetamide under these conditions, but reacts with triflamide being converted to a rearrangement product.[421, 422]

Until recently, nothing was known about the oxidative amidation of unsaturated triflamide derivatives.[423] An attempt at the oxidative triflamidation of *N*-propargyltriflamide[424] gave only iodination products: *N*-(3-iodoprop-2-yn-1-yl)triflamide and *N*-[(2*E*)-2,3-diiodoprop-2-en-1-yl]triflamide. For recently studied oxidative amidation reactions of *N*-allyl- and *N*,*N*-diallyltriflamides with triflamide and arenesulfonamides, the formation of various linear and heterocyclic products was demonstrated.[425] For comparison, the reactions of the same substrates with trifluoroacetamide were studied.[426] It was found that the reaction of *N*-allyltriflamide with trifluoroacetamide, like the reactions with sulfonamides, gives piperazine **10.111** as the only product;[426] the product structure was established by X-ray diffraction. Thus, trifluoroacetamide acts only as the chlorine atom transferring agent (Scheme 215).

Scheme 215

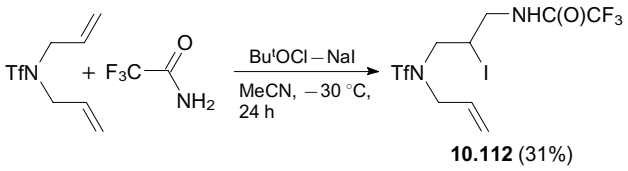


Conversely, *N*,*N*-diallyltriflamide reacts with trifluoroacetamide giving iodoamidation product, amide **10.112**, in a moderate yield (Scheme 216).[426]

The second double bond cannot be involved in the reaction even with excess acetamide, similarly to what was observed previously for reactions with arenesulfonamides.[425]

The presented analysis of the available data on the behaviour of trifluoroacetamide and its derivatives towards

Scheme 216



reactions with aromatic, heterocyclic and unsaturated compounds catalyzed by metal complexes in the presence of oxidants demonstrated the growing interest in these reactions. New methods for C—N bond formation were developed and diverse nitrogen heterocyclic systems were synthesized. Owing to easy trifluoroacetyl deprotection, trifluoroacetamide serves as a synthetic equivalent of ammonia and is a convenient synthon for the synthesis of various amines, including heterocyclic ones, which are of undoubted interest for pharmacological and medicinal chemistry.

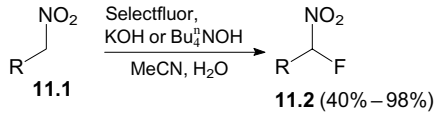
11. Chemistry of α-fluoro nitro compounds

This chapter is devoted to the synthesis and reactivity of compounds containing a fluorine atom and a nitro group at the same carbon atom. The attention is focused on the papers that appeared in the last 10 – 15 years — exactly in this period, organofluorine chemistry, including the chemistry of fluoro nitro compounds, started to develop more intensively (for earlier papers, see Refs 427 – 429). Specific cases such as, for example, transformations of polyfluorinated derivatives [430, 431] are not discussed here. Similarly, the reactions of compounds containing a fluorodinitromethyl group are not included in the discussion: they are regarded as promising energetic compounds,[432] but, their use as intermediates in organic synthesis appears problematic.

11.1. Synthesis of α-fluoronitroalkanes and their transformations proceeding with retention of the fluoronitromethyl moiety

Aliphatic nitro compounds **11.1** are key substrates for the synthesis of α-fluoronitroalkanes **11.2**. They readily undergo electrophilic fluorination under alkaline conditions (KOH, Bu^n_4NOH, NaH). Easily accessible and convenient-to-handle Selectfluor, that is, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), is used most often for this purpose (Scheme 217). Using this reagent, both non-functionalized products[433] and fluoro nitro compounds containing carbonyl,[434, 435] phosphonate[436] and sulfonic groups[437, 438] were obtained. Other

Scheme 217



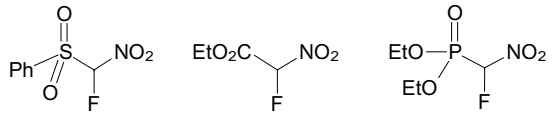
11.1 **11.2** (40% – 98%)

R = Alk, Bn, Bz

known fluorinating agents include *N*-fluorobenzenesulfonimide (NFSI),[439] acetyl hypofluorite (AcOF)[440] and perchloryl fluoride ($FClO_3$).[441] The main side process accompanying fluorination is obviously difluorination,[434, 439, 442] which is usually minimized by selecting the appropriate reactant ratio.[433, 440] The addition of chiral quinine-derived amines allows fluorination to be conducted with a moderate optical induction.[443]

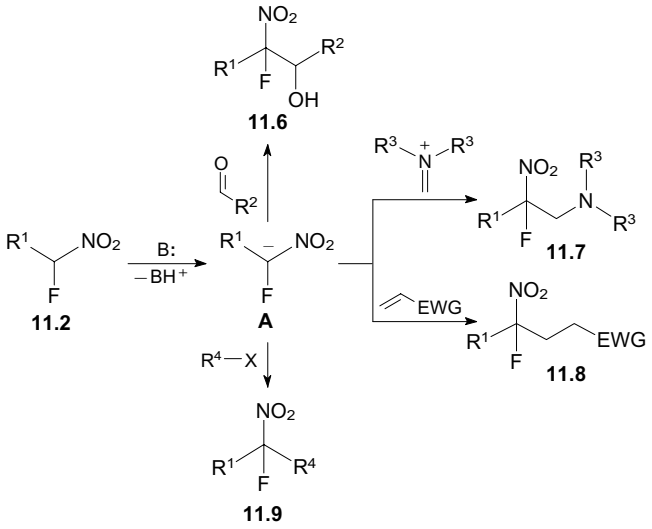
The main reactivity of fluoro nitro compounds is associated with the anionic site on the α-carbon atom (structure **A**, Scheme 218). Although the anion could be stabilized by the nitro group alone, additional functions are often used. For example, fluoronitro(phenylsulfonyl)methane (FNSM, **11.3**),[438, 444 – 447] fluoronitroacetate (**11.4**)[448 – 450] and fluoronitrophosphonate **11.5**[436] are used as reagents. It is noteworthy that the introduction of a fluorine atom reduces, most often, the acidity of nitro compounds and, hence, hampers the formation of anion **A**;[451, 452] the acidity of difluoronitromethane CF_2HNO_2 is as much as two orders of magnitude lower than that of nitromethane.[453] One more peculiar feature of anion **A** is the ability to eliminate the fluoride ion, which may give decomposition products. Perhaps, this accounts for the moderate yields in the synthesis of reagents **11.4** and **11.5**.[436, 448]

Structures 11.3 – 11.5



11.3 **11.4** **11.5**

Scheme 218



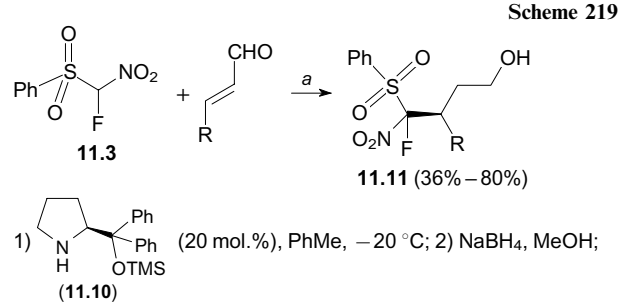
R^1, R^2, R^3, R^4 = Alk; EWG is electron-withdrawing group

Like non-fluorinated analogues, simple and functionalized fluoronitroalkanes can participate in the Henry,[454] Mannich[446] and Michael[436, 450, 455] reactions to give products **11.6** – **11.9** (see Scheme 218). The Michael reaction was found to be efficiently catalyzed by the ruthenium hydride $RuH_2(PPh_3)_4$.[456] For phosphonate **11.5**, successful examples of C-alkylation have been reported,[436] while for FNSM **11.3**, cases of Tsuji – Trost allylation are known.[457]

Currently, the attention of researchers engaged in the chemistry of fluoro nitro compounds is focused on the development of asymmetric reactions for generation of a quaternary stereocentre bearing a fluorine atom. Reactions of this type were carried out for arylfluoronitromethanes,[458, 459] FNSM **11.3**[438, 444, 445, 447] and fluoronitroacetate **11.4**,[448, 449] which were allowed to react with compounds with an activated multiple bond such as α,β-unsaturated carbonyl compounds,[444, 445, 447, 449] nitroalkenes[448, 458] and N-Boc-imines.[438, 459] Some examples of these transformations are described below.

Thus, in the presence of prolinol **11.10** as a catalyst, FNSM **11.3** undergoes Michael addition reaction with unsaturated aldehydes (Scheme 219).[445] For more convenient isolation, adducts are then reduced with sodium borohydride. This procedure has been used to prepare alcohols **11.11** with high enantiomeric purity [enantiomeric ratio (*er*) from 81 : 19 to 99 : 1], although the diastereoselectivity of the reaction is moderate: the diastereomeric ratio (*dr*) varies from 1 : 1 to 5 : 2.

Scheme 219



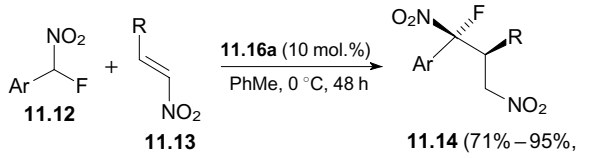
R = Ar, Alk

The asymmetric Michael reactions of arylnitromethanes **11.12** and fluoronitroacetate **11.4** with conjugated nitroalkenes **11.13** giving compounds **11.14** and **11.15** are catalyzed by thiourea derivatives **11.16a**,**b**.[448, 458] In the latter case, the best performance was observed for catalyst **11.16b**.[448] Adducts **11.14** and **11.15** were formed in high yields and with high diastereo- and enantioselectivity (Scheme 220).

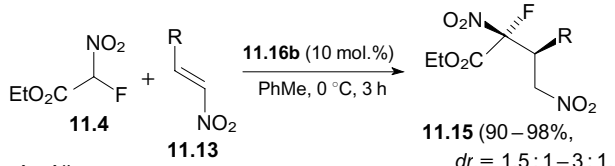
Apart from the above-indicated asymmetric reactions of C – C bond formation, asymmetric classical alkynylation of FNSM **11.3** yielding product **11.17** and proceeding with a moderate enantioselectivity in the presence of catalyst **11.18** has been reported (Scheme 221).[460]

In the above reactions, anion **A** is generated by abstraction of the proton of the fluoro nitro compound. However, this does not exhaust approaches to species of this type. An alternative pathway is the retro-Henry reaction.[430, 439] An unusual transformation was described for difluoronitroacetophenone (**11.19**).[434] With lithium bromide and diisopropylethylamine as catalysts, the molecule undergoes C – C bond cleavage. The resulting difluoronitromethyl anion **B**

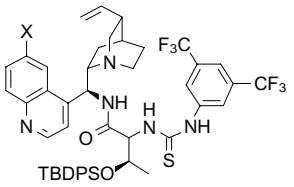
Scheme 220



R = Ar, Alk

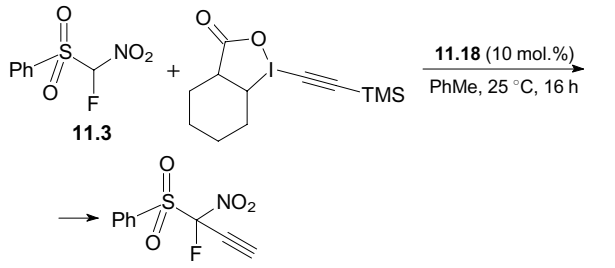


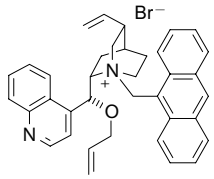
R = Ar, Alk;

11.16a,**b** =  [X = H (**11.16a**), OMe (**11.16b**)];

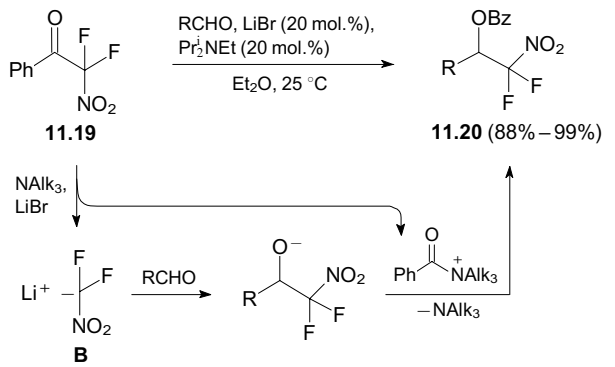
TBDPS is *tert*-butyldiphenylsilyl

Scheme 221



11.18 = 

Scheme 222



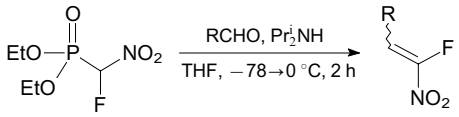
R = 1-Naph, 3-$MeOC_6H_4$, 4-XC_6H_4 (X = Br, CN, NO_2)

can be attacked by an aldehyde molecule and the intermediate alcoholate is benzoylated, thus completing the process and giving products **11.20** (Scheme 222).

11.2. Synthesis of α-fluoronitroalkenes and their transformations with retention of the fluoronitromethyl moiety

The chemistry of α-fluoronitroalkenes **11.21** started to be developed relatively recently. A probable reason is the lack of convenient methods for the preparation of these substrates. The Henry reaction involving carbonyl compounds and fluoronitromethane (CH_2FNO_2) could serve as a simple approach. However, no such reactions were reported in the literature, which is attributable to two main reasons. First, fluoronitromethane is rather difficult to obtain;[452, 461] second, it is unstable in a basic medium.[452] In this connection, the first general approach to the synthesis of nitroalkenes **11.21** included the reaction of carbonyl compounds with fluoronitromethylphosphonate **11.5**, a synthetic equivalent of fluoronitromethane (Scheme 223).[436] The involvement of phosphonate **11.5** into the Horner – Wadsworth – Emmons reaction resulted in the preparation of fluoronitroalkenes **11.21** in good yields and with moderate *Z*,*E*-selectivity. Among the studied ketones, only trifluoroacetophenone reacted successfully.

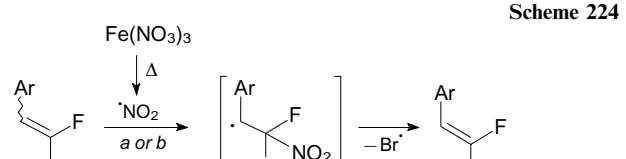
Scheme 223



RCHO = PhCHO, n-$C_6H_{13}CHO$, citronellal, 4-ClC_6H_4CHO, 4-$MeOC_6H_4CHO$, 4-$O_2NC_6H_4CHO$, 3-(3,5-$Cl_2C_6H_3O$)C_6H_4CHO

Another method for the preparation of fluoronitroalkenes **11.21** is the radical substitution of a nitro group for the bromine atom in bromofluorostyrenes **11.22** (Scheme 224).[462] The required nitrogen dioxide is generated *in situ* by thermal decomposition of iron(III) nitrate. The key benefit of this method is its diastereoselectivity: in all cases, only *Z*-isomer of nitroalkene **11.21** was formed irrespective of the diastereomeric composition of substrate **11.22**. However, the need to use an aryl substituent capable of stabilizing the radical centre in intermediate **C** is a

Scheme 224



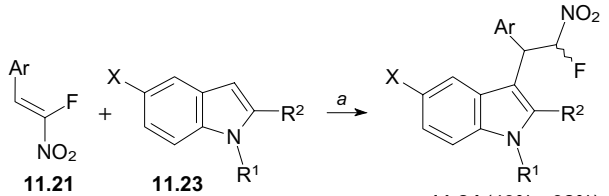
(*a*) $Fe(NO_3)_3 \cdot 9H_2O$, TEMPO (0.2 equiv.), MS 4 Å, 1,2-dichloroethane; (*b*) $Fe(NO_3)_3 \cdot 9H_2O$, 1,4-dioxane, 80 – 100 °C, 0.5 – 4 h;
TEMPO is 2,2,6,6-tetramethylpiperidin-1-yloxyl, MS are molecular sieves

limitation. For oxidation-sensitive substrates, a procedure with milder silver nitrate was proposed.[462]

Like their non-fluorinated analogues, fluoronitroalkenes **11.21** can act as Michael acceptors. They successfully react with nucleophiles such as sodium borohydride,[436, 462] amines, benzenethiol and dimethyl malonate,[462] being converted to the addition products.

The reaction of compounds **11.21** with indoles **11.23** has been studied (Scheme 225).[463] It was shown that the reactivity of substrates **11.21** and **11.23** is sufficient for the successful formation of adducts **11.24** without a catalyst. The reaction can proceed for a broad range of nitroalkenes and indoles, in particular, those substituted at the N(1), C(2) and C(5) atoms.

Scheme 225



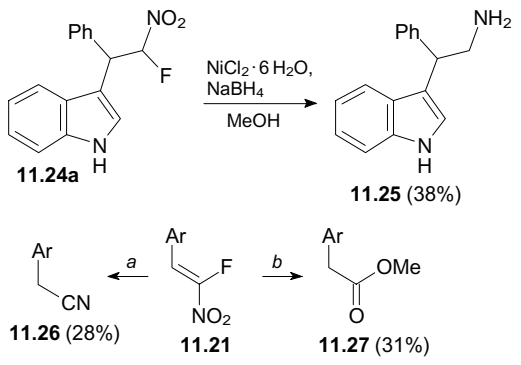
(*a*) H_2O, 100 °C, 7 h; R^1 = H, Me; R^2 = H, Me, Ar; X = H, Hal

11.3. Reactions of α-fluoro nitro compounds proceeding without retention of the fluoronitromethyl moiety

This subchapter describes the synthetic techniques affecting the fluoronitromethyl moiety. These transformations should largely determine the utility of fluoro nitro compounds for targeted organic synthesis.

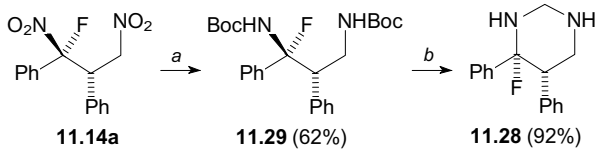
The reduction of the nitro group in fluoro nitro compounds appears to be a promising approach to α-fluorinated amine derivatives. However, an obvious obstacle is the lack of stability of the reaction products. Often, the reaction cannot be stopped when required and elimination of a fluorine atom takes place as a result of donation of the liberated lone pair of nitrogen to the σ^*_{C-F} antibonding orbital.[436, 448, 458, 462, 463] Indeed, the reduction of fluoronitroalkane **11.24a** affords amine **11.25**, while hydrogenation of fluoronitroalkenes **11.21** results in isolation of nitrile **11.26** and ester **11.27** in moderate yields (Scheme 226).

Scheme 226



(*a*) H_2 (1 atm), Ni-Ra, EtOH (Ar = 4-$MeOC_6H_4$); (*b*) H_2 (1 atm), Ac_2O, Pd/C, MeOH (Ar = 4-ClC_6H_4); Ni-Ra is Raney nickel

Scheme 227

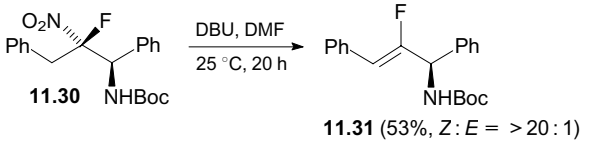


(*a*) H_2 (15 atm), Pd/$BaSO_4$, Boc_2O, MeOH, MS 4 Å, AcOH, 25 °C, 48 h; (*b*) 1) CF_3CO_2H, CH_2Cl_2, 25 °C, 2 h; 2) CH_2O (aq.), THF, 25 °C, 12 h

Among successful attempts to trap fluoroamines, the synthesis of perhydropyrimidine **11.28** deserves attention (Scheme 227).[458] In this case, fluoride elimination was prevented by protecting the arising amino group. The authors also note that during isolation of product **11.29** the temperature should not rise above 20 °C in order to avoid a decrease in the product yield.

One more possible transformation of fluoro nitro compounds is elimination of nitrous acid giving rise to a double bond.[464] For instance, substrate **11.30** is converted to fluoroalkene **11.31** with high *Z*,*E*-selectivity (Scheme 228).[459]

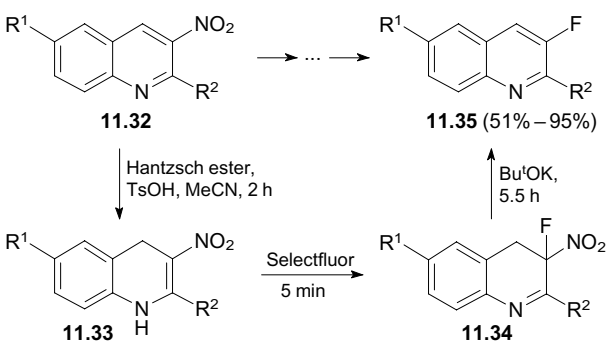
Scheme 228



Elimination of nitrous acid can be used to construct heterocycles. The formal replacement of the nitro group in 3-nitroquinolines **11.32** by a fluorine atom was accomplished in this way.[465] All three steps of the process — reduction, fluorination and elimination — were carried out without isolation of intermediate products **11.33** and **11.34**, which made it possible to obtain target fluoroquinolines **11.35** in moderate to high yields (Scheme 229).

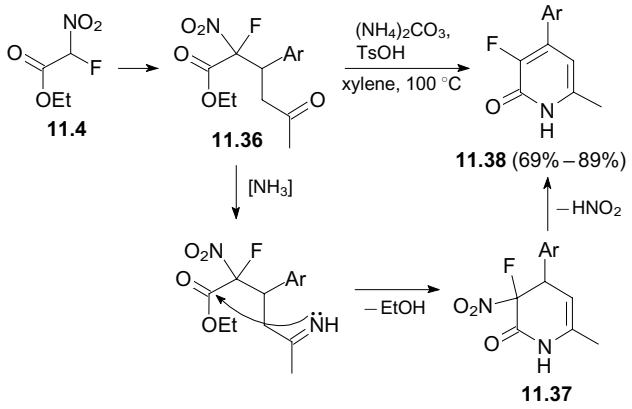
In a similar way, adducts **11.36** undergo cyclization to fluorine-substituted pyridones (Scheme 230).[450] One of the proposed mechanisms comprises the initial cyclization to give lactams **11.37**, which subsequently eliminate HNO_2 being converted to products **11.38**.

Scheme 229



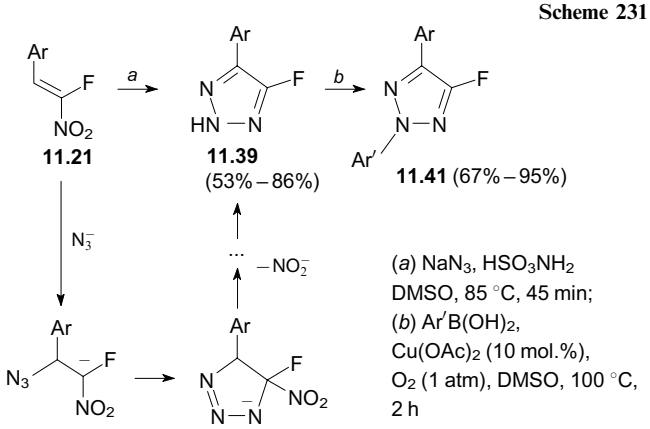
R^1 = H, MeO; R^2 = Ar, $ArCH_2CH_2$, Bu^n

Scheme 230

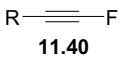


Elimination of nitrous acids may occur as a part of a tandem process including many transformations of geminal fluoro nitro compounds. In this connection, special mention should be made of the prospects of using fluoronitroalkenes **11.21** for the synthesis of diverse fluorine-containing heterocycles. It was shown by a single example that nitroalkenes **11.21** can be involved in the Barton – Zard pyrrole synthesis.[462] By the reaction with sodium azide, a series of previously unknown fluorinated 1,2,3-NH-triazoles **11.39** was prepared (Scheme 231).[466] A putative mechanism of the reaction includes the Michael addition of the azide anion, cyclization and aromatization with elimination of the nitrite anion. Thus, the overall process corresponds to formal [3 + 2]-cycloaddition of azide in which fluoronitroalkenes **11.21** act as synthetic equivalents of relatively unstable fluoroacetylenes **11.40**.

Scheme 231



Structures 11.40

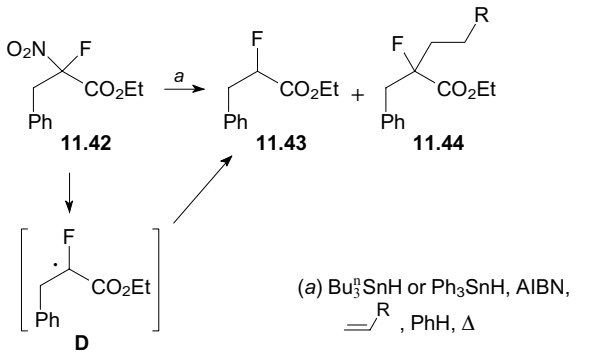


11.40

A typical feature of triazoles **11.39** is the ability to undergo selective functionalization at the N(2) atom, which favourably distinguishes them from non-fluorinated analogues.[466, 467] Scheme 231 presents an example of their Chan – Lam arylation with arylboronic acids to give diaryltriazoles **11.41**.

In some cases, it is possible to carry out reductive radical denitration of fluoro nitro compounds **11.42** on treatment with the Bu^n_3SnH – AIBN system [AIBN is azobis(isobutyronitrile)],[448, 468] which is depicted in Scheme 232. The intermediate radical **D** can be stabilized, apart from hydrogen atom transfer (product **11.43**), by being trapped with an alkene to give a new C – C bond (products **11.44**).[459, 468, 469] Thus, in the introduction of a fluorinated substituent, the nitro group can serve for activation and then can be eliminated from the target molecule.

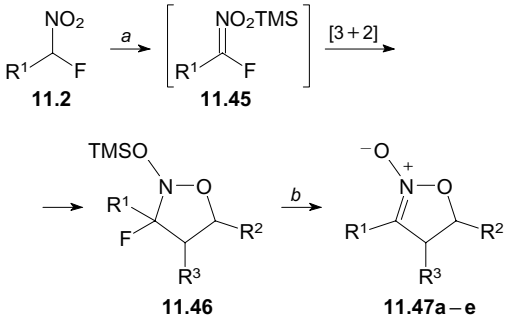
Scheme 232



Reagent	R	Yield of **11.43** (%)	Yield of **11.44** (%)
Bu^n_3SnH	CN	51	9
Bu^n_3SnH	Ac	44	14
Bu^n_3SnH	Ph	30	47
Ph_3SnH	CN	–	–
Ph_3SnH	Ph	18	68

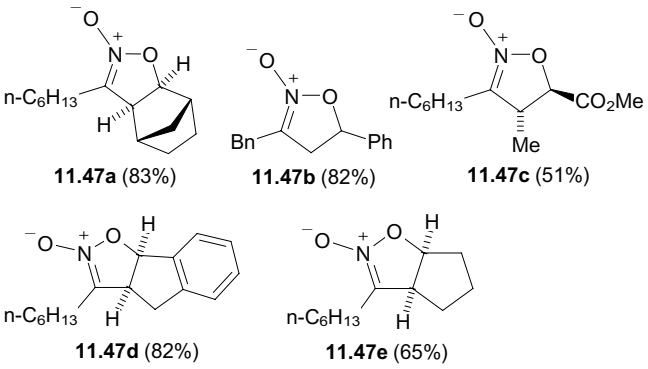
At the end of this chapter, we will consider data on the transformations of fluoro nitro compounds aimed at the synthesis of N,O-containing products. The silylation of fluoronitroalkanes **11.2** in the presence of dipolarophiles provides a route to isoxazoline *N*-oxides (Scheme 233).[470] Unlike many examples considered above in which the nitro group acts as an activator for the introduction of a fluorine-containing moiety and is then removed from the target molecule, in this case, the fluorine atom serves for generation of the ONO moiety. The first step is the formation of silyl nitronates **11.45**, which are subjected to [3 + 2]-cycloaddition with alkenes without isolation. The presence of the

Scheme 233



(*a*) TMSCl, Et_3N, $R^2CH{=}CHR^3$, pentane, 25 °C, 7 days;
(*b*) MeCN, Δ, 1 h

Structures 11.47



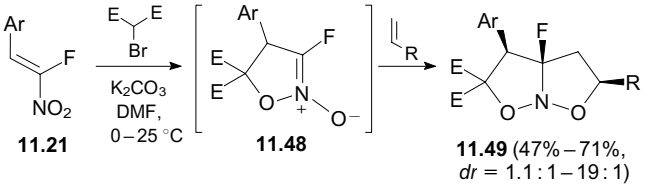
11.47a (83%) **11.47b** (82%) **11.47c** (51%)

11.47d (82%) **11.47e** (65%)

fluorine atoms markedly distinguishes the reaction sequence **11.2** → **11.45** → **11.46** → **11.47** from that observed for non-fluorinated analogues. First, nitronates **11.45** are rather unstable and cannot be isolated in a pure state. Second, nitronates **11.45** undergo 1,3-dipolar cycloaddition 2 – 3 orders of magnitude faster, which is also confirmed by quantum chemical calculations. (This circumstance made it possible to accomplish the reaction with 1,2-disubstituted alkenes.) Third, adducts **11.46** proved to be fairly stable; elimination of trimethylfluorosilane from the adducts required refluxing in acetonitrile.

Similarly, high reactivity of fluoronitronates allowed the synthesis of bicyclic nitroso acetals (Scheme 234).[471] The [4 + 1]-annulation of nitroalkenes **11.21** with bromomalonate in the presence of potassium carbonate afforded five-membered nitronates **11.48**. They proved to be unstable and failed to be isolated in a pure state; however, they were successfully introduced into [3 + 2]-cycloaddition giving products **11.49**. The diastereoselectivity of the reaction depended on the dipolarophile employed: the highest characteristics (*dr* = > 7 : 1) were attained for styrene derivatives, while less beneficial results (*dr* = 5 : 1 – 6 : 1) were obtained for alkyl-substituted alkenes and ethyl vinyl ether. A modest selectivity (*dr* = 1 : 1 – 3 : 1) was observed for electron-withdrawing alkenes, *e.g.* methyl acrylate and acrylonitrile.

Scheme 234

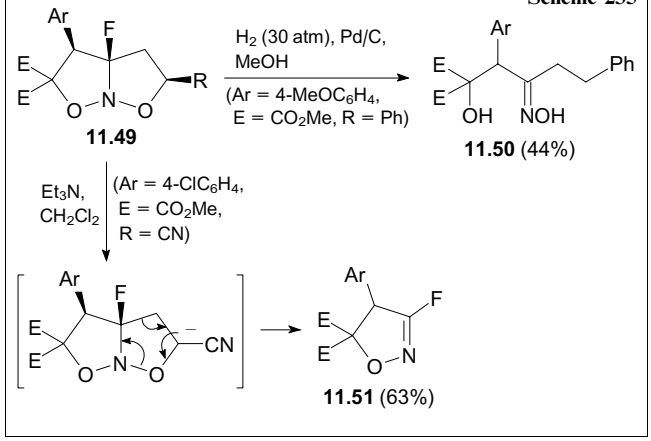


11.21 **11.48** **11.49** (47% – 71%, *dr* = 1.1 : 1 – 19 : 1)

E = CO_2Me; R = Ar, Alk, OEt, CN, CO_2Me

Some chemical properties of fluorinated nitroso acetals **11.49** have been studied (Scheme 235). As shown above for the reduction of fluoro nitro compounds (see Scheme 226), the catalytic hydrogenation is accompanied by defluorination of the substrate to give functionalized oxime **11.50** as the major product. One more interesting transformation was found for cyano-substituted nitroso acetals **11.49**: on treatment with triethylamine, base-catalyzed cyclofragmentation takes place to give 3-fluoroisoxazoline **11.51**.[471]

Scheme 235



11.49 **11.50** (44%) **11.51** (63%)

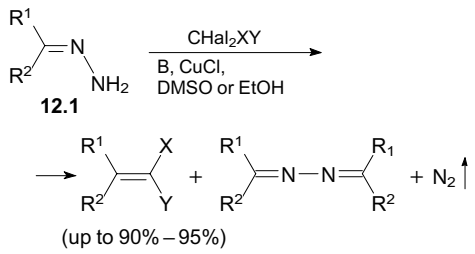
As follows from the material presented in this chapter, geminal fluoro nitro compounds are useful intermediates for organic synthesis. The involvement of these reagents into classical reactions of nitro compounds allows the synthesis, including asymmetric synthesis, of a broad range of fluorinated polyfunctional products containing carbonyl, ester, sulfonic, amine and other groups. A separate line of research is the design of fluorine-containing heterocycles, which has already been accomplished for pyridones, quinolines and triazoles; in the future, these reactions can be extended to the preparation of other products. Thus, the activating properties of the nitro group facilitate the introduction of a fluorine-containing moiety into the target molecule. Meanwhile, the preparation of α-fluorinated amine derivatives is one of the remaining challenges. Discovery of new transformations reflecting the interplay of the fluorine atom and the nitro group may also be expected; this would further expand the synthetic potential of these compounds.

12. Catalytic olefination using freons: a convenient tool for the synthesis of fluorinated compounds

This chapter covers the preparation of fluorinated alkenes based on catalytic olefination by freons and synthesis of diverse fluorinated compounds using these alkenes. Haloalkenes proved to be valuable substrates for organic chemistry and were successfully used in the synthesis of various alkenes, alkynes, carboxylic acid derivatives and carbo- and heterocyclic compounds.[472] The strategy of the synthesis of haloalkenes relies on the olefination reactions of carbonyl compounds, in particular, the Wittig, Peterson and Julia reactions,[472 – 474] which have become ingrained in both synthetic practice and organic chemistry handbooks. Nevertheless, the catalytic olefination (Nenajdenko – Shastin reaction) discovered in 1999 has become a simple alternative to the above-mentioned classical methods of alkene synthesis.[475, 476] The essence of the reaction is the transformation of N-unsubstituted aldehyde and ketone hydrazones **12.1** (in some cases, formed *in situ*) into alkenes on treatment with polyhaloalkanes catalyzed by copper salts. The reaction is accompanied by nitrogen evolution, the ratio of isomeric alkenes reaches 21 : 1 (Scheme 236), and symmetrical azines, which are readily separated by column chromatography, are formed as the only side products.

The reaction is versatile: variation of carbonyl compounds and polyhaloalkanes over wide limits allows effi-

Scheme 236



R^1 = Ar, Alk; R^2 = Alk, H; Hal = Cl, Br; X = F, Cl, Br, H; Y = F, Cl, Br, CN, CO_2Et

cient syntheses of diverse alkenes, including functionally substituted ones.[477 – 493]

A considerable advantage of the catalytic olefination of hydrazones **12.1** over classical methods is the experimental simplicity. Indeed, there is no need to use inert atmosphere, anhydrous solvents or equimolar amounts of reducing metals or organoelement compounds. The reaction proceeds smoothly at room temperature. Furthermore, we demonstrated that this reaction can be conducted in ionic liquids and the yield of target alkenes does not decrease for up to 5 repeated reaction cycles.[494]

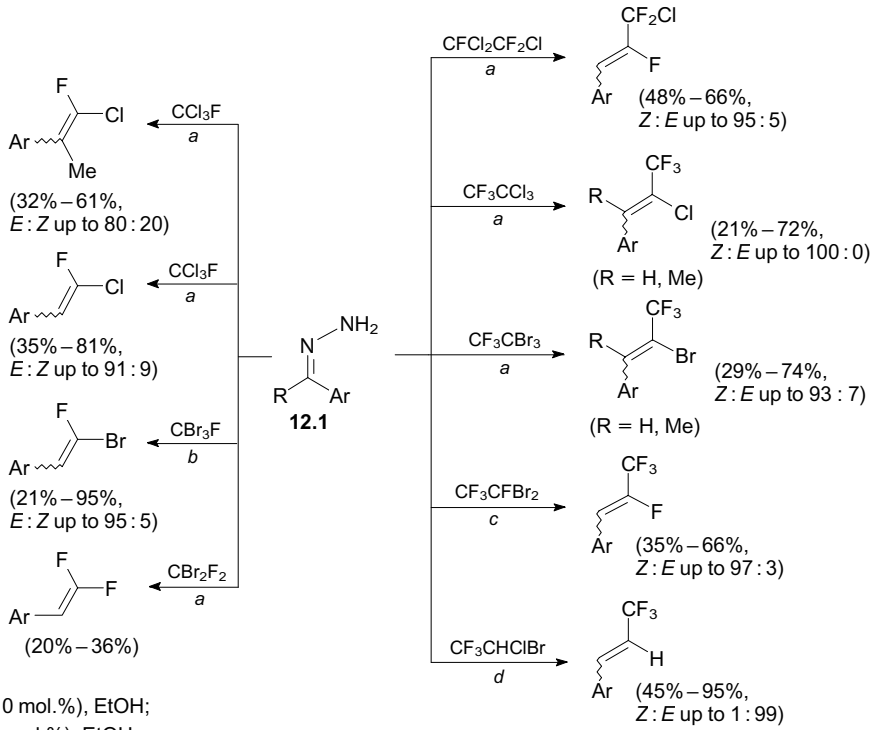
An important milestone in the development of the catalytic olefination of hydrazones is the start of the use of freons, which opens the access to fluorinated alkenes as convenient building blocks for the preparation of fluorine-containing products.[495] The present chapter covers the synthesis of fluorinated alkene *via* catalytic olefination and their application for the preparation of various fluorinated derivatives.

12.1. Olefination of carbonyl derivatives with fluoroalkanes (freons)

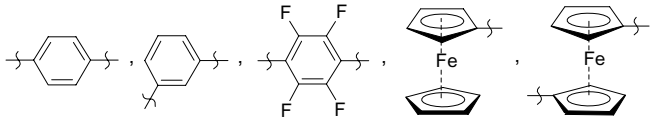
Using C_1-freons as olefinating reagents, approaches to the synthesis of various β-fluorostyrenes have been devised. Thus β-chloro- and β-bromo-β-fluorostyrenes were prepared by reactions of hydrazones **12.1** with $CFCl_3$ (freon 11)[496] and $CFBr_3$ (Refs 497 – 499). The reaction is stereoselective and gives good yields of products, with predominant formation of the less sterically hindered *E*-isomers. The use of dibromodifluoromethane CBr_2F_2 (freon 12B2) as the olefinating reagent resulted in *gem*-difluorostyrenes being formed in good yields (Scheme 237).[500]

The use of C_2-freons for the catalytic olefination of hydrazones **12.1** resulted in the development of new approaches to the synthesis of β-CF_3- and β-CF_2Cl-styrenes. The involvement of CF_3CFBr_2, CF_3CCl_3 and CF_3CBr_3 resulted in β-fluoro-,[501] β-chloro-[502] and β-bromo-β-trifluoromethylstyrenes[503] in high yields. When

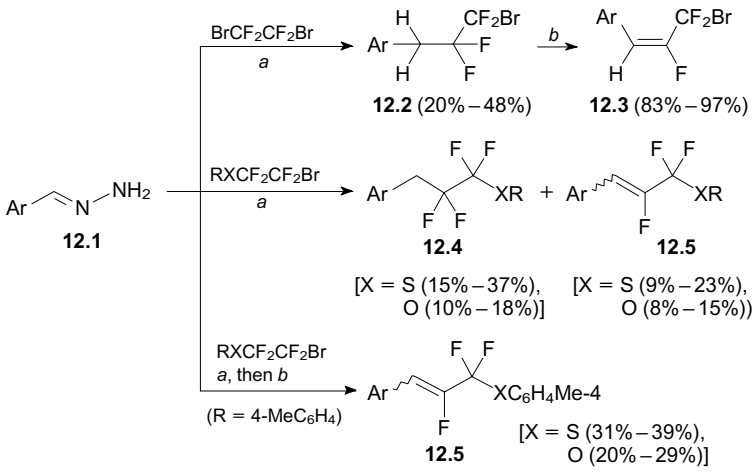
Scheme 237



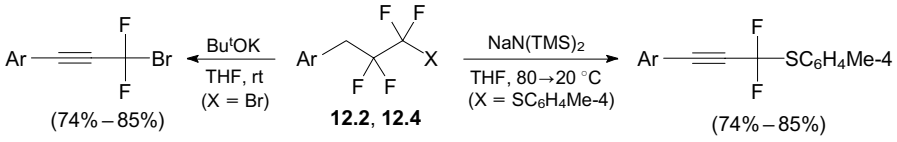
(*a*) $NH_2(CH_2)_2NH_2$, CuCl (10 mol.%), EtOH;
(*b*) $NH_2(CH_2)_2NH_2$, CuCl (1 mol.%), EtOH;
(*c*) NH_3, CuCl (10 mol.%), DMSO;
(*d*) $NH_2(CH_2)_2NH_2$, $CuCl_2$ (1 мол.%), $HOCH_2CH_2OH$;
Ar = 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-ClC_6H_4, 3-ClC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, Ph, 4-NCC_6H_4, 4-MeC_6H_4, 4-FC_6H_4, 2-FC_6H_4, 2-ClC_6H_4, 4-$Me_2NC_6H_4$, 2-$MeOC_6H_4$, 2,4-$Cl_2C_6H_3$, 4-EtC_6H_4, 4-$Bu^nC_6H_4$, 4-$MeO_2CC_6H_4$, 4-$F_3CC_6H_4$, 2-$O_2NC_6H_4$, 4-$MeSC_6H_4$, 4-$Bu^tC_6H_4$, 4-HOC_6H_4, 2-MeC_6H_4, 4-PhC_6H_4, 3-HOC_6H_4, 2-HOC_6H_4, 3,4-$(MeO)_2C_6H_3$, 3,5-$(MeO)_2C_6H_3$, 1-Naph, 2-Naph,



Scheme 238



(*a*) $NH_2(CH_2)_2NH_2$, CuCl, EtOH, 45 – 50 °C, 5 h; (*b*) 50% NaOH, Δ, 4 – 5 h;
Ar = 4-ClC_6H_4, 4-BrC_6H_4, 4-EtC_6H_4, 4-$Bu^nOC_6H_4$, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 3-ClC_6H_4, 3-BrC_6H_4, 3-$O_2NC_6H_4$, 3-$MeOC_6H_4$, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$; R = Ar, Alk



$CFCl_2CF_2Cl$ served as the olefinating reagent, β-chlorodifluoromethyl-β-fluorostyrenes were formed.[502] The reaction with $CF_3CHClBr$ (halothane, freon 123B1) provided an efficient approach to the synthesis of (*E*)-β-trifluoromethylstyrenes.[504] The stereoselectivity of olefination with C_2-freons depends on the nature of the carbonyl compound. Aldehyde olefination is stereoselective, giving predominantly the less sterically hindered isomer containing a trifluoromethyl or chlorodifluoromethyl group and the aryl moiety in the *trans*-positions relative to each other. Conversely, olefination of ketones with CF_3CBr_3 affords a mixture of *cis*- and *trans*-isomers of β-bromo-β-trifluoromethyl-α-methylstyrenes in equal amounts (see Scheme 237).[503, 505]

Olefination of hydrazones involving $BrCF_2CF_2Br$ (freon 114B2) follows an unusual pathway. In this case, the reaction gave arylbromotetrafluoropropanes **12.2**, instead of the expected alkenes **12.3** (Scheme 238).[506] Nevertheless, treatment of the resulting alkanes with NaOH in ethanol smoothly afforded β-bromodifluoromethyl-β-fluorostyrenes **12.3** in high yields as only *Z*-isomers. The reaction with $RSCF_2CF_2Br$ or $ROCF_2CF_2Br$ proceeds in a similar way with the only difference that it affords a mixture of the corresponding alkane (**12.4**) and alkene (**12.5**), which can be converted to the pure alkene in a moderate yield upon the addition of 50% NaOH.[507, 508] On treatment with strong bases [Bu^{t}OK (Ref. 506) or $NaN(TMS)_2$ (Refs 507, 508)], it was possible to eliminate two HF molecules from the obtained fluorinated alkanes **12.2** and **12.4**, resulting in the synthesis of the corresponding fluorinated alkynes (see Scheme 238).

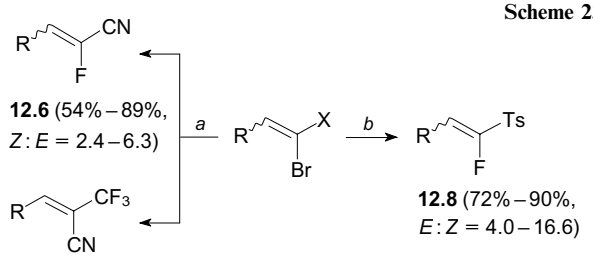
Thus, new synthetic routes to fluorine-containing alkanes, alkenes and alkynes were developed on the basis of catalytic olefination of hydrazones with various freons.

12.2. Synthesis of fluorinated compounds based on β-halo-β-trifluoromethylstyrenes and β-bromo-β-fluorostyrenes

β-Bromo-β-fluorostyrenes and β-chloro-/β-bromo-β-trifluoromethylstyrenes are convenient substrates for the introduction of additional functional groups *via* nucleophilic displacement of a halogen atom. This makes these compounds useful building blocks for the preparation of diverse fluorinated alkenes and carbo- and heterocyclic compounds.[509]

For example, in the reaction of fluorine-containing alkenes with CuCN, bromine is displaced by the cyano group to give α-fluoro- (**12.6**) and α-trifluoromethylacrylonitriles (**12.7**) in high yields. The reaction is stereoselective and affords mixtures of isomeric α-fluoroacrylonitriles **12.6** with the *Z*-isomer predominating, whereas α-trifluoromethylacrylonitriles are isolated as only *E*-isomers (stereospecificity) (Scheme 239).[510] Similarly, α-fluoro-β-arylvinyl sulfones **12.8** were stereoselectively synthesized in high yields by the reaction of β-bromo-β-fluorostyrenes with

Scheme 239

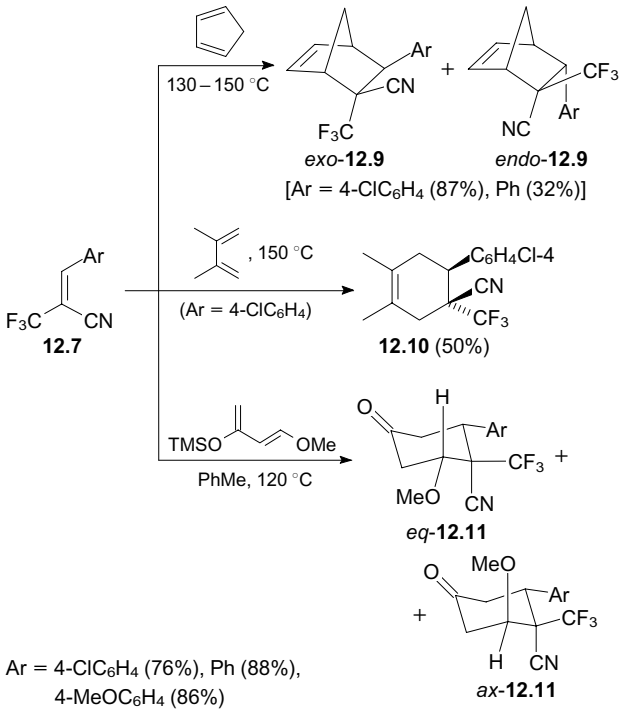


(*a*) CuCN, DMF, 150 – 155 °C; (*b*) 4-$MeC_6H_4S(O)ONa \cdot 2H_2O$, *N*-methylpyrrolidin-2-one (NMP), 180 – 185 °C;
R = 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, 4-$MeO_2CC_6H_4$, 4-ClC_6H_4, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$; X = F, F_3C

sodium 4-methylphenylsulfinate.[511] It is noteworthy that the versatile nature of this approach makes it suitable for the synthesis of acrylonitriles and sulfones containing both electron-donating and -withdrawing substituents in the aromatic ring (see Scheme 239).

The pronounced electron deficiency of the double bond in fluorinated acrylonitriles and sulfones makes them promising for the Diels – Alder reaction. It was shown that α-trifluoromethylacrylonitrile **12.7** (R = 4-ClC_6H_4) reacts with cyclopentadiene on heating to give a mixture of *endo*- and *exo*-adducts **12.9** in 1 : 1 ratio. The reaction with dimethylbuta-2,3-diene stereoselectively yields cyclohexene derivative **12.10**. Finally, the reaction of Danishefsky diene with these fluorinated nitriles affords the only regioisomer of the expected ketones **12.11**. It is formed as a ~2 : 1 mixture of diastereomers with equatorial (*eq*) and axial (*ax*) positions of the MeO group (Scheme 240).[510]

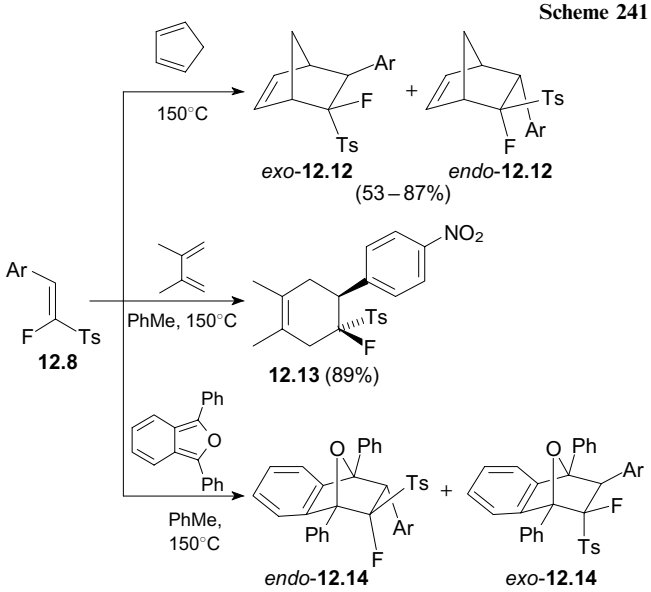
Scheme 240



α-Fluoro-β-arylvinyl sulfones **12.8** also proved to be fairly reactive dienophiles, which was utilized to prepare adducts of cyclopentadiene (**12.12**), dimethylbuta-2,3-diene (**12.13**) and 1,3-diphenylisobenzofuran (**12.14**) in good to high yields. Cyclopentadiene adducts were prepared as 3 : 2 diastereomer mixtures with the predominance of the *exo*-F-*endo*-Ts-*exo*-Ar diastereomer. The reaction with 1,3-diphenylisobenzofuran was more stereoselective, giving predominantly *endo*-F-*exo*-Ts-*endo*-Ar diastereomers, the proportion of which was up to 89% (Scheme 241).[511]

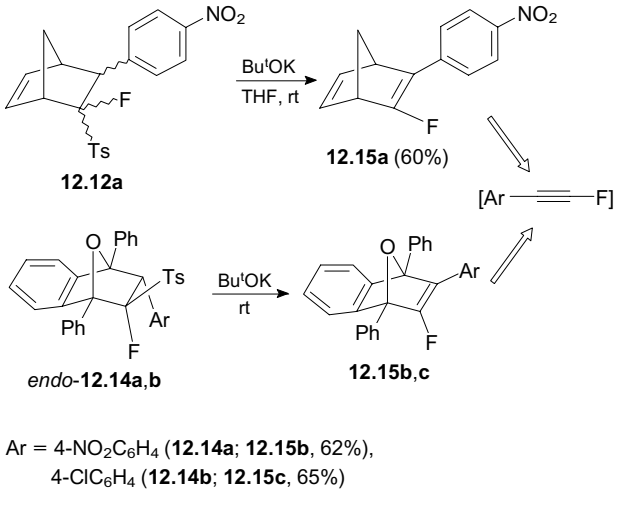
An attempt was made to affect the elimination of the 4-methylphenylsulfonyl group from the obtained adducts. This transformation was found to easily proceed on treatment with Bu^{t}OK in THF at room temperature giving the corresponding cyclic fluoroalkenes in good yields (Scheme 242). Compounds **12.15a – c** are formally the Diels – Alder reaction products involving dienes and fluoroacetylenes, which are very rare and still poorly studied.[511]

Scheme 241



Ar	*endo* : *exo*	Yield of **12.14** (%)
4-$O_2NC_6H_4$	75 : 25	94
4-ClC_6H_4	89 : 11	82

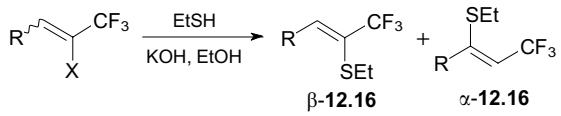
Scheme 242



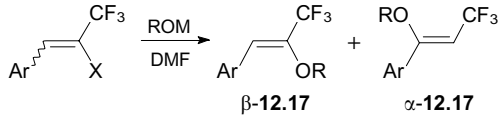
12.3. Reactions of β-halo-β-trifluoromethylstyrenes with thiols and metal alkoxides

It was found that β-chloro- and β-bromo-β-trifluoromethylstyrenes readily react with ethanethiol and metal alkoxides to afford isomeric vinyl sulfides **12.16** and alkoxystyrenes **12.17**, respectively. The reactions are versatile, permitting stereoselective synthesis of fluorinated styrenes with both electron-donating and -withdrawing substituents in the aromatic ring (Scheme 243).[512] The halogen nature in the starting styrenes does not affect the ratio of substitution products **12.16** (from 33 : 67 to 100 : 0) or the total yield, which in some cases reaches 100%. The crucial influence on the ratio of regioisomers is made by electronic and steric properties of the aryl(hetaryl) substituent. The presence of electron-withdrawing and sterically hindered substituents in the starting alkene stimulates the formation of

Scheme 243



X = Cl (64% – 96%), Br (76% – 96%); R = 4-$O_2NC_6H_4$, 4-ClC_6H_4, 4-MeC_6H_4, Ph, 4-$MeOC_6H_4$, 4-$MeO_2CC_6H_4$, 2-$MeOC_6H_4$, 2-Py, 3-ClC_6H_4, 3-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, 2-BrC_6H_4, 3-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$

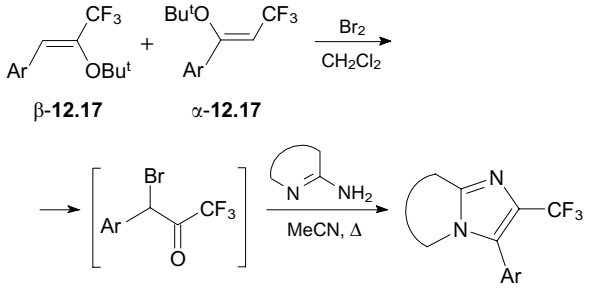


ROM = MeONa, Bu^tOK; X = Cl, Br;
R = Me (76% – 89%), Bu^t (41% – 97%)

β-regioisomer **12.17** (β : α ratio varies from 67 : 33 to 100 : 0). Conversely, an increase in the electron-donating properties of substituents is accompanied by increasing proportion of the α-regioisomer. It is noteworthy that in the case of sterically hindered *tert*-butoxide, the percentage of the α-regioisomer decreases (see Scheme 243).[513] Although the starting styrenes are *Z*- and *E*-isomer mixtures with the former predominating, the corresponding α- and β-regioisomers of reaction products **12.16** and **12.17** were isolated as single *Z*-isomers. The impurity of the *E*-isomer was observed only for styrenes with electron-withdrawing substituents in the *ortho*-position of the aromatic ring (see Scheme 243).

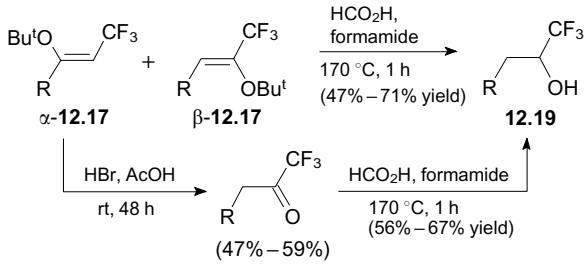
The well-known relative stability of the *tert*-butyl cation and, consequently, easily occurring reactions involving this cation were successfully used to prepare fluorinated derivatives from *tert*-butoxystyrenes. It was found that the reaction of *tert*-butoxystyrenes with bromine in dichloromethane gives rise to α-bromo-α-aryltrifluoromethyl ketones, which are converted, without isolation, to heterocyclic compounds by reactions with dinucleophiles. This strategy resulted in the preparation of a broad range of CF_3-containing heterocycles **12.18**, derived from imidazopyridine, imidazopyrimidine, imidazobenzimidazole, imidazothiazole and thiazole, in moderate to high yields. Even in those cases where regioisomeric *tert*-butoxystyrenes were introduced in the reaction, the final heterocycle was formed as a single regioisomer (Scheme 244).[513] This is probably attributable to low stability of the second ketone regioisomer in the course of heterocyclization.

Scheme 244



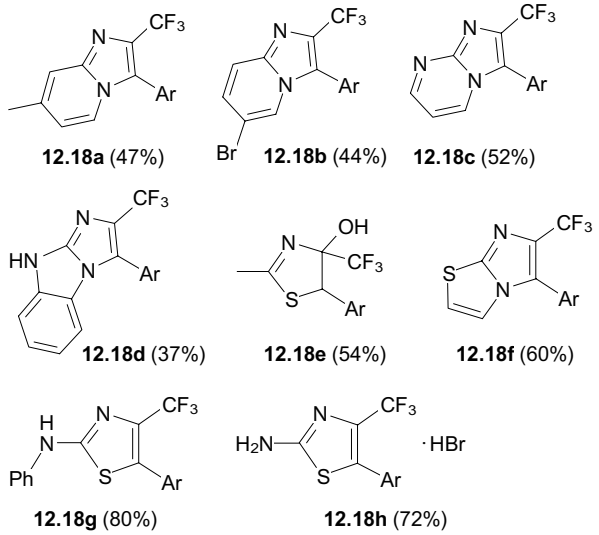
It was expected that *tert*-butoxystyrenes would act as synthetic equivalents of trifluoromethyl benzyl ketones in the Leuckart – Wallach reaction, which would open the route to trifluoromethyl-substituted phenethylamines. However, heating of *tert*-butoxystyrenes **12.17** with formic acid in formamide unexpectedly gave α-trifluoromethyl-substituted alcohols **12.19** in good yields (Scheme 245). Nevertheless, the assumption that *tert*-butoxystyrenes could be employed as synthetic equivalents of trifluoromethyl benzyl ketones proved to be true, since the introduction of analogous trifluoromethyl benzyl ketones (R = 4-ClC_6H_4, 4-$O_2NC_6H_4$, 3-$MeOC_6H_4$) into the Leuckart – Wallach reaction afforded the same trifluoromethylated acohols **12.19**.[514]

Scheme 245

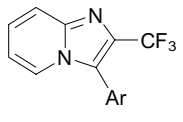


R = 4-ClC_6H_4, 4-$O_2NC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 2-BrC_6H_4, 4-BrC_6H_4, Ph

Structures 12.18



Ar = 4-ClC_6H_4



12.18 (27 – 53%)

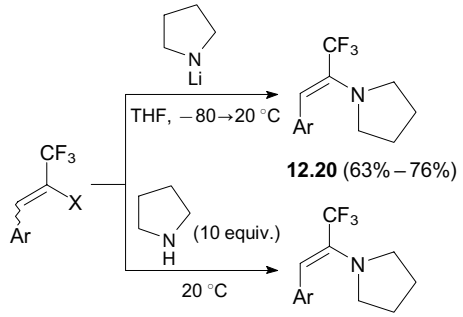
Ar = 4-$O_2NC_6H_4$, 4-ClC_6H_4, Ph, 3-$O_2NC_6H_4$, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-BrC_6H_4

12.4. Reactions of β-halo-β-trifluoromethylstyrenes with amines

Reactions of β-halo-β-trifluoromethylstyrenes with amines have been investigated. It was found that the nature of

processes and the composition of products depend not only on the electronic properties of substituents in the aromatic ring, but also on the nature of the amine. As in the reactions with thiols and metal alkoxides, electron-withdrawing styrenes produce, as expected, β-regioisomeric substituted products. Similarly, the reaction of amines with elecron-donating styrenes starts with the formation of the α-regioisomer, which undergoes a cascade of subsequent transformations (unlike reactions with other nucleophiles), which ends in the complete loss of the fluorine atom or cleavage of the carbon – carbon double bond. When the process is carried out in an excess of the most reactive secondary amine, pyrrolidine, the displacement of the halogen atom of electron-withdrawing styrenes gives (*Z*)-trifluoromethyleneamines **12.20** in high yields and with high regio- and stereoselectivity (Scheme 246). For the preparation of trifluoromethyleneamines from elecron-donating styrenes (R = 4-ClC_6H_4, Ph, 4-$MeOC_6H_4$), it is necessary to use the lithium salt of pyrrolidine, since the

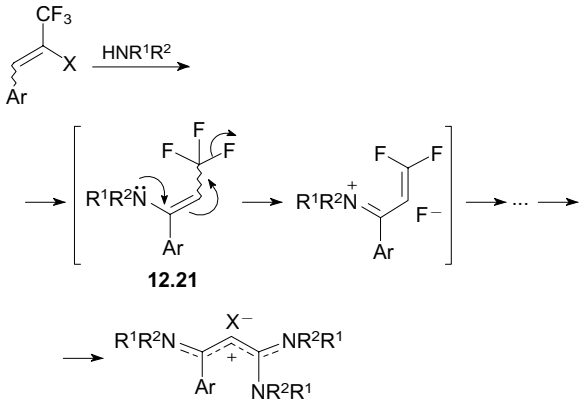
Scheme 246



12.20 (63% – 76%)

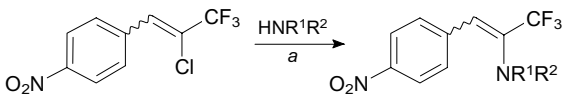
12.20 (68% – 98%)

X = Cl, Br; Ar = 4-$O_2NC_6H_4$, 4-ClC_6H_4, 2-BrC_6H_4, 3-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, 4-$MeO_2CC_6H_4$, Ph, 4-$MeOC_6H_4$



12.22 (35% – 87%)

Ar = 4-ClC_6H_4, Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 2-BrC_6H_4; $R^1 - R^2$ = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_6$; $R^1 = R^2$ = Et



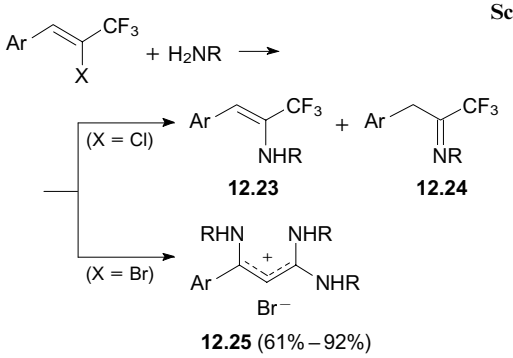
12.20 (52% – 92%)

(*a*) 1) EtOH, Δ; 2) no solvent, 85 °C;
3) no solvent, 125 °C; $R^1 - R^2$ = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_6$, $(CH_2)_2O(CH_2)_2$, $(CH_2)_2NH(CH_2)_2$; $R^1 = R^2$ = Et, Pr^n

reaction with pyrrolidine gives vinylogous guanidinium salts. A similar reaction with less reactive secondary amines is accompanied by the loss of fluorine atoms from α-isomer **12.21** and produces guanidinium salts **12.22**. Only in the case of the most electron-withdrawing styrene with the 4-nitrophenyl substituent, it is possible to synthesize trifluoromethyleneamines **12.20** with *Z*- and *E*-isomer ratios ranging from 83 : 17 to 96 : 4 (see Scheme 246).[515]

Similar trends can be followed in the reaction of β-halo-β-trifluoromethylstyrenes with primary amines. Only in the case of styrenes with nitrophenyl groups, does the reaction give β-regioisomers as a mixture of tautomeric trifluoromethyleneamine **12.23** and trifluoromethylimine **12.24** in 88 : 12 to 67 : 33 ratio (71% – 96% total yield), whereas the reactions of other styrenes end in the formation of vinylogous guanidine salts **12.25** in good yields (Scheme 247).[516]

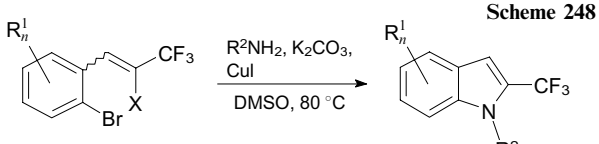
Scheme 247



12.23, **12.24**: Ar = 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 2-$O_2NC_6H_4$;
12.25: Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$; R = Me, Pr^i, Bu^s, Cy, $Ph(CH_2)_2$, (*S*)-PhCHMe, $(MeO)_2CHCHMe$, Bn

With a second bromine atom in the styrene *ortho*-position, it was possible to carry out intramolecular cyclization of imines formed upon the reaction with primary amines. The reaction of β-halo-2-bromo-β-trifluoromethylstyrenes with primary aliphatic amines proceeds as two successive nucleophilic substitutions giving 2-trifluoromethylindole derivatives **12.26** in good to high yields (Scheme 248).[517]

Scheme 248

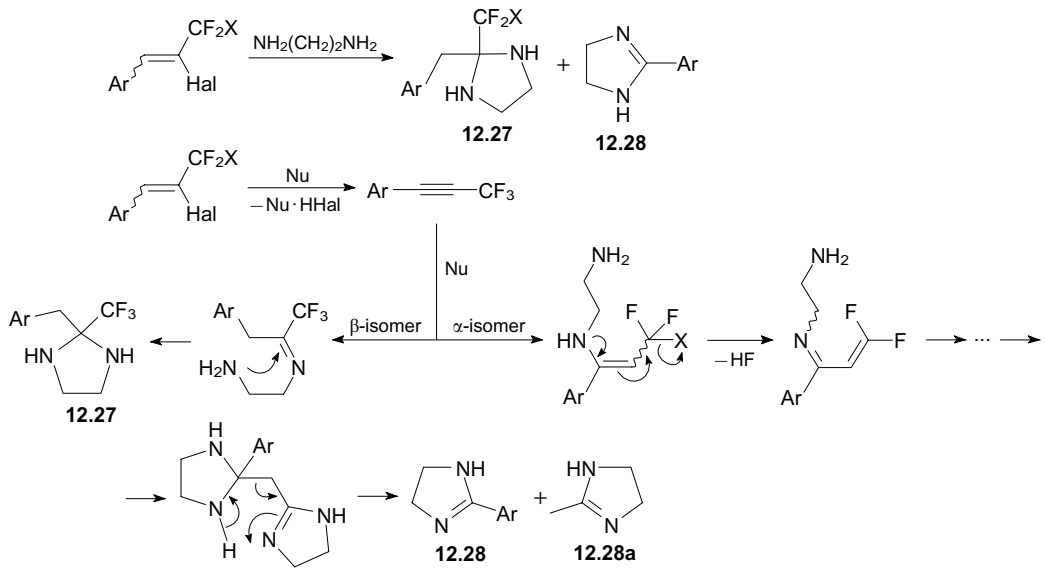


12.26 (39% – 74%)

X = Cl, Br; R_n^I = H, 5-MeO, 5-EtO, 5,6,7-$(MeO)_3$;
R^2 = Et, Pr^i, n-C_6H_{13}, $Ph(CH_2)_2$, $MeO(CH_2)_2$, $MeO(CH_2)_3$, 2-(3,4-dimethoxyphenyl)ethyl, 2-(3,4-diethoxyphenyl)ethyl

The pathway of the reaction with N,N- and N,O-dinucleophiles is also dictated by the nature of the substituent in the aromatic ring. Thus the reaction of electron-withdrawing styrenes with ethylenediamine affords fluorinated derivatives of imidazolidines **12.27** in high yields (Scheme 249). The reactions of styrenes possessing pro-

Scheme 249



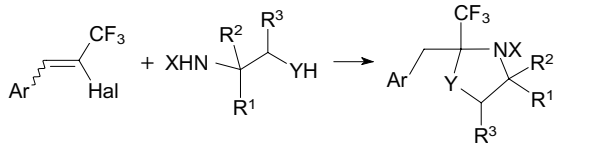
X = F: Hal = F, Cl, Br; X = Cl, Hal = F; Nu = $NH_2CH_2CH_2NH_2$

Ar	Yield of **12.27** (%)	Yield of **12.28** (%)
2-BrC_6H_4, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 2-$O_2NC_6H_4$	55 – 97	–
4-ClC_6H_4, Ph, 4-FC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$	1 – 30	39 – 80
4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$	–	54 – 61

nounced electron-donating properties with nucleophiles is accompanied by unexpected fragmentation, resulting in non-fluorinated imidazolines **12.28**. In the case of styrenes with aryl substituents exhibiting no strong electron-donating or -withdrawing properties, a mixture of both products is formed (see Scheme 249). The putative mechanism of the reaction can be represented in the following way. The first elementary step of the reaction is elimination of hydrogen halide, resulting in acetylenes. The latter add an ethylenediemine molecule to give β-regioisomer (of the corresponding imine), which cyclizes to imidazolidine (electron-withdrawing styrenes). In the case of electron-donating styrenes, the addition of ethylenediamine affords α-regioisomeric enamine, which undergoes a cascade of rearrangements, ending in the C – C bond cleavage to give aryl- (**12.28**) and methylimidazolines (**12.28a**) devoid of fluorine atoms (see Scheme 249).[518]

Ethylenediamine and ethanolamine derivatives were also successfully reacted with electron-withdrawing styrenes, which, as expected, led to fluorinated derivative of imidazolidine (**12.27**) and oxazolidine (**12.29**) in good yields (Scheme 250).[518]

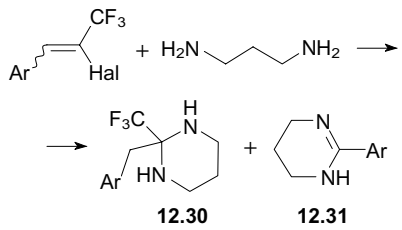
Scheme 250



12.27, **12.29** (32% – 91%)

Ar = 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 2-$O_2NC_6H_4$; X = H, Me; Y = NMe, NH, O; $R^1R^2C(NHX)CHR^3YH$ is *N*-methylethyenediamine, *N,N′*-dimethylethyenediamine, ethanolamine, 1,2-diaminocyclohexane, 2-aminobutanol, 2-amino-2-methylpropanol

Scheme 251



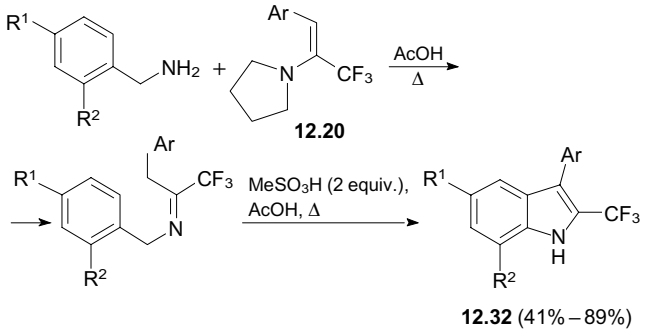
Ar	Hal	Yield of **12.30** (%)	Yield of **12.31** (%)	**12.30** : **12.31**
4-ClC_6H_4	Br	30	51	37 : 63
4-$O_2NC_6H_4$	Cl	62	–	100 : 0
4-$MeOC_6H_4$	Br	–	42	0 : 100

Finally, the reaction of β-halo-β-trifluoromethylstyrenes with 1,3-diaminopropane provided the synthesis of six-membered heterocyclic compounds **12.30** and **12.31** in good yields (Scheme 251).[518]

Owing to the presence of the pyrrolidine moiety, which is a good leaving group in acid medium, CF_3-enamines were successfully used as convenient synthetic equivalents of trifluoromethyl benzyl ketones in the Fischer, Pictet – Spengler and Leimgruber – Batcho reactions and in trifluoromethylphenetylamine synthesis.

It was found that CF_3-enamines react with arylhydrazines in acetic acid giving the corresponding hydrazones, which can be converted, without isolation, to 2-trifluoromethylindoles by adding two equivalents of stronger methanesulfonic acid (Fischer reaction). The proposed method is versatile and can be used for the synthesis of 3-aryl-

Scheme 252

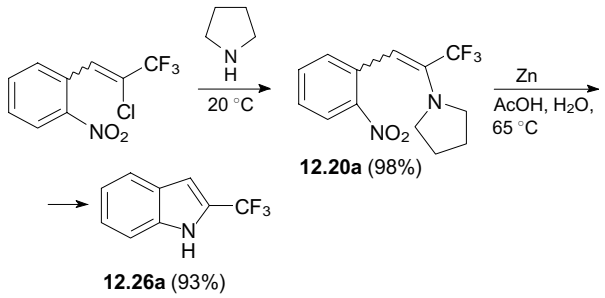


R^1 = Cl, F, NC, Me, MeO; R^2 = H, Cl, Me;
Ar = 4-$O_2NC_6H_4$, 4-ClC_6H_4, Ph, 4-$MeO_2CC_6H_4$, 2-BrC_6H_4, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$

2-trifluoromethylindoles **12.32** containing different combinations of electron-withdrawing and -donating substituents in the aryl and indole rings, which are formed in good to high yields (Scheme 252).[519]

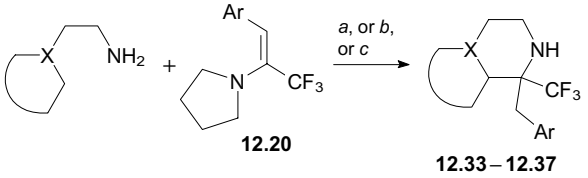
A facile and efficient method for the preparation of 2-trifluoromethylindole **12.26a** was developed on the basis of β-chloro-β-trifluoromethylstyrene with an *ortho*-nitro group. In the first step, the reaction with pyrrolidine gives enamine **12.20a** in a quantitative yield; treatment of this product with zinc dust in acetic acid (Leimgruber – Batcho indole synthesis) affords 2-trifluoromethylindole (**12.26a**) in a high yield (Scheme 253).[520]

Scheme 253



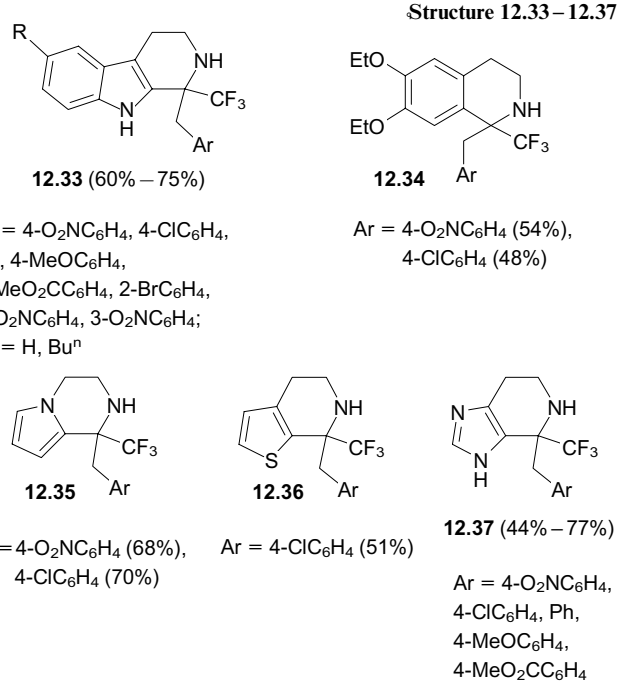
The application of CF_3-enamines as the carbonyl component in the Pictet – Spengler reaction proved to be fruitful. Indeed, compounds **12.20** react, under mild conditions, with a number of ethylamines containing aryl or hetaryl substituents activated towards the electrophilic attack to give fluorinated heterocyclic derivatives — compounds **12.33**, **12.34** (conditions *a*), **12.35**, **12.36** (conditions *b*) and **12.37** (conditions *c*) in good yields (Scheme 254).[519]

Scheme 254



(*a*) CH_2Cl_2, CF_3CO_2H, 20 °C; (*b*) AcOH, 20 °C;
(*c*) 1) EtOH, $RNH_2 \cdot HCl$, Δ; 2) KOH, Δ; X = CH, N

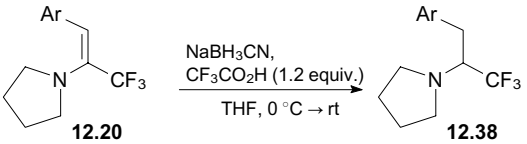
Structure 12.33 – 12.37



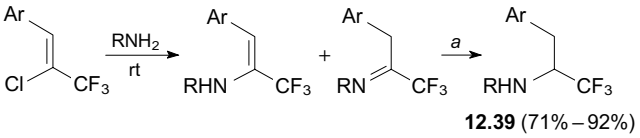
Ar = 4-$O_2NC_6H_4$, 4-ClC_6H_4, Ph, 4-$MeOC_6H_4$, 4-$MeO_2CC_6H_4$, 2-BrC_6H_4, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$; R = H, Bu^n

One more application of CF_3-enamines is the synthesis of α-trifluoromethylphenetylamines; two strategies of this synthesis have been developed. The first one is based on the reduction of CF_3-enamines, which are directly introduced in the reaction. Using CF_3-enamines obtained from both secondary and primary amines, which react with $NaBH_3CN$ in THF under mild conditions, α-trifluoromethylphenetylamines **12.38** and **12.39** are synthesized in good to high yields (Scheme 255).[521]

Scheme 255



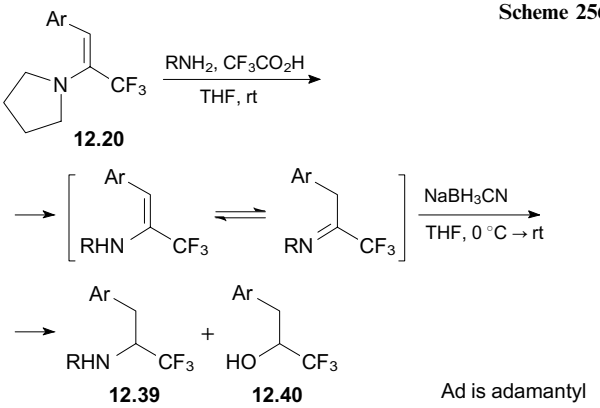
Ar = 4-$O_2NC_6H_4$ (85%), 2-BrC_6H_4 (68%), 2-$O_2NC_6H_4$ (70%)



(*a*) $NaBH_3CN$, CF_3CO_2H (1.2 equiv.), THF, 0 °C → rt;
Ar = 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$; R = Me, Pr^i

The second strategy is based on transamination, which was found to occur on treatment of CF_3-enamines **12.20** with primary amines in THF in the presence of trifluoroacetic acid giving rise to a mixture of CF_3-enamine and CF_3-imine tautomers. The resulting tautomer mixtures are reduced with $NaBH_3CN$ in THF, which gives α-trifluoromethylphenetylamines **12.39** in moderate to good yields. The crucial factors determining the composition and the yields of products in this reaction include the steric hindrance of the reactants (amine and styrene) and electronic

Scheme 256



Ar	R	Yield of **12.39** (%)	Yield of **12.40** (%)
4-$ON_2C_6H_4$	Bn, $BnCH_2$, 4-$MeOC_6H_4$	62 – 82	15 – 27
4-$O_2NC_6H_4$	1-Ad, 2-Py	0	90 – 100
2-$O_2NC_6H_4$	Bu^n, Bn, $BnCH_2$, 4-$MeOC_6H_4$, 4-$MeOC_6H_4CH_2$, 4-$FC_6H_4CH_2$	19 – 41	20 – 40
2-BrC_6H_4	Bn	53	33
4-$MeO_2CC_6H_4$	Bn	23	61
4-ClC_6H_4	Bn	0	69

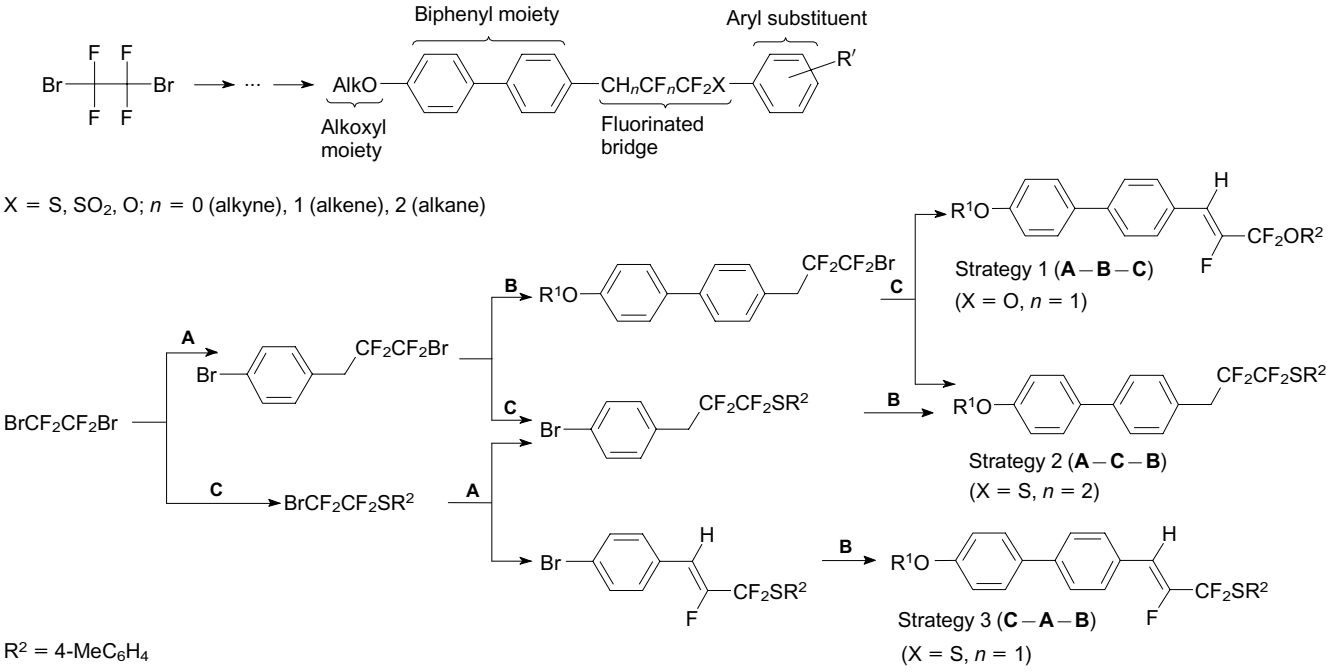
properties of substituents in styrene. A decrease in the steric hindrance of the reactants and the presence of the electron-withdrawing nitro group in the styrene aromatic ring increase the yield of the amine and decrease the yield of α-trifluoromethylphenylethanol **12.40**, which is formed as a side product (Scheme 256).[521]

12.5. Design and synthesis of a new class of fluorinated liquid crystalline compounds

Fluorinated-bridged compounds are known to possess good liquid-crystalline (LC) properties.[522] Using published data,[523] we designed and prepared a new family of liquid-crystalline compounds based on 1,2-dibromotetrafluoroethane, which is a simple and accessible compound. The structure of this family is based on aryl and biaryl moieties linked by a fluorinated bridge (Scheme 257). The target compounds were prepared using three synthetic strategies comprising different combinations of the anomalous olefination reaction (AOR), giving alkanes; bromine displacement from $BrCF_2CF_2Br$ by thiolates and phenolates; and Suzuki cross-coupling reaction. For alkyne synthesis, elimination of hydrogen fluoride was carried out in the final step by treatment of alkane or alkene with a strong base (see Scheme 257).[508]

Thus, the catalytic olefination reaction proved to be an excellent tool for the synthesis of fluorinated alkanes, alkenes and alkynes — convenient building blocks for the preparation of fluorinated molecules. Using these compounds, facile methods were developed for the synthesis of

Scheme 257



Reaction	**A** (AOR)	**B** (Suzuki coupling)	**C** (nucleophilic substitution)
Reagent	Br–C6H4–CHO	R^1O–C6H4–$B(OH)_2$	HXR^2 (X = O, S)

diverse fluorinated alkenes, carbo- and heterocyclic compounds, which are of practical value.

13. Methods of synthesis and some reactions of fluoroaliphatic and fluoroaromatic silanes

Organofluorine silicon compounds, R_FSiMe_3, which are, most often, stable and relatively high-boiling liquids, can be called without exaggeration universal reagents for the introduction of fluorinated aliphatic, aromatic or unsaturated groups into organic, organoelement and organometallic compounds of various classes.[11, 88, 524, 525] The possibility of generating C-anions, including polyhalogenated ones, using these reagents was already demonstrated at the early stage of studies of the silane reactivity.[526 – 530] However, only markedly later, at the end of 1980s, Ruppert and co-workers[531] and other researchers[532 – 535] accomplished the nucleophilic perfluoroalkylation of carbonyl compounds with perfluoroalkyl(trimethyl)silanes. The simplicity of practical use of these reagents immediately aroused considerable interest in the studies of their properties. Currently, the results of these studies have been specified in detail in numerous reviews and monographs.[11, 88, 524, 525, 536 – 539] Meanwhile, the search for simple and efficient methods for the synthesis of fluorinated silanes is becoming an important task. The present chapter describes the most recent advances in this area.

The rampant development of the chemistry of organosilicon polymers in the early 1950s and the critical need of industry for thermally and chemically stable materials stimulated the synthesis of fluorinated silicon derivatives.[540 – 542] During the subsequent 10 years, quite a number of studies along this line were accomplished, the key synthetic routes to organofluorine compounds were defined[526] and hundreds of compounds of this class were prepared and covered in detail in a review.[543] During this period, fluorinated silanes with a perfluorinated substituent (R_F) separated from the silicon atom by a hydrocarbon group came to the forefront. The synthesis of these compounds proved to be most appropriate for industry[544 – 547] and the first samples of fluorinated rubbers based on them, mainly containing the $CF_3CH_2CH_2Si$ and $R_FCH_2CH_2Si$ groups, attracted close attention of researchers owing to their unique properties.[548]

The early attempts to prepare silanes in which the perfluorinated aliphatic substituent is directly linked to silicon had little success. The direct Rochow synthesis using the silicon – copper alloy[540, 549, 550] and hydrosilylation of fluoroolefins ($CF_2{=}CF_2$, $CF_3CF{=}CF_2$, $CF_2{=}CFCl$, *etc.*)[526, 551 – 555] have not become popular. Higher performance was demonstrated by the standard organometallic approach consisting in the silylation of the C-anions, generated by two-electron reduction of organic halides, using chlorotrimethylsilane. Depending on the substrate nature, this reaction was in some cases performed step-by-step with intermediate trapping of the C-anion as organometallic compounds such as Grignard reagent and so on, or, in many cases, the best results were achieved by performing the synthesis under the Barbier reaction conditions, where the substrate was reduced by metal with further silylation of the C-anion *in statu nascendi* (Scheme 258).

Scheme 258

$$R{-}X \xrightarrow{e} [R{-}X]^{-\bullet} \longrightarrow R^{\bullet} + X^{-} \xrightarrow{e} R^{-} \xrightarrow{ClSiMe_3} RSiMe_3$$

However, even the first attempts at the synthesis of perfluoroalkylsilanes by this method revealed several problems. It was found that, unlike aliphatic organomagnesium compounds, their perfluorinated analogues have very low stability.[556, 557] In addition, very unexpectedly, chlorotrimethylsilane often did not react with either perfluorinated Grignard reagents or perfluoroalkyl halides in the presence of magnesium in diethyl ether.[558, 559] For this reason, the focus of researchers initially shifted from magnesium derivatives to lithium compounds. Indeed, one of the first syntheses of perfluoroalkylsilanes R_FSiR_3 ($R_F = C_3F_7$, *etc.*) was performed by the Barbier reaction of the appropriate iodides or bromides with Me_3SiCl in the presence of lithium and by silylation of perfluoroalkyllithuium derivatives obtained by transmetallation with MeLi.[560 – 562] Later, it was found that on switching to a more donor solvent (THF), perfluoroalkylsilanes can also be prepared using magnesium (by the Barbier reaction) and Grignard reagent.[558, 562 – 565]

At the same time, the first silanes containing a perfluorovinyl group [$Si(CF{=}CF_2)_4$,[559] $CF_2{=}CFSiMe_3$ (Refs 564, 566)] or a pentafluorophenyl group[567, 568] were synthesized using Mg and Li organic compounds.

Twenty years later, when all the main trends of the thermal stability of organosilicon polymers seemed to be already known, Ruppert *et al.*[569] turned back to the problem of synthesis of fluorinated rubbers containing a CF_3Si group. The authors supposed that these polysiloxanes should possess high stability.

Shortly before that, Marchenko *et al.*,[570, 571] who used tris(diethylamino)phosphine as an organic reducing agent instead of the active metals (Li, Mg), developed an efficient and general process for the synthesis of perhalogenated silanes, including fluorine-containing ones. Using a similar approach, in 1984, Ruppert *et al.*[569] synthesized trimethyl(trifluoromethyl)silane CF_3SiMe_3 (Ruppert reagent) from trifluoromethyl bromide and chlorotrimethylsilane. Subsequently, this method was successfully scaled up and extended to the synthesis of higher perfluoroalkyl-,[531, 572 – 575] perfluoroalkenyl-[576, 577] and perfluoroaryl(trimethyl)silanes,[578, 579] which stimulated a lot of studies of the properties of these compounds. Also, tetrakis(dimethylamino)ethylene (TDAE) was shown to be applicable as the reducing agent; however, in this case, high yields of perfluoroalkylsilanes can be obtained only from iodides.[580, 581]

Extensive practical implementation of the indicated methods for the synthesis of organofluorine silanes is hampered by the difficulty of scaling and high cost and toxicity of the applied chemicals. For solving these issues, electrochemical synthetic procedures were proposed in 1994. In this case, the C-anion was generated upon the cathodic reduction of alkyl halide in the presence of sacrificial aluminium or zinc anode.[582, 583] Although electrochemical synthesis is applicable for the preparation of both diverse polyfluorinated aliphatic silanes (including functionalized ones) and aromatic, heteroaromatic and vinylic silanes,[584 – 586] the preparation of the most demanded trimethyl(trifluoromethyl)silane from trifluoromethyl bromide requires a special autoclave cell,[587] which markedly complicates the practical use of this method.

While studying the electrochemical synthetic strategy towards trifluoromethyl-containing organic compounds and relying on the published data on the synthesis and reactivity of trifluoromethyl derivatives of metals (first of all, zinc),[588, 589] Grobe and Hegge[590] demonstrated in 1995 that under conditions of the Barbier reaction, trifluoromethyl bromide can react with chlorotrimethylsilane in the presence of zinc or aluminium in *N*-methylpyrrolidone to give CF_3SiMe_3 without electrochemical assistance (Scheme 259). Later, Prakash's research team[591] extended this method to the synthesis of some Ruppert reagent analogues — compounds **13.1**.

Scheme 259

$R_FHal + ClSiMe_3 \xrightarrow{a,\ or\ b,\ or\ c} R_FSiMe_3$

13.1

(*a*) $P(NEt_2)_3$ or TDAE, PhCN or diglyme, $-30\ ^\circ C \rightarrow$ rt; (*b*) Zn or Al (anode)/Ni or SS (cathode), Et_4N^+, DMF, MeCN or PhOMe, HMPA; (*c*) Zn or Al, NMP, rt $\rightarrow$ 50 °C; SS is stainless steel, HMPA is hexamethylphosporamide

The last method for the preparation of the Ruppert reagent (conditions *c*) is most beneficial from the practical standpoint. While it was scaled up, it was shown that the synthesis of CF_3SiMe_3 using zinc or aluminium has a number of considerable drawbacks for industrial application such as low yield of trifluoromethylsilane and the need to dispose inorganic products.[592] For solving these problems, it was proposed to change the nature of the silylating reagent, namely, to use silanes $ROSiMe_3$ [R = $CF_3C(O)$ or $MeSO_2$], instead of Me_3SiCl, traditionally employed in the synthesis of fluorinated silanes (Scheme 260).[593] This change proved to be significant and allowed researchers to develop an efficient CF_3SiMe_3 production process from trifluoromethyl bromide in a standard reactor operating at a slight excess pressure. Later, it was shown that this method is suitable for the synthesis of various fluorinated silanes **13.1** from appropriate halides.[594 – 597]

Scheme 260

$R_FHal + R^1OSiR^2_3 \xrightarrow[DMF\ or\ NMP]{Zn/Cu} R_FSiR^2_3$

13.1

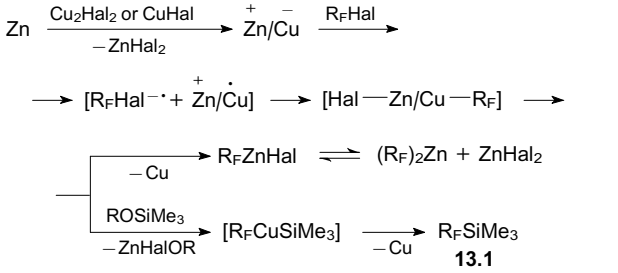
Hal = Br, I; $R^1 = CF_3C(O)$, $MeSO_2$; R^2 = Me: $R_F = CF_3$ (67%), C_2F_5 (80%), n-C_3F_7 (81%), iso-C_3F_7 (57%), n-C_4F_9 (60%),

n-C_6F_{13} (89%), n-C_8F_{17} (77%),  (80%),  (65%),

CF_2CO_2Me (70%), CF_2CO_2Et (40%), $CF_2CF_2OCF{=}CF_2$ (50%), $CF_2[CF_2OCF(CF_3)]_nCO_2Me$ [*n* = 1 (51%), 2 (71%)];
$R_F = CF_3$: $R^2_3 = Et_3$ (45%), $Me_2(CH{=}CH_2)$ (63%)

Experimental results suggest that the catalytic role of copper in this process is determined by its high oxidation potential; in the Zn/Cu galvanic couple, copper bears the negative charge.[598] The reduction of R_FHal with the zinc/copper couple gives rise to zinc – copper complexes, the subsequent fate of which depends on the absence or presence of silyl ethers in the reaction medium: in the former case, organofluorine zinc derivatives are formed *via* copper elimination, while in the latter case, fluorine-containing silanes are generated *via* a reaction with the silylating agent[595] (Scheme 261).

Scheme 261



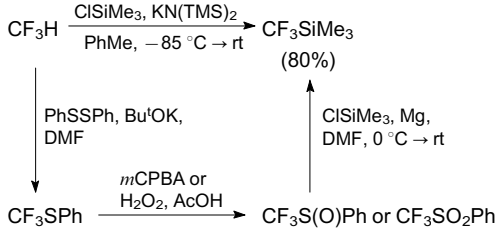
Somewhat earlier, Jairaj and Burton[599] demonstrated the efficient use of trifluorovinylcopper, generated *in situ* by transmetallation of trifluorovinylzinc iodide, in the synthesis of trimethyl(trifluorovinyl)silane.

The generation and the subsequent silylation of C-anions from fluorinated halides can also be accomplished in the presence of inorganic reducing agents, for example, SmI_2.[600]

Starting from the 1960s, trifluoromethyl bromide (Halon 1301, R13B1) has been a widely used fire extinguisher manufactured in large amounts; therefore, the use of this compound as a raw material for the production of the Ruppert reagent seemed quite reasonable. However, since the beginning of the 21st century, which was marked by global banning of ozone depleting substances, the use of CF_3Br in industry became impossible. This brought about the necessity to develop new methods for the synthesis of the Ruppert reagent without the use of banned halofluorocarbons.

A candidate source of the CF_3 anion is the ozone-safe fluoroform (trifluoromethane, HFC-23) — a by-product of the large-scale production of chlorodifluoromethane (HCFC-22) and tetrafluoroethylene. The synthetic route to CF_3SiMe_3 proposed by Prakash's research team[601 – 604] includes either the replacement of the hydrogen atom in CF_3H by a better leaving group, *e.g.* , S(O)R or SO_2R, followed by generation and silylation of the CF_3 anion or the silylation of the CF_3 anion generated directly from fluoroform (pK_a = 25 – 28) on treatment with strong bases (Scheme 262).

Scheme 262



*m*CPBA is *m*-chloroperoxybenzoic acid

Recently, one more method was proposed for CF_3H deprotonation using either DMSO potassium or sodium salt as the base or benzyl sodium and 18-crown-6 ether in the presence of hexamethylborazine. Although in this case, the generation and subsequent silylation of the CF_3 anion no longer require deep cooling, the practical possibility to

prepare CF_3SiMe_3 by this method has not been elucidated.[605, 606]

For many years, attempts were made to obtain the Ruppert reagent by decarboxylation of $CF_3CO_2SiMe_3$. However, the data available from the literature imply that no conditions under which this reaction would give the target product in high yield have been selected as yet.[607]

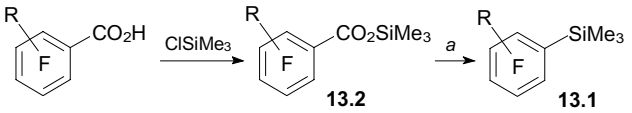
In 2014, modification of this approach resulted in an original and simple method for the preparation of trimethyl(trifluoromethyl)silane involving decarboxylation of trimethylsilyl trichloroacetate followed by Swartz fluorination of the resulting trimethyl(trichloromethyl)silane (Scheme 263).[608, 609] It is noteworthy that the syntheses of silicon and fluorine organic compounds by the Swartz reaction have also been reported earlier; however, it is only now, when 60 years passed after the first studies, that the synthetic potential of this method starts to be implemented.[543, 610] Currently, this method is apparently the most cheap and easily implementable synthetic route to the Ruppert reagent.

Scheme 263

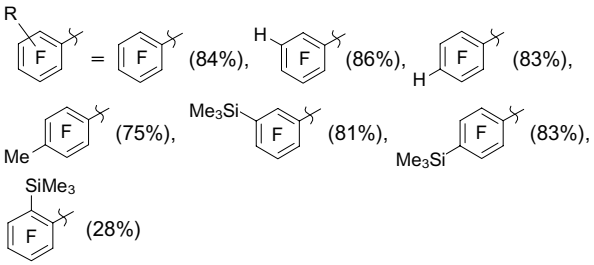
$$CCl_3CO_2SiMe_3 \xrightarrow[MeCN,\ 40\ ^\circ C]{CCl_3CO_2Na} CCl_3SiMe_3\ (90\%) \xrightarrow[100-138\ ^\circ C]{SbF_3,\ Br_2} CF_3SiMe_3\ (76\%)$$

In the beginning of the 2000s, these studies revealed the fact that, unlike silyl esters of perfluoroaliphatic carboxylic acids, their polyfluoroaromatic analogues **13.2** are decarboxylated to give polyfluoroaryl(trimethyl)silanes in high yields.[592] Considering the ready accessibility of the starting compounds, fluoroaromatic acids, and simple experimental equipment, this opens up the way to extensive use of compounds of this class (Scheme 264).[597, 611 – 613]

Scheme 264



(*a*) KCl (Cat.), sulfolane, 120 °C;



For example, trimethyl(pentafluorophenyl)silane can be employed in the synthesis of valuable intermediates such as pentafluorobenzaldehyde, pentafluorostyrene and pentafluorophenol,[597, 614] and other analogous compounds, as described in detail in a review.[615]

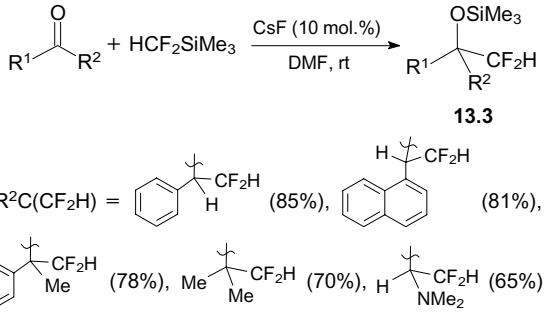
During more than 30-years of investigations, the Ruppert reagent was shown to be suitable for not only nucleophilic[616] but also radical[617 – 619] trifluoromethylation; also it can be converted to electrophilic trifluoromethylating reagents[620] or used for difluoromethylation,[621, 622] generation of difluorocarbene[623, 624] and synthesis of other trifluoromethylating reagents, *e.g.*, the Togni reagent.[10] Meanwhile, the reduction of the Ruppert reagent to (difluoromethyl)trimethylsilane with $NaBH_4$ discovered in 2010 markedly expanded the range of practical applications of CF_3SiMe_3 in organic synthesis.[625, 626] Subsequently this reaction was used to prepare DCF_2SiMe_3[627] and also scaled up for batch[597] and flow processes (Scheme 265).[628]

Scheme 265

$$CF_3SiMe_3 \xrightarrow[diglyme\ or\ sulfolane]{NaBH_4\ or\ NaBD_4} HCF_2SiMe_3\ or\ DCF_2SiMe_3\ (50\% - 70\%)\ (40\%)$$

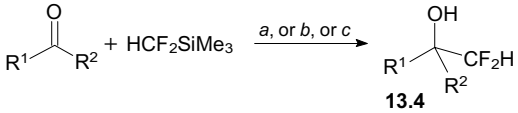
At that time, (difluoromethyl)trimethylsilane was seldom employed as a difluoromethylating agent in organic synthesis because it was poorly accessible and had low reactivity, considerably differing from those of other halogenated silanes.[529, 530, 629, 630] Of course, the availability of HCF_2SiMe_3 enhanced the research interest in this reagent. Thus it was found that difluoromethylation of aldehydes and ketones with HCF_2SiMe_3 giving ethers **13.3** can be accomplished under mild conditions using caesium salts, for example, CsF and Cs_2CO_3, as nucleophilic catalysts (Scheme 266).[631]

Scheme 266



Further investigation of this reaction expanded the range of suitable substrates and gave rise to alcohols **13.4** (Scheme 267).[632 – 637]

Scheme 267



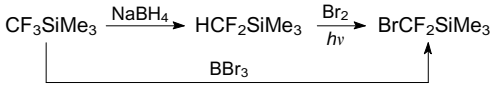
(*a*) CsF or Bu^{t}OCs, 18-crown-6, THF or DME, −78 °C → rt;
(*b*) CsF, HMPA or DMPU, THF, rt;
(*c*) Bu^{t}N=P[N=P(NMe$_2$)$_3$]$_3$, DMF, rt;
R^1, R^2 = H, Alk, CH=CH$_2$, Ar, Het;
DMPU is *N*,*N*′-dimethylpropyleneurea

Since then, the chemistry of (difluoromethyl)trimethylsilane started to rapidly develop, mainly, as reproduction of the transformations involving the Ruppert reagent. For example, reactions of HCF_2SiMe_3 with imines[632, 638, 639] and N-oxides[640] were studied; methods of difluoromethylation of unsaturated,[627, 641 – 643] aromatic[627, 641, 642, 644, 645]

and heterocyclic compounds[646 – 648] were developed. Quite a few papers were devoted to S-difluoromethylation.[649 – 654] Syntheses of HCF_2-selenium-[655] and HCF_2-tellurium-containing compounds[656] were reported. Like CF_3SiMe_3, its difluoromethyl analogue started to be used in the synthesis of organometallic compounds,[657 – 660] which were utilized in difluoromethylation reactions.[661 – 664]

Apart from the direct synthetic use of HCF_2SiMe_3, the chemists' toolkit was supplemented by a number of other useful fluorinated silicon reagents, the synthesis of which was markedly simplified. Among them, worthy of note is $BrCF_2SiMe_3$, the convenient syntheses of which were developed by several research groups (Scheme 268).[665 – 667]

Scheme 268



The scope of applicability of these reagents is comprehensively described in review publications[668 – 671] and is evidently far from being exhausted.

14. New reagents for nucleophilic difluoroalkylation

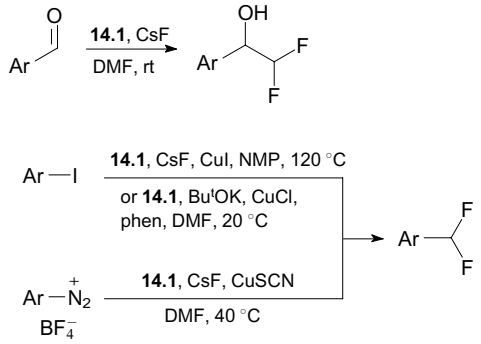
Among numerous approaches to the introduction of fluorinated groups into an organic molecule,[20, 537] nucleophilic fluoroalkylation reactions gain the highest popularity.[672, 673] These reactions are mainly based on the use of trimethyl(trifluoromethyl)silane, which is readily accessible and can act as a trifluoromethyl carbanion equivalent under mild conditions.[11, 524] Meanwhile, compounds containing a difluoromethyl group and a difluoromethylene unit attract increasing interest in medicinal chemistry.[674, 675] However, methods for the introduction of a difluoroalkyl group are much less studied, which is due to poor accessibility or/and limited stability of the relevant carbanionic reagents.

During the last decade, numerous papers appeared devoted to difluoroalkylation reactions.[624, 676] This chapter considers the most efficient methods for difluoroalkylation and for the introduction of alkyl groups containing two fluorine atoms at the α-carbon atom.

Fluorosilicon reagents find wide use in difluoroalkylation reactions.[525, 670, 677, 678] The difluoromethyl carbanion can be introduced into a molecule using the silicon reagent HCF_2SiMe_3 (**14.1**). A convenient procedure for the preparation of this reagent comprising reduction of CF_3-substituted silane with sodium brohydride was published only in 2011 (see Scheme 265).[626] Recently this reaction was implemented in a flow reactor.[628] Despite the fact that the mechanism of this reaction is not obvious, this method makes silane **14.1** rather accessible and now it is manufactured also in Russia.

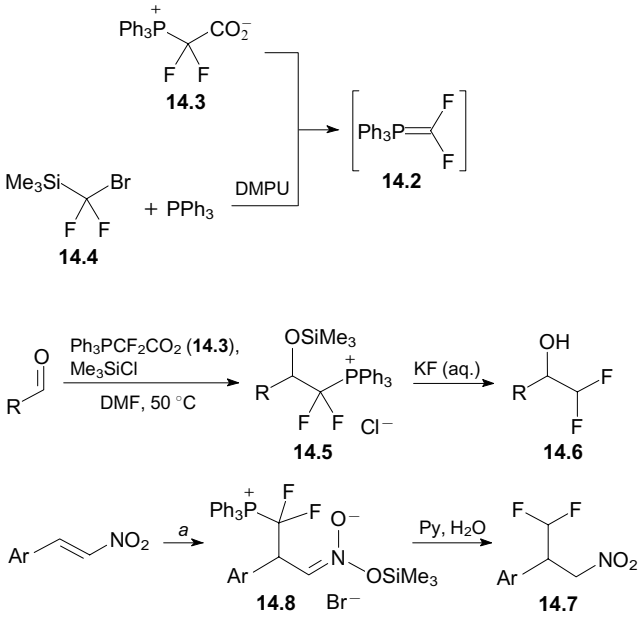
(Difluoromethyl)trimethylsilane was employed for difluoromethylation of carbonyl compounds and *N*-sulfonylimines[631 – 634] (Scheme 269). However, these reactions require sufficiently basic conditions needed for activating the silicon – carbon bond. Reagent **14.1** was also employed for generation of the difluoromethylcopper intermediate, which reacted with aryl halides[627, 642, 679] and diazonium salts.[644]

Scheme 269



phen is phenanthroline

Scheme 270



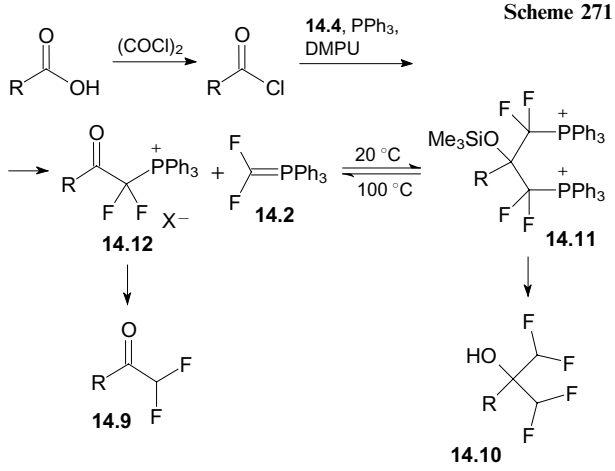
(*a*) Me_3SiCF_2Br (**14.4**), PPh_3, DMPU, MeCN, rt

A convenient and facile method for nucleophilic difluoromethylation of carbonyl compounds is based on the use of difluoro-substituted phosphonium ylide **14.2** (Scheme 270).[680, 681] This ylide is unstable and can be generated *in situ* by decarboxylation of phosphobetaine **14.3**[682] or by the reaction of (bromodifluoromethyl)trimethylsilane **14.4** and triphenylphosphine in the presence of *N*,*N*′-dimethylpropyleneurea.[681] It is noteworthy that phosphobetaine **14.3** is smoothly formed from the readily accessible potassium bromodifluoroacetate and triphenylphosphine; it is a crystalline air-stable compound.[682] The reaction of reagent **14.3** with aldehydes in the presence of chlorotrimethylsilane gives difluoro-substituted phosphonium salts **14.5**. The subsequent hydrolysis of the carbon – phosphorus bond is conducted under basic conditions, which affords difluorinated alcohols **14.6**.[680] The nucleophilic difluoromethylation of nitroalkenes giving nitro compounds **14.7** can be implemented in the reaction with silane **14.4**, which is followed by protodephosphorylation of the intermediate phosphonium salt **14.8**.[681] Generation of ylide **14.2** by coupling trimethyl(trifluorome-

thyl)silane with triphenylphosphine has also been reported; however, this method has a limited range of applicability.[622] Phosphonium salts **14.5** can be used as precursors to generate difluorinated radicals *via* the single-electron reduction of the carbon – phosphorus bond under photoredox conditions; the radicals can be trapped by either electron-enriched or electron-deficient double bonds.[683]

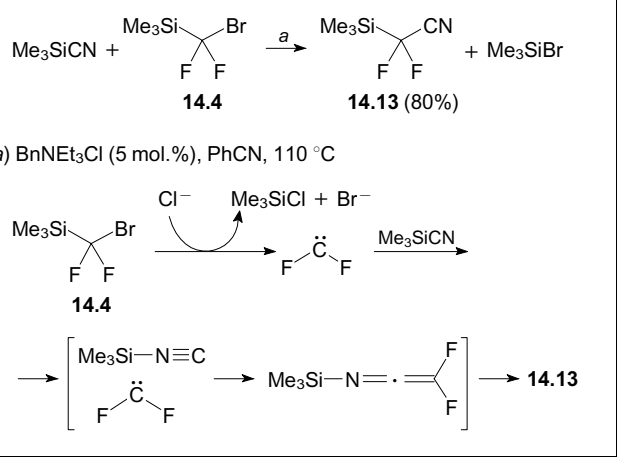
The reaction of acid chlorides with silane **14.4** and triphenylphosphine can afford difluoromethyl ketones **14.9** or bis(difluoromethyl)-substituted alcohols **14.10** depending on the reaction conditions (acid chlorides are conveniently generated *in situ* by treatment of carboxylic acids with oxalyl chloride)[684] (Scheme 271). When the reaction is carried out at room temperature, bis-phosphonium salts **14.11** are formed and are then hydrolyzed to alcohols **14.10**. However, heating of salts **14.11** to 100 °C is accompanied by elimination of one phosphorane **14.2** molecule to give monophosphonium salts **14.12**.

Scheme 271



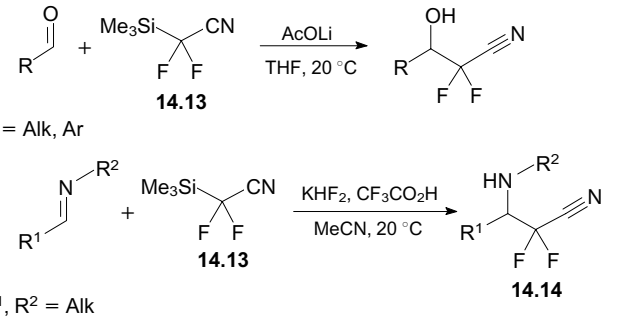
The standard route to fluorosilicon reagents includes silylation of carbanionic intermediates. However, this approach proved to be poorly suitable for the synthesis of cyano-substituted difluoromethylsilane (Me_3SiCF_2CN, **14.13**). This silane was prepared by insertion of difluorocarbene into the silicon – carbon bond of trimethylsilyl cyanide (Scheme 272).[665] It is evident that difluorocarbene is generated in this reaction from silane **14.4** under the action of chloride anion on heating.[685] However, the mechanism of its reaction with silyl cyanide has not been studied. Presumably, the isonitrile form of silyl cyanide is coupled with difluorocarbene and then 1,3-shift of the trimethylsilyl group takes place.

Scheme 272



Silane **14.13** can undergo nucleophilic difluoroalkylation upon Lewis base activation (Scheme 273).[665] The alkylation of aldehydes is carried out in the presence of lithium acetate, while the addition to N-alkyl- and N-aryl-imines requires a combination of potassium hydrogen difluoride with trifluoroacetic acid, which activates not only the fluorosilicon reagent, but also the azomethine component.

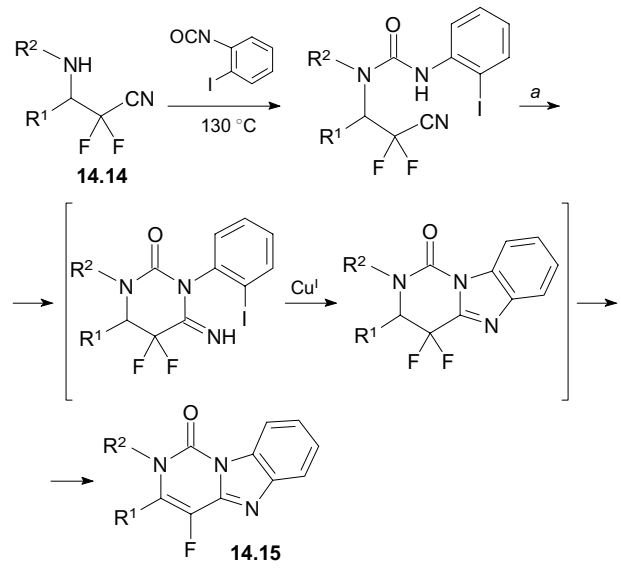
Scheme 273



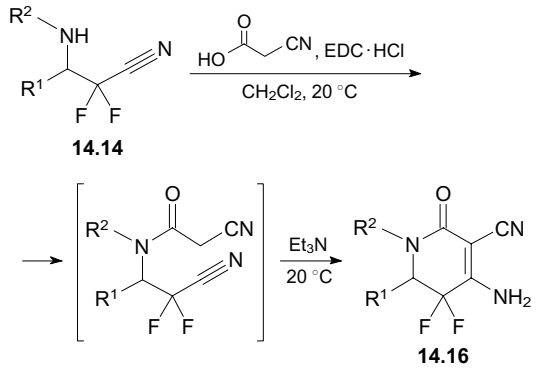
Amines **14.14** can act as building blocks for the preparation of fluorinated heterocyclic compounds (Scheme 274). For example, they react with *o*-iodophenyl isocyanate on heating to give a six-membered ring. The addition of a base and a catalytic amount of copper iodide and proline makes it possible to carry out intramolecular amination, while elimination of a hydrogen fluoride molecule affords tricyclic products **14.15**.[686]

The acylation of amines **14.14** using cyanooacetic acid and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC · HCl) gives dinitriles, which undergo cycli-

Scheme 274



Scheme 275

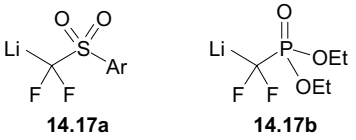


R^1, R^2 = Alk

zation under mild conditions to give 4-amino-3-cyano-5,6-dihydropyridin-2(1*H*)-ones **14.16** (Scheme 275).[687]

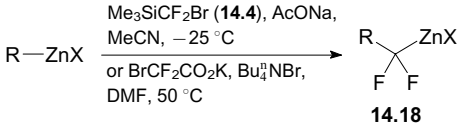
The key problem arising in nucleophilic difluoroalkylation is the instability of difluorinated organolithium and -magnesium reagents. Often, these reagents are also unstable even at very low temperatures. The high metal – fluorine bond energy in combination with the polarity of the metal – carbon bond promotes fast α-scission. For such difluorinated lithium and magnesium reagents to be generated and used as nucleophiles, a neighbouring electron-withdrawing group should be present in the molecule. Thus lithium derivatives **14.17a**,**b**, containing a sulfonyl[688] or phosphoryl[689] group are known. After they react with electrophiles, the functional group can be replaced by a hydrogen atom; therefore, the final reaction outcome corresponds to the introduction of a difluoromethyl carbanion.

Structures 14.17



On going from lithium and magnesium, to zinc-based fluorine-containing compounds, stability of the reagents increases, but simultaneously they become less reactive. Recently a new approach was proposed for generation of α,α-difluorinated organozinc reagents *via* insertion of the difluoromethylene moiety into the carbon – zinc bond (Scheme 276). The optimal source of the CF_2 moiety is silane **14.4**, which reacts with an organozinc compound at −25 °C upon activation with sodium acetate in acetonitrile.[690] A more readily accessible reagent, potassium bromodifluoroacetate in dimethylformamide,[691] can also be used; however, the reaction with this compound occurs only at elevated temperature because decarboxylation is required and the yields of products **14.18** are somewhat lower than those attained with silane **14.4**. Primary and secondary benzyl and alkyl organozinc compounds easily participate in the reaction, with various functional groups such as ester, nitrile as well as the pinacolboryl group and a halogen atom in the aromatic ring remaining intact. The mechanism of insertion of the difluoromethylene unit into the carbon – zinc bond has not been studied; however, it is quite probable that difluorocarbene is formed intermediately and then reacts with nucleophilic zinc compounds as an electrophile.

Scheme 276

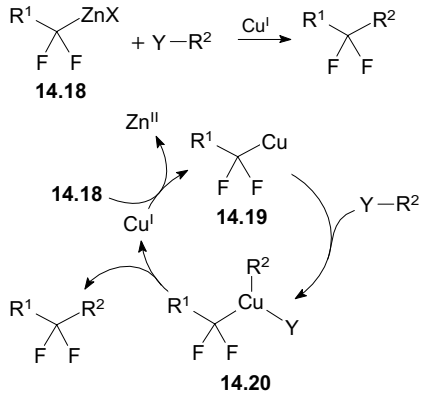


R = Alk, $ArCH_2$; X = Br, Cl, I

The stability of products **14.18** is largely determined by the nature of the solvent. In the case of acetonitrile, ~75% of benzyldifluoromethylzinc bromide ($BnCF_2ZnBr$, **14.18a**) decomposes within 2 h at room temperature, whereas in dimethylformamide, this reagent is much more stable. For example, upon the addition of dimethylformamide (5 equiv.) to compound **14.18a**, only 25% of the reagent decomposes within 2 h at 40 °C.

Due to the presence of two fluorine atoms, Zn derivatives **14.18** have moderate nucleophilicity. For their coupling with carbon-centred nucleophiles (YR^2), copper(I) salts must be used as catalysts (Scheme 277). The putative mechanism of the reaction includes zinc – copper exchange to give intermediate **14.19**. This is followed by oxidative addition, resulting in the formation of short-lived copper(III) intermediate **14.20**. This intermediate rapidly undergoes reductive elimination to give the cross-coupling product with simultaneous regeneration of the catalytically active copper(I) species.

Scheme 277

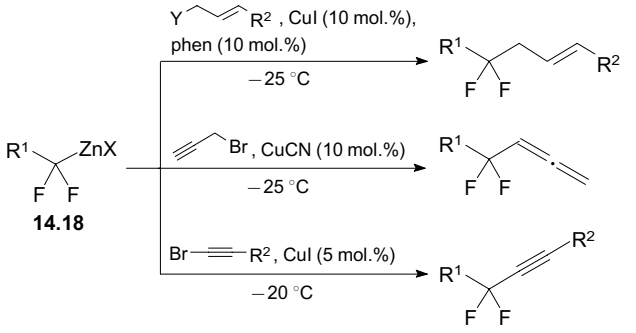


R^1, R^2 = Alk; X, Y = Hal

Reagents **14.18** are smoothly cross-coupled with allyl[692] and propargyl electrophiles[693] and with 1-bromoacetylenes (Scheme 278).[694] In the case of unsymmetrically substituted allylic substrates, the product is formed without the allyl rearrangement (the nucleophile adds to the carbon atom bearing the leaving group). Probably, this is due to fact that in the copper(III) allylic intermediate (such as **14.20**), the 1,3-allylic rearrangement is faster than the reductive elimination. In the case of propargyl bromide, only the allene product is formed. Apparently, this means that the reductive elimination is very fast.

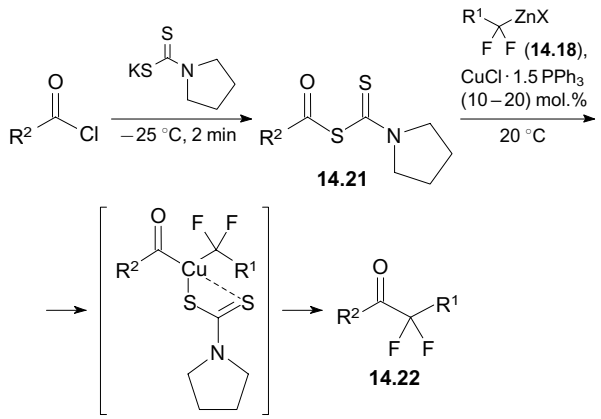
The reactions of compounds **14.18** with acylating agents have been investigated.[695] The reaction with acetyl chloride (in particular, in the presence of catalysts) did not lead to the target products. S-Acyl dithiocarbamates **14.21** proved

Scheme 278



R^1, R^2 = Alk; X, Y = Cl, Br

Scheme 279



R^1, R^2 = Alk; X = Cl, Br

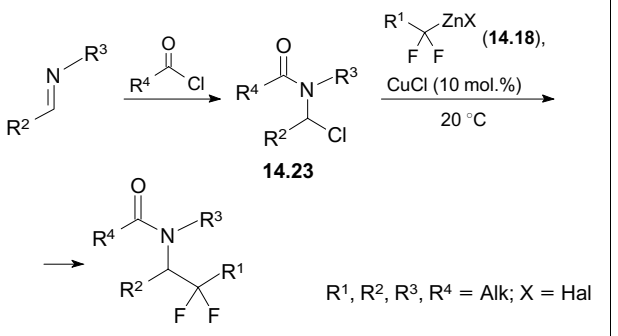
to be optimal components for the cross-coupling (Scheme 279). These intermediates are generated upon the reaction of acyl chlorides with potassium dithiocarbamate at low temperature during several minutes. This can be followed by their cross-coupling with reagents **14.18** catalyzed by a copper(I) chloride complex with triphenylphosphine. The performance of compounds **14.21** in the cross-coupling may be related to the efficiency of the oxidative addition step, which yields a copper(III) intermediate with an additional stabilizing interaction between the copper atom and the thiocarbamate moiety. It is also noteworthy that this method smoothly affords α,α-difluoro-substituted ketones **14.22**, which are of interest for medicinal chemistry as proteolytic enzyme inhibitors.

Reagents **14.18** are unreactive as nucleophiles towards imines. However, imines can be activated by treatment with acyl chlorides, resulting in generation of acyliminium chlorides **14.23** (Scheme 280). These species react with **14.18** in the presence of copper(I) chloride to give difluorinated N-acylamine derivatives.[696]

Compounds **14.18** can react with heteroatomic electrophiles. The iodination and bromination with these reagents proceed readily and give the corresponding products with bromo- and iododifluoromethyl groups.[690, 691] Nitrosation of reagents **14.18** on treatment with the butyl nitrite – chlorotrimethylsilane system[697] and the reaction with disulfides[695] have been reported.

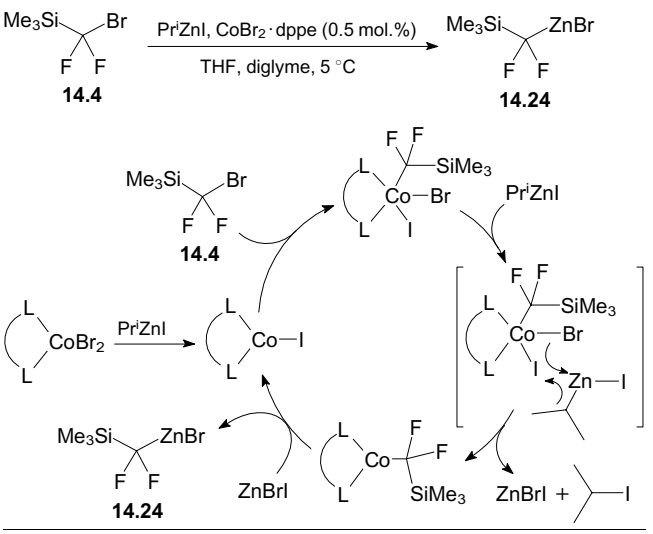
Silane **14.4** reacts with isopropylzinc iodide in the presence of the cobalt bromide complex (0.5 mol.%) with

Scheme 280



1,2-bis(diphenylphosphino)ethane (dppe) to generate organozinc reagent **14.24** (Scheme 281). For this compound, X-ray diffraction data were obtained, according to which the bromine atom instead of the expected iodine atom is connected to the zinc atom in the molecule of **14.24**.[698] The proposed mechanism of the bromine – zinc exchange includes the generation of a cobalt(I) complex as the catalytically active species. Its oxidative addition to the carbon – bromine bond with subsequent attack by the isopropyl group on the iodine atom affords a Co – C bonded complex, and this bond exchanges with zinc halide at the final step.

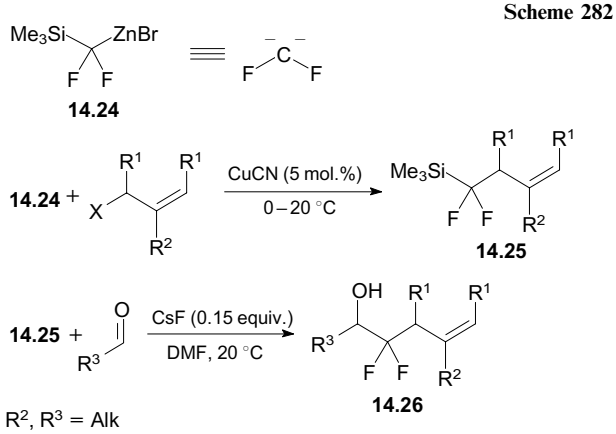
Scheme 281



Reagent **14.24** can be considered as an equivalent of difluoromethylenebis(carbanion) in reactions with two different electrophiles (Scheme 282). The allylation at the zinc – carbon bond occurs in the presence of the catalytic amount of copper cyanide; this leads to difluoro-substituted silicon derivatives **14.25**, which were isolated in a pure state. These silanes react with aldehydes in the presence of caesium fluoride as the catalyst to give alcohols **14.26**.[698] It was also reported that reagent **14.24** can act as a nucleophile in the conjugated addition reaction with arylidene Meldrum's acid derivatives.[699]

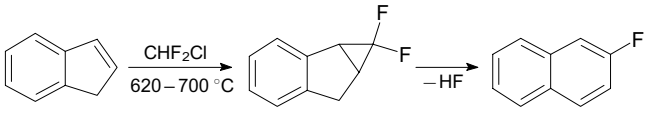
One more application of fluoro-substituted carbenes is the reaction with alkenes followed by transformations of the cyclopropane moiety. For example, pyrolysis of chlorodifluoromethane in the presence of indene affords 2-fluoro-

Scheme 282



R^1, R^2, R^3 = Alk

Scheme 283



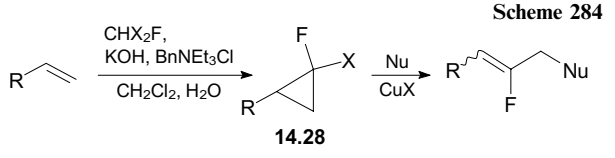
14.27 (68% – 80%)

napthtalene (**14.27**) in a good yield (Scheme 283). Using this reaction, diverse mono- and difluoroaromatic compounds were obtained.[700] Despite the high reaction temperature (~700 °C), this method is of interest for industrial use,[701] because it is based on the use of a large-scale product, that is, the initial freon. In addition, this process can be implemented in a flow system; first, this allows decreasing the effect of high temperature on the reactants and products and, second, this is attractive for the design of large-scale production.

The cyclopropanation involving bromofluorocarbene and chlorofluorocarbene is conveniently conducted under phase transfer catalysis (Scheme 284).[702] The cyclopropanation of a broad range of alkenes by treatment with bromofluorocarbene can also be accomplished by using sodium dibromofluoroacetate and silver complexes as catalysts.[703] The cyclopropanes **14.28** thus formed may undergo opening of the three-membered ring upon the reaction with nucleophilic reagents in the presence of copper(I) salts. The role of copper is to induce detachment of the halide anion, which is accompanied by conrotatory opening of the cyclopropyl moiety. When amines are employed as nucleophiles, the reaction gives allylamines containing a fluorine atom at the double bond;[704] these products are of interest for medicinal chemistry. Apart from amines, other suitable nucleophiles include alcohols, carboxylic acids, water or chloride anion; these reactions allow the synthesis of fluoro-substituted allyl ethers, alcohols or halides.[705 – 707]

Thus, during the last several years, a considerable progress was made in the nucleophilc difluoroalkylation

Scheme 284



X = Cl, Br; Nu = R'_2NH, R′OH, Cl^-

reactions. Chemically different reagents have been used. Among numerous compounds, reagents with a silicon – carbon bond are most air-stable and, therefore, they are most convenient for handling. However, because of the low reactivity of the carbon – silicon bond towards electrophiles in reactions involving silanes, addition of bases is required for activation.

Zinc-based reagents can be easily prepared *via* insertion of difluorocarbene into the carbon – zinc bond; they are able to undergo cross-coupling reactions with various electrophiles. Since the organozinc and electrophilic components can be varied independently of each other, this approach is suitable for the preparation of quite a number of difluorinated compounds.

It is noteworthy that the above-described reactions take place under mild conditions, require commercially available organofluorine reagents and provide a multitude of products needed for medicinal chemistry. However, an important challenge is the search for high-performance processes that would be useful for industrial scale implementation. Conducting the enantioselective nucleophilic difluoromethylation is also a fundamental challenge.

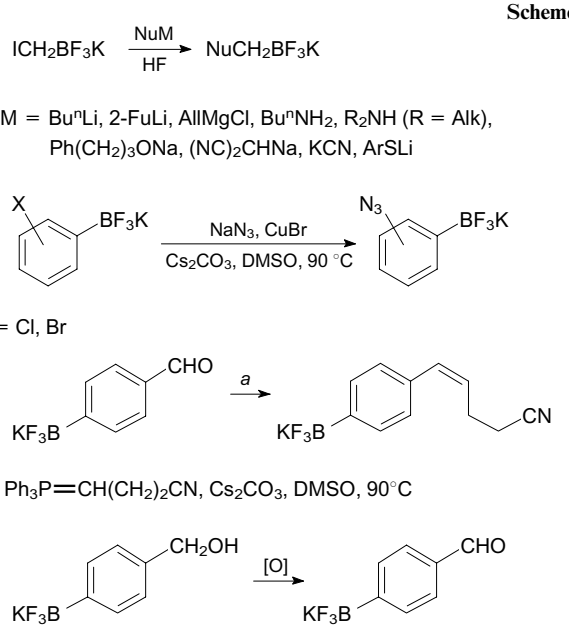
15. Transformations of the organic moiety of polyfluorinated organoboranes and borates with retention of the carbon – boron bond

In the 1960s, a new line of research has formed at the boundary between the chemistry of organofluorine and organoboron compounds, namely, the chemistry of polyfluorinated organoboron compounds. These compounds possess 'non-linear combinations' of properties inherent in organic compounds of fluorine and boron. Before the 1980s, this research area did not attract much attention of chemists, until it was found that tris(pentafluorophenyl)-borane is a strong Lewis acid, behaves as a homogeneous catalyst and, what is more important, is promising as a co-catalyst of olefin polymerization. Since then, the number of publications on this topic has started to sharply increase. The reviews[708 – 710] published in 2007 – 2010 analyze the achievements of the chemistry of polyfluorinated organoboranes and borates and consider the key differences between these derivatives and non-fluorinated analogues determining the specific character of their synthesis and reactivity. Some methods for the preparation of both types of compounds are similar in appearance, as, for example, nucleophilic addition of organolithium and -magnesium compounds to tris(alkoxy)boranes and subsequent conversion to fluoroborates.[711 – 715] However, in most cases, it was necessary to either considerably modify the known methods or develop completely new synthetic approaches. The same is true for the reactivity of polyfluorinated organoboranes and -borates. Using these compounds, xenon(II,IV) organic derivatives[716, 717] and alkenyl and alkynyl bromine(III,V) and iodine(III,V) derivatives[718 – 720] that cannot be prepared from boron hydrocarbon derivatives were synthesized for the first time. The C – C bond formation by cross-coupling of organoboronic acids or the corresponding trifluoroborates with organic electrophiles catalyzed by transition metal compounds (Suzuki – Miyaura reaction), which is widely used in the hydrocarbon series, proved to be inapplicable for perfluoroalkylation on treatment with perfluoroalkyltrifluoroborates. Only under specially selected conditions, was it possible to carry out perfluorovinylation

and polyfluoroarylation of aryl halides by means of the corresponding organotrifluoroborates.[710, 721 – 725]

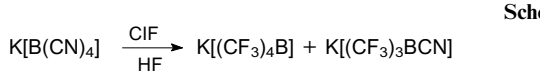
Transformation of organic groups without C – B bond cleavage are well-known for hydrocarbon borane derivatives.[726] Several recent publications report some analogous reactions of organotrifluoroborates. Mainly, these are nucleophilic substitution reactions[727 – 730] or transformations of the functional group remote from boron (Scheme 285).[731, 732]

Scheme 285



The methods of synthesis of trifluoromethylborates by oxidative fluorination of cyanoborates described by Bernhardt *et al.*[733] are worthy of particular note (Scheme 286).

Scheme 286



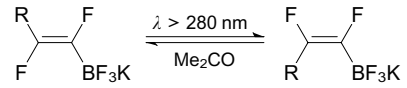
This chapter addresses modifications of the polyfluorinated organic groups at the boron atom involving transformations of polyfluorinated alkenyl, alkynyl and aryl moieties with retention of the C – B bond.

15.1. Transformations of polyfluorinated alkenyl or alkynyl moiety

The major method for the synthesis of polyfluoroalkenyltrifluoroborates is nucleophilic addition of polyfluoroalkenyllithium to $B(OAlk)_3$ followed by alkoxy group displacement by fluorine. The configuration of the alkenyl moiety is retained in this case.[708] An attempt to isomerize the $RCF{=}CFBF_3K$ salts by treatment with Me_4NF in diglyme was unsuccessful,[734] although catalysis of *Z*/*E* isomerization of polyfluoroalkenes by fluoride anions is a common approach.[735] However, irradiation of solutions of single salts in acetone affords a mixture of *Z*- and *E*-isomers, with the position of equilibrium depending on the nature of the substituent R (Scheme 287).[734]

Photoinduced isomerization takes place also in methanol and acetonitrile, but markedly more slowly. In the presence of bromine, the reaction rate increases, although no brominated products are formed throughout irradiation.

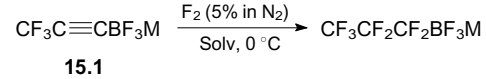
Scheme 287



R = H, Cl, Prn, Bun, Ph, C_nF_{2n+1} (n = 2 – 6), OC_3F_7-n

The addition of halogens (fluorine, chlorine and bromine) to the carbon – carbon multiple bonds of polyfluoroalkenyl- and polyfluoroalkynyltrifluoroborates was reported by Bardin *et al.*[736, 737] Passing fluorine (5% in nitrogen) through a dilute solution of $CF_3C{\equiv}CBF_3M$ (**15.1**) in MeCN[736] or 1,1,1,3,3-pentafluorobutane (PFB)[737] affords perfluoropropyltrifluoroborate in 50% – 60% yield and is accompanied by partial fluorodeboration. The intermediate perfluoropropyleneborate was not detected, as under the conditions employed, this compound and its homologues rapidly add fluorine at the C=C bond (Scheme 288).

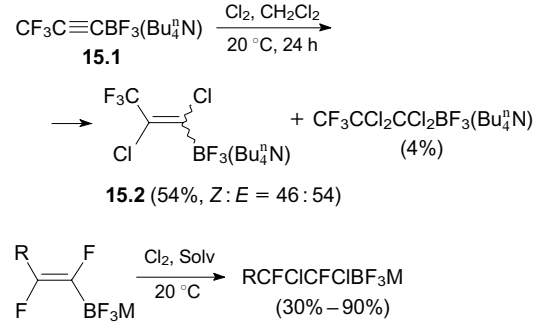
Scheme 288



Solv = MeCN, M = K; Solv = PFB, M = Bu^n_4N

Chlorination of salt **15.1** proceeds in a similar way, but tetra-n-butylammonium 1,2-dichloro-3,3,3-trifluoropropenyltrifluoroborate (**15.2**) resulting from the primary addition is the major reaction product in this case. This is due to the known stability of chlorinated alkenes to the action of chlorine. However, perfluoroalkenyltrifluoroborates easily add chlorine under these conditions to give perfluoroalkyl-1,2-dichlorotrifluoroborates (Scheme 289).[736, 737]

Scheme 289

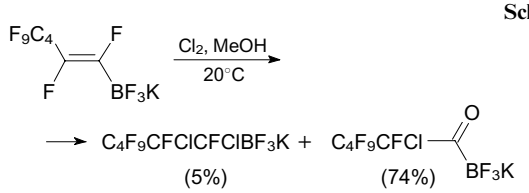


R = F, C_4F_9, Bun; Solv = CH_2Cl_2, MeCN, sulfolane

Chlorination of polyfluoroalkenyltrifluoroborates in methanol has a specific feature: the solvent acts as a nucleophile, as follows from the nature of the products (Scheme 290). [736]

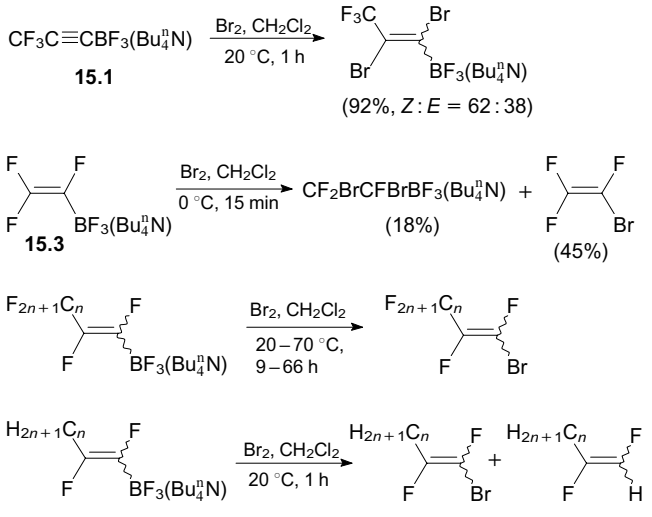
The reaction of salt **15.1** with bromine starts with addition of two bromine atoms, which is followed by bromodeboration to give tribromotrifluoropropene and $(Bu^n_4N)BF_4$. Alkenyltrifluoroborates undergo only bromo-

Scheme 290



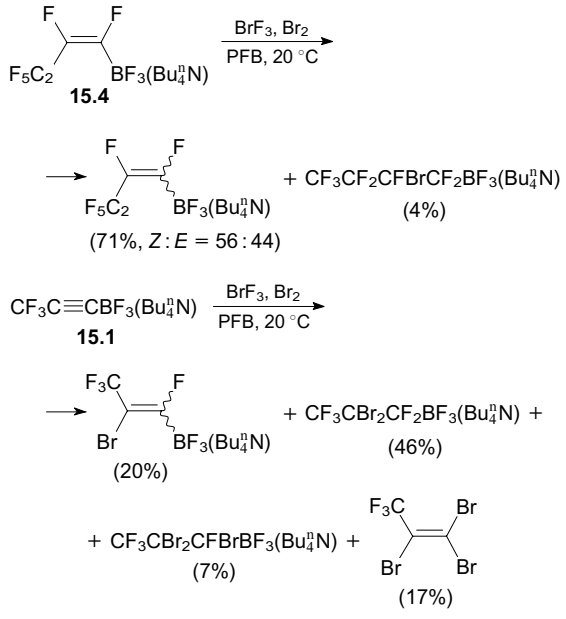
deboration on treatment with bromine in CH_2Cl_2 or $CHCl_3$, and only conversion of salt **15.3** gives some amount of the product of C=C bond bromination (Scheme 291).

Scheme 291



An equimolar mixture of BrF_3 and Br_2, which acts as an equivalent of [BrF], is an efficient bromofluorinating reagent.[738] The reaction of [BrF] with salt **15.4** results in partial isomerization of the alkenyl moiety of organoborate and bromofluorination of the C=C bond. However, when the perfluoroalkyl group is replaced by less electronegative substituents R, displacement of boron by bromine is the only reaction pathway. It is noteworthy that conversion of

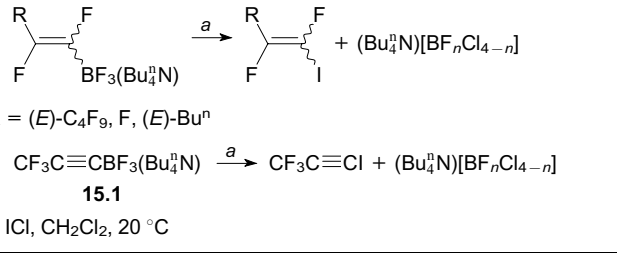
Scheme 292



salt **15.1** gives both bromofluorination and bromination products of the C≡C bond (Scheme 292).

The reaction of polyfluoroalkenyl- and polyfluoroalkynyltrifluoroborate salts with ICl gives only iododeboration products (Scheme 293).[738]

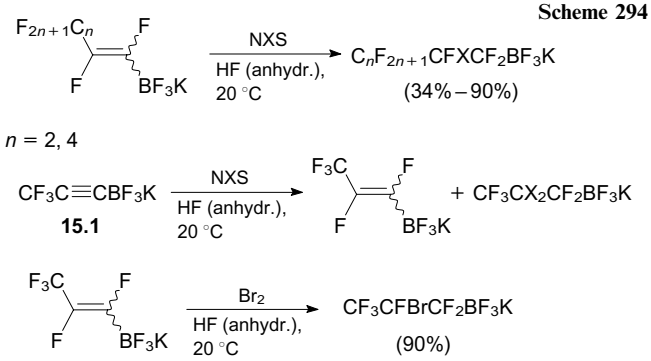
Scheme 293



Unlike tetra-n-butylammonium perfluoroalkenyltrifluoroborates, which are well soluble in chlorohydrocarbons and PFB, similar potassium salts are virtually insoluble in them and do not react with chlorine or bromine. However, (*E*)-RCF=CFBF$_3$K (R = Bu^n, Ph) undergo complete halodeboration. The salt CF_2=$CFBF_3K$ occupies an intermediate position and, along with halodeboration products, it forms the corresponding 1,2-dichloro- and 1,2-dibromotrifluoroethyltrifluoroborates. It is quite probable that these reactions occur on the surface of borates.[737]

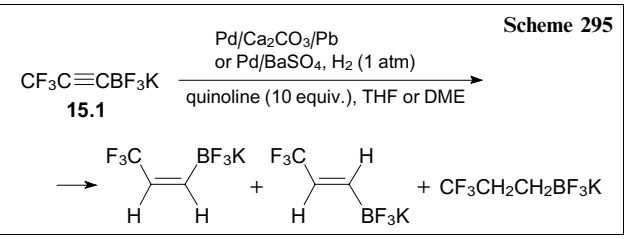
It was found [736, 739] that on treatment with strong protic acids HX, the salts K[RBF$_3$] split into RH and K[BF$_3$X], and the reaction rate depends appreciably on the nature of the organic group R. Nevertheless, electrophilic halofluorination of perfluoroalkenyl- and alkynyltrifluoroborates was accomplished by treatment with *N*-halosuccinimides (NXS) or bromine in anhydrous HF (Scheme 294).[736]

Scheme 294



Palladium-catalyzed hydrogenation of compound **15.1** with hydrogen was implemented. The outcome of the reaction considerably depends on the solvent [THF, MeOH, 1,2-dimethoxyethane (DME)], the composition of the catalyst and the reaction duration. Under optimal conditions, it is possible to obtain virtually pure *Z*- or

Scheme 295

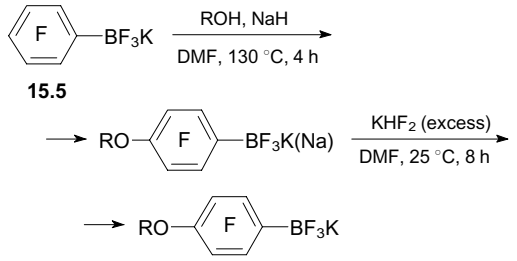


E-isomer contaminated with potassium 3,3,3-trifluoropropyltrifluoroborate (Scheme 295).[740]

15.2. Transformations of the polyfluorinated aryl moiety

In the series of polyfluoroaromatic boron derivatives, nucleophilic substitution reactions of aryltrifluoroborates are best studied. Potassium pentafluorophenyltrifluoroborate (**15.5**) does not react with sodium methoxide in refluxing methanol, while in the absence of a nucleophile it undergoes hydrodeboration in pentafluorobenzene.[741] On treatment of salt **15.5** with sodium alkoxides in polar aprotic solvents (DME, DMF, DMSO), 4-alkoxytetrafluorophenyltrifluoroborates are formed in more than 80% yields (Scheme 296).[742]

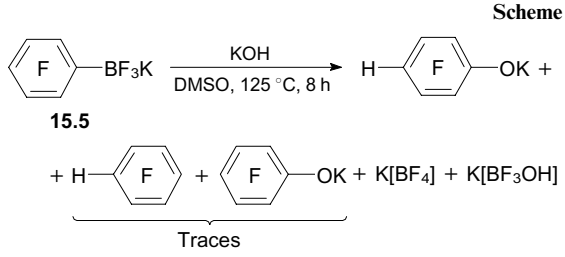
Scheme 296



R = Me (88%), Et (81%), Pr^n (87%), Pr^i (86%), Bu^n (89%), Bu^t (88%), Bn (80%), All (87%), Ph (82%)

In the presence of a threefold excess of the nucleophile, 2,4- and 3,4-dialkoxy derivatives are formed, apart from the major product, in approximately the same amount.[743] In view of these results, it was unexpected that compound **15.5** was stable to KOH in DMSO at 80 °C and that the C–B bond was cleaved at higher temperature (Scheme 297).[742]

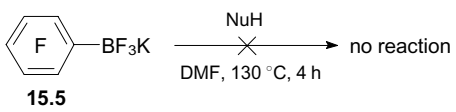
Scheme 297



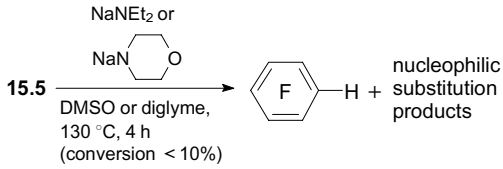
Further studies confirmed the dependence of the nucleophilic substitution pathway on the reagent nature. Indeed, salt **15.5** does not react with diethylamine and morpholine in DMF at 130 °C, while at 150 °C, it is cleaved to give pentafluorobenzene and the products of its reaction with the nucleophile. The reaction of borate **15.5** with sodium amides occurs in a similar way (Scheme 298).[744]

Conversely, treatment of $C_6F_5BF_3K$ with potassium or sodium azolides (NaAz) smoothly gives 4-azolyltetrafluorophenyltrifluoroborates.[744] The displacement of the second fluorine atom in the aromatic ring proceeds more slowly than that induced by O-nucleophiles. Even in the presence of excess reagent, the content of bis(azolyl)trifluorophenyltrifluoroborate in the final product does not exceed several percent (Scheme 299).

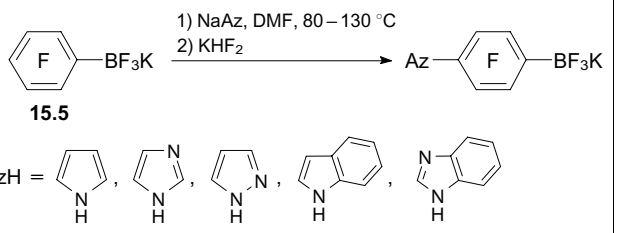
Scheme 298



NuH = Et_2NH, morpholine

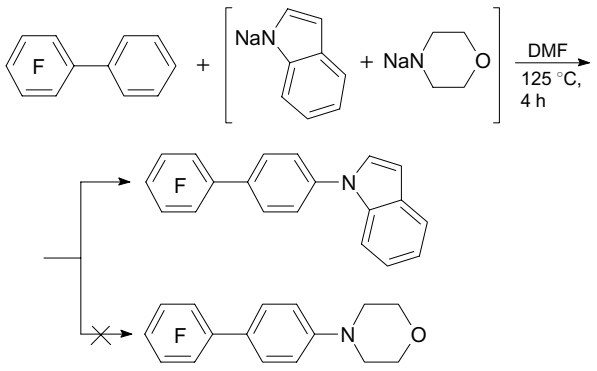


Scheme 299



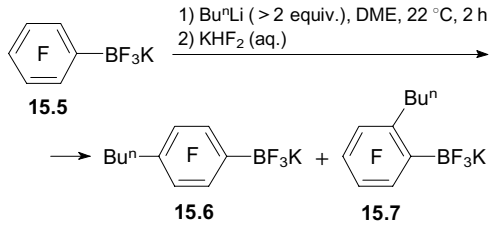
While analyzing the cause for higher reactivity of sodium azolides compared with sodium amides, Shabalin *et al.*[744] carried out the competitive reaction of these nucleophiles with 2,3,4,5,6-pentafluorobiphenyl as a model electrophile. It can be seen from Scheme 300 that the rate of fluorine atom replacement by sodium indolide is much higher than the replacement rate by sodium morpholide, which determines the outcome of the reaction with compound **15.5**. Note that the comparative nucleophilicity of alkali metal amides was not investigated before.

Scheme 300



Shabalin *et al.*[743] analyzed nucleophilic substitution of fluorine atoms in compound **15.5** under the action of organolithium compounds (C-nucleophiles). Since this borate is insoluble in diethyl ether or hexane, but is rather readily soluble in DME, the reaction was carried out in a solvent mixture. It was found that the reaction with methyllithium gives 4-methyltetrafluorophenyltrifluoroborate (**15.6**), but together with isomer **15.7**, which results from displacement of the fluorine atom in the *ortho*-position to boron, the product ratio being ~10 : 1. The reaction with Bu^{n}Li in a DME – hexane mixture proceeds in a similar way

Scheme 301

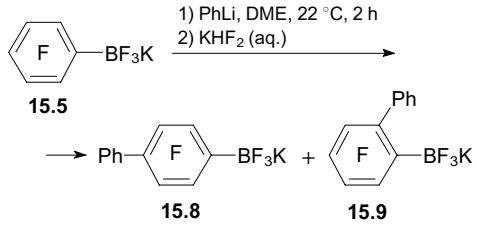


to give derivatives **15.6** and **15.7** in the same ratio (Scheme 301).

Two fluorine atoms are not displaced even with excess nucleophile. Only at 55 – 60 °C, 2,4- and 2,5-di-n-butyltrifluorophenyltrifluoroborates appear in minor amounts.

The results of reaction of compound **15.5** with phenyllithium are qualitatively similar to those described above, but the contribution of *ortho*-substitution is much higher and the **15.8** : **15.9** ratio of isomers is ~ 1 : 1 (Scheme 302).

Scheme 302

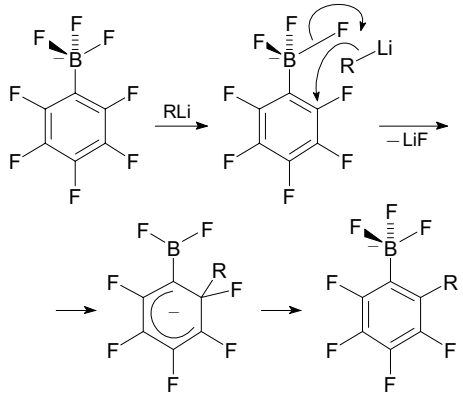


Lithium phenylacetylenide does not react with borate **15.5** (DME, 58 °C, 5 h), which is in line with the published data pointing to relatively low nucleophilicity of this reagent.[743]

Thus, the pattern of fluorine displacement in borate **15.5** by C-nucleophiles differs from that observed for O- and N-nucleophiles, first, by the formation of 2-$RC_6F_4BF_3K$ isomers and, hence, by higher stability of the primary substitution products, $RC_6F_4BF_3K$, to the displacement of the second fluorine atom. It is assumed that displacement of the *ortho*-fluorine atom by organolithium reagents is due to lithium coordination by the fluorine atom attached to boron, as shown in Scheme 303.

Enrichment of the reaction mixture obtained from salt **15.5** and PhLi with isomer **15.9** is due to additional

Scheme 303



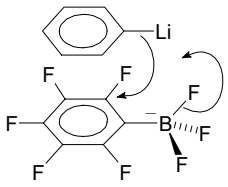


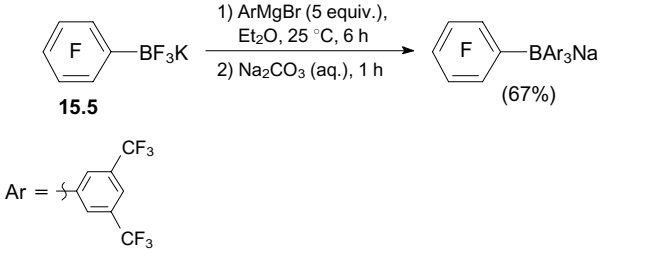
Figure 2. Transition state for the reaction of borate **15.5** with phenyllithium (see Scheme 303).

stabilization of the transition state by the donor – acceptor interaction of the phenyl group with the pentafluorophenyl moiety of the organyltrifluoroborate *via* π-stacking (Fig. 2).

The absence of this reaction channel in the reaction of salt **15.5** with MOR or MAz (M = Na, K) is attributed to lower affinity of these cations to the fluoride anion.

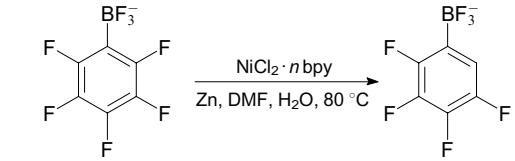
It is of interest that the reaction of borate **15.5** with 3,5-bis(trifluoromethyl)phenylmagnesium bromide gives fluorine-containing tetraarylborate rather than the product of nucleophilic substitution in the pentafluorophenyl group (Scheme 304).[745, 746] In the authors' opinion, this is a consequence of slow reversible dissociation of the borate to give KF and aryldifluoroborane, which is captured by the weakly nucleophilic reagent.

Scheme 304



The doubts concerning the inertness of the BF_3^- group towards hard metal cations are supported by hydrodefluorination of $C_6F_5BF_3K$ on treatment with zinc in the presence of a nickel salt (Scheme 305).[747]

Scheme 305

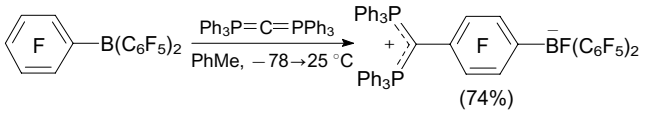


bpy is bipyridine

Previously, such regioselective activation of the C – F bond was observed for pentafluorobenzoic acid derivatives $C_6F_5C(O)X$ (X = OH, NH_2, OEt)[748] and pentafluoroaniline C_6F_5NHAc;[749] the first step of this reaction is the coordination of the carbonyl oxygen atom to the nickel atom. However, the possible participation of the trifluoroborate group in a process of this type was demonstrated for the first time.

Unlike the reactions of borates, similar transformations of polyfluorinated organylboranes have been scarcely

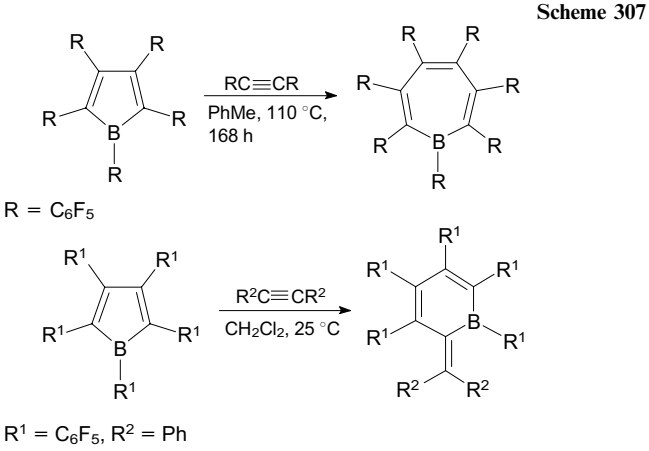
Scheme 306



studied. Consider two examples. On treatment with hexaphenylcarbodiphosphorane in toluene, one fluorine atom of $B(C_6F_5)_3$ is displaced to give a zwitter-ion product (Scheme 306).[750]

Long-term heating of perfluoropentaphenylborole with perfluorodiphenylacetylene leads to ring expansion giving perfluoroheptaphenylborepin. The reaction with diphenylacetylene rapidly proceeds at room temperature; however, along with borepins, the reaction gives boracyclohexadiene with the *exo*-methylene group as the major product (Scheme 307).[751]

Scheme 307



The examples presented in this chapter demonstrate the high potential of development of the chemistry of fluorinated organoboron compounds, which have found use in various fields of science and technology. Recently, a convenient approach was proposed for the preparation of aromatic and fluoroaromatic difluoroboranes by reactions of potassium trifluoroborates with ionic liquids containing the tetrachloroaluminate anion and free dissolved aluminium chloride. A study of the catalytic properties of the resulting aryldifluoroboranes in model reactions of phenol alkylation revealed their dependence on the nature of substituents in the aromatic ring.[752] A new synthetic platform was proposed for the preparation of ionic liquids (IL) with specific properties based on the polyfluorophenyltrifluoroborate anion $Q[4\text{-}XC_6F_4BF_3]$ (Q is 1,3-dialkylimidazolium; X = F, AlkO).[753] Convenient preparative approaches to these ionic liquids, including IL with chiral substituents, have been developed. The salts $4\text{-}RC_6F_4BF_3M$ are efficient reagents for palladium-catalyzed cross-coupling with organic halides, which opens up new synthetic opportunities for the design of materials with unique properties.[754]

Thus, fluorinated organoboron compounds represent a special class of organoelement compounds possessing a number of unique properties, which are caused by partial or complete replacement of hydrogen atoms in boron-bound organic groups by fluorine atoms. The latter circumstance stimulates the search for new fluorinated organoboron compounds and development of synthetic routes to them.

16. Catalysts of olefin metathesis with unsymmetrical fluorine-containing NHC ligands

During the last decade, metathesis of olefins, as an important method for the formation of carbon – carbon bonds, has become one of the most vigorously developing issues of organic chemistry. This process has already made an invaluable contribution to the synthesis of physiologically active natural products, pharmaceuticals, functional materials and polymers. The discovery of efficient ruthenium carbene complexes (Fig. 3), distinguished by high stability with respect to moisture and air oxygen and by high tolerance to various functional groups in the substrate, resulted in the development of quite a few important synthetic processes such as ring closing metathesis, cross-metathesis, ring opening metathesis polymerization and so on.[755]

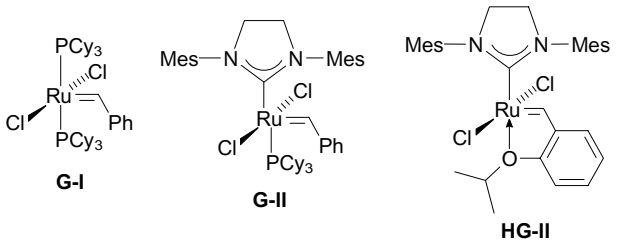


Figure 3. Commercially available catalysts for olefin metathesis: Grubbs I (**G-I**) and II (**G-II**) and Hoveyda – Grubbs II (**HG-II**) (Mes = 2,4,6-$Me_3C_6H_2$) catalysts.

The recent progress in the development of new ruthenium-based metathesis catalysts is related, most of all, to modification of the N-heterocyclic carbene (NHC) ligand in the commercially available complexes **G-II** and **HG-II**, which makes it possible to directly affect the catalyst performance.[756 – 758] In recent years, unsymmetrical NHC ligands have become significant. In this case, desymmetrization makes it possible to rapidly perform further fine tuning of the catalytic properties. For example, the introduction of functional groups possessing chelating, chiral or shielding properties can considerably affect the catalyst stability, reactivity and selectivity, thus stimulating researchers to develop new efficient catalytic systems.[759, 760]

Meanwhile, it is well known that organofluorine compounds are now widely used virtually in all fields of science and technology, including medicine and manufacture of new materials.[9, 522, 761, 762] This is related, first of all, to the fact that the introduction of a fluorine atom or a fluoroalkyl group into an organic molecule considerably changes its physicochemical parameters, often resulting in increasing lipophilicity and thermal and proteolytic stability. In addition, fluorine atoms can form rather strong hydrogen bonds with neighbouring functional groups and coordination bonds with metals.[283, 763 – 765]

In the case of ruthenium carbene complexes, the steric and electronic influence of fluorine atoms and fluoroalkyl groups on the catalytic properties was mainly studied using

fluorine-modified phosphine and styrene ligands and replacement of chlorine atoms directly bound to ruthenium by fluoroalkoxyl groups.[766 – 770] Complexes containing fluorinated NHC ligands are barely studied and the range of catalysts with unsymmetrical fluorinated NHC ligands is limited to only a few examples.[771 – 773] Therefore, the development of new efficient catalysts for olefin metathesis with NHC ligands modified by fluorine-containing functional groups is a topical issue of modern organic and organometallic chemistry.

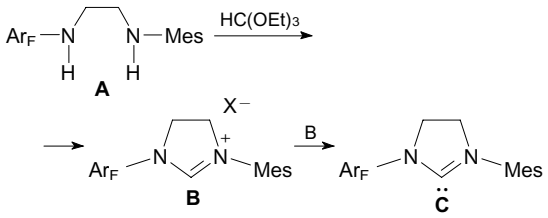
More than 20 years ago investigations were started towards the development of α-CF_3-containing cyclic α-amino acids, which are of interest as potential inhibitors of pyridoxal phosphate-dependent enzymes and are also meant for modification of bioactive peptides in order to increase their conformational rigidity and protease stability.[774, 775] The synthetic strategy chosen for this purpose is based on the use of accessible CF_3-containing α-imino- and α-diazocarboxylates for the design of diverse unsaturated linear α-amino acid derivatives, which are then subjected to intramolecular ring closing metathesis reactions catalyzed by ruthenium carbene complexes. This is exemplified by ring closing olefin metathesis and ring closing enyne metathesis (RCM and RCEYM),[776 – 779] combinations of these types of metathesis with cyclopropanation[780] (RCEYM/cycloprop) and with the Diels – Alder reaction[781] (RCEYM/D-A), ring opening/ring closing metathesis sequence[782] (ROM/RCM) and cross enyne metathesis/Diels – Alder reaction sequence[783] (CEYM/D-A) (Scheme 308).

Subsequently, efficient synthetic routes were developed to new ruthenium carbene complexes with unsymmetrical trifluoromethyl-containing NHC ligands and the catalytic activity of the complexes in the intra- and intermolecular metathesis of olefins was sudied.

16.1. Synthesis of ruthenium carbene complexes with unsymmetrical fluorine-containing NHC ligands based on *N*,*N*′-diarylimidazoline

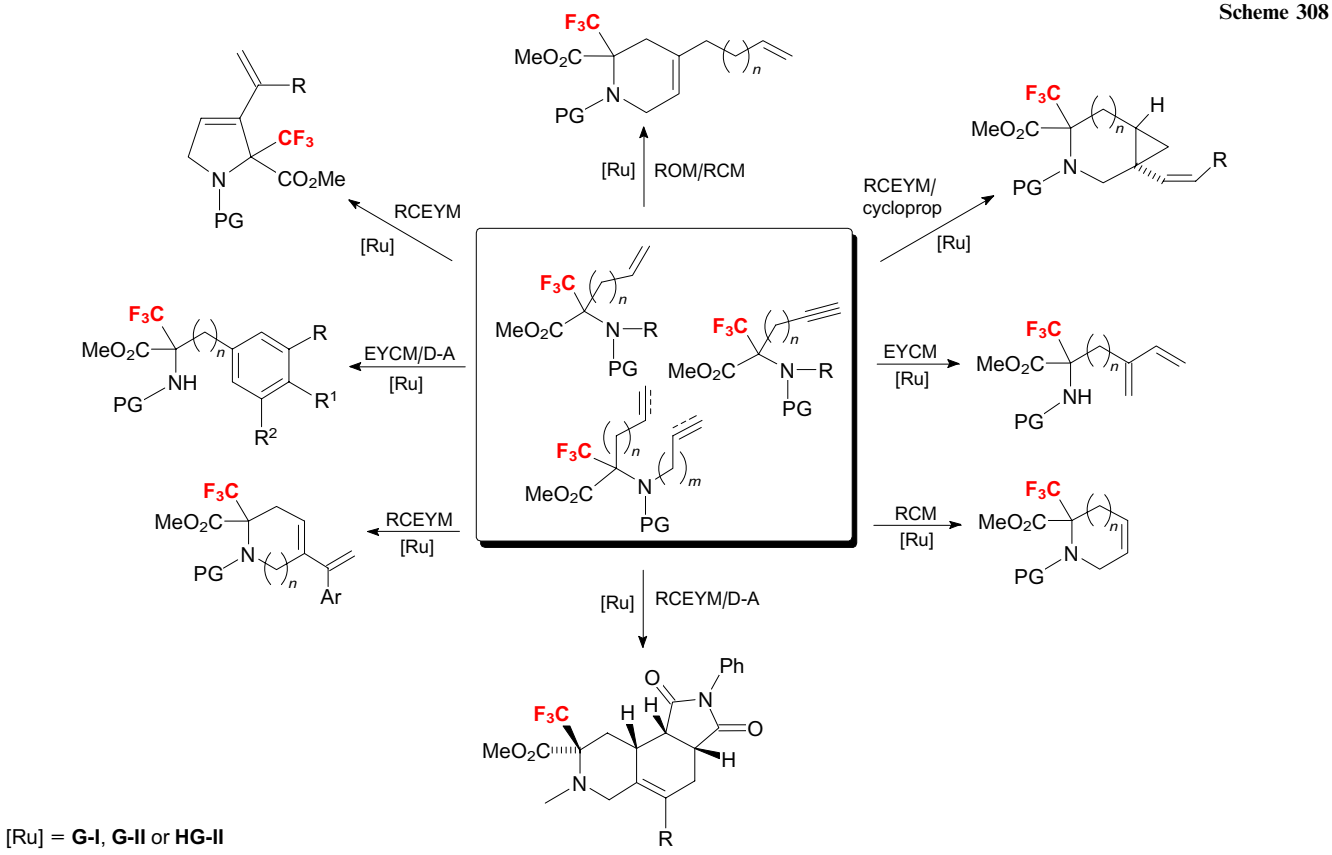
Among the known metathesis catalysts, the highest activity was found for the ruthenium carbene complexes with NHC ligands based on 4,5-dihydroimidazole with *ortho*-substituted N-aryl groups. Therefore, the strategy chosen for the synthesis of unsymmetrical N-heterocyclic carbenes includes the preparation of unsymmetrical bis(aryl)ethylenediamine **A** and the subsequent heterocyclization giving imidazolinium salt **B** as the precursor of carbene **C** (Scheme 309).

Scheme 309



Since it is known that an increase in the steric bulk of the substituent at the nitrogen atom in the NHC ligand, most often, increases the stability of the corresponding ruthenium complex and, as a consequence, improves its performance, it appeared reasonable to obtain an unsymmetrical imidazolinium salt containing a hexafluoroisopropylalkoxy group in the *ortho*-position of the N-aryl substituent.[784] The presence

Scheme 308

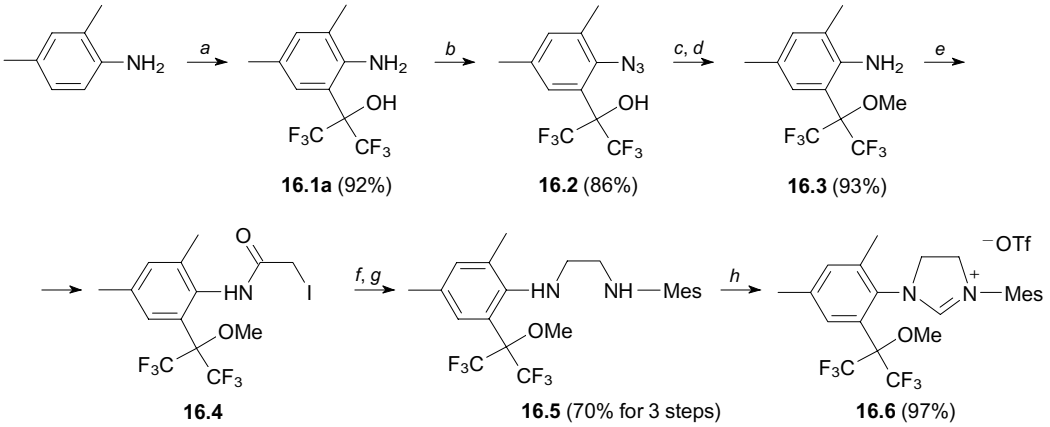


[Ru] = **G-I**, **G-II** or **HG-II**

of a bulky fluorinated group with an anionic centre in the close vicinity to the ruthenium atom may provide the complex with enhanced stability by shielding the metal site from the adverse effects of the environment and by the possible formation of an additional Ru – O coordination bond. Also, the presence of two lipophilic CF_3 groups in the catalyst molecule can endow it with better solubility in industrially important alkanes or monomers.[785, 786]

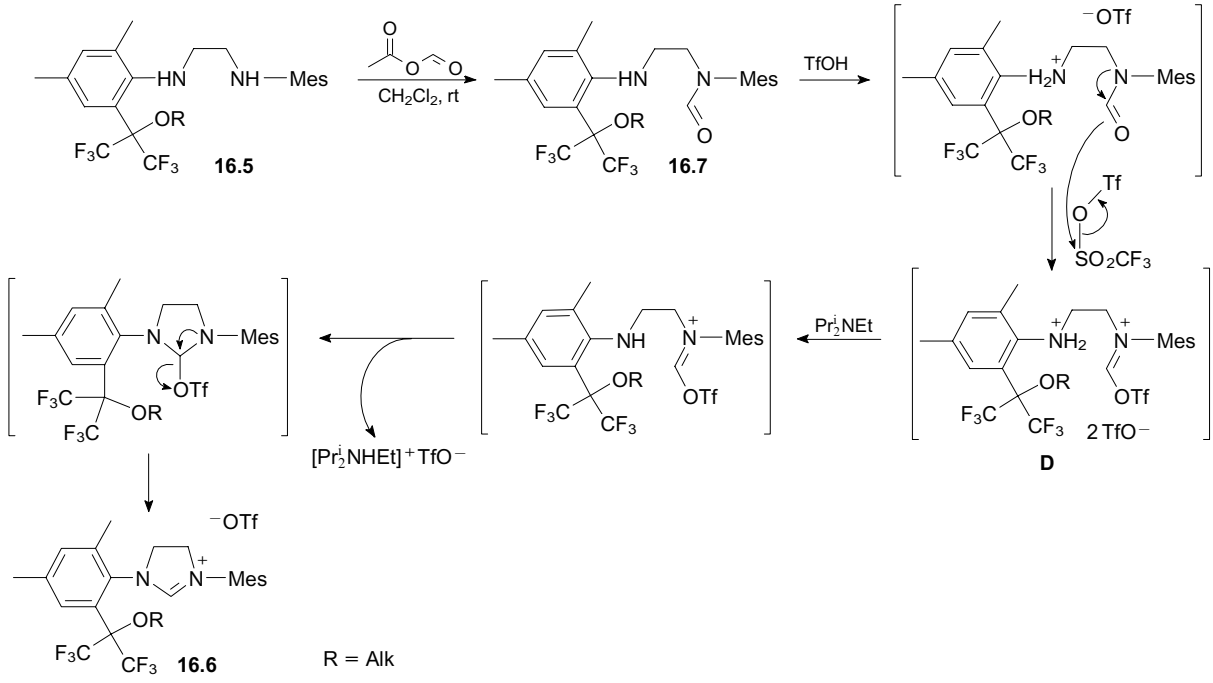
For this purpose, fluorinated aniline **16.1a** was initially synthesized (Scheme 310) using a simple procedure, which included alkylation of 2,4-dimethylaniline with commercially available hexafluoroacetone hydrate in the presence of *para*-toluenesulfonic acid as the catalyst (step *a*). Further, the synthetic manoeuvre including preliminary transformation of substrate **16.1a** to azide **16.2** by successive treatment with sodium nitrite and azide served for the selective design of the key diamine. The O-methylation under standard conditions was followed by reduction of the azido group in the MeO derivative by treatment with sodium borohydride, using cobalt chloride catalyst in the presence of cetyltrimethylammonium bromide (CTAB), needed for stabilization of the cobalt-containing catalyst species. This afforded aniline **16.3**. The subsequent synthetic sequence included N-acylation with chloroacetic acid chloride and chlorine atom replacement by iodine according to the Finkelstein reaction to give iodide **16.4** (steps *d*, *e*). The condensation of iodide **16.4** with mesitylamine and the reduction of the amide keto group (steps *f*, *g*) resulted in the formation of unsymmetrical ethylenediamine **16.5** in a high yield (70% for steps *e* – *g*).

Scheme 310



(*a*) $(CF_3)_2CO \cdot 1.5\,H_2O$, TsOH (1 mol.%), 100 °C; (*b*) $NaNO_2$, H_2SO_4, then NaN_3; (*c*) MeI, K_2CO_3, MeCN, 70 °C, then HCl, H_2O, rt; (*d*) $NaBH_4$, $CoCl_2$, CTAB, H_2O, MeOH; (*e*) $ClCH_2C(O)Cl$, DMAP, CH_2Cl_2, then NaI, Me_2CO, rt; (*f*) $MesNH_2$ (15-fold excess), rt; (*g*) $BH_3 \cdot SMe_2$, THF; (*h*) AcOCHO, Et_2O, rt, then TfOH, Tf_2O, Pr^i_2NEt, 70 °C; DMAP is 4-dimethylaminopyridine

Scheme 311



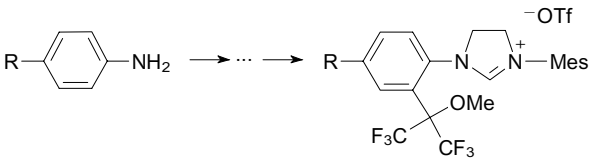
The first attempts to carry out heterocyclization of diamine **16.5** to the desired 4,5-dihydroimidazole derivative **16.6** using traditional methods were, unfortunately, unsuccessful. Nevertheless, this problem was solved by modifying the synthesis of sterically crowded imidazolinium salts reported by Organ and co-workers.[787] It was found that diamine **16.5** can be selectively formylated at the sterically more accessible amino group by treatment with mixed acetic and formic anhydride to give the corresponding derivative **16.7** in a high yield. The successive treatment of formylated diamine **16.7** with a stoichiometric amount of trifluoromethanesulfonic acid and its anhydride followed by the addition of excess tertiary amine leads to desired triflate salt **16.6** in a quantitative yield (Scheme 311).

The mechanism of formation of salt **16.6** includes the covalent activation of the amide function under the action of the $TfOH-Tf_2O$ mixture (intermediate **D** in Scheme 311); this creates conditions for the intramolecular Vilsmeier – Haack reaction. The use of the Hünig's base (ethyldiisopropylamine) was the optimal choice for the final step of cyclization.

The found conditions proved to be also applicable for the synthesis of salts containing no methyl group in the *ortho*-position.[788, 789] Thus the synthetic strategy shown in Scheme 310 was used to prepare the corresponding triflates **16.8ab** in reasonable overall yields starting from commercially available *p*-toluidine and *p*-anisidine (Scheme 312).

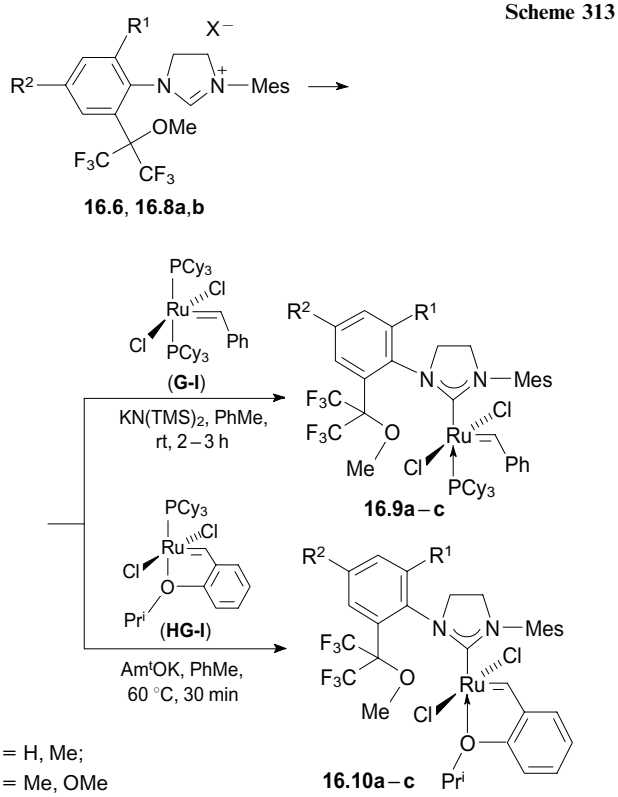
It is noteworthy that all steps of the developed method for the synthesis of salts **16.6** and **16.8a**,**b** are readily scaled up to 10-gram amounts without the use of chromatographic purification techniques.

Scheme 312

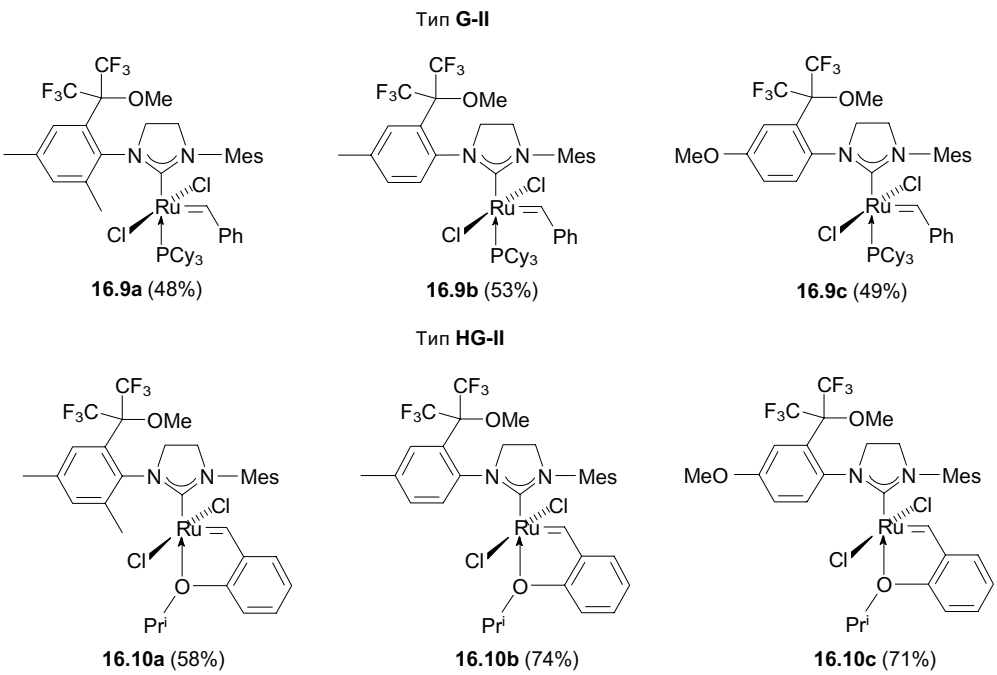


R = Me (**a**, 67%), OMe (**b**, 62%) **16.8a**,**b**

Scheme 313



Structures 16.9, 16.10



of commercially available first-generation Grubbs (**G-I**) and Hoveyda – Grubbs (**HG-I**) complexes to the reaction mixture.

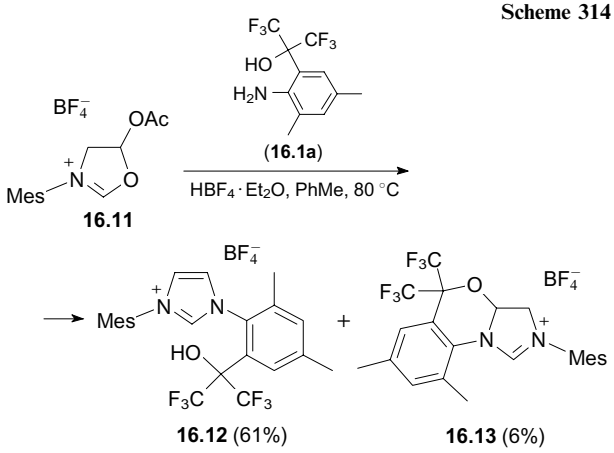
As a rule, completion of the ligand exchange reaction requires stirring of the reaction mixture for 2 h at room temperature or for 30 min at 60 °C. Complexes **16.9a – c** and **16.10a – c** were isolated in moderate to good yields by column chromatography on silica gel as coloured dark brown powders (**16.9**) and dark green powders, the colour being typical of phosphine-free complexes (**16.10**).

16.2. Synthesis of ruthenium carbene complexes with unsymmetrical fluorinated NHC ligands based on *N*,*N*′-diarylimidazole

The examples of non-equivalently substituted 1,3-diarylimidazole-based NHC ligands are limited only to compounds with trivial aromatic substituents.[790] This is attributable to the fact that the synthesis of their precursors, imidazolium salts, by quaternization of N-aryl-substituted imidazoles is now mainly available only for simple aryl halides,[791] while sterically hindered alkyl and aryl halides are virtually inapplicable for this process. In 2006, Fürstner *et al.*[792] developed an original approach based on heterocyclic interconversion of oxazolinium salts under the action of aromatic amines. However, they described only two examples of synthesis of imidazolium salts with sterically crowded N-mesityl and N-diisopropylphenyl (DIPP) groups. Subsequently only few such salts were prepared by this method and were used to synthesize metal complexes, including ruthenium carbene complexes.[793, 794] A later study of the reaction of N-mesityl-substituted oxazolinium Fürstner salt **16.11** with dinucleophilic arylamine **16.1a** (Scheme 314) provided a new type of functionally substituted precursors of the NHC ligands.[795]

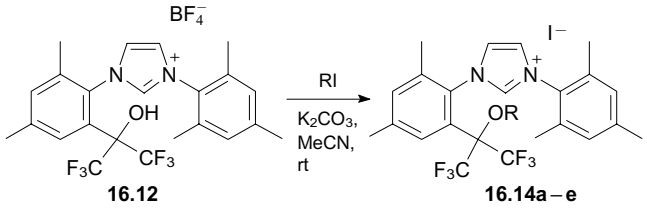
The reaction proceeds in the presence of Brønsted acids (HBF_4) and affords a mixture of the expected hydroxyl-containing imidazolium salt **16.12** with the tricyclic product **16.13** in 10 : 1 ratio (see Scheme 314). The formation of product **16.13** is apparently due to the fact that an additional opportunity for heterocyclization at the hydroxyl group arises during the reaction. Salt **16.12** is easily isolated in a pure state in a reasonable yield, even in amounts of tens of grams, by single recrystallization from a chloroform – diethyl ether mixture.

Scheme 314



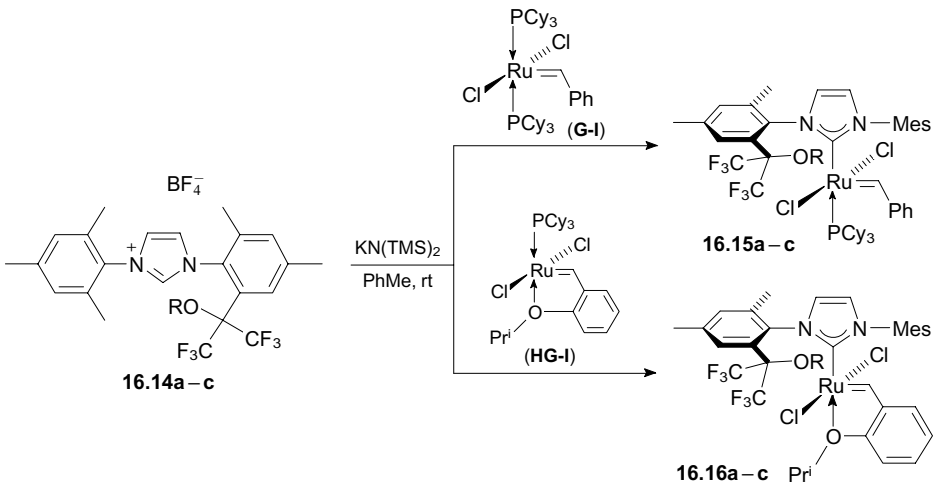
The presence of a free hydroxy group in imidazolium salt **16.12** stimulated studies of the possibility of its direct functionalization. For this purpose, salt **16.12** was treated with an excess of potassium carbonate in the presence of methyl iodide (2 equiv.) at room temperature, which led to the selective formation of O-methylated product **16.14a** in a high yield. The chosen conditions also proved to be optimal for other alkyl iodides such as ethyl, butyl and isoamyl iodides and ethyl iodoacetate (Scheme 315).

Scheme 315



RI	Product **16.14**	Yield (%)
MeI	**a**	92
EtI	**b**	83
Am^iI	**c**	70
Bu^nI	**d**	74
ICH_2CO_2Et	**e**	71

Scheme 316



Compound	R	Yield of **16.15** (%)	Yield of **16.16** (%)
a	Me	53	57
b	Et	52	51
c	Am^i	46	50

Like imidazolinium salts **16.6** and **16.8**, unsaturated analogues **16.14a – c** were also used as precursors of NHC ligands for the synthesis of ruthenium complexes *via* replacement of the tricyclophosphine ligand in the commercially available **G-I** and **HG-I** catalysts. In all cases, the reactions were conducted at room temperature and were completed in 2 h, giving products **16.15a – c** and **16.16a – c** in reasonable yields [796] (Scheme 316).

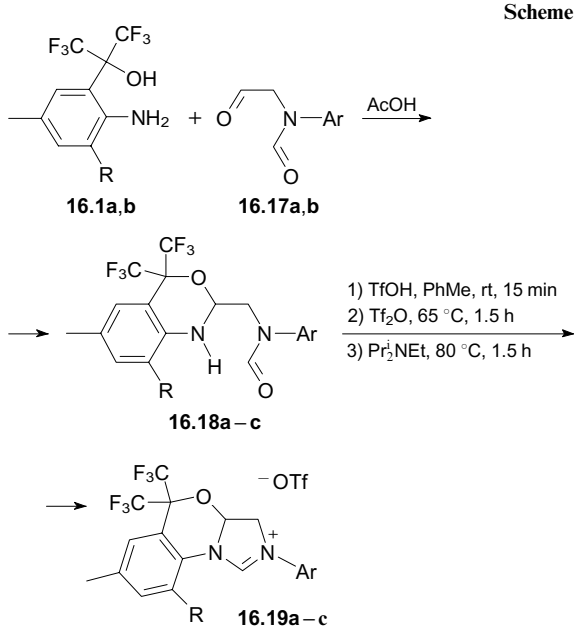
16.3. Ruthenium alkylidene complexes with sterically rigid NHC ligands

As noted above, upon the reaction of Fürstner salt **16.11** with aniline **16.1a,** apart from the OH-containing imidazolium salt **16.12**, the formation of unusual side product **16.13** was observed (see Scheme 314). The rigid tricyclic structure of the latter appeared interesting for the design of the corresponding ruthenium complexes and for studying their catalytic activity.

After several unsuccessful attempts to change the pathway of the reaction of compounds **16.11** and **16.1a** towards predominant formation of product **16.13** by varying the reaction conditions, an alternative two-step synthesis to this product as the triflate salt was found (Scheme 317). The method includes condensation of anilines **16.1a**,**b** with readily accessible N-aryldialdehydes **16.17a**,**b** [797, 798] with selective formation of the corresponding benzoxazines **16.18a – c**. The subsequent intramolecular heterocyclization upon the covalent activation of the keto group under conditions selected for the preparation of salts **16.6** (see Scheme 311) affords target tricyclic products **16.19a – c** in high yields.[799]

The resulting triflate salts **16.19a – c** proved to be efficient NHC-precursors, generation of which under standard

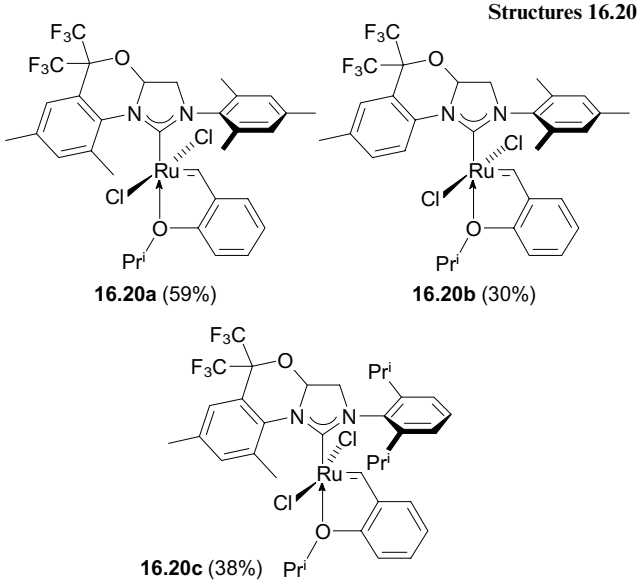
Scheme 317



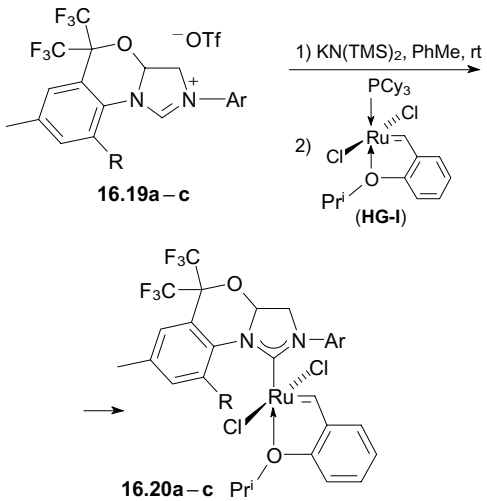
16.1: R = Me (**a**), H (**b**); **16.17**: Ar = Mes (**a**), DIPP (**b**)

Compound	R	Ar	Yield of **16.18** (%)	Yield of **16.19** (%)
a	Me	Mes	80	75
b	H	Mes	62	82
c	Me	DIPP	71	98

Structures 16.20



Scheme 318



conditions in the presence of phosphine-containing complexes **HG-I** ends in the formation of ruthenium carbene complexes **16.20a – c** (Scheme 318).

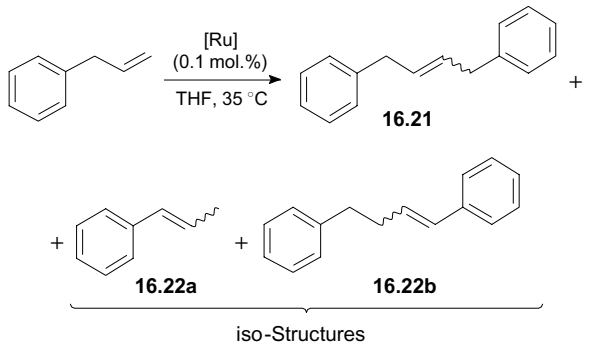
16.4. Catalytic activity of the obtained complexes

The influence of structural and electronic features of unsymmetrical fluorinated NHC ligands on the catalytic activity of new ruthenium carbene complexes was studied in classical model reactions of intra- and intermolecular olefin metathesis such as ring closing metathesis (RCM) involving diallyl- and allylmethallylmalonates and cross metathesis (CM) of allylbenzene with 1,4-diacetoxybut-2-ene. Commercially available second-generation Grubbs (**G-II**) and Hoveyda – Grubbs (**HG-II**) catalysts, which are used most often in transformations of this type, were chosen as reference compounds. As a result, it was found that the activity of the new complexes is comparable with (and in some cases, is higher than) the activities of the reference catalysts.[784, 788, 789, 796, 799] In particular, fluoroalkyl-containing phosphine-free complexes with a mono-*ortho*-aryl substituent in the NHC ligand (**16.10b**,**c**) demonstrate unusually high initiation rate in the CM reaction involving

allylbenzene, with the conversion being higher than that for **HG-II** by more than 10%.[788] Phosphine-containing complexes with unsaturated NHC ligands **16.15a – c** proved to be much more active in the RCM involving diallyl- and allylmethallylmalonates[796] than their symmetrical analogue **G-II**.

The most interesting activity was demonstrated by complexes **16.20a – c** with sterically rigid NHC ligands in the homometathesis of allylbenzene.[799] Most of available **G-II** and **HG-II** catalysts induce isomerization of both the starting allylbenzene and the metathesis product during the reaction, due to easy migration of the double bond, thus giving an inseparable mixture of isomeric products.[800, 801] It was found that complexes **16.20a – c** virtually do not cause

Scheme 319



Scheme 320

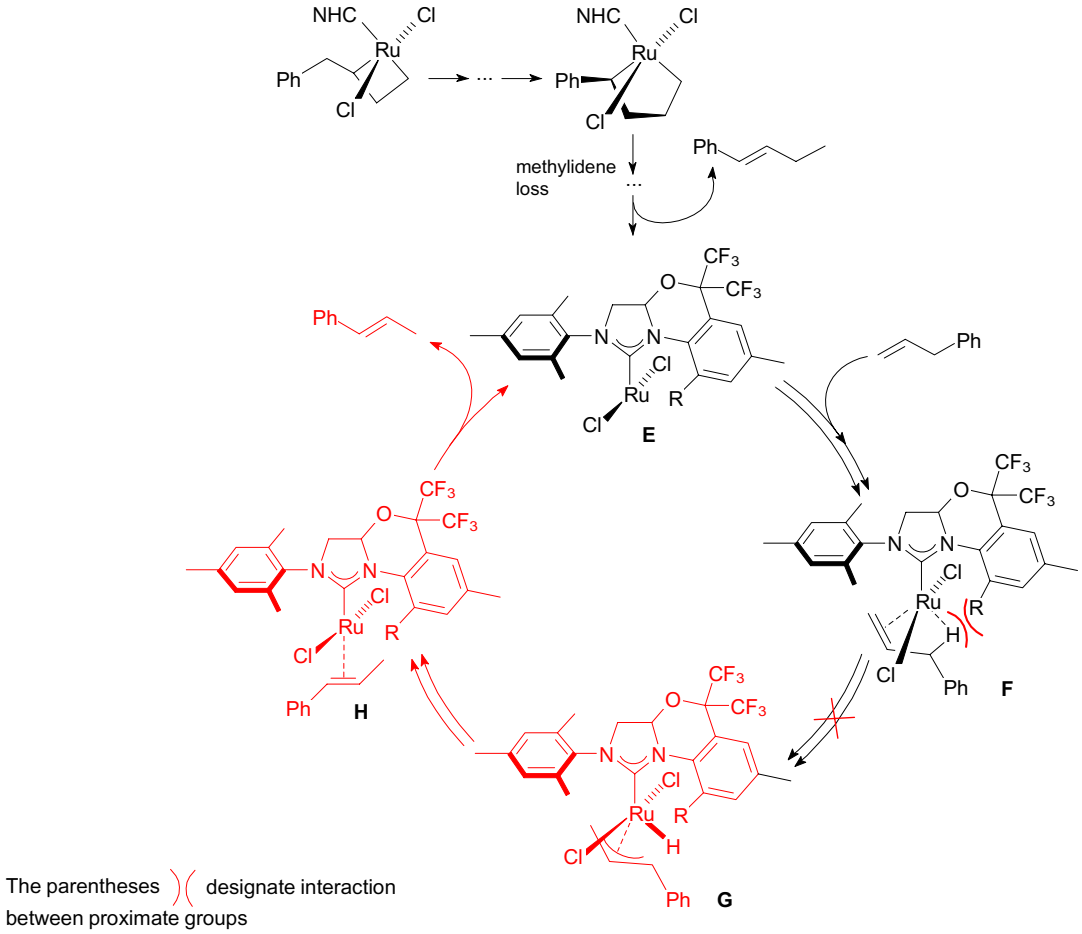


Table 2. Catalysis of homometathesis of allylbenzene by Ru complexes (see Scheme 319).[799]

Ru catalyst	Time /h	Conversion (%)	Yield of **16.21** (%)	Yield of **16.22a,b** (%)	**16.21** : **16.22a,b**
HG-II	1	88.0	83.8	16.1	5
HG-II	4	98.1	76.4	23.6	3
16.20a	1	76.1	**99.9**	**0.1**	**760**
16.20a	4	81.3	99.6	0.4	270
16.20b	1	75.3	**99.9**	**0.1**	**752**
16.20b	4	82.3	98.8	1.2	81
16.20c	1	74.3	99.2	0.8	123
16.20c	4	80.1	98.9	1.1	88

Note. Conditions: THF as solvent, the allylbenzene concentration was 3 mol litre^{-1}; the conversion and the yields were determined by ^{1}H NMR spectroscopy and GC/MS; the *E*- to *Z*-isomer ratio was in the range from 4 : 1 to 5 : 1 in all cases.

the isomerization in this process and show high selectivity and high yields of the target homometathesis product **16.21** (Scheme 319, Table 2).

The observed selectivity may be related to the rigid structure of the NHC ligand, which ensures the proximity of its aromatic part to Ru. This hampers isomerization by the known hydride pathway, which is considered to be the most likely mechanism for this undesirable transformation.[802] The mechanism of isomerization yielding compounds **16.22a**,**b** (see Scheme 319) includes decomposition of the catalytic species *via* the formation of ruthenacyclopentane followed by the loss of the methylidene group to give intermediate **E** (Scheme 320). The subsequent coordination of complex **E** to allylbenzene initiates double bond isomerization along the **F** → **G** → **H** pathway to give a side product. The rigid structure of the tricyclic ligand can prevent the hydride ion transfer with the formation of intermediate **H**, thus preventing isomerization of allylbenzene. A similar mechanism can also be implemented in the case of isomerization of homometathesis product **16.21**.

Thus, effective methods were developed for the synthesis of unsymmetrical 1,3-bis(aryl)-4,5-dihydroimidazolium salts and their unsaturated analogues containing a bulky hexafluoroisopropylalkoxy group in the *ortho*-position of one of the N-aryl substituents. The resulting salts proved to be unique precursors of the corresponding N-heterocyclic carbenes, which made it possible to prepare quite a few new alkylidene ruthenium complexes with unsymmetrical fluorine-containing NHC ligands. Most of the synthesized complexes demonstrated high catalytic activity, which was comparable with and, in some cases, higher than the activity of the commercial Grubbs II and Hoveyda – Grubbs II catalysts in the model intra- and intermolecular olefin metathesis. The structural and electronic features of the obtained complexes, which are associated, first of all, with the unsymmetrical structure of the NHC ligand and the presence of a bulky functional trifluoromethyl-containing group near the Ru site, endow them with high stability both in the solid state and in solution and enable fast tuning of their catalytic properties. Generally these results can be used in the design and synthesis of new selective catalysts of olefin metathesis.

17. Fluorinated quinolines and their aza-analogues

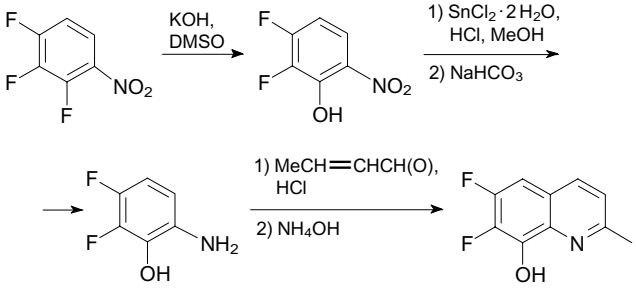
The enhanced interest in fluorinated quinoline derivatives is due to the fact that the introduction of fluorine atoms into the benzazine ring enhances the biological activity and gives rise to other useful properties.[803] The medicinal applications of these compounds include the antimalarial agent fluoroquin, the antitumour drug Brequinar®, the drug flosequinan relaxing the smooth muscles of arteries and veins and, undoubtedly, modern antibacterial agents with broad spectrum of action — fluoroquinolones.[804, 805] A number of fluorine-containing quinolines are used in agriculture and in technology, for example, as components of liquid crystal mixtures.[806] It is also known that by introducing a fluorine atom into the benzene ring, it is possible to tune the colour and emission intensity of aluminium complexes with 8-hydroxyquinolines.[807]

In recent years, fluorinated aza-analogues of quinolines — quinazolines and quinoxalines — have attracted increased interest.[808] The expediency of studies aimed at the synthesis of new fluorinated quinolines and the prospects for the search for new pharmaceutical drugs among these compounds are evidenced by biological activity data for fluoroquinazolinones.[809 – 814] Many fluorine-containing quinazolines show high antiviral and antifungal activities and possess anti-arteriosclerotic and anti-inflammatory properties. Compounds with neuroprotector properties, effective for treatment of degenerative changes in the central nervous system, were identified. Products with high antitumour activity were found among annulated quinazolines.[815] Fluorine-containing benzodiazines are promising for agriculture and technology, for example, as light-sensitive materials, dyes and thermally-resistant oligomers.[806]

17.1. Fluorinated quinolines

Published data on approaches to the synthesis of fluoroquinolines and their most significant derivatives, exhibiting various types of biological activity, have been summarized.[803, 806] A key method for the synthesis of quinolines containing fluorine atoms in the benzene ring is cyclocondensation of *ortho*-unsubstituted aniline with reagents containing an active three-carbon moiety. 6,7-Difluoro-8-hydroxy-2-methylquinoline (**17.1**) was synthesized for the first time by transformations of 2,3,4-trifluoronitrobenzene (Scheme 321). 2,3-Difluoro-6-nitrophenol was reduced with $SnCl_2$, and the resulting aminodifluorophenol was introduced into the Skraup reaction with crotonaldehyde.[816]

Scheme 321



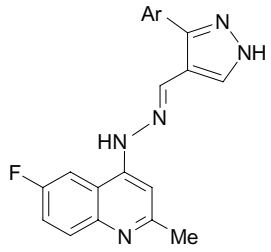
17.1 (51%)

The synthesis of fluorinated 4-phenylquinolines by the reaction of 3- or 4- fluoroaniline with PhCH=CHC(O)R (R = H, *p*-Tol) catalyzed by AgOTf and TfOH was developed.[817] Selective trifluoromethylation of 6-fluoroquinoline at position 2 by treatment with trimethyl(trifluoromethyl)-silane in the presence of trifluoroacetic acid, KHF_2 and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidine at room temperature was described.[818]

Compounds possessing antituberculosis activity were found among hydrazones **17.2**. In particular, according to *in silico* molecular docking data, compound **17.2** with Ar = 3-ClC_6H_4 [the minimal inhibitory concentration (MIC) is 12.5 μg ml^{-1}] is characterized by strong binding to cytochrome P450 type enzymes (CYP121) and thymidine monophosphate kinase (TMPK) from *Mycobacterium tuberculosis*.[819] 3-Fluoro-6-methoxyquinoline **17.3** is a new non-fluoroquinolone bacterial topoisomerase II and IV inhibitor.[820] 2-Diarylpyrazolyl-substituted 6-fluoroquinoline **17.4** was shown to be active against the Dengue virus.[821]

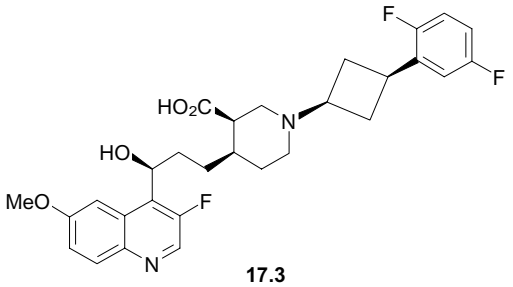
4-(*p*-Chlorophenyl)-3-(*m*-cyanophenylsulfo)-7-fluoroquinoline **17.5** behaves as an allosteric modulator of the gluta-

Structures 17.2 – 17.11

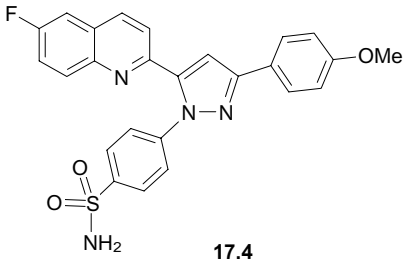


17.2

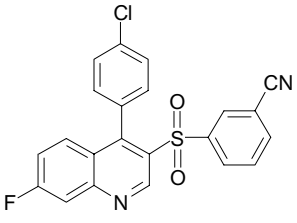
Ar = RC_6H_4 (R = H, 4-F, 4-Cl, 4-Br, 4-OMe, 4-Me, 3-Cl)



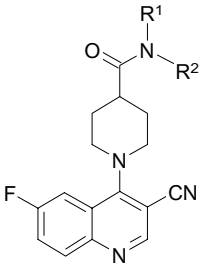
17.3



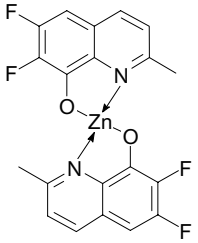
17.4



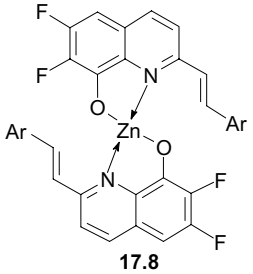
17.5



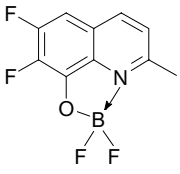
17.6 (R^1, R^2 = Alk)



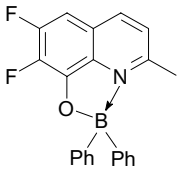
17.7



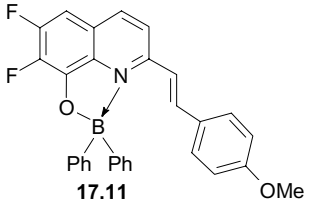
17.8



17.9



17.10

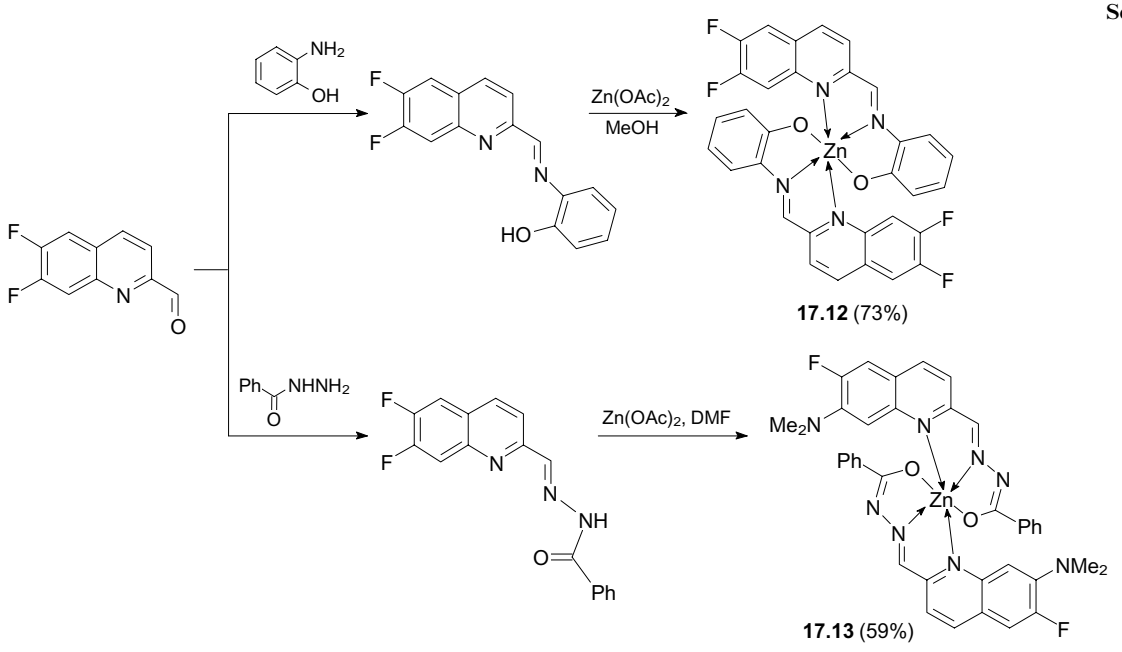


17.11

mate receptor mGluR5, which prompts the use of this compound as an antidepressant drug.[822] 6-Fluoro-4-piperidinoquinoline-3-carbonitrile derivatives **17.6** are promising for the treatment of some diseases of the central nervous system, as they show properties of muscarinic receptor M_4 positive allosteric modulators.[823]

Some fluorine-containing quinolines proved to be useful structural components for the design of new materials. Alapour *et al.*[824] investigated the structure and photophysical properties of a number of 4-arylethynyl-2,8-bis(trifluoromethyl)quinolines and concluded that the introduction of a fluorine atom increases the flexibility of the

Scheme 322



17.12 (73%)

17.13 (59%)

molecule and decreases the number of intermolecular contacts, thus enhancing the blue emission.

Complex **17.7**, prepared by the reaction of 8-hydroxy-2-methyl-6,7-difluoroquinoline (**17.1**) with zinc acetate in aqueous DMF on heating, is characterized by green fluorescence at (λ_{fl}) 522 nm.[825] On the basis of quinoline **17.1**, 2-styryl derivatives and their zinc complexes **17.8** were synthesized. The introduction of fluorine atoms into the benzene ring of the complex induces a blue shift of the emission maximum, whereas the introduction of fluorine into the ligand structure leads to the red shift of the emission peak.[816] New N,O-bidentate difluoro- and diphenylborate complexes **17.9** – **17.11** with a five-membered chelate ring were obtained from 8-hydroxy-2-methyl- and 8-hydroxy-2-styrylquinolines; diphenylborate complex **17.10** shows the most intense fluorescence.[826]

Zinc complexes **17.12** and **17.13** (Scheme 322) based on N,N,O-tridentate ligands, hydroxyazomethines and (6-fluoro-7-dimethylaminoquinolin-2-yl)methylenebenzohydrazide, also exhibited photoluminescence, the intensity of which markedly increased at low temperature.[827, 828]

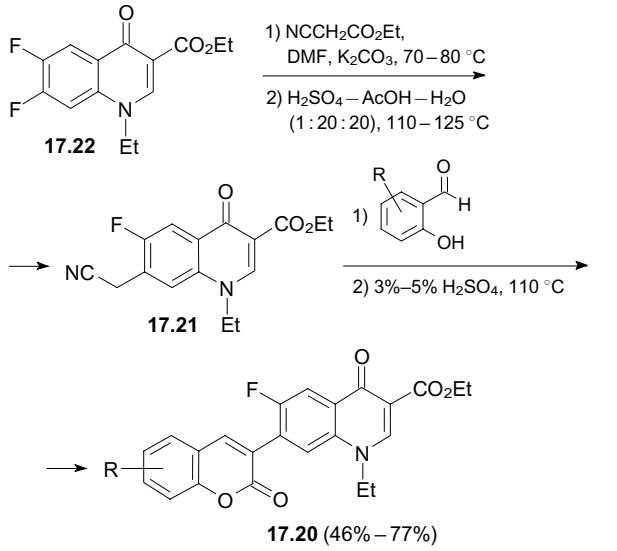
17.2. Fluoroquinolones

During as long as three decades, fluoroquinolones have retained the status of the most active synthetic antibacterial chemotherapeutic agents and are still attracting attention of researchers.[804] Numerous studies were performed in recent years in the field of both bicyclic 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid derivatives and annulated fluoroquinolones. Dual action antibiotics — heterodimers composed of fluoroquinolones and other antibacterial agents — are being actively developed;[829] studies of fluoroquinolones with other types of biological activity (antifungal, antiviral and antitumour activities) are in progress.[830]

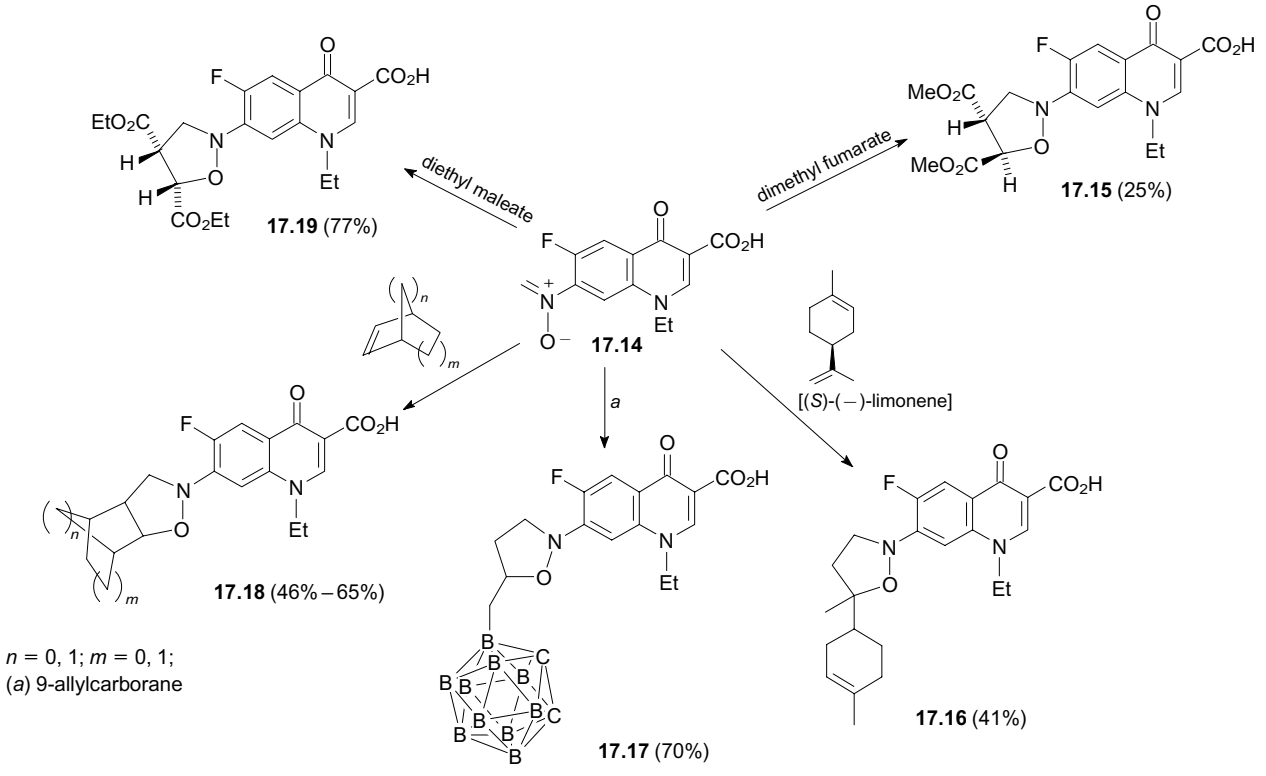
1,3-Dipolar cycloaddition is an efficient strategy for structural modification of 6-fluoro-4-quinolone-3-carboxylic acids, since this makes it possible to introduce various heterocyclic moieties into position 7. In particular cycloaddition of azomethine oxide **17.14** to alkenes proceeds regio- and stereoselectively to give diverse 7-isoxazolidinoquinolones **17.15** – **17.19** (Scheme 323).[831 – 833]

A method was developed for the synthesis of new 7-coumarinylfluoroquinolones **17.20** comprising the aldol condensation of 7-cyanomethylfluoroquinolone **17.21** (obtained from 6,7-difluoro derivative **17.22**) with aromatic hydroxyaldehydes and intramolecular cyclization on heat-

Scheme 324



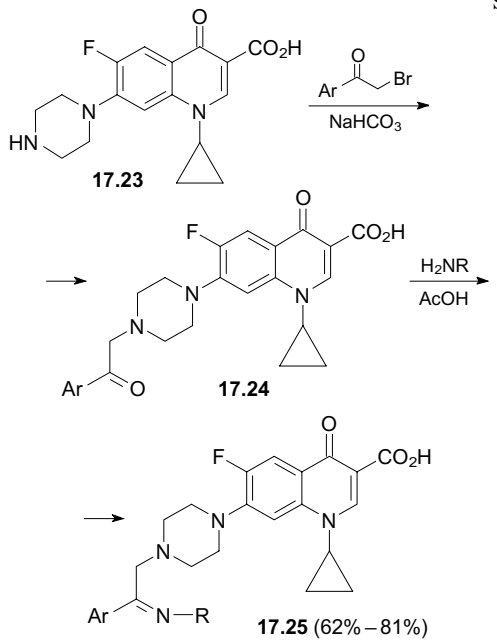
Scheme 323



ing in acid medium (Scheme 324). Fluoroquinolone **17.20** containing 8-ethoxy-substituted coumarin showed the highest activity towards the mycobacterium strains $H_{37}R_V$, *Avium* and *Terrae* and a clinical multidrug resistant strain (MIC = 0.7 – 1.5 μg ml^{-1}).[834]

Modification of ciprofloxacin by alkylation of compound **17.23** with bromoacetophenone derivatives and subsequent reaction of intermediates **17.24** with N-nucleophiles gives fluoroquinolones **17.25** (Scheme 325).[835]

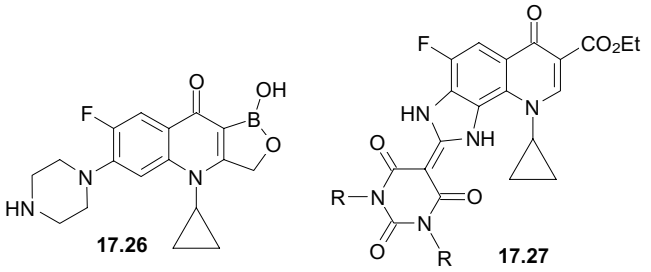
Scheme 325



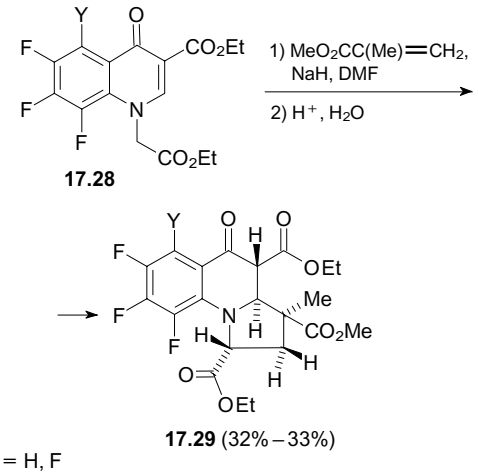
Methods for the preparation of original fused fluoroquinolones have been reported. For example, tricyclic oxaborole-[*b*]fused fluoroquinolone **17.26** was synthesized from 3-bromo-2-hydroxymethylquinolone and trimethoxyborane.[836] Imidazo-[*h*]fused fluoroquinolones **17.27** were prepared by cyclocondensation of 7,8-diamino-6-fluoroquinolone with 5-bis(ethylthio)methylenebarbituric acids.[837]

Most attention was devoted to the synthesis of new [*a*]- and [*i*,*j*]fused fluoroquinolones.[838, 839] We employed the reaction of 1-ethoxycarbonylmethylquinolones **17.28** with methyl methacrylate in the presence of sodium hydride to propose a synthesis of pyrrolo-[*a*]fused fluoroquinolones **17.29** (Scheme 326).[840]

Structures 17.26, 17.27



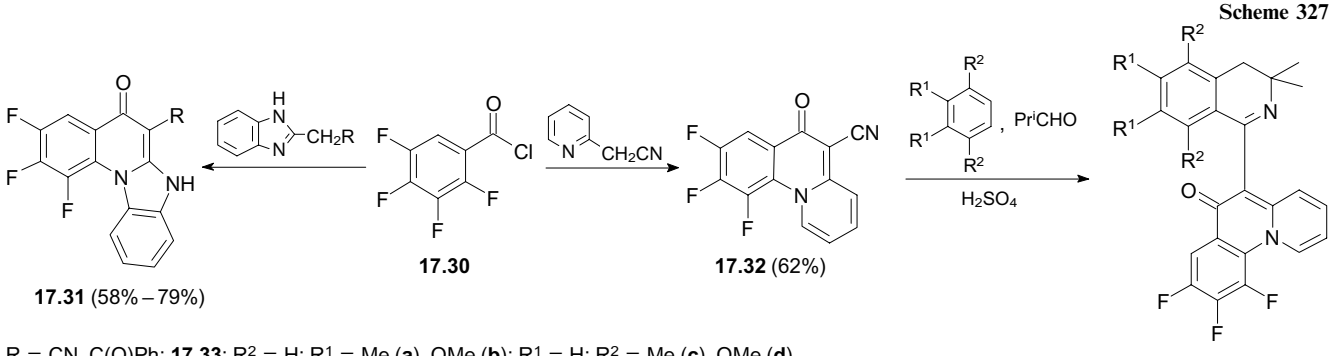
Scheme 326



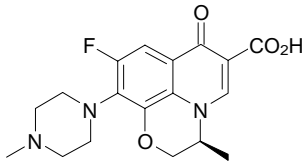
The reaction of *o*-fluorobenzoyl chloride (**17.30**) with C,N-dinucleophiles (2-cyanomethyl- and 2-benzoylmethylbenzimidazoles and 2-cyanomethylpyridine) results in [*a*]fused quinolones **17.31** and **17.32** (Scheme 327).[841 – 844] 3,4-Dihydroisoquinolines **17.33** containing the 8,9,10-trifluoro-6*H*-pyrido[1,2-*a*]quinolin-6-one moiety were synthesized by the three-component reaction of arenes, isobutyraldehyde and fluoroquinolone **17.32** in sulfuric acid (see Scheme 327).[845]

One of the best known [*i*,*j*]fused fluoroquinolones is levofloxacin.[804] A series of studies is devoted to the kinetic resolution of racemic 2-methylbenzoxazine and other heterocyclic amines.[846 – 849] Racemic (*R*,*S*)-7,8-difluoro-3-methyl-2,3-dihydro-4*H*[1,4]benzoxazine was separated using naproxen, N-sulfonyl-substituted (*R*)-proline and (2*S*)-(6-methoxy-2-naphthyl)propionyl chloride. The opti-

Scheme 327



Structure of levofloxacin



cally active *S*-isomer of 2-methylbenzoxazine obtained by this method was used for the synthesis of levofloxacin.[846]

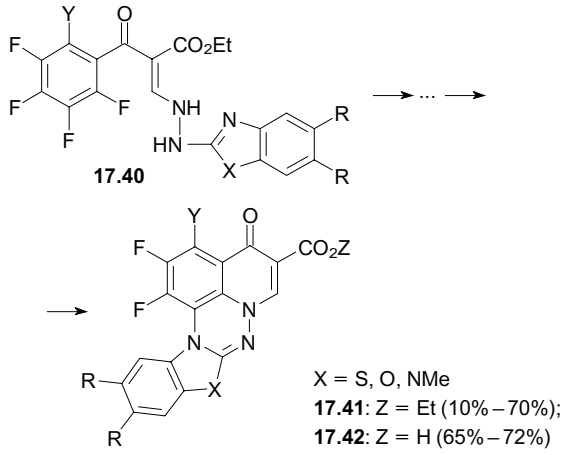
The condensation of 2-(polyfluorobenzoyl)-3-ethoxyacrylates **17.34** with hydrazides, thiosemicarbazides and amidrazones as 1,4-difunctional nucleophiles *via* the formation of compounds **17.35** and **17.36** resulted in the synthesis of [*i*,*j*]fused fluoroquinolones **17.37** (Scheme 328).[850 – 853]

Derivatives exhibiting antibacterial and tuberculostatic activities were detected among the tricyclic fluoroquinolones **17.38** and **17.39**.[854 – 856] Compound **17.37** (X = S, Y = F, R = pyrrolidino) showed the highest antitumour activity and was selected by the US National Cancer Institute (NCI) for the *in vivo* hollow fibre assay.[857]

The cyclocondensation of 2-polyfluorobenzoylacrylates **17.40** containing 2-hydrazinobenzazole residues in position 3 can be used to perform the [*i*,*j*]annulation of the quinoline core with the benzazolotriazine moiety (Scheme 329). It should be noted that pentacyclic compounds **17.41** and **17.42** are characterized by long-range spin – spin coupling constants ^{7}J(F,F) and ^{6}J(F,H) and by considerable differences in the reactivity of the fluorine atoms in comparison with tri- and tetracyclic derivatives.[858]

Compound **17.42** (X = NMe, Y = R = F) showed the highest antitumour activity[857] and was selected for the next stage of *in vivo* tests using the xenograft model (in the OVCAR-3 and other cell lines); growth retardation for solid tumors was observed for test animals administered with a quinolone solution in comparison with control animals.[859]

Scheme 329



17.3. Aza-analogues of fluorine-containing quinolines. Fluorinated quinazolines and quinazolin-4-ones

The published data concerning different approaches to the synthesis of fluorinated quinazolines and biological activity of the most important representatives of compounds of this class have been summarized.[815, 839, 842, 844, 860, 861]

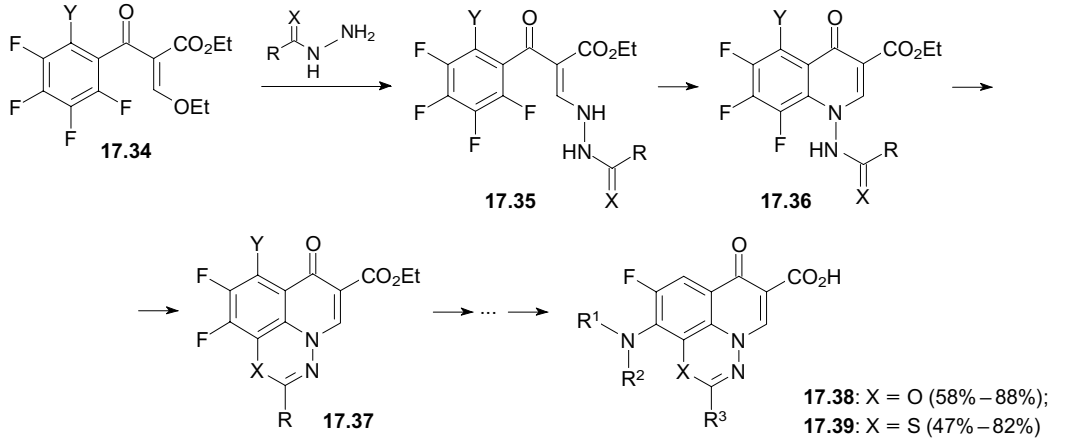
Several convenient methods were proposed for the synthesis of quinazoline derivatives containing fluorine atoms: cyclocondensation involving fluoroanthranilic acid derivatives; transformation of fluorinated 3,1-benzoxazin-4-ones to quinazolinones; and modification of substituents in the heterocycle.[815]

2-Amino-6-fluorobenzonitrile **17.43** was shown to be applicable for the synthesis of 5-fluoroquinazolin-4(3*H*)-ones (Scheme 330).[862, 863] Hydrolysis of nitrile **17.43** affords 2-amino-6-fluorobenzamide **17.44**, which was allowed to react with acid chlorides to give 2-substituted quinazolinones **17.45** or 2,6-bis(5-fluoro-1,4-dihydroquinazolin-4-on-2-yl)pyridine (**17.46**). The reaction of nitrile **17.43** with phenyl isothiocyanate gives disulfide **17.47**, the structure of which was confirmed by X-ray diffraction analysis. Heating of 2-aminonitrile **17.43** with formic acid afforded 5-fluoroquinazolin-4-one (**17.48**).

A general method was proposed for the first time for the preparation of 3*H*-quinazolin-4-ones with different numbers of fluorine atoms in the benzene ring by the reaction of *o*-fluorobenzoic acid chlorides **17.49** with S-alkylisothioureas as N,N′-dinucleophiles giving fluorine-containing 2-alkylthioquinazolin-4-ones **17.50** (Scheme 331).[864, 865]

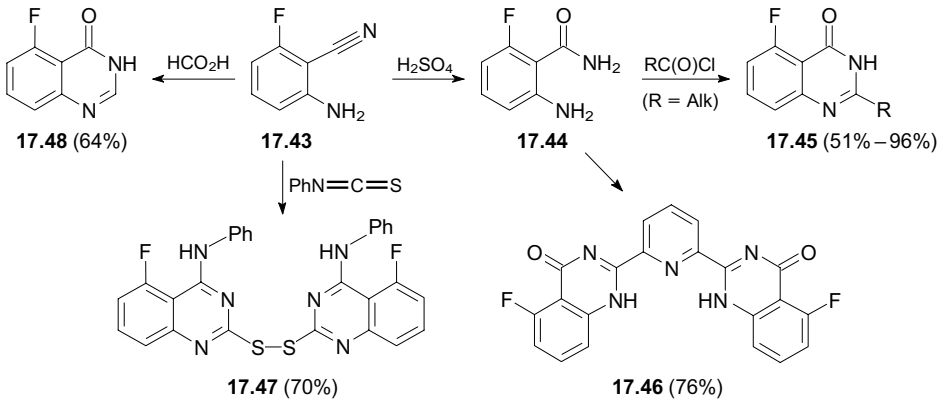
6,7,8-Trifluoroquinazolinones **17.51** and **17.52** containing phenyl substituents in position 1 or 3 were prepared by cyclocondensation of tetrafluorobenzoyl chloride **17.49**

Scheme 328

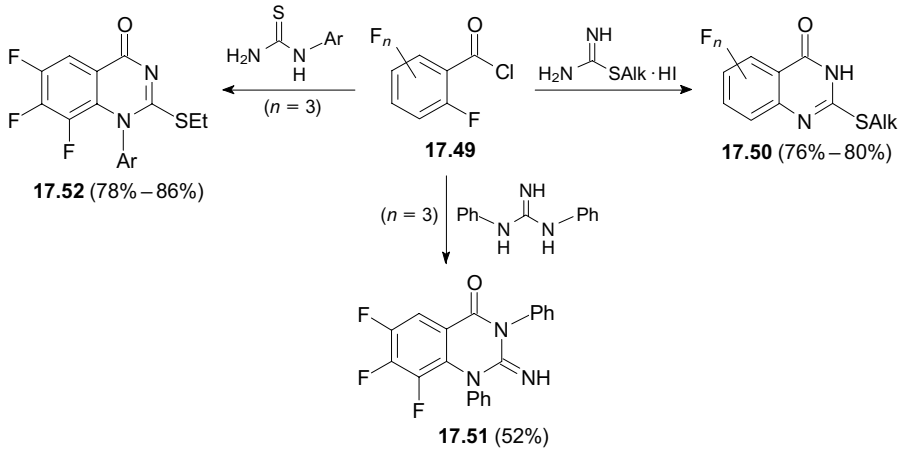


X = O, S, NH; Y = H, F; R, R^3 = Alk, 1-pyrrolidino; R^1, R^2 = Alk

Scheme 330



Scheme 331

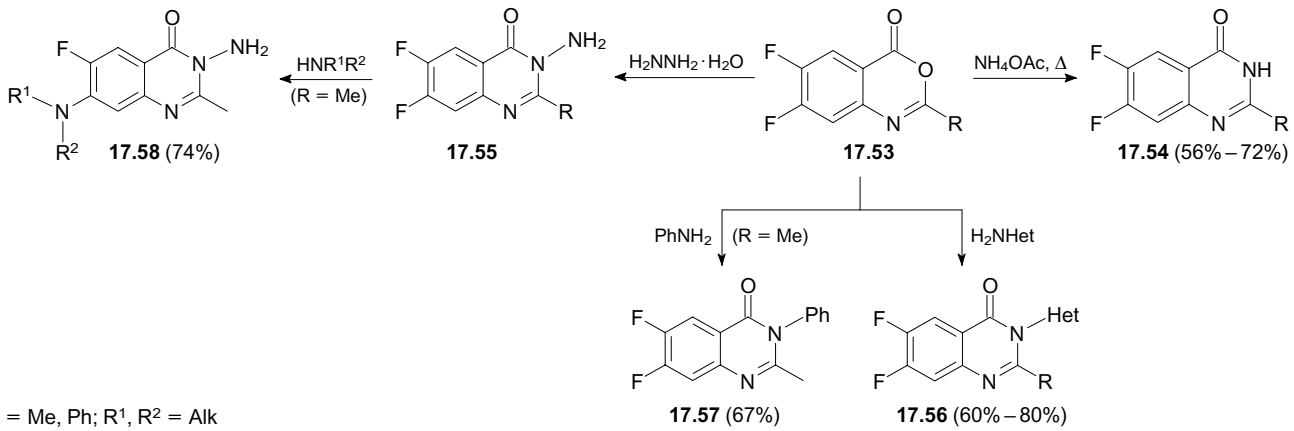


with *N*,*N*′-diphenylguanidine or *N*-(*p*-tolyl)thiourea, respectively.[865, 866]

By transformation of 3,1-benzoxazin-4-ones **17.53**, several 6,7-difluorine-substituted quinazolin-4-ones were synthesized (Scheme 332).[867] Thus fusing benzoxazinones **17.53** with ammonium acetate followed by refluxing in a KOH solution led to 3-unsubstituted difluoro-3*H*-quinazolin-4-ones **17.54**. The reaction of benzoxazinones **17.53** with hydrazine hydrate in refluxing ethanol yielded 3-amino derivatives **17.55**. Heating of compounds **17.53** with 2-aminopyridine or aniline in pyridine afforded quinazolinones **17.56** and **17.57**. Nucleophilic substitution reaction in 3-aminoquinazolinone **17.55** (R = Me) with displacement of the F atom in position 7 resulted in the synthesis of 3*H*-quinazolin-4-ones **17.58**, analogues of known DNA gyrase inhibitors.[868]

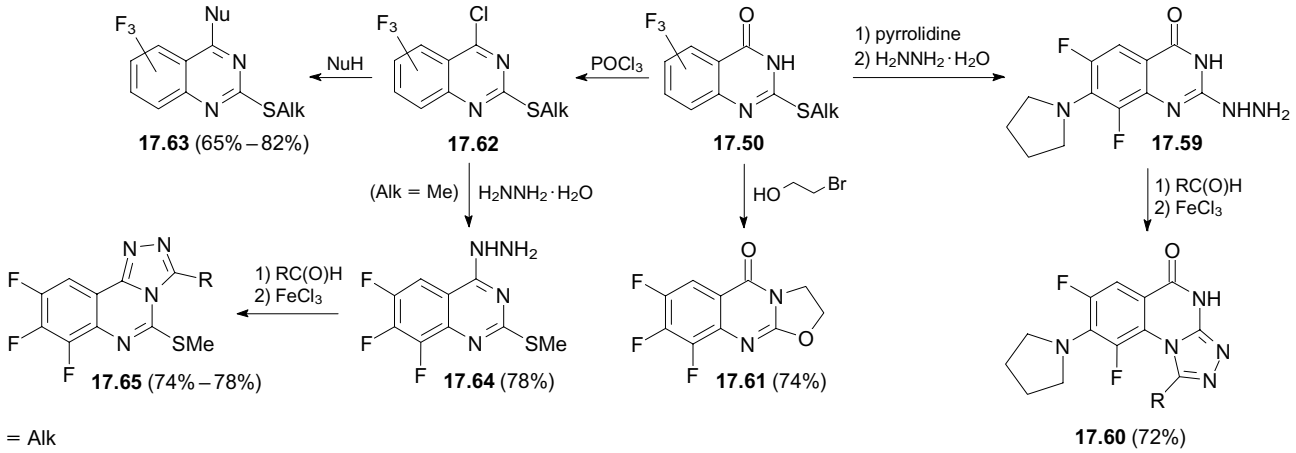
Modification of 3*H*-quinazolin-4-ones **17.50** at positions 2, 4 and 7 produces a series of new derivatives (Scheme 333).[869] The nucleophilic displacement of the halogen atom at C(7) and the SAlk group in position 2 generated compound **17.59**, which was converted to 1,2,4-triazolo[4,3-*a*]quinazoline **17.60**. The reaction of sulfide **17.50** with 2-bromoethanol involves N-alkylation and intramolecular nucleophilic displacement of the alkylthio

Scheme 332



R = Me, Ph; R1, R2 = Alk

Scheme 333



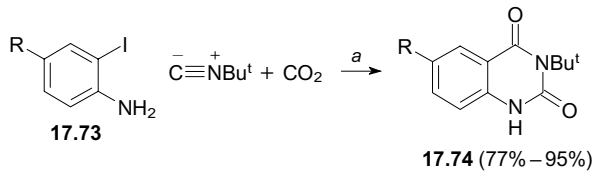
group, thus yielding 2,3-dihydrooxazolo[2,3-*b*]quinazolin-5-one system **17.61**; this was confirmed by X-ray diffraction data. Treatment of quinazolinone **17.50** with phosphorus(V) oxychloride followed by the reaction of 4-chlorinated derivative **17.62** with N- or C-nucleophiles give 4-substituted quinazolines **17.63**. The hydrazine group in position 4 of compound **17.64** enables the annulation of the quinazoline core at the [*c*]-face and gives 1,2,4-triazolo[4,3-*c*]quinazoline **17.65**.

The reactions of tetrafluorobenzoyl chloride **17.49a** with 2-aminoazoles or 2-aminoazines served for the synthesis of a series of [*a*]-annulated quinazolinones **17.66** – **17.72** (Scheme 334).[866, 870, 871]

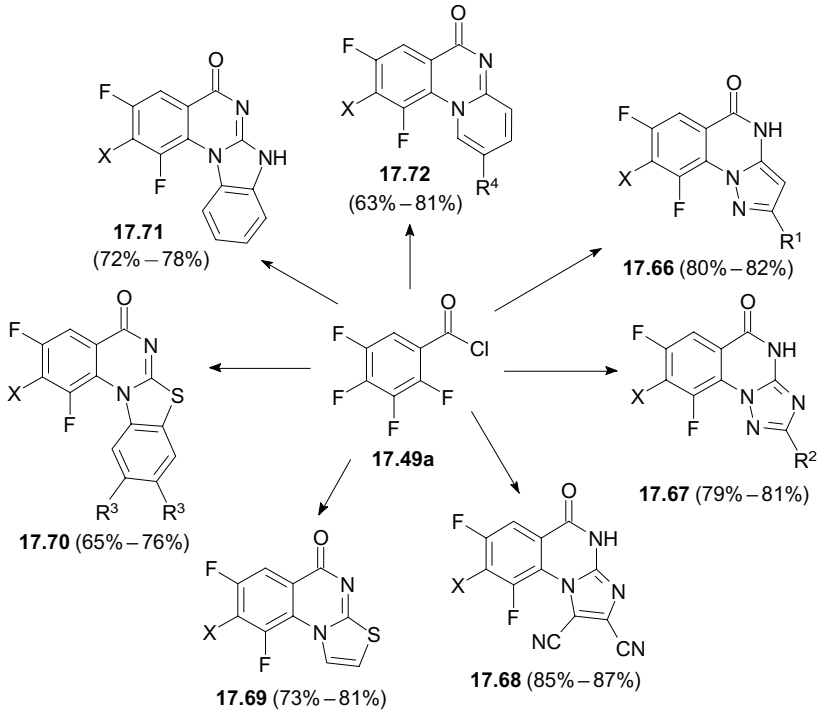
A recent publication[872] describes the conversion of iodoanilines **17.73** to fluorine-containing quinazolinones **17.74** by means of two C-building blocks, isocyanides and CO_2, under mild conditions (Scheme 335).

Compounds **17.47**, **17.52**, **17.57**, **17.58**, **17.63** , **17.66** and **17.72** possessing high tuberculostatic activity were detected among fluorine-containing quinazolines and quinazoli-

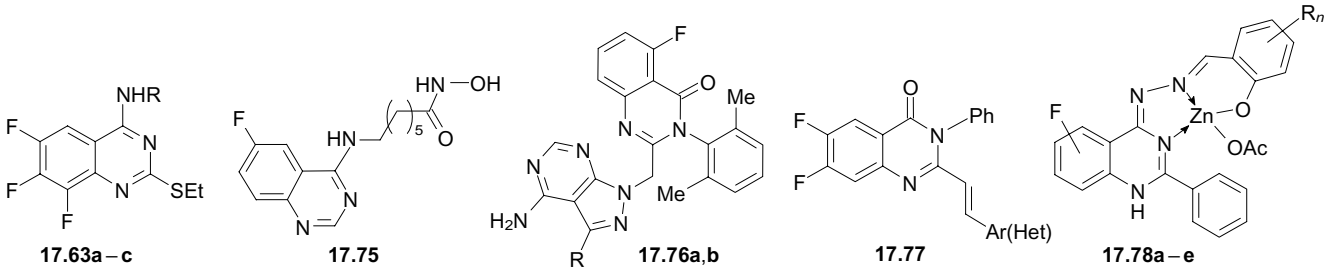
Scheme 335



Scheme 334



Structures 17.63, 17.75 – 17.78



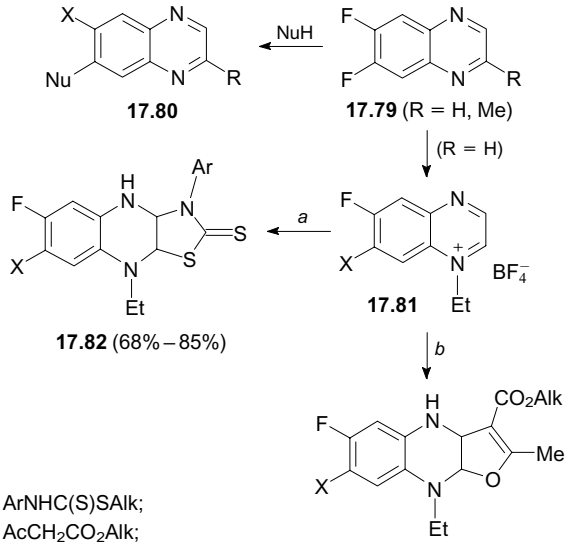
17.63a – c **17.75** **17.76a,b** **17.77** **17.78a – e**

17.63: R = Ph (**a**), 2-ClC_6H_4 (**b**), 3,4-$F_2C_6H_3$ (**c**); **17.76**: R is indol-5-yl (**a**), 3,4-dimethoxyphenyl (**b**);
17.78: 5-isomer: R_n = H (**a**), 4-OH (**b**), 3,5-Br_2 (**c**); 6- and 7-isomers: R_n = H (**d**), 5-NO_2 (**e**)

nones.[856] The minimal inhibitory concentration against the laboratory *M. tuberculosis* strain $H_{37}R_V$ was 0.36 μg ml^{-1}. 4-Arylaminoquinazolines **17.63a – c** showed a high antiviral activity against the pox virus family.[873] 6-Fluoroquinazoline **17.75** containing the hydroxamic group in position 4 was described as a new selective histone deacetylase (HDAC) inhibitor with a higher activity compared with the known SAHA agent.[813] Quinazolinones **17.76a**,**b** with a pyrazolo[3,4-*d*]pyrimidine moiety in position 2 showed a high activity as selective phosphoinositide 3-kinase PI3Kδ inhibitors [the half-maximal inhibitory concentration (IC_{50}) is 8.6 nmol $litre^{-1}$ for **17.76a** and 8.4 nmol $litre^{-1}$ for **17.76b**].[814]

A broad range of styryl derivatives **17.77** possessing fluorescent properties with an emission maximum at 410 – 540 nm in acetonitrile was synthesized starting from quinazolin-4-ones.[874, 875] Zinc complexes **17.78a – e** were prepared on the basis of 2-hydroxybenzaldehyde (2-phenylquinazolin-4-yl)hydrazones.[876] The structure of the products was confirmed by X-ray diffraction analysis (performed for compound **17.78c**) and is represented as a coordination polymer with acetate bridges and a five-coordinate zinc atom. In acetonitrile solution, these compounds exhibit blue or green photoluminescence with an emission maximum in the range of 465 – 549 nm.

Scheme 336



17.80 **17.79** (R = H, Me) **17.82** (68% – 85%) **17.81** **17.83** (72% – 86%)

(*a*) ArNHC(S)SAlk;
(*b*) $AcCH_2CO_2Alk$;
X = F, Nu (Nu is morpholino or thiomorpholino)

17.4. Fluorinated quinoxalines

Various cyclocondensations are widely used for the synthesis of quinoxalines. 6,7-Difluoroquinoxalines **17.79** were prepared by the reaction of 1,2-diamino-4,5-difluorobenzene with 1,2-dioxo compounds (Scheme 336).[839, 877] The reactions of these substrates with nucleophiles lead to displacement of one or two fluorine atoms, depending on the nature of the reagent, giving derivatives **17.80**. New approaches to the synthesis of annulated fluoroquinoxalines were developed. Quaternization of quinoxaline **17.79** and the subsequent reaction of salt **17.81** with 1,3-dinucleophiles yield thiazolo[4,5-*b*]- and furo[2,3-*b*]tetrahydroquinoxalines **17.82** and **17.83** (see Scheme 336).[878] The condensation of 2-amino-3-cyano- and 2-amino-3-(aminocarbonyl)-6,7-difluoroquinoxalines **17.84** with DMAD and $HC(OEt)_3$ generated fluorine-containing pyrido[2,3-*b*]- and pyrimido[4,5-*b*]quinoxalines **17.85** and **17.86** (Scheme 337).

A new approach to the synthesis of pyrrolo[2,3-*b*]- and indolo[2,3-*b*]quinoxalines **17.87** and **17.88** from aminoquinoxaline **17.84** was implemented, using the intramolecular substitution strategy with displacement of hydrogen in position 3.[879, 880]

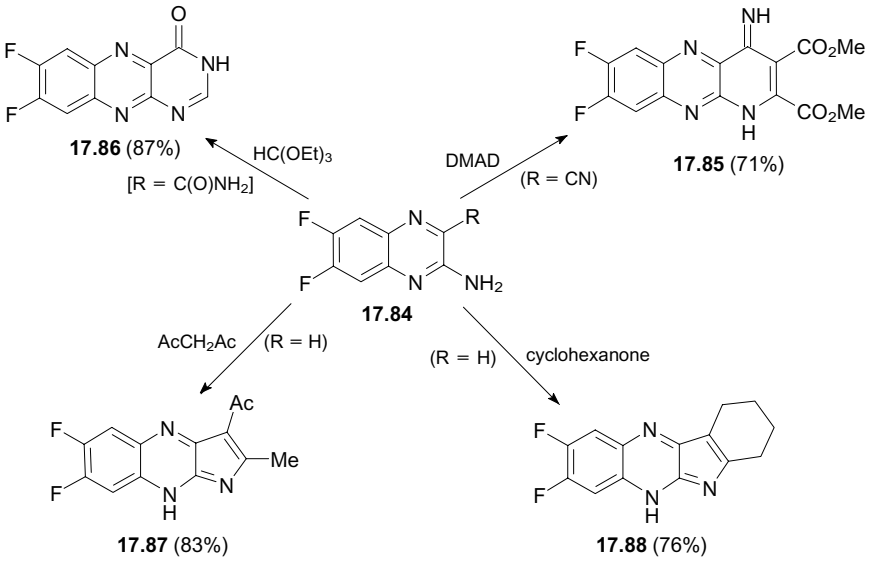
6,7-Difluoroquinoxaline 1,4-dioxides **17.89**, prepared by the transformation of 5,6-difluorobenzofuroxans **17.90** in the presence of diketones, were used as key compounds for the synthesis of new quinoxaline dioxide derivatives **17.91 – 17.94** (Scheme 338).[881]

2-Chloro-3-(cyclopentyloxy)-7-fluoroquinoxaline *N*-oxide **17.95**, synthesized by the annulation reaction of 4-fluoroaniline with 1,1,2-trichloro-2-nitroethylene followed by O-alkylation, was introduced[882] into Pd-catalyzed cross-coupling with arylboronic acids for the preparation of 2-arylquinoxaline *N*-oxides **17.96** (Scheme 339). The carbene-catalyzed aroylation of fluoroquinoxaline *N*-oxide **17.95** with aromatic aldehydes affords 2-aroylquinoxaline *N*-oxides **17.97**.[883]

6,7-Difluoroquinoxalin-2-one **17.98** reacts with resorcinol (pyrogallol), indoles, 5,5-dimethylcyclohexane-1,3-dione or 3-methyl-1-phenylpyrazol-5-one on heating in acetic acid to give substitution products at the hydrogen atom in position 3 of the pyrazine ring (compounds **17.99 – 17.102**) (Scheme 340).[884] The treatment of compounds **17.100** with *N*-methylpiperazine on heating allowed the synthesis of 7-(4-methylpiperazino) derivatives.

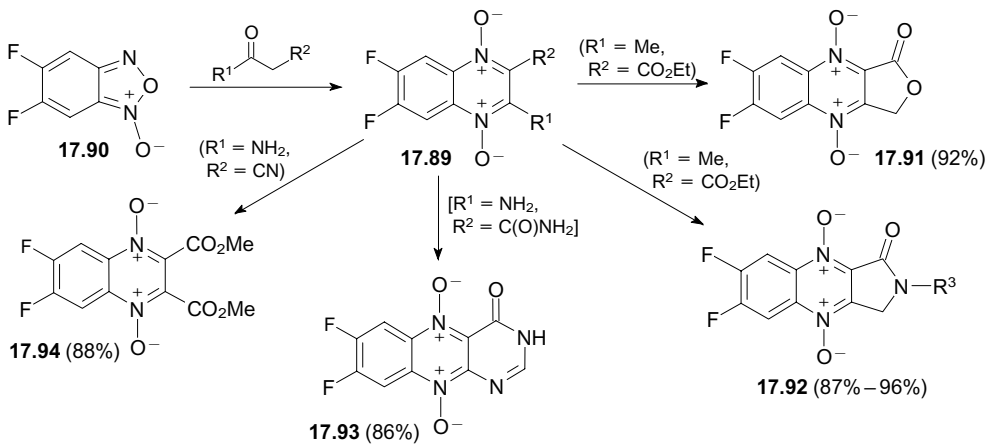
Among new fluorine-containing quinoxalines, compounds exhibiting various types of biological activity were

Scheme 337

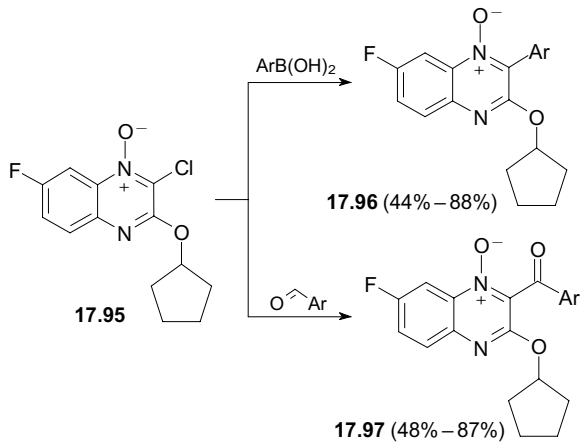


DMAD is dimethyl acetylenedicarboxylate

Scheme 338



Scheme 339



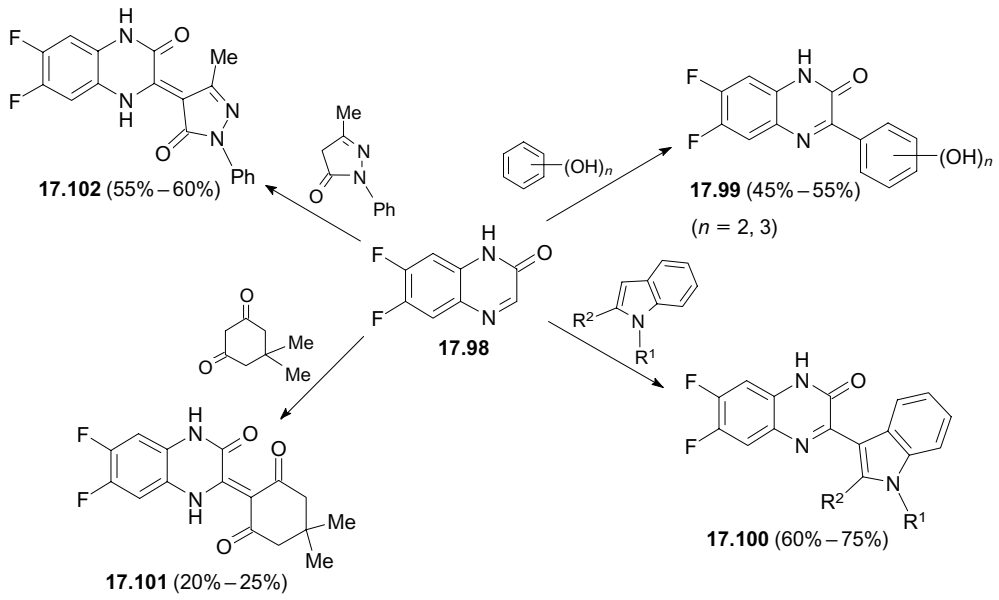
17.95: Ar = Ph, substituted phenyl, Th;
17.97: Ar = Ph, substituted phenyl, Naph, Py, Th

found. Thus 2-(2-oxo-3-phenylthioquinoxalin-1-yl)acetic acids **17.103** demonstrated high activity as aldose reductase (ALR2) inhibitors.[885] 6-Chloro-7-fluoroquinoxalines **17.104** are promising HIV inhibitors.[886] Phosphodiesterase 10A inhibitors with high activity were found among mono- and difluoroquinoxalines **17.105**.[887]

Styryl 6,7-difluoroquinoxaline derivatives **17.106** exhibit green or yellow-orange fluorescence with an emission maximum in acetonitrile at 425 – 570 nm;[888] zinc complex **17.107** based on 2-(6,7-difluoroquinoxalin-2-ylmethylidenamino)phenol shows intense red fluorescence with an emission maximum at 657 nm in 2-methyltetrahydrofuran at 77 K.[827]

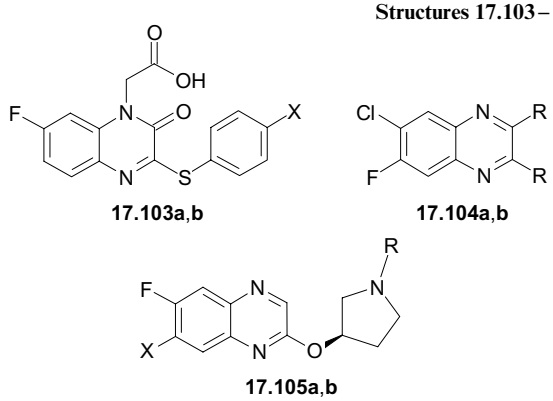
The presented analysis of published data indicates that the interest in fluorine-containing quinoline derivatives and, in general, benzazines is not only persits, but also continues to grow. New approaches to the synthesis of these compounds were developed; new medicinal agents based on them were designed; new types of biological activity were identified; the search for technological applications of these products is in progress, first of all, as photoactive compounds and luminophores. Fluorine-containing quinolines

Scheme 340



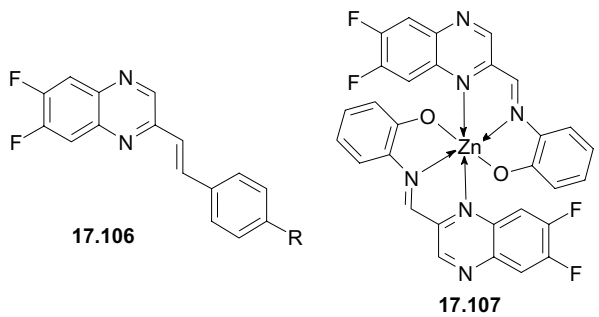
n = 2, 3; R^1, R^2 = Alk

Structures 17.103 – 17.105



17.103: X = Br (**a**), Cl (**b**); **17.104**: R = Ph (**a**), 4-FC_6H_4 (**b**); **17.105**: X = H, R = Boc (**a**); X = F, R is 6,7-dimethoxyquinazolin-4-yl (**b**)

Structures 17.106, 17.107



R = Alk, Hal, *etc.*

and benzazines are most promising; they have formed the base for the whole family of antibacterial agents and are meant for the creation of libraries of new biologically active compounds. One problem in this field that needs to be solved is extension of the possibility for their screening.

A promising line of research deals with metal complexes of fluoroquinolones as biologically active compounds and as agents for quantitative determination of fluoroquinolones and for elucidation of the role of cations in their interaction with DNA.[889]

18. Polyfluorinated 1,2-diaminobenzenes and derived aza-heterocycles for chemistry, materials science and biomedicine

Complete replacement of hydrogen atoms of arenes and hetarenes by fluorine atoms affects little their aromaticity,[890, 891] but crucially changes many other properties — physical, chemical and biological.[5, 124, 522] The molecular electrostatic potential and quadrupole moment are modified, which allows arenes and polyfluoroarenes to be involved in π-stacking interactions with each other to give $C_6H_6 \cdot C_6F_6$ type complexes important for supramolecular chemistry, crystal engineering and molecular recognition.[522, 892, 893] In place of electrophilic substitution, fluorinated derivatives are typically involved in nucleophilic substitution.[124, 522] Apart from aromatics, many other classes of organic compounds become less toxic to living organisms and acquire better metabolic stability and pharmacokinetic characteristics upon introdiction of F atoms.[5, 894] In this connection, the development of synthetic methods and study of properties of fluorinated heterocyclic compounds are relevant issues.[2 – 4, 895, 896]

Aza-heterocyclic compounds derived from 1,2-diaminobenzenes, *i.e.*, benzoannulated 1,3-diazoles (benzimidazoles), 1,2,3-triazoles, 1,2,5-chalcogenadiazoles (E = S, Se, Te), 1,4-diazines (quinoxalines), 1,5-diazepines, *etc.*, are important not only for organic chemistry and materials science,[897, 898] but also for biomedicine.[899 – 904] The synthesis, properties and practical applications of these compounds in the series of hydrocarbons are well known. However, this is not the case for fluorine derivatives. This chapter summarizes recent advances related to the synthesis of polyfluorinated 1,2-diaminobenzenes and derived aza-heterocycles and to redox properties, cytotoxicity and

apoptotic activity. These polyfunctional compounds, especially heterocycles, are of interest for chemistry, materials sciences and biomedicine.

Until recently, the number of polyfluorinated 1,2-diaminobenzenes first synthesized in the mid-20th century by reduction of the corresponding nitro derivatives was very limited.[905,906] A much more efficient method was proposed back in 1990,[907] but was further developed only in the last five years.[908–910] The method consists in *ortho*-amination of polyfluorinated anilines in which the key role is played by 2,1,3-benzothiadiazoles, a convenient protective form of 1,2-diamines, which can be easily recovered by reduction (Scheme 341). The reduction of thiadiazoles to the target diamines readily occurs on treatment with usual reducing agents such as $SnCl_2 \cdot 2H_2O$, Zn, $LiAlH_4$ and $NaBH_4$.[907–913]

If the *ortho*-positions of the carbocycle are non-equivalent, the heterocyclization is highly regioselective, being probably orbital controlled. Since only one fluorine atom is needed for ring closure, this method is applicable not only for fluorocarbon compounds, but also for hydrocarbon derivatives.[911–913]

For preparation of polyfluorinated 1,2,5-thiadiazole from the already available 1,2-diamine, SF_4 and $(PhSO_2N)_2S$ are well suited for cyclization, while $SOCl_2$ is somewhat less efficient (unlike the hydrocarbon series).[908,914,915]

The synthesis of heterocycles from polyfluorinated 1,2-diaminobenzenes is rather simple. The 1,3-diazole, 1,4-diazine and 1,5-diazepine rings are closed under the action of carbonyl compounds — carboxylic acids or aldehydes in the presence of mineral acids (Philipp method) or diketones (Körner – Hinsberg and related reactions). The 1,2,3-triazole ring is formed upon diazotization. In the case of 1,2,5-selenadiazoles, the cyclization is induced by SeO_2 and $SeCl_4$; the use of $SeOCl_2$ is also efficient. 1,2,5-Telluradiazoles were prepared using $TeCl_4$ (Scheme 342).[907–910,913,916–919]

The nucleophilic substitution typical of polyfluorinated arenes and hetarenes[124] can serve for additional functionalization of the synthesized compounds. (Note that cyclization of $Ar-N=S=N-SiMe_3$ to thiadiazoles shown in Scheme 341, which is induced by fluoride ions and involves unusual thiazylamides, $Ar-N^- -S\equiv N$,[920–922] also follows the nucleophilic substitution mechanism). In particular, one to four MeO or Me_2N groups, including their combinations, can be introduced into thia(selena)diazoles and diazines. The first and second groups regioselectively enter positions 5(6) of diazoles and 6(7) of diazines (Scheme 343). The substitution is somewhat more selective in selenadiazoles than in thiadiazoles. According to density functional theory (DFT) calculations, the regioselectivity is due to the concerted action of kinetic and thermodynamic factors of the substitution reaction.[909]

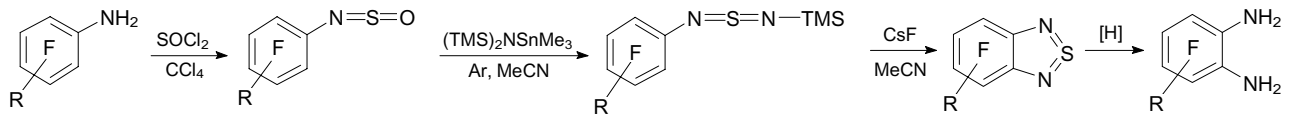
The reduction of functionalized thia(selena)diazoles may afford new diamines, which can be converted to other heterocycles, for example, compounds **18.1** and **18.2** (Scheme 344).[909,916,917]

Functionalization of 1,3-di- and 1,2,3-triazoles, 1,4-diazines and 1,5-diazepines can also involve the heterocycle, for example, they can be acylated at the nitrogen atom and give products **18.3** (Scheme 345).[913,916] 2-Substituted 1,3-diazoles **18.4** can be synthesized from 1,2-diamines. If the group R is not an alkyl, the oxidation of the intermediate Schiff base under special conditions is required.[923]

Thus, the method for the synthesis of fluorinated 1,2-diaminobenzenes and derived aza-heterocycles is exceptionally flexible. Since complete replacement of fluorine atoms converts the considered compounds from the fluorocarbon to hydrocarbon series, this approach may also be promising for the preparation of difficult-to-obtain non-fluorinated compounds — polymethoxylated, polydimethylaminated and mixed derivatives.[909] If a functional group is required, it can be introduced by nucleophilic displacement of fluorine atoms.

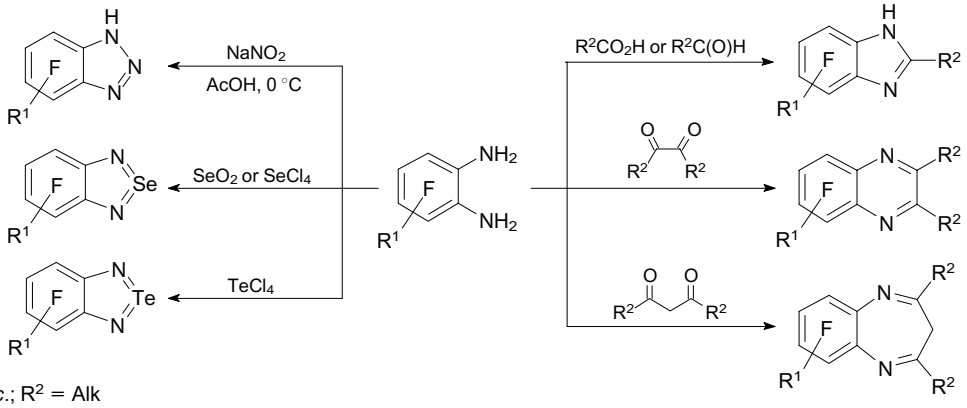
Redox-active π-heterocycles are useful in the design and synthesis of diverse molecular functional materials.[897,924,925] Polyfluorinated arenes and hetarenes have positive electron affinity; therefore, their radical anions (RAs) are thermodynamically preferred over neutral mole-

Scheme 341



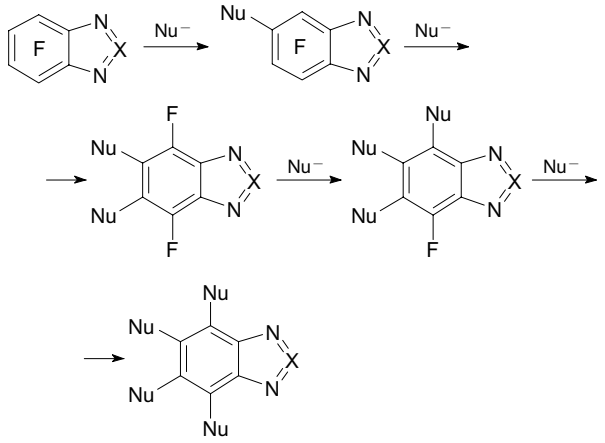
R = Alk, H, Hal, *etc*.

Scheme 342



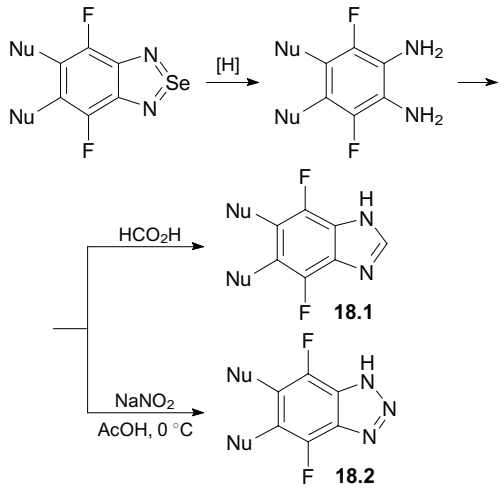
R^1 = H, Alk, Hal, *etc*.; R^2 = Alk

Scheme 343



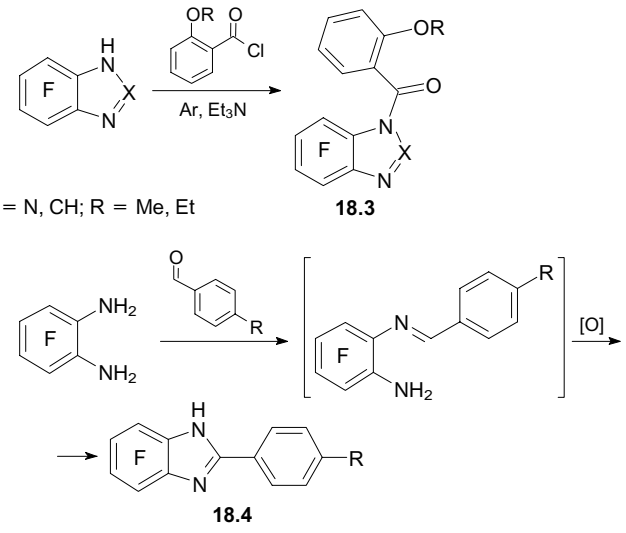
X = S, Se, HC – CH; Nu = OMe, NMe_2

Scheme 344



Nu = OMe, NMe_2

Scheme 345

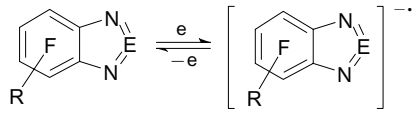


X = N, CH; R = Me, Et

R = F, Br, NO_2, OMe

cules.[926, 927] However, the RAs of compounds such as C_6F_6, $C_{10}F_8$ and C_5F_5N are very unstable in solution under ambient conditions because they either easily eliminate a fluoride ion or undergo radical recombination.[928] Conversely, the electrochemical reduction of polyfluorinated 2,1,3-benzothia(selena)diazoles and 1,4-benzodiazines under ambient conditions is, most often, reversible (Scheme 346), and their long-lived RAs were characterized by EPR spectroscopy in combination with DFT calculations. In these RAs, the single-occupied π*-molecular orbital is delocalized over the whole molecule, but the charge and spin density is largely concentrated on electron-withdrawing heterocycles and is decreased on the carbocyclic moieties, which hampers both fluoride elimination and RA recombination to give a C – C bond.[929 – 931]

Scheme 346



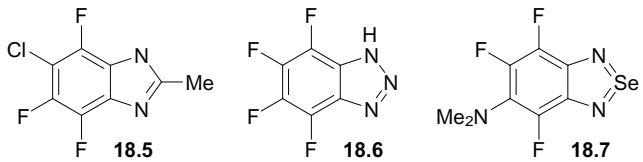
E = S, Se, HC – CH

Studies of the redox properties of other analogous fluorinated aza-heterocycles are now in progress. The possibility of using them as components of redox-active polymers and charge transfer complexes is under research.

Telluradiazoles are poorly soluble in aqueous media and, unlike thia(selena)diazoles, they tend to be hydrolyzed to diamines; therefore, they have not been considered for biomedical purposes. The properties of polyfluorinated diazepines are little studied as yet. Other synthesized aza-heterocycles, being of low toxicity towards normal cells, showed pronounced cytotoxicity and high apoptotic activity† towards laryngeal cancer cells (Hep2),[910, 916, 917] which is difficult to cure by surgery or radiation treatment.[934] No such properties are inherent in their hydrocarbon analogues.[910]

The cytotoxicity and apoptotic activity of compounds depend on the type of heterocycle and the pattern of substitution. The highest effect of low concentrations was found for diazoles, selenadiazoles and triazoles (Fig. 4, shown for compounds **18.5** – **18.7**); in the case of selenadiazoles, the cell death was already detected in the first hours

Structures 18.5 – 18.7



of the experiment. The penetration of the agent into the cells was detected by its fluorescence.[910]

† Apoptosis is programmed death of eukaryotic cells mitigating the adverse effects of drugs when involved in their action.[932, 933]

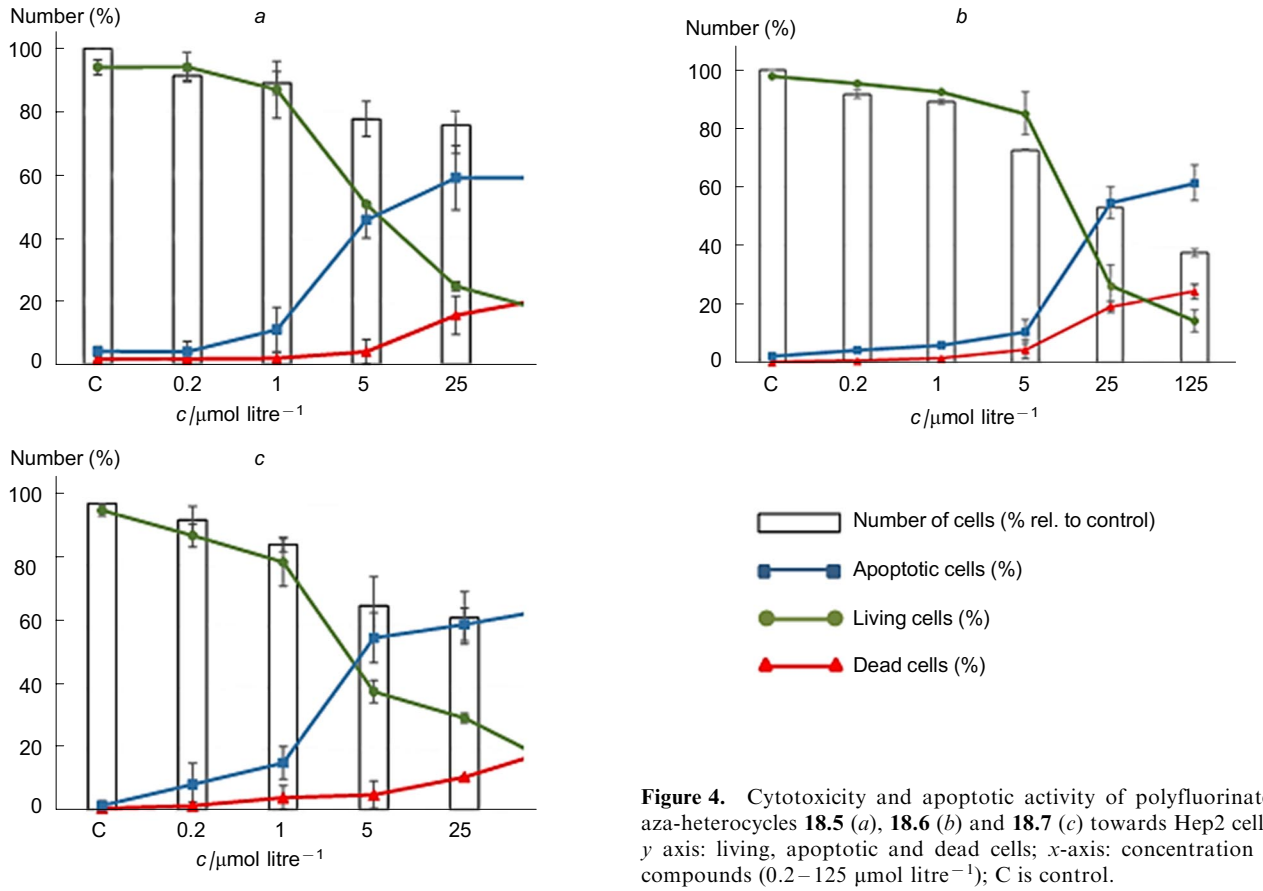


Figure 4. Cytotoxicity and apoptotic activity of polyfluorinated aza-heterocycles **18.5** (*a*), **18.6** (*b*) and **18.7** (*c*) towards Hep2 cells. *y* axis: living, apoptotic and dead cells; *x*-axis: concentration of compounds (0.2 – 125 μmol litre^{-1}); C is control.

The parent 1,2-diamines also induce apoptosis of Hep2 cells, but less efficiently than fluorinated diazoles, selenadiazoles or triazoles. The overall cytotoxic effect of heterocycle closing is that diazoles and triazoles are more toxic and thia(selena)diazoles and diazines are less toxic than the parent diamines; the diazole ring shows a more pronounced desired effect than the triazole ring.[910]

It was noted above that the cytotoxicity and apoptotic activity of compounds depend on not only the type of aza-heterocycle, but also the substituents in carbo- and heterocyclic moieties. Therefore, the choice of substituents is very important for biomedical issues. This choice can be done empirically, *e.g.*, by introducing pharmacophore groups with desired properties. However, there is also a rational approach, namely, the molecular docking approach. In particular, the structures of 1-(2-alkoxybenzoyl)-substituted diazoles and triazoles **18.3** (see Scheme 345) were selected for the synthesis relying on the results of evolutionary *in silico* modelling using libraries of chemical groups for the binding site of the PAS domain of the HIF transcription factor.[916] The cytotoxic activity of these compounds in different cancer cell lines is still under study.

In general, aza-heterocycles fused with a fluorinated benzene ring in combination with various substituents show high cytotoxicity and apoptotic activity towards cancer cells.[910, 916, 917]

Thus, an original general method was developed for the synthesis of polyfluorinated 1,2-diaminobenzenes and derived aza-heterocycles, difficult to prepare by other methods, covering benzoannulated 1,3-diazoles (benzimidazoles), 1,2,3-triazoles, 1,2,5-chalcogenadiazoles (S, Se, Te), 1,4-diazines (quinoxalines) and 1,5-diazepines functionally substituted at carbo- and heterocyclic moieties. In some cases, the method is applicable for the preparation of both fluorocarbon and hydrocarbon derivatives. The structures of typical representatives of synthesized compounds were confirmed by X-ray diffraction.[908 – 911, 916, 917, 919] This is important not only for reliable identification of compounds, but also for the use of real molecular geometry in the molecular docking study of their interaction with cell receptors.

The above-mentioned compounds are polyfunctional. Some of them are markedly cytotoxic and have high apoptotic activity towards cancer cells,[910, 916, 917] which makes them promising for further research. A possible trend of development of this field of chemistry is the synthesis of symmetrical (containing two identical heterocycles annulated with a fluorinated benzene ring) and unsymmetrical (containing two different heterocycles) tricyclic systems, which may enhance (not excepting the synergistic effect) the apoptotic activity.[917] One more trend is preparation of derivatives combining fluorine atoms with other halogen atoms in the benzene ring,[910] which also attract enhanced attention for biomedicine.[935]

Fluorinaed thia(selena)diazoles and diazines exhibit redox activity and good (judging by the low electrochemical reduction potentials) electron-withdrawing properties.[929 – 931] In addition, they show fluorescence, which is useful not only for the study of their cytotoxic and apoptotic activities.[908 – 910] Similar properties are expected of other classes of aza-heterocycles. In this connection, all these compounds are of interest for the design and synthesis

of functional molecular materials. For example, actual or potential applications of materials based on non-fluorinated thia(selena)diazoles include luminescence (in particular, in near-IR range) and electroluminescence, photovoltaics (solar batteries), chemical sensors and fluorescent thermometers for living systems.[898] Tellurium-containing analogues are much less studied; however, the supramolecular chromotropic properties of polyfluorinated 2,1,3-benzotelluradiazole are worthy of note.[919] Polyfluorinated 1,2-diaminobenzenes are novel redox-active ligands in metal complexes promising for the design of field effect transistors[936] (the demands of coordination chemistry for polyfluorinated aromatic ligands are traditionally high).[937]

19. Fluorinated pyrroles and pyridines

The unique properties of organofluorine compounds, in particular, their high solubility in lipids (lipidophilicity) and easy transport through cellular membranes account for the ever increasing interest in these compounds of synthetic chemists, pharmacologists, physicians and materials scientists. This is the reason for increased attention that is now paid to the chemistry of fluorinated heterocycles,[3, 4, 806, 938 – 941] especially pyrrole and pyridine derivatives as the most fundamental life-supporting molecular systems. The fluorinated derivatives of pyrroles are extensively investigated as promising biologically active compounds — pharmaceuticals, fungicides, insecticides and herbicides.[942] In these compounds, the fluorine atom can occur both in the pyrrole ring and in the functional group. Fluorinated pyrrolopyrimidines containing a fluorine atom in the pyrrole ring are studied as gonadotropin-releasing hormone receptor antagonists.[943] Vonoprazan and its analogue, the 3-fluoro-2-(2-fluoro-3-pyridyl)pyrrole derivative, behave as potassium-competitive acid blockers with long duration of action and were recommended for the treatment of *Helicobacter pylori*-associated gastritis and gastric ulcer.[944] Novel chlorfenapyr analogues, trifluoromethylpyrrole derivatives, possess insecticidal and herbcidal activities.[945]

Fluorinated azines, especially quinolines and their derivatives, are also investigated because of their high biological activity. It is known that fluoroquinolones are important antibiotics (ciprofloxacin, moxifloxacin, gatifloxacin and levofloxacin), while some trifluoromethyl quinolines are efficient antimalarial agents (mefloquine and fluoroquin). Direct fluorination and reactions of fluorinated reagents do not always ensure introduction of a fluorine atom or fluorine-containing group into the desired position of a pyrrole or pyridine ring. Therefore, the synthon approach (molecular assembly from building blocks containing fluorine atoms) is becoming more and more popular. In recent years, this strategy has been successfully used to prepare various fluorinated heterocycles. This is often done using fluorinated aminoenones[946] and electron-deficient acetylenes.[947 – 951]

This chapter, because of its limited size, does not claim to be an exhaustive presentation of studies in this field. Only the most significant publications characterizing the modern trends in the chemistry of fluorinated pyrroles and pyridines are analyzed. These trends include systematic investigation of pyrrole trifluoroacetylation and application of the acylated products thus formed as active fluorine-containing synthons.

In the field of fluorinated pyridine structures, popularity is gained by the approach based on the use of 1,3-dipolar adducts (zwitter-ions) of pyridine bases with electron-deficient fluorinated acetylenes as triggers of cascade annulation reactions that afford fused heterocyclic systems.

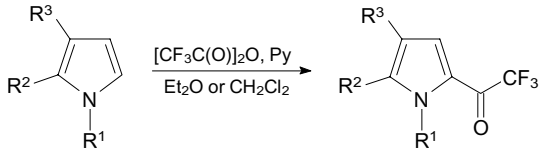
The first trend acquired popularity when α-unsubstituted pyrroles became available, being easily prepared in one step from ketoximes (ketones) and acetylenes in the presence of KOH – DMSO superbasic catalyst (Trofimov reaction).[952]

The systematic development of the second trend started when the 1,3-dipolar adducts, in essence, vinylic carbanions, were conceptually recognized as promising intermediates for the synthesis of fluorinated pyridine derivatives.

19.1. Trifluoroacetylpyrroles and their derivatives

The trifluoroacetylation of pyrroles with trifluoroacetic anhydride usually smoothly proceeds at room temperature and gives 2-trifluoroacetylpyrroles in high yields (Scheme 347).[952 – 954]

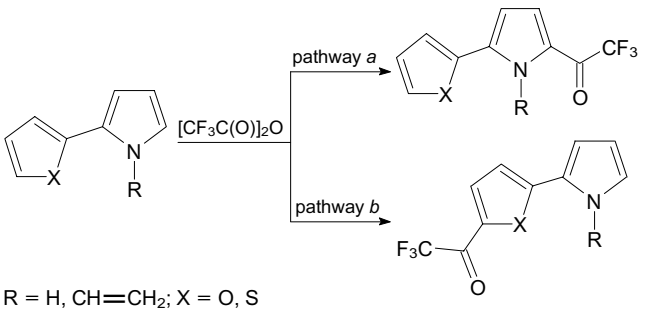
Scheme 347



R^1 = H, Et, $(CH_2)_2SEt$, $(CH_2)_2SiEt_3$, CH=CH_2;
R^2 = Me, Ph, 4-MeC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 2-Naph; R^3 = H, Me, Et, Pr^n, Am^n, n-C_9H_{19};
$R^2 - R^3$ = $(CH_2)_4$

The trifluoroacetylation was used to compare the reactivities of pyrrole, furan and thiophene towards electrophilic substitution.[955] The trifluoroacetylation rates of these heterocycles are related as $(5.3 \times 10^7) : (1.4 \times 10^2) : 1$. Hence, it was expected that 2-(2-furyl)- and 2-(2-thienyl)pyrroles and their N-vinyl derivatives will be acylated only into position 5 of the pyrrole ring (Scheme 348, pathway *a*).[952]

Scheme 348



R = H, CH=CH_2; X = O, S

Indeed, it was found that 2-(2-furyl)- and 2-(2-thienyl)-pyrroles are trifluoroacetylated only into the pyrrole ring. A different behaviour towards trifluoroacetylation was found for *N*-vinyl-2-(2-furyl)pyrrole. Whereas *N*-vinyl-2-(2-thienyl)pyrrole is acylated only according to pathway *a*, the major trifluoroacetylation pathway of *N*-vinyl-2-(2-furyl)-pyrrole is the attack on the α-position of the furan moiety (see Scheme 348, pathway *b*). The products of trifluoroace-

tylation into the furan and pyrrole rings are formed in 9 : 1 ratio.[952]

Here three factors should be taken into account: (1) markedly higher nucleophilicity of the furan ring compared with the thiophene ring; (2) decrease in the electron density in the pyrrole ring due to the competitive conjugation of the vinyl group with the nitrogen lone pair and due to its negative inductive effect; (3) the possible steric hindrance created by the N-vinyl group for the attack on the α-position. The absence of double acylation products attests to very strong deactivating influence of the trifluoroacetyl substituent, which is translated from the pyrrole α-position to the furan α-position. The mechanism of this long-range action (through seven covalent bonds) is not evidently limited to the inductive effect, but involves the formation of the common system of conjugation (Scheme 349).

The introduction of the trifluoroacetyl substituent into the pyrrole ring of tetrahydropyrrolo[3,2-*c*]pyridine **19.1** required more drastic conditions: heating in toluene for 3 h (Scheme 350).[956]

Pyrrole-2-carbaldehydes are not trifluoroacetylated under conditions suitable for other pyrroles.[952–954] This is caused by a strong electron-withdrawing effect of the aldehyde group, which deactivates the pyrrole ring against the electrophilic attack.

5-Trifluoroacetylpyrrole-2-carbaldehydes **19.2a**,**b** were prepared[957] by preliminary protection of the aldehyde group of pyrrole-2-carbaldehydes **19.3a**,**b** with 2,2-dimethylpropane-1,3-diol, the subsequent trifluoroacetylation of acetals **19.4a**,**b** and the final acid-catalyzed hydrolytic acetal deprotection (Scheme 351).

Despite the fact that high yields of trifluoroacetylpyrroles are achieved in most cases, the trifluoroacetylation of unsubstituted pyrrole results in the formation of side trifluoromethyl and trifluoroacetyl dimers and trimers **19.6** – **19.10**.[958] Tripyrrole **19.7** is also formed (in 10% yield) upon the reaction of trifluoroacetylpyrrole and pyrrole at room temperature.

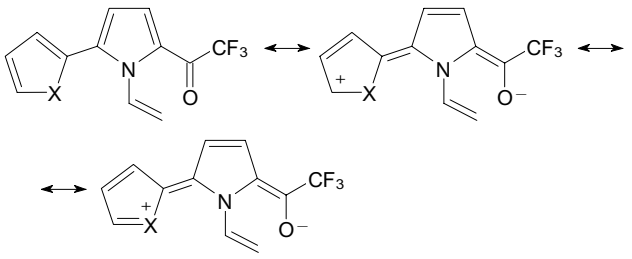
2-Trifluoroacetyl-4,5,6,7-tetrahydroindole can be prepared *via* two steps: the reaction of 4,5,6,7-tetrahydroindole with 1-ethoxy-2,2,2-trifluoroethanol and oxidation of 2-hydroxy(trifluoromethyl)-4,5,6,7-tetrahydroindole **19.11** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 352).[959]

The reactivity of trifluoroacetylpyrroles is determined exceptionally by the trifluoroacetyl group, as the pyrrole ring is deactivated by the strong electron-withdrawing effect of this group.

Trifluoroacetylpyrroles are easily reduced to give pyrrolyltrifluoroethanols **19.12** (Scheme 353).[952]

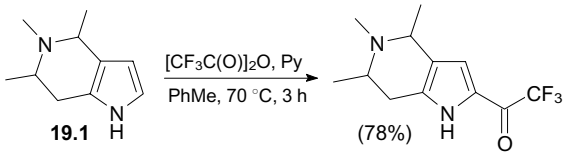
Pyrroles **19.12** were used in the original synthesis of boradiazaindacene fluorophore (boron-dipyrromethenes, BODIPY) with a *meso*-CF_3-group — compounds **19.13** (Scheme 354).[960] In comparison with non-fluorinated analogues, fluorescence of BODIPY **19.13** is shifted to red spectral range (600 – 670 nm) and has a high quantum yield (~1.0), which opens up new prospects for the use of these compounds as biological labels.

Scheme 349

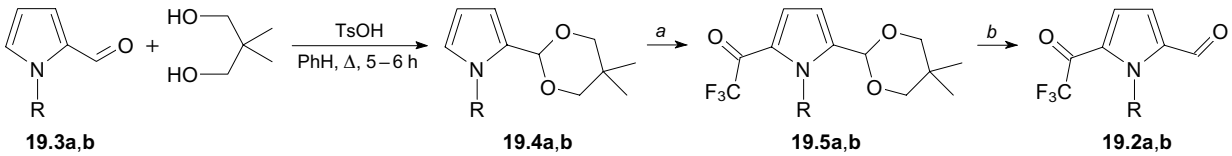


X = O, S

Scheme 350



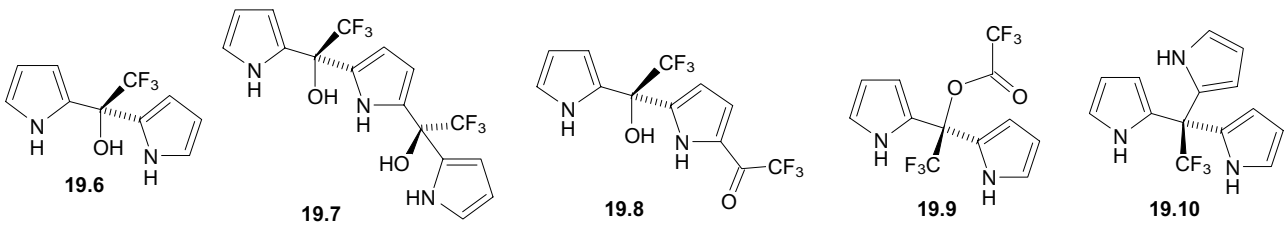
Scheme 351



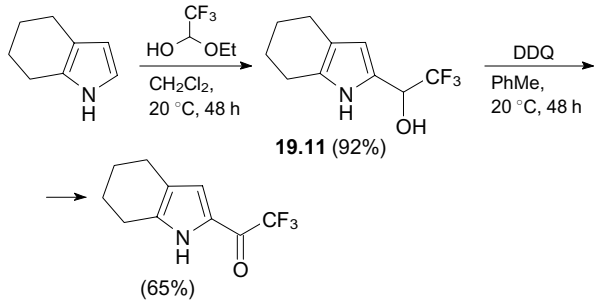
(*a*) $[CF_3C(O)]_2O$, Py, Et_2O, from −15 to 20 °C, 4.5 h;
(*b*) H^+, H_2O, Me_2CO, 16 h

Compound	R	Yield of **19.4** (%)	Yield of **19.5** (%)	Yield of **19.2** (%)
a	H	45	96	48
b	Et	44	51	36

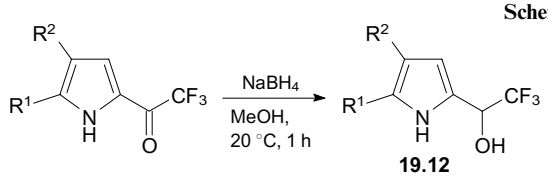
Structures 19.6 – 19.10



Scheme 352

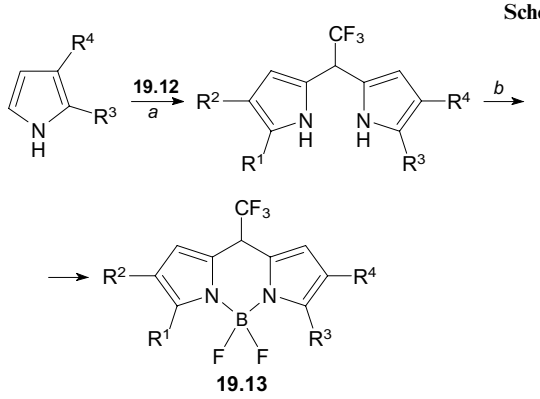


Scheme 353



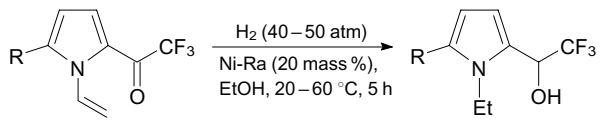
R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-PhC_6H_4, 4-$Me_2NC_6H_4$, 4-$H_2NC_6H_4$, 3-$H_2NC_6H_4$, 2-Th; R^2 = H, Ph; $R^1 - R^2 = (CH_2)_4$

Scheme 354



(*a*) P_2O_5, CH_2Cl_2, rt, 15 – 16 h; (*b*) 1) DDQ, CH_2Cl_2, rt, 1 h; 2) $BF_3 \cdot Et_2O$, Pr^i_2NEt, CH_2Cl_2, rt, 1 h;
R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-PhC_6H_4, 4-$Me_2NC_6H_4$, 4-$H_2NC_6H_4$, 3-$H_2NC_6H_4$, 2-Th; R^2 = H, Ph; R^3 = H, Ph, 2-Th; R^4 = H, Ph

Scheme 355

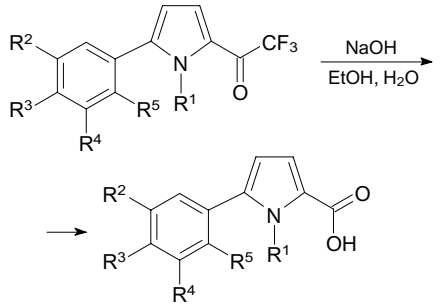


R = Me, Ph, 4-MeC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4

When *N*-vinyl-2(5)-trifluoroacetylpyrroles are hydrogenated with hydrogen at elevated pressure, not only the trifluoroacetyl, but also the vinyl group is reduced (Scheme 355).[952]

The haloform reaction of 2-trifluoroacetylpyrroles can be used to prepare diverse pyrrolecarboxylic acids (Scheme 356),[952 – 954] which are key intermediates in the synthesis of HIV-1 inhibitors.[953, 954]

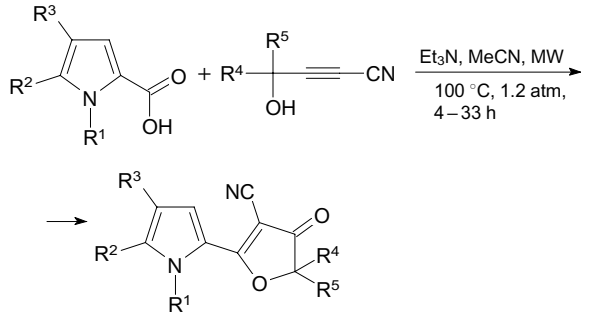
Scheme 356



R^1 = H, CH=CH_2; R^2 = H, F, OMe; R^3 = H, Me, Et, OMe, CF_3, F, Cl; R^4, R^5 = H, F

The cascade reaction of arylpyrrolecarboxylic acids with cyanoacetylenic alcohols opens up a simple pathway to functionalized pyrrolylfuranones, potential anti-HIV agents (Scheme 357).[961]

Scheme 357

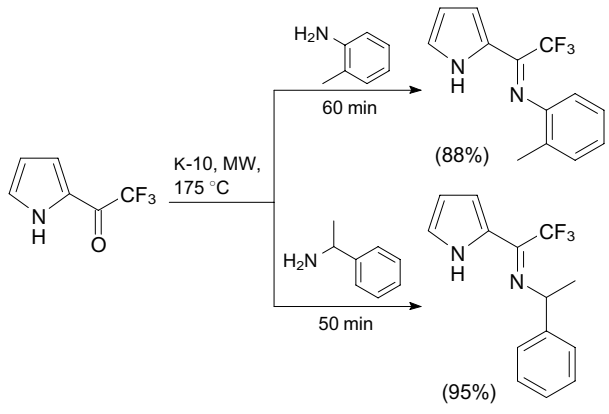


R^1 = H, CH=CH_2; R^2 = H, Ph, 4-ClC_6H_4; R^3 = H, Et; R^4 = Me, Et; R^5 = Me; $R^4 - R^5 = (CH_2)_4$;
MW is microwave radiation

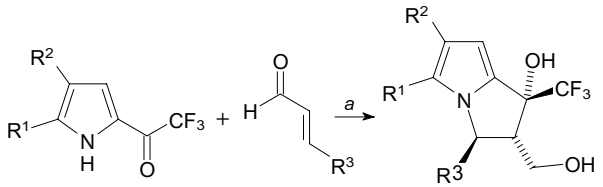
The microwave-assisted reaction of 2-trifluoroacetylpyrrole with primary amines in the presence of montmorillonite K-10 affords pyrrolyltrifluoroimines in high yield (Scheme 358).[962]

4,5-Dibromo-2-trifluoroacetylpyrrole and 4-cyano-2-trifluoroacetylpyrrole react with α,β-unsaturated aldehydes in the presence of the optically active catalyst, trimethylsilyl

Scheme 358



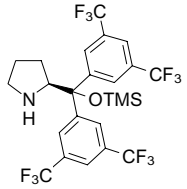
Scheme 359



19.14 (61 – 88%)

(*a*) 1) Cat (20 mol.%); 2) $PhCO_2H$ (40 mol.%), PhMe (0.1 M), from −10 to −30 °C, 18 h; 3) $NaBH_4$ (100 mol.%), EtOH (0.1 M), from −10 to −30 °C, 0.5 h

Cat =



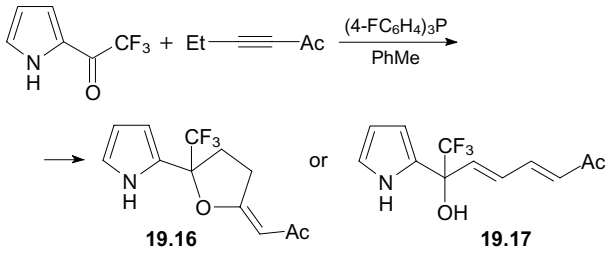
R^1 = H, Br; R^2 = CN, Br; R^3 = Me, Pr^n, CH_2OMe, $(CH_2)_3N(Boc)Cbz$; Cbz is benzyloxycarbonyl

ether of (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol. The subsequent reaction with $NaBH_4$ gives chiral pyrrolizines **19.14** with high enantioselectivity (90% – 98% *ee*) (Scheme 359).[963]

The condensation of 2-trifluoroacetylpyrrole with triphenylphosphine and dimethyl acetylenedicarboxylate yields N-substituted 2-trifluoroacetylpyrrole **19.15**. The intramolecular Wittig reaction of adduct **19.15** generates (after elimination of triphenylphosphine oxide) 1-trifluoromethyl-3*H*-pyrrolizine-2,3-dicarboxylate (Scheme 360).[964]

Tris(4-fluorophenyl)phosphine-catalyzed (20 mol.%) [3 + 2]-cycloaddition (65 °C, 72 h) of 2-trifluoroacetylpyrrole to hexynone affords cycloadduct **19.16** in 43% yield. At 10 °C (144 h), only δ-adduct **19.17** was isolated (67% yield). The same adduct is also formed in 38% yield (10 °C, 72 h) in the presence of an equimolar amount of 2-bromo-4-fluorophenol additive (Scheme 361).[965]

Scheme 361



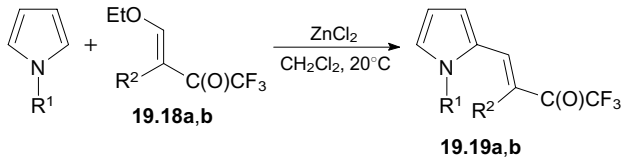
19.16 **19.17**

19.2. Trifluoroacetylethenyl- and trifluoroacetylethynylpyrroles

Trifluoromethylethylene and trifluoromethylacetylene ketones are convenient reagents for the introduction of trifluoroacetylethylene and trifluoroacetylacetylene substituents into the pyrrole ring. Owing to their high reactivity, these compounds may in the future become multitarget building blocks for the synthesis of diverse pharmaceutically oriented pyrrole derivatives functionalized with trifluoromethyl substituents. Indeed, a combination of the pyrrole ring with the trifluoromethyl ketone moiety and a double or triple bond in one conjugated molecule opens up extensive prospects for drug development.

Pyrrolylethenyl trifluoromethyl ketones were prepared by the reactions of pyrroles with functionalized trifluorobutenones.[966, 967] The reaction of 1*H*- and 1-methylpyrroles with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**19.18a**) and 3-(ethoxymethylene)-1,1,1,5,5,5-hexafluoropentane-2,4-dione (**19.18b**) readily proceeds in the presence of $ZnCl_2$ with ethoxy group displacement giving 2-[(2-trifluoroacetyl)ethenyl]pyrroles **19.19a**,**b** in 53% and 88% yields, respectively. In the case of ketone **19.18a**, the reaction is stereospecific and gives the *E*-isomer (Scheme 362).[966, 967]

Scheme 362



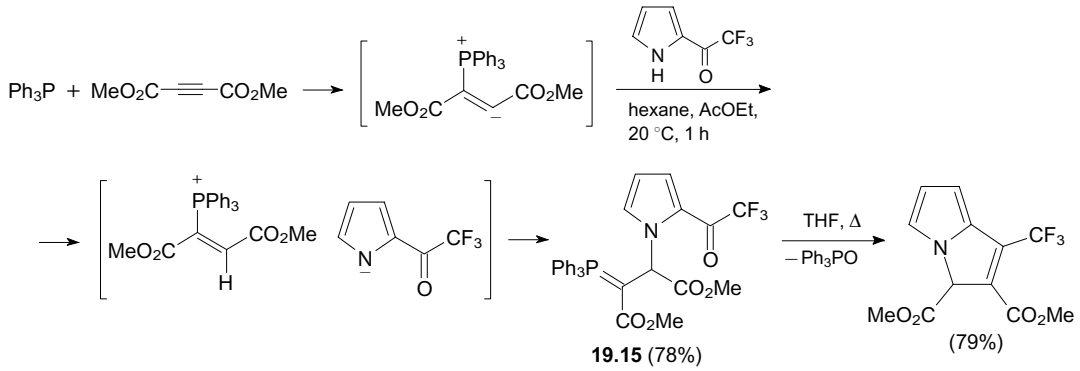
19.18a,**b** **19.19a**,**b**

R^1 = H, Me; R^2 = H (**a**), $C(O)CF_3$ (**b**)

Pyrrole **19.19a** is also formed in 84% yield from 1*H*-pyrrole and 1,1,1-trifluoro-4-(phenylsulfonyl)but-3-ene-2,2-diol (**19.20**), which is easily obtained by oxidation of trifluoroacetylated vinyl sulfide (Scheme 363).[966, 967] Both reactions follow the same pathway: the addition of the pyrrole nucleophile to an activated double bond followed by elimination of EtOH or $PhSO_2H$.

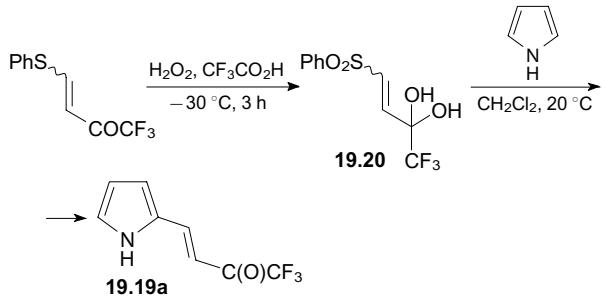
A general approach to the synthesis of ethynylpyrroles with electron-withdrawing functional groups in the acetylene substituent is non-catalyzed cross-coupling of pyrroles with haloacetylenes in a solid oxide or metal salt medium

Scheme 360



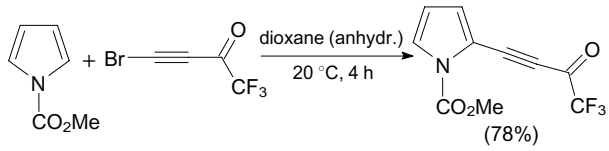
19.15 (78%) (79%)

Scheme 363



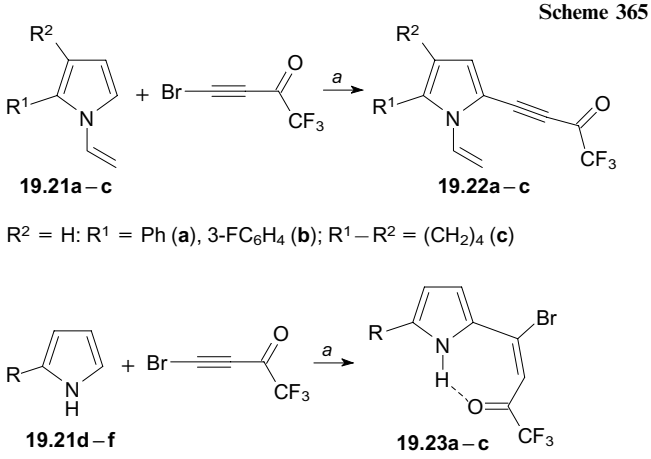
(alternative to the Sonogashira reaction).[968] This procedure was used to prepare trifluoromethyl pyrrolylethynyl ketone by the reaction between pyrrole with the protected NH group and bromo(trifluoroacetyl)acetylene (Scheme 364).[196]

Scheme 364



The direct chemo- and regioselective reactions of pyrroles **19.21a – f** with bromo(trifluoroacetyl)acetylene in solid Al_2O_3 give *N*-vinyl-2-(trifluoroacetylethynyl)pyrroles **19.22a – c** in up to 58% yields or (*E*)-2-(1-bromo-2-trifluoroacetylethenyl)pyrroles **19.23a – c** in 12% – 21% yields (Scheme 365).[969, 970] The reactions take place under mild conditions in the absence of a catalyst and solvent.

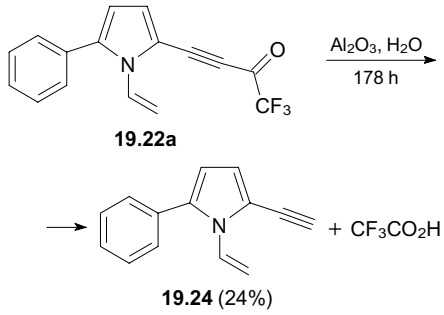
Scheme 365



The expected ethynylation of pyrroles is observed only for N-vinylpyrroles **19.21a – c**, whereas NH-pyrroles **19.21d – f** are functionalized by only the 1-bromo-2-trifluoroacetylethenyl substituent. The synthesis of 2-(1-bromo-2-trifluoroacetylethenyl)pyrroles **19.23a – c** is not only chemo- and regioselective, but also stereoselective, giving only *E*-isomers of the products.

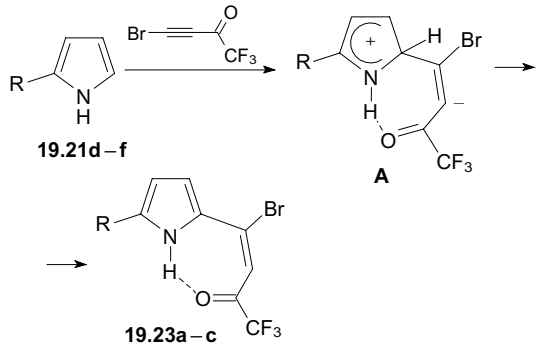
N-Vinyl-2-(trifluoroacetylethynyl)pyrroles **19.22a – c** and (*E*)-2-(1-bromo-2-trifluoroacetylethenyl)pyrroles **19.23a – c** are stable when stored in the pure state (3 months in a refrigerator). On long-term contact (7 days) of pyrrole **19.22a** with Al_2O_3, the trifluoroacetyl group is eliminated (apparently, as trifluoroacetic acid or aluminium trifluoroacetate) to give 2-ethynylpyrrole **19.24** in 24% yield (Scheme 366).

Scheme 366



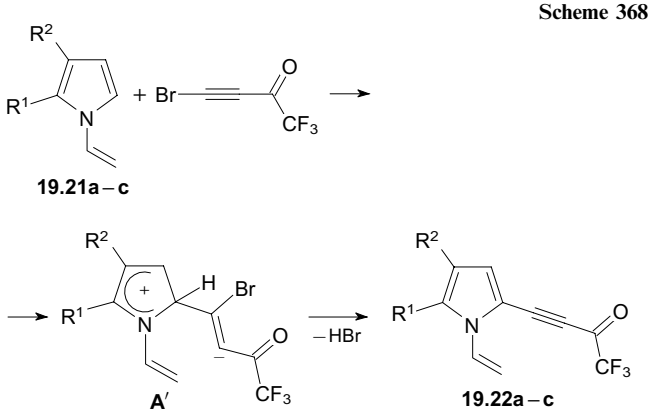
The chemoselectivity of ethynylation observed for NH-pyrroles **19.21d – f** is caused by the structural features of the resulting adducts **19.23a – c**. The pronounced downfield shift of the NH proton signals (13 – 14 ppm) in the ^{1}H NMR spectra of pyrroles **19.23a – c** attests to strong intramolecular NH···O interaction in the energetically favourable *E*-configuration (see Scheme 365). Similarly, an intramolecular hydrogen bond can exist in zwitter-ion **A**, in which this bond stabilizes the *E*-configuration (Scheme 367). Since no HBr elimination takes place as zwitter-ion **A** is formed, the proton transfer from position 2 of the pyrrole ring to the carbanionic centre is facilitated by stabilization of this centre by the trifluoroacetyl group.

Scheme 367



In the reaction of N-vinylpyrroles **19.21a – c** with bromo(trifluoroacetyl)acetylene, intramolecular hydrogen bond in the reaction products is impossible. Moreover, the formation of *E*-4-bromo-1,1,1-trifluoro-4-(1-vinylpyrrol-2-yl)but-3-en-2-ones is sterically impeded by the mutual repulsion of the N-vinyl and trifluoroacetyl groups. Possibly, the steric strain effect already destabilizes the *E*-form of intermediate zwitter-ion **A′** (Scheme 368), thus making the *Z*-form energetically favourable. In the final step, bromide anion elimination and deprotonation of position 2 of the

Scheme 368

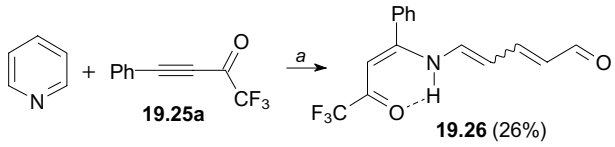


pyrrole ring transform zwitter-ion **A′** into trifluoroacetylethynylpyrroles **19.22a – c** (see Scheme 368).

19.3. Reactions of azines with fluorinated carbonyl compounds

The reaction of pyridine with phenyl(trifluoroacetyl)acetylene (**19.25a**) carried out in the presence of water under very mild conditions (0 °C), instead of the possible annulation, leads to pyridine ring opening to give trifluoroacetylated 5-aminopenta-2,4-dienal **19.26** (Scheme 369).[971]

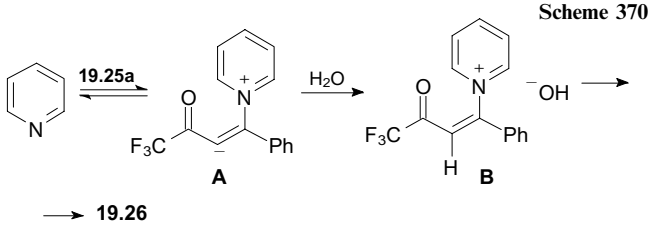
Scheme 369



(*a*) H_2O, MeCN, 0 °C, 24 h

The *Z*-stereoselectivity [relative to the phenyl(trifluoroacetyl)ethenyl moiety] is virtually 100% and the *E*,*E*- to *E*,*Z*-isomer ratio in the pentadienal moiety reaches 95 : 5. According to the data on pyridine ring opening on treatment with non-fluorinated electron-deficient acetylenes,[972 – 974] the reaction includes the formation of 1,3-dipole complex **A** of pyridine with acetylene **19.25a**. The proton transfer from the water molecule to the carbanionic centre of this complex leads to ammonium intermediate **B**, which then rearranges with N – C(2) bond cleavage to give aminopentadienal **19.26** (Scheme 370).

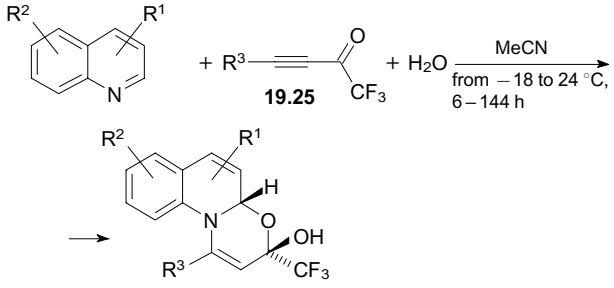
Scheme 370



The milder temperature conditions of this reaction in comparison with analogous reactions with other acylacetylenes are, as expected, caused by the enhanced electrophilicity of phenyl(trifluoroacetyl)acetylene **19.25a**. This simple one-pot synthesis opens up the way for introducing a enone moiety containing the trifluoromethyl pharmacophore group into 5-aminopenta-2,4-dienals, which are important intermediates in the synthesis of natural alkaloids.[975]

When fused pyridines (quinolines) are used in this reaction, the expected azide ring opening does not take place, but the reaction gives (under the same very mild conditions) 1,2-functionalized quinolines **19.27** annulated with the 1,3-oxazine ring in up to quantitative yields (Scheme 371; the substituent position in the substrate is indicated).[976] The reaction is diastereoselective, giving 1,3-oxazinoquinolines as single diastereomers.

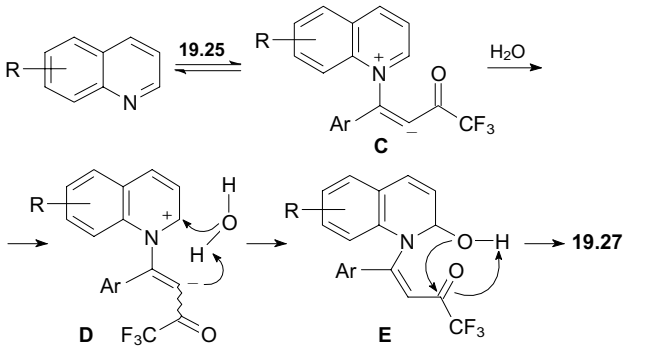
Scheme 371



R^2 = H: R^1 = H, 3-Me, 5-CN, 6-Cl, 3-Br, 5-Br; R^1 = 4-Cl, R^2 = 7-Cl; R^3 = Ph, 4-MeC_6H_4, 3,4-$Me_2C_6H_3$, 4-$Bu^tC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-$MeSC_6H_4$, 4-MeONaph

As in the reaction with pyridine, the annulation mechanism includes the reversible formation of 1,3-dipolar intermediate **C**, which adds a water molecule to positions 1 and 4 (this is likely a concerted process), yielding hemiaminal **E**. This is followed by 1,3-oxazine ring closure *via* intramolecular nucleophilic addition of the hydroxide ion to the carbonyl group (Scheme 372).

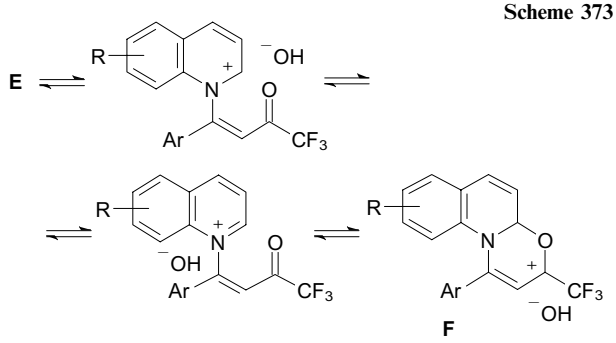
Scheme 372



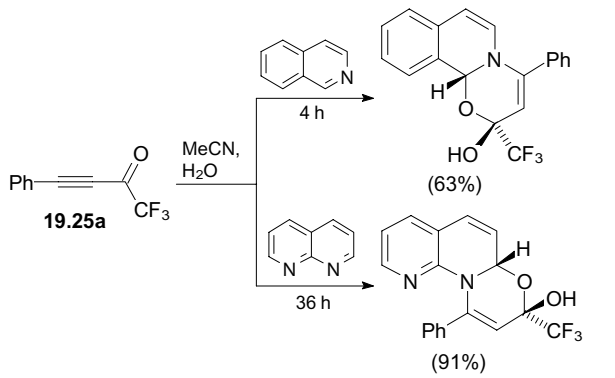
The stereoselectivity of the reaction can be explained by considering the ionic form of cyclic intermediate **F** (Scheme 373). Since the cationic oxazine moiety in structure **F** is nearly orthogonal to the quinoline ring plane, the attack by the hydroxide anion on the carbocationic centre in structure **E** should occur from the least sterically hindered side. It is noteworthy that the resulting diastereomers can be additionally stabilized by the anomeric effect.

This cascade annulation is possible also for other compounds containing a pyridine ring. Isoquinoline and

Scheme 373



Scheme 374



1,8-naphthyridine undergo similar reaction under the same conditions to give pyridine systems fused with the 1,3-oxazine ring (Scheme 374).[976]

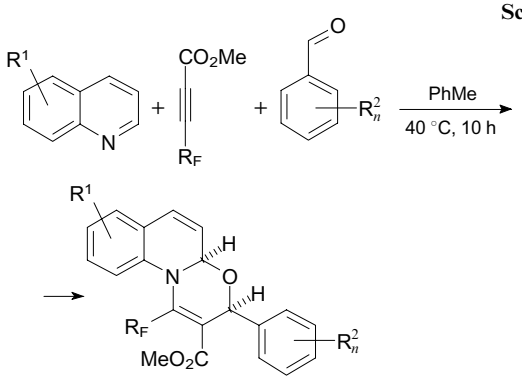
A crucially different behaviour of quinolines and their analogues in this reaction as compared with pyridines is caused by the basicity difference between them [pK_a(BH)$^+$ is 5.14 for pyridine and 4.85 for quinoline]. In the case of more basic pyridine, the N – C(2) bond in the primary dipolar complex should be more polarized than that in analogous complexes formed from its fused derivatives (quinolines, isoquinoline, naphthyridine). Hence, the ammonium intermediate **B** (see Scheme 370) is more prone to N – C(2) bond cleavage than that in quinoline intermediate **D** (see Scheme 372).

1,3-Oxazine structures are attractive for drug design; this is even more true for fluorinated oxazinoquinolines. A 1,3-oxazine of this type with a trifluoromethyl group is already used in medical practice as the anti-HIV agent efavirenz. The above-considered diastereoselective three-component one-pot assembly of hydroxyl-containing trifluoromethyl-1,3-oxazinoquinolines and their analogues opens up wide opportunities for the synthesis of these compounds. Good prospects of this reaction are due to the fact that it is fully diastereoselective, proceeds without catalysts under physiological conditions (at room temperature) as a one-pot procedure and gives high yields of the desired fluorinated oxazinoquinolines. This fully complies with the requirements imposed on the modern organic synthesis by the Parliamentary Assembly of Council of Europe (PASE) paradigm.[977]

In recent years, other approaches to the synthesis of 1,3-oxazinoquinolines have also been developed. Three-component reactions involving quinoline, dimethyl acetylenedicarboxylate and fluorinated carbonyl compounds were reported; the carbanionic centre of the primary 1,3-dipole is captured by the carbonyl group and this is followed by the attack by the oxygen-centred anion on the quinoline position 2 (Scheme 375).[978]

The same pathway is implemented in the reaction of quinolines with perfluoroalkylacetylenecarboxylates and carbonyl compounds to give 1,3-oxazinoquinolines in the yields ranging from trace to high (92%) (Scheme 376).[948]

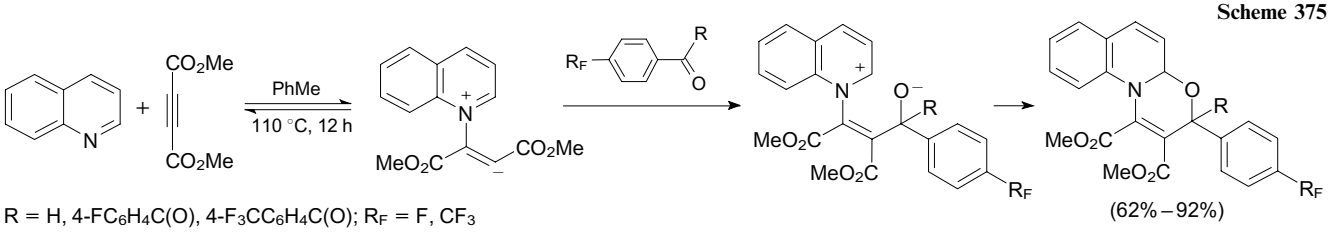
Scheme 376



R^1 = H, 4-Me, 6-Me, 5-OMe, 6-OMe; R^2_n = H, 4-Me, 4-CF_3, 4-CO_2Me, 3-CN, 4-CN, 4-F, 4-Cl, 2,3-Cl_2, 2,4-Cl_2, 3,4-Cl_2, 4-Br, 4-OMe, 2-NO_2, 3-NO_2, 4-NO_2; R_F = CF_3, C_2F_5, n-C_3F_7

The studies dealing with fluorine-containing pyrroles and pyridines carried out in the last decade, which are briefly analyzed in this chapter, indicate that the prospective trends in the chemistry of fluorinated derivatives of these fundamental heterocycles are largely determined by trifluoroacetylation reactions (in the case of pyrrole and its derivatives) and by cascade reactions involving pyridine bases (especially for quinolines and their analogues) and fluorinated electron-deficient acetylenes and/or fluorinated carbonyl compounds. The trifluoroacetylation of α-unsubstituted pyrroles, which have become widely available, discloses new approaches to the synthesis of trifluoromethyldipyrromethanes, important synthons for the assembly of diverse pyrrole systems with a trifluoromethyl substituent, including highly efficient boradiazaindacene (BODIPY)

Scheme 375



R = H, 4-FC_6H_4C(O), 4-$F_3CC_6H_4C$(O); R_F = F, CF_3

fluorophores, prodigiosin type trifluoromethylated oligopyrroles, and macrocyclic compounds like porphyrin and its analogues promising in many respects.

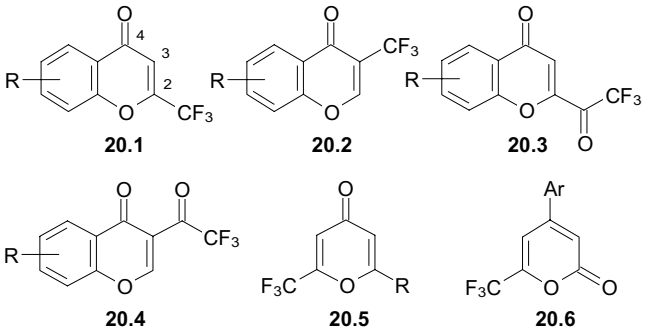
The possibilities of using fluorinated electron-deficient acetylenes for the synthesis of new functionalized fused pyridine structures *via* the formation of 1,3-dipolar vinyl carbanions are far from being exhausted. The large synthetic potential of these reactions has only started to be implemented. The most promising trend is the involvement of new electrophiles for capture of a carbanionic centre of the forming 1,3-dipolar intermediate.

20. Chemistry of trifluoromethylated chromones and pyrones

Within the framework of the synthon strategy, CF_3-containing chromones and pyrones are of interest as simple and highly reactive molecules for the introduction of the trifluoromethyl group into definite positions of various heterocyclic systems. Owing to their natural origin, chromones have long attracted attention of chemists and are well-studied oxygenated heterocycles. Reviews devoted to their biological activity[979, 980] and application in the synthesis of more complex compounds[981 – 986] have been published. Evidently, the introduction of the electron-withdrawing CF_3 group into the pyrone ring of chromones and into 2- and 4-pyrones not only considerably increases their reactivity towards nucleophiles, but makes them valuable CF_3-containing synthons suitable for the preparation of diverse heterocyclic compounds with a potential biological activity.

The present chapter is devoted to the synthetic potential of 2(3)-trifluoromethyl- and 2(3)-trifluoroacetylchromones **20.1** – **20.4** and 6-trifluoromethyl-4(2)-pyrones **20.5** and **20.6** and covers publications of the last 15 years. The primary attention is concentrated on the reactions that are inherent only in trifluoromethylated chromones and pyrones and do not proceed for their methylated analogues. The material is arranged according to the position of the fluorinated substituent relative to the pyrone carbonyl group, because this determines the chemical behaviour of these compounds.

Structures 20.1 – 20.6



The most reactive site in chromones **20.1** – **20.4** is the C(2) atom; hence, most reactions with mono- and dinucleophiles start with the attack on this atom. The trifluoromethyl group in position 2 markedly increases the reactivity of 2-trifluoromethylchromones **20.1**, despite the arising steric hindrance; this is manifested as a number of new transformations that are absolutely not typical of 2-methylchromones. The additional carbonyl group in chromones **20.3** and **20.4** increases their synthetic potential, which is attributable to the presence of three electrophilic centres [C(2), C(4) atoms and the $CF_3C(O)$ substituent] and a good leaving group, which is represented by the phenoxide anion. Owing to the easy cleavage of the O – C(2) bond, the nucleophilic reactions of chromones **20.1** – **20.4** are, most often, accompanied by pyrone ring opening and ring closure involving the carbonyl groups present in the molecule. Much of the above is also true for 6-trifluoromethyl-4(2)-pyrones **20.5** and **20.6** with the only difference that for these compounds it may be difficult to identify the site of the initial attack.

The use of chromones **20.1** – **20.4** and pyrones **20.5** and **20.6** in organic synthesis considerably expands the range of the available CF_3-containing building blocks and demonstrates real prospects and extensive capabilities of these compounds for selective introduction of the trifluoromethyl group into various heterocycles, which is of obvious interest for medicinal chemistry.

20.1. 2(3)-Trifluoromethylchromones

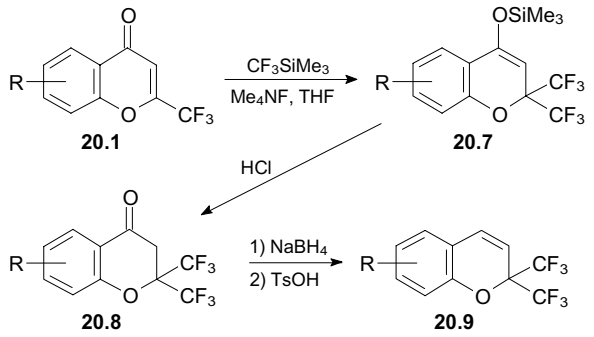
2-Trifluoromethylchromones **20.1** were first obtained in 1951 by condensation of substituted 2-hydroxyacetophenones with ethyl trifluoroacetate followed by dehydration of the initially formed β-diketones in an acid medium.[987] However, the first publication[988] dealing with their high reactivity towards amines appeared only 30 years later. In recent years, the chemical properties of chromones **20.1** have received considerable attention; as a result, a number of new synthetic routes to diverse trifluoromethylated heterocycles were developed.[989, 990] It was shown that the replacement of the methyl group in 2-methylchromones by the trifluoromethyl group makes chromones **20.1** valuable CF_3-containing building blocks with high synthetic potential.

The reaction of chromones **20.1** with the Ruppert reagent was the first example of conjugate trifluoromethylation of the α,β-enone system.[991] It was shown that in the presence of the nucleophilic initiator Me_4NF (THF, 0 °C, 4 h), 2-CF_3-chromones **20.1** react with CF_3SiMe_3 almost quantitatively and with high regioselectivity according to the 1,4-addition pathway to give trimethylsilyl ethers **20.7**, which are then hydrolyzed to 2,2-bis(trifluoromethyl)chroman-4-ones **20.8**. It is clear that successful implementation of this reaction is possible only because of high electrophilicity of the C(2) atom bound to the CF_3 group. The reduction of chromanes **20.8** with sodium borohydride followed by dehydration in the presence of *p*-toluenesulfonic acid leads to 2,2-bis(trifluoromethyl)-2*H*-chromenes **20.9** (Scheme 377).[992]

Currently, the 1,4-nucleophilic trifluoromethylation reaction, which was further developed in recent publications,[11, 677] is the simplest and the most efficient pathway to partially fluorinated analogues of natural chromanones, chromanes and chromenes with a *gem*-dimethyl group at the C(2) atom.

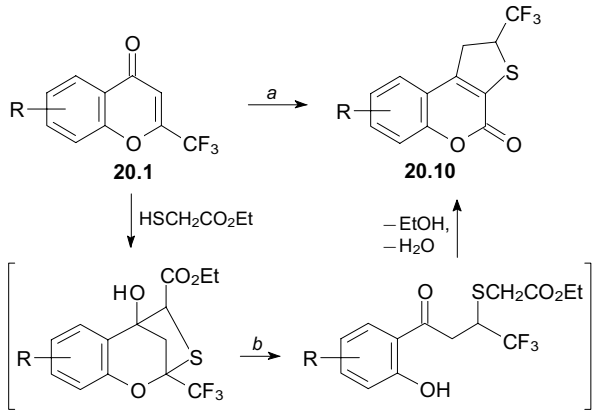
One of the most unexpected reactions of chromones **20.1** is the reaction with excess ethyl thioacetate in the presence of Et_3N, which results in 2-trifluoromethyl-1,2-dihydro-4*H*-thieno[2,3-*c*]chromen-4-ones **20.10** (66% – 93% yield) and diethyl 3,4-dithiaadipate, which attests to the redox nature of this transformation (Scheme 378).[993] This reaction is typical of only 2-CF_3-substituted chromones and no longer

Scheme 377



R = H, Me, OMe (here and below, in different positions)

Scheme 378

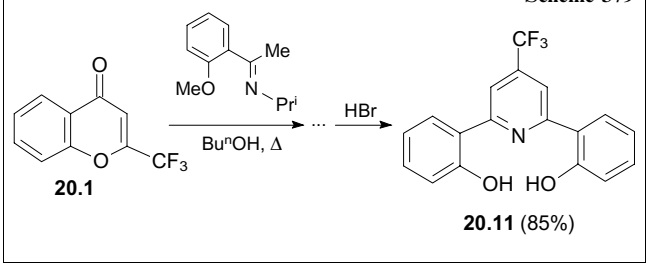


(*a*) $HSCH_2CO_2Et$ (3 equiv.), $-(SCH_2CO_2Et)_2$, $-EtOH$, $-H_2O$;
(*b*) $HSCH_2CO_2Et$ (2 equiv.), $-(SCH_2CO_2Et)_2$;
R = H, Me, OMe, NH_2, Cl, Br

proceeds when the trifluoromethyl group is replaced by the methyl or another polyhaloalkyl group.

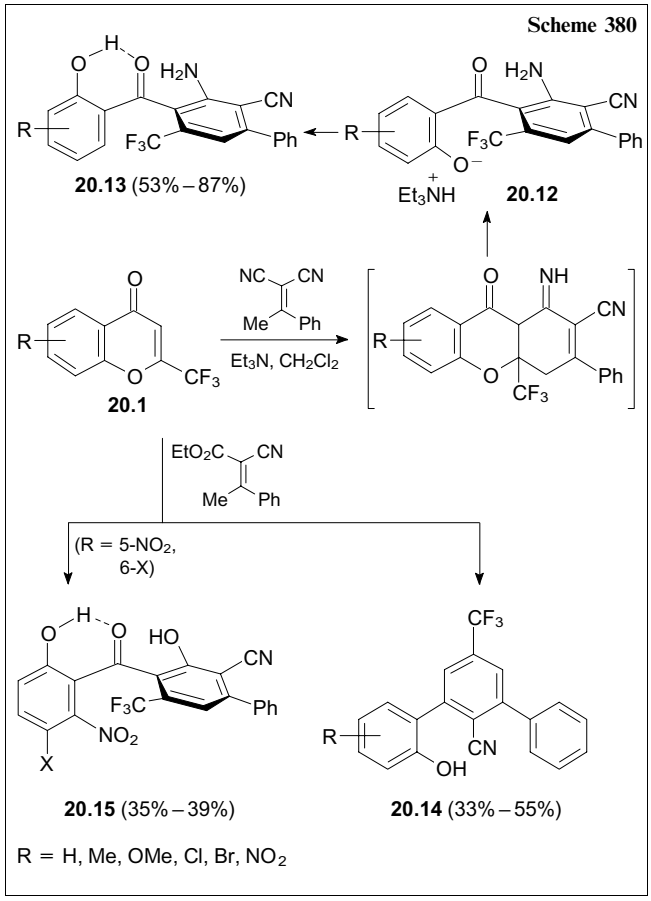
Methyl aryl ketone imines react with 2-CF_3-chromones **20.1** on refluxing in butanol to give pyridines. This reaction was used to prepare a broad range of 4-(trifluoromethyl)-pyridines, including 2,6-bis(2-hydroxyphenyl)-4-(trifluoromethyl)pyridine (**20.11**), which is of interest as a chelating ligand (Scheme 379).[994]

Scheme 379



The reaction of chromones **20.1** with ambiphilic ylidene malononitriles containing both nucleophilic and electrophilic centres results in new polyfunctional benzophenones. Thus the reaction with 2-(1-phenylethylidene)malononitrile proceeded *via* the formation of salts **20.12** and gives 2-amino-2′-hydroxybenzophenones **20.13**, resulting from formal [4 + 2]-cycloaddition, in 53% – 87% yield. Note that the reaction with ethyl α-cyano-β-methylcinnamate proceeds as formal [3 + 3]-cycloaddition to give *m*-terphenyls **20.14**, while the expected 2,2′-dihydroxybenzophenones **20.15** were isolated only in two cases, if X = Me and MeO (Scheme 380).[995]

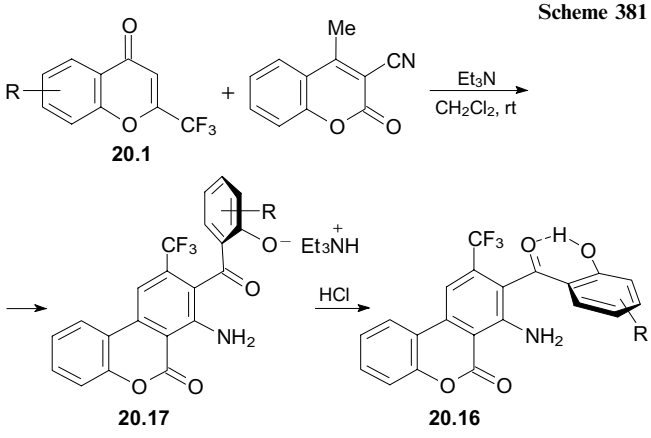
Scheme 380



R = H, Me, OMe, Cl, Br, NO_2

A similar transformation involving 3-cyano-4-methylcoumarin gives benzo[*c*]coumarins **20.16**. This is a tandem of the Michael reaction and the intramolecular condensation of the intermediate enolate anion involving the cyano group giving first salts **20.17**, which are hydrolyzed on

Scheme 381

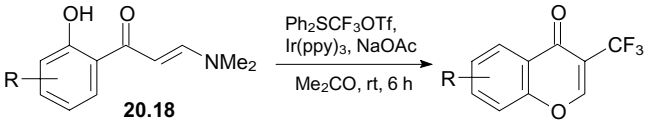


R = H, Me, OMe, Cl, Br, NO_2

treatment with hydrochloric acid to give final products **20.16** (Scheme 381).[996]

It is noteworthy that 3-trifluoromethylchromones **20.2** were synthesized quite recently by radical cyclization of 3-dimethylamino-1-(2-hydroxyaryl)prop-2-en-1-ones **20.18** on irradiation with visible light with Ph_2SCF_3OTf as the source of the trifluoromethyl radical (Scheme 382);[997] however no data about chemical properties of such products are yet available in the literature.

Scheme 382

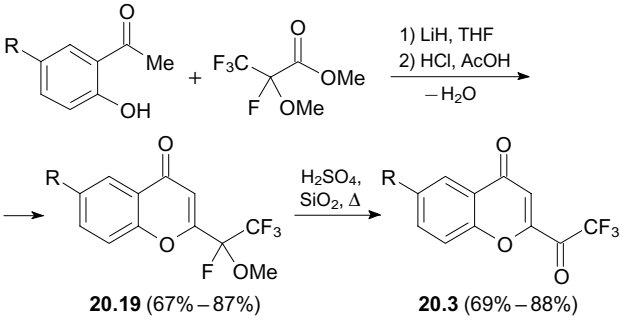


R = H, Me, MeO, F, Cl, Br, 4-$MeOC_4H_4$, 4-$EtO_2CC_6H_4$;
ppy is 2-phenylpyridine

20.2. 2-Trifluoroacetylchromones

2-Trifluoroacetylchromones **20.3** belong to the class of CF_3-containing chromones and behave as highly reactive trifluoromethyl 1,2-diketones. The two-step synthesis of these compounds from 2-hydroxyacetophenones and methyl 2-methoxy-2,3,3,3-tetrafluoropropionate with subsequent acid hydrolysis of chromones **20.19** containing a protected trifluoroacetyl group was first described by Irgashev *et al.*[998] in 2009. On treatment of chromones **20.19** with concentrated sulfuric acid in the presence of silicon oxide, the protection is readily removed, and 2-trifluoroacetylchromones **20.3** thus formed exist mainly as hydrates (Scheme 383).

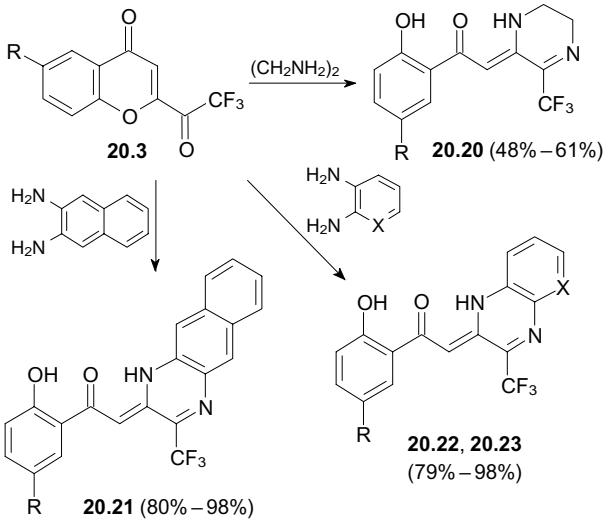
Scheme 383



R = H, Me, Cl

2-Trifluoroacetylchromones **20.3** react with 1,2-diamines with pyrone ring opening to give trifluoromethylated pyrazine derivatives. For example, the reaction with ethylenediamine in the presence of acetic acid in methanol at room temperature gives 5,6-dihydro-1*H*-pyrazine derivatives **20.20**. In a similar way, the reaction of chromones **20.3** with aromatic 1,2-diamines such as 2,3-diaminonapthtalene, *o*-phenylenediamine and 2,3-diaminopyridine on refluxing in acetic acid for 4 h affords benzo[*g*]quinoxalines **20.21**, quinoxalines **20.22** and pyrido[2,3-*b*]pyrazines**20.23**, respectively, in 79% – 98% yields.[999] In the last-mentioned case, a mixture of two regioisomers is formed; however, when the reaction is conducted at room temperature for 7 days, the selectivity markedly increases and the content of isomer **20.23** reaches 85% – 94%. It is evident that the initial attack by the most reactive β-NH_2 group is mainly directed at the C(2) atom of the chromone system (Scheme 384).

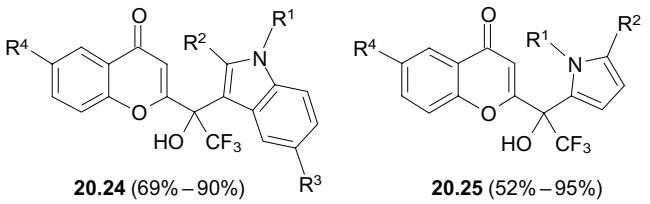
Scheme 384



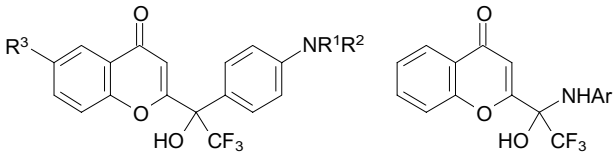
R = H, Me, Cl; X = CH (**20.22**), N (**20.23**)

In addition, 2-trifluoroacetylchromones **20.3** smoothly react with indoles and pyrroles at 90 °C for 5 h without solvents or catalysts thus forming (indol-3-yl)(chromon-2-yl)trifluoromethylcarbinols **20.24** and (pyrrol-2-yl)(chromon-2-yl)trifluoromethylcarbinols **20.25**.[1000] Aromatic amines behave as C- or N-nucleophiles, depending on the conditions, when react with chromones **20.3**. In the solvent-free reaction carried out at 100 °C for 12 – 18 h, they act as C-nucleophiles and afford bis[(het)aryl]carbinols **20.26**, whereas in refluxing toluene, primary arylamines add *via* the amino group to give the corresponding hemiaminals **20.27**.[1001]

Structures 20.24 – 20.27



R^1 = H, Me; R^2 = H, Me, Ph; R^3 = H, OMe; R^4 = H, Me, Cl



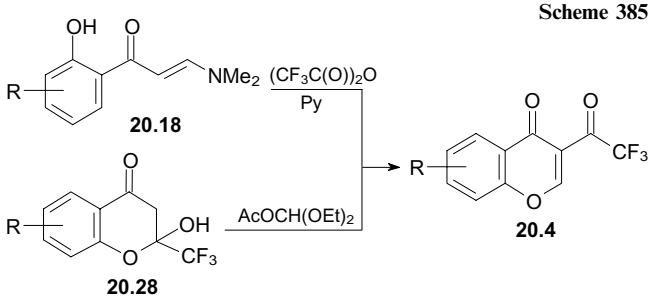
R^1, R^2, R^3 = H, Me

Ar = Ph, 4-$MeOC_6H_4$

20.3. 3-Trifluoroacetylchromones

3-Trifluoroacetylchromones **20.4** containing a β-dicarbonyl moiety and a latent formyl group have now found much wider use in organic synthesis than 2-trifluoroacetylchromones **20.3**. There are two key methods for their synthesis — trifluoroacetylation of amino enones **20.18** (Ref. 1002) and formylation of 2-hydroxy-2-trifluoromethylchroman-4-ones **20.28** under the action of diethoxymethyl acetate, which acts as the formylating agent and as the solvent (Scheme 385).[1003]

Scheme 385

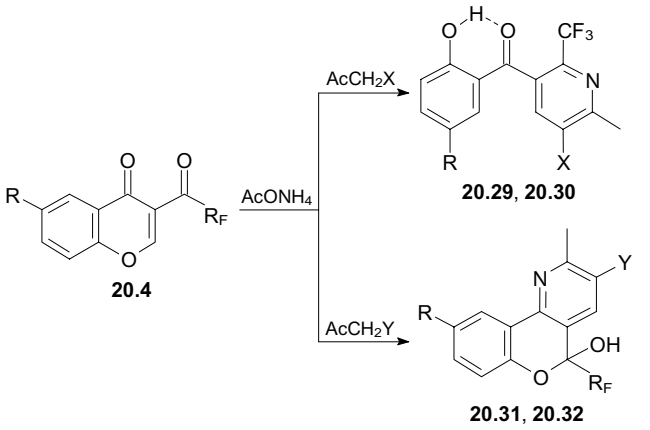


R = H, Me, OMe, Br, NO_2

The three-component reaction of chromones **20.4** with acetoacetamide and ethyl acetoacetate in ethanol in the presence of ammonium acetate is directed to the C(2) atom and is accompanied by pyrone ring opening followed by ring closure giving pyridines **20.29** and **20.30**. Meanwhile, the similar reaction of 3-R_FCO chromones with β-aminocrotononitrile and ethyl acetoacetate leads to 5-polyfluoroalkyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitriles **20.31** and **20.32** (Scheme 386).[1004]

Chromones **20.4** react with heterocyclic amines **20.33a** – **o** giving four types of products depending on the nature of the 1,3-C,N-dinucleophile and the solvent. In the case of aminoheterocycles **20.33a**,**i**,**j**,**l**, fused pyridines **20.34** were obtained, whereas **20.33e** – **h** were predominantly converted to chromeno[4,3-*b*]pyridines **20.35**. Refluxing of chromones **20.4** with amines **20.33b**,**k**,**m** – **o** in DMF gave chromanones **20.36** as the major products; refluxing with amines **20.33a** – **e** in acetic acid afforded pyridines **20.34** and **20.37**. These results provided the conclusion that α- and γ-CF_3-pyridines are formed from less aromatic heterocycles **20.33a** – **j**,**l**.[1005]

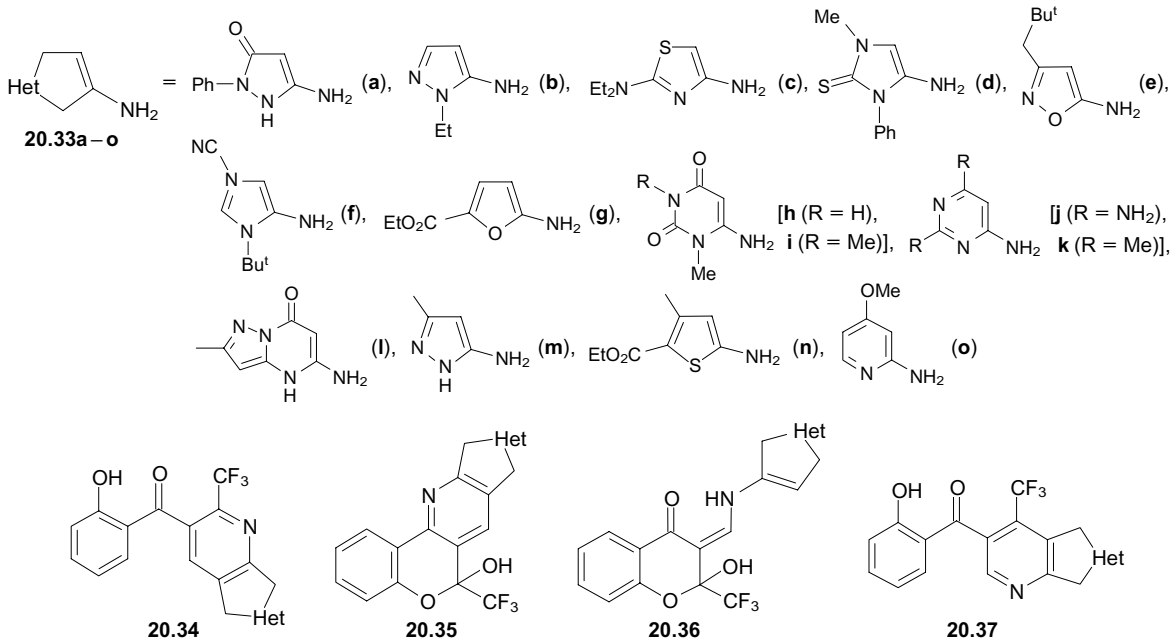
Scheme 386



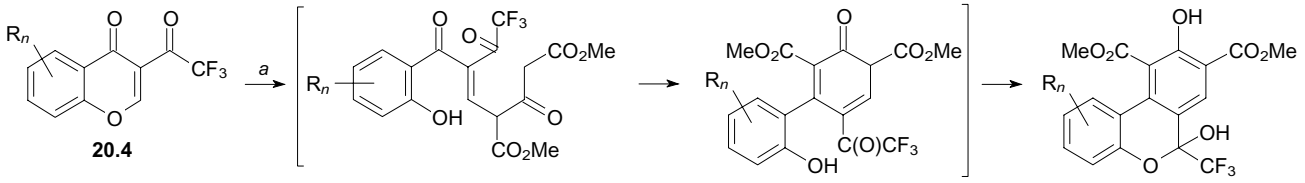
R_F = CF_3, CF_2H, $(CF_2)_2H$; R = H, Me, Cl;
20.29, **20.30**: X = $C(O)NH_2$ (46% – 50%), CO_2Et (18% – 20%);
20.31, **20.32**: Y = CN (23% – 42%), CO_2Et (26% – 69%)

Whereas chromones **20.4** react with enamines mainly at the $CF_3C(O)$ group to afford pyridine derivatives, the reaction of **20.4** with dimethyl acetonedicarboxylate follows the pathway leading to 6*H*-benzo[*c*]chromenes **20.38**. This heterocyclic system results from the initial 1,4-addition and subsequent pyrone ring opening, the attack by the second CH_2 group on the benzoyl carbon atom and cyclization involving the phenol hydroxyl group and the trifluoroacetyl group (Scheme 387). The same reaction is possible for polyfluoroacylchromones with R_F = C_2F_5 and C_3F_7.[1006]

Structures 20.33 – 20.37

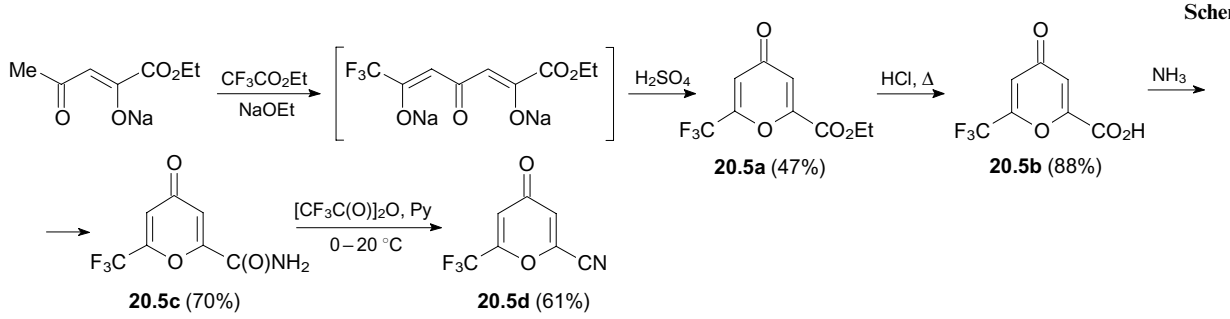


Scheme 387



(*a*) $(MeO_2CCH_2)_2CO$, DBU; R_n = H, Me, MeO, Cl, Br, benzo

Scheme 388



20.4. 6-Trifluoromethyl-4-pyrones

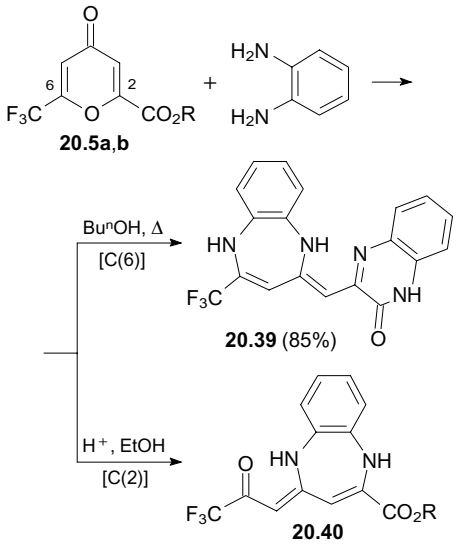
4-Pyrones are highly reactive latent tricarbonyl compounds, which have long been utilized for the synthesis of various derivatives *via* reactions with polynucleophiles. As in the case of chromones, the introduction of the CF_3 group into the pyrone ring increases not only the electrophilicity of the carbon atom attached to it, but also the reactivity of the molecule as a whole.[1007]

Ethyl 6-trifluoromethylcomanate **20.5a** was prepared in our study by the reaction of ethyl 2,4-dioxopentanoate with ethyl trifluoroacetate in the presence of NaOEt. This ester is readily hydrolyzed to acid **20.5b** on refluxing in 20% HCl and is converted to amide **20.5c** on treatment with 20% aqueous NH_3.[1008] The reaction of the amide with trifluoroacetic anhydride in the presence of pyridine yields nitrile **20.5d** (Scheme 388).[1009]

High reactivity of 6-trifluoromethylcomanic acid derivatives **20.5** is determined by the presence of two electron-withdrawing groups in positions 2 and 6. Because of similar electrophilicities of these reaction centres, the regio- and chemoselectivity of reactions can be switched between them. Indeed, even a minor change in the conditions (temperature, acidity and the nature or the solvent or the nucleophile) often crucially changes the direction of the initial attack.

One example is the reaction of 4-pyrones **20.5a,b** with *o*-phenylenediamine, which demonstrates the possibility to obtain different products depending on the medium acidity. Refluxing of compounds **20.5a,b** with *o*-phenylenediamine in Bu^nOH leads to quinoxalinone **20.39**, which is formed *via* the initial attack on the C(6) atom followed by pyrone ring opening and reaction with a second *o*-phenylenediamine molecule.[1010, 1011] An important feature of this reaction is the fact that all four reaction centres are involved in the design of the heterocyclic assembly — this is the first such example in the 4-pyrone chemistry. Conduction of the reaction in EtOH with the addition of hydrochloric acid changes the process pathway and results in the formation of benzodiazepines **20.40** *via* the attack on the C(2) atom (Scheme 389).

Scheme 389

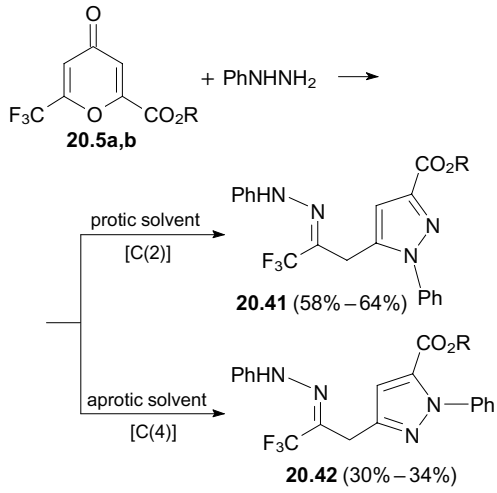


R = H (29%), Et (60%)

The reaction of pyrones **20.5a,b** with phenylhydrazine demonstrates that not only the medium acidity, but also the variation of the solvent nature can change the reaction selectivity. In polar protic solvents (EtOH for ester **20.5a** and a H_2O + HCl mixture for acid **20.5b**), this reaction leads to pyrazole-3-carboxylic acid derivatives **20.41**, whereas in aprotic media (toluene for ester **20.5a** and dioxane for acid **20.5b**), pyrazole-5-carboxylic acid derivatives **20.42** are formed.[1012, 1013] Different regiochemistry of this transformation is associated with the attack by the phenylhydrazine molecule on the C(2) atom in a protic medium and on the C(4) atom in an aprotic medium (Scheme 390).

The introduction of the cyano group into position 2 not only increases the reactivity of 2-cyano-6-trifluoromethyl-4-pyrone (**20.5d**), but also changes the selectivity of its reaction with nucleophiles. For example, the reaction of pyrone **20.5d** with hydrazine and phenylhydrazine on cool-

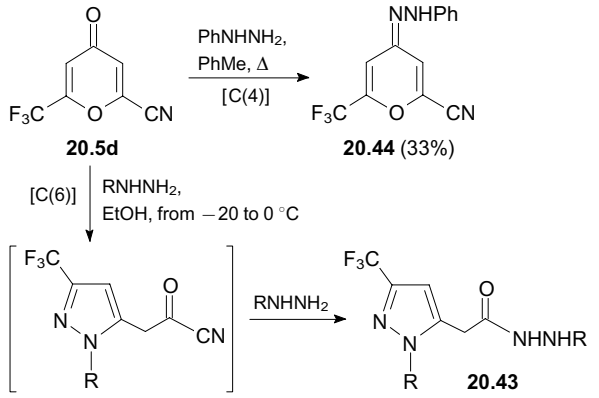
Scheme 390



R = H, Et

ing from −20 to 0 °C produced fluorine-containing pyrazoles **20.43**.[1009] A possible reaction mechanism includes the attack by the nucleophile on position 6 with the subsequent ring opening giving intermediate acyl cyanide, which then reacts with a second hydrazine molecule with displacement of the cyano group. Conduction of the reaction in toluene leads to hydrazone **20.44**; unlike analogous transformation of pyrones **20.5a**,**b**, this is not followed by pyrazole ring closure (Scheme 391).

Scheme 391



R = H (44%), Ph (70%)

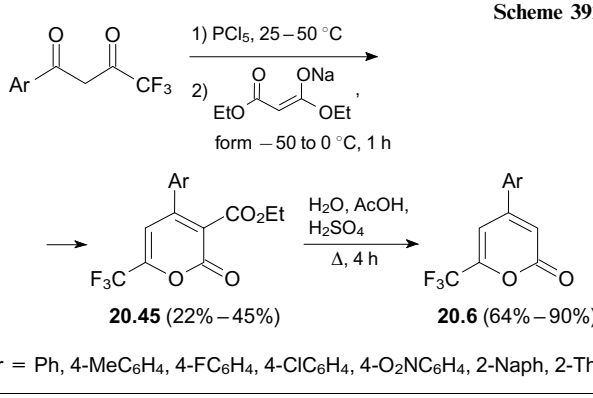
20.5. 6-Trifluoromethyl-2-pyrones

Previously, it was shown [1014, 1015] that successive treatment of 1-aryl-4,4,4-trifluorobutane-1,3-diones with phosphorus pentachloride and sodium diethyl malonate on cooling to −50 °C gives rise to ethyl 4-aryl-2-oxo-6-trifluoromethyl-2*H*-pyran-3-carboxylates **20.45**, which are converted to 4-aryl-6-trifluoromethyl-4-pyrones **20.6** on refluxing in aqueous acetic acid with addition of H_2SO_4 (Scheme 392).

In 2014, a method was proposed [1016] for the synthesis of pyrones **20.6** from phenylthioacetic acids and α,β-unsaturated trifluoromethyl ketones, which included the Michael addition catalyzed by isothiourea **20.46**, lactonization and elimination of benzenethiol (Scheme 393).

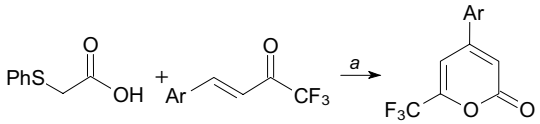
In particular, unlike 6-trifluoromethyl-4-pyrones **20.5**, which may react with nucleophiles at all three electrophilic

Scheme 392

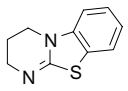


Ar = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 2-Naph, 2-Th

Scheme 393

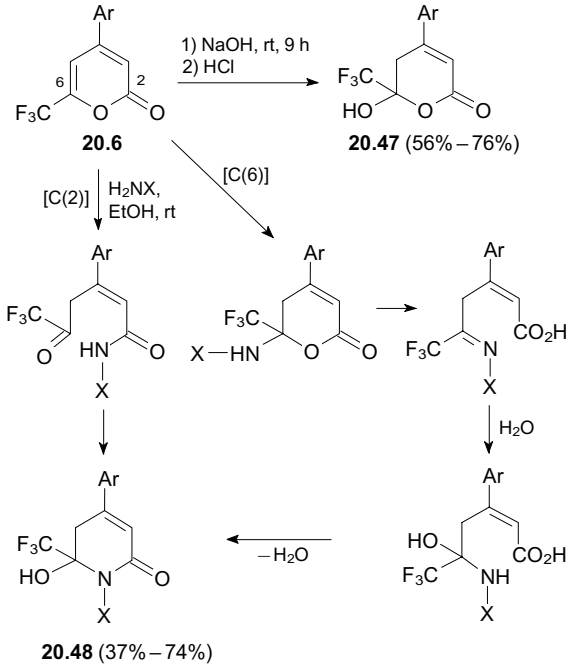


(*a*) 1) $Bu^tC(O)Cl$, Pr^i_2NEt; 2) **20.46**, MeCN, rt, 24 h;

20.46 =  ; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2-Th, 2-Fu, 2-Naph

centres of the pyrone ring [C(2), C(4) and C(6) atoms], 6-trifluoromethyl-2-pyrones **20.6** react with mono- and dinucleophiles only at the C(6) and/or C(2) atom. According to our recent data,[1017] reactions with sodium hydroxide, hydrazine and hydroxylamine proceed in ethanol at room temperature and give compounds **20.47** and **20.48**. Two possible mechanisms of formation of dihydropyridones **20.48** were proposed: the attack by the primary amino group on the C(2) atom to give amide, which cyclizes to

Scheme 394

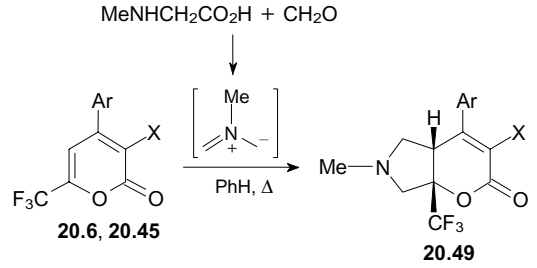


X = NH_2, OH

the final product **20.48** or the addition to the C(6) atom followed by ring opening, hydration and ring closure (Scheme 394).

One more important feature of 2-pyrones **20.6**, related to the presence of the trifluoromethyl group, is the ability to act as dipolarophiles in the [3 + 2]-cycloaddition reactions. It was shown that azomethine ylide generated *in situ* from sarcosine and formaldehyde reacts with pyrones **20.6** (X = H) and **20.45** (X = CO_2Et) on refluxing in benzene to give pyrano[2,3-*c*]pyrrolidines **20.49** only as the *cis*-diastereomers (Scheme 395).[1018]

Scheme 395

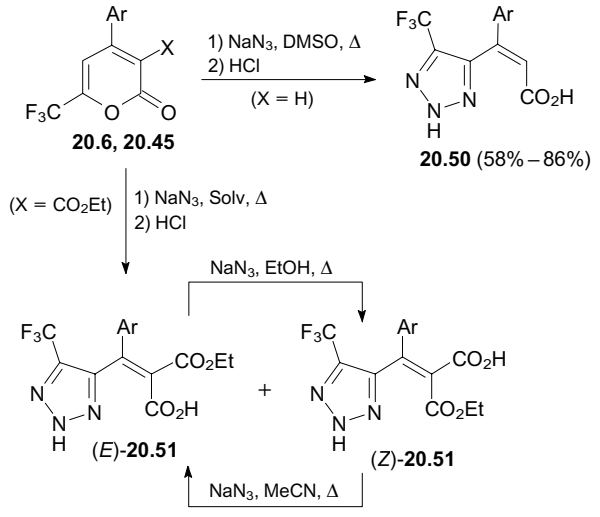


20.6, **20.45** **20.49**

Ar = Ph, 4-ClC_6H_4, 4-FC_6H_4; X = H (42% – 56%), CO_2Et (66% – 71%)

The [3 + 2]-cycloaddition reaction of sodium azide and pyrones **20.6** in DMSO affords (*Z*)-β-triazolylcinnamic acids **20.50**, while the presence of an ester group in pyrone position 3 (pyrones **20.45**) gives rise to a mixture of *E*- and *Z*-isomers **20.51** in a ratio considerably depending on the nature of the solvent. Conduction of the reaction in acetonitrile leads to *E*-isomers **20.51** as the only products (79% – 91% yield), which precipitate as the sodium salts. Salts of both isomers are soluble in ethanol, which promotes the formation of the sterically less hindered triazole (*Z*)-**20.51** [(*E*)-**20.51** : (*Z*)-**20.51** = 4 : 96 – 25 : 75; 67% – 81% yield]. The isomers (*E*)-**20.51** and (*Z*)-**20.51** are interconverted on refluxing in the corresponding solvent in the presence of sodium azide (Scheme 396).[1019]

Scheme 396



20.6, 20.45 **20.50** (58% – 86%)

(*E*)-**20.51** (*Z*)-**20.51**

Ar = Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 2-Naph

The introduction of the trifluoromethyl group into the pyrone system has a dual benefit. On the one hand, its electron-withdrawing effect increases the electrophilicity of the substrate, thus making it more reactive towards nucleophiles compared with non-fluorinated analogues, while on the other hand, quite a number of specific features of CF_3-containing compounds such as binding properties, metabolic stability and lipophilicity allow considering this group as a pharmacophore substituent and expect a beneficial effect in the search for biologically active molecule.

A brief survey of the latest data on the chemistry of trifluoromethylated chromones and pyrones indicates that these compounds are practically useful as small and accessible building blocks, which considerably expand the range of CF_3 synthons available to date. These compounds are finding increasing use in the synthesis of new derivatives of partially fluorinated heterocycles, many of which are of interest for medicinal chemistry as potential biologically active compounds. A characteristic feature of the CF_3 synthons is their high reactivity, which provides the possibility of using a large set of mono- and dinucleophiles, and high regioselectivity of their reactions, which allows the synthesis of single products in good yields.

Currently, the chemical properties of 2-trifluoromethyl- and 3-trifluoroacetylchromones have been studied rather comprehensively, whereas the studies of other chromones and pyrones considered in this chapter are at their infancy. Nevertheless, it is already clear that 2-trifluoroacetylchromones behave towards N- and C-nucleophiles as 1,2-diketones with one protected carbonyl group, while 6-trifluoromethyl-4(2)-pyrones attract attention as dipolarophiles and chameleonic substrates, possessing several electrophilic centres and capable of selectively reacting at one of these centres, depending on the reaction conditions or the reagent nature. Generally, it can be concluded that the chemical behaviour of trifluoromethylated chromones and pyrones has not been fully investigated and their synthetic potential has been only partly identified.

21. Conclusion

The ability of the fluorine atom to considerably affect the chemical and physicochemical properties of organic compounds accounts for the broad range of practical applications of fluorine derivatives. One of the most needed applications of organofluorine compounds is medicinal chemistry. In this connection, it is not surprising that the studies of the last decade are largely focused on the development of synthetic strategies towards molecules containing a fluorine atom or fluorinated group. The approaches based on modification of fluorinated substrates and on introduction of a ready organofluorine moiety into the molecule were actively formed. The latter approach included the active development of the chemistry of organoelement compounds, which act as convenient synthetic equivalents for direct introduction of fluorinated groups. These reactions are most conveniently performed using silicon derivatives, which, on the one hand, can be stored in air and, hence, are attractive as commercial chemicals, and, on the other hand, can be involved into various transformations under mild conditions. Apart from the trifluoromethyl group, considerable interest is aroused by compounds with a difluoromethylene moiety or difluorohalomethyl group.

A lot of attention was paid to the preparation and structural modification of heterocyclic compounds, which is also caused by their importance for medicinal chemistry and agrochemistry. Therefore, investigations of fluorinated pyridines, quinolines and chromones are highly significant.

The fluorine atom can substantially affect the reactivity of neighbouring functional groups. Owing to the strong electron-withdrawing effect, the fluorine atom and especially the trifluoromethyl group substantially increase the reactivity of double and triple bonds, carbonyl groups and the azomethine moiety. For this reason, fluorine-substituted alkenes, acetylenes, carbonyl compounds and imines possess unique properties.

Apart from synthetic applications, fundamental aspects of the reactivity of organofluorine intermediates have been actively studied. In particular, the studies addressed reactions involving carbocations and carbanions containing fluorinated substituents, reactions involving difluorocarbenes and reactions of radical anion species based on fluorine-substituted arenes.

It is evident that achievements of the Russian organofluorine chemistry of the last fifteen years, which are reflected in this review, are largely based on the foundation laid by scientific schools of the second half of the 20th century. Meanwhile, the vigorous growth of the number of works in organofluorine chemistry observed all over the world in the last decade created conditions for the initiation of new trends of this research area in Russia. The ever increasing significance of fluorine compounds brings the development of high-performance synthetic methods to the forefront; the knowledge accumulated to date creates prerequisites for further growth.

Chapter 2 (by L.V.Politanskaya, G.A.Selivanova, E.V.Panteleeva and E.V.Tretyakov) was written with the financial support of the Russian Science Foundation (RSF) (Project No. 18-13-00173) and the Russian Foundation for Basic Research (RFBR) (Project No. 19-53-53003); chapter 7 (by Ya.V.Burgart, E.V.Shchegolkov and V.I.Saloutin) was written with the financial support of the RSF (Project No. 16-13-10255); chapter 8 (by V.B.Sokolov and A.Yu.Aksinenko) was prepared within the state assignment of the Ministry of Education and Science of Russia for 2018–2020 (theme No. 0090-2017-0023); chapter 11 (by A.A.Tabolin and S.L.Ioffe) was written with the financial support of the RFBR (Project No. 18-03-00810); chapter 12 (by V.M.Muzalevskiy, E.S.Balenkova, A.V.Shastin and V.G.Nenajdenko) was written with the financial support of the RFBR (Project No. 16-03-00936-a); chapter 15 (by N.Yu.Adonin and V.V.Bardin) was written with the financial support of the RFBR (Project No. 16-29-10762 ofi_m); chapter 16 (by S.N.Osipov, D.V.Vorobyeva and S.M.Masoud) was written with the financial support of the RSF (Project No. 16-13-10364); chapter 17 (by E.V.Nosova, G.N.Lipunova and V.N.Charushin) was written with the financial support of the RSF (Project No. 15-13-00077-P) and within the state assignment of the Ministry of Education and Science of Russia for 2018 – 2020 (theme No. 4.6351.2017/8.9); chapter 19 was written with the financial support of the RFBR (by K.V.Belyaeva, Project No. 18-03-00762) and within the state assignment of the Ministry of Education and Science of Russia (B.A.Trofimov and L.N.Sobenina; theme No. V.44.5.6); chapter 20 (by V.Ya.Sosnovskikh, D.L.Obydennov and S.A.Usachev) was written with the financial support of the RFBR (Project No. 17-03-00340).

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