Mendeleev Commun., 2006, **16(3)**, 121–128

A new methodology for the preparation of fluoroaromatic compounds based on fluorinated dihalocarbenes and polyhaloolefins as building blocks

Oleg M. Nefedov* and Nikolai V. Volchkov

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 495 135 6390; e-mail: volchkov@ioc.ac.ru

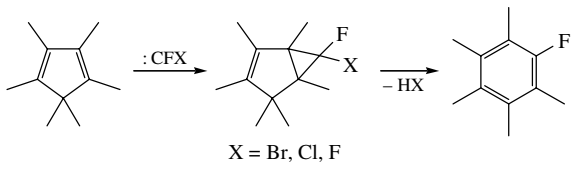
DOI: 10.1070/MC2006v016n03ABEH002362

A new general methodology has been developed for the synthesis of diverse fluoroaromatic compounds based upon the utilization of fluorohalocarbenes and fluorinated polyhaloolefins as fluoro-containing building blocks, on the one hand, and unsaturated or polyunsaturated cyclic or acyclic compounds (cyclopentadiene and its derivatives, indenes, allylbenzenes, styrenes and acyclic 1,3-dienes), on the other hand. In most cases, the process can occur as one or two step reaction involving sequential cycloaddition, isomerisation with ring expansion, and aromatisation accompanied by dehydrohalogenation. Examples of the use of the resulting fluoroaromatic compounds for the preparation of important biologically active compounds are presented.

Owing to the unique effect of fluorine on physicochemical and biological properties, fluorinated organic compounds are widely used as efficient medicines, agrochemicals and engineering materials.[1,2] Practically useful fluorine-containing medicines and agrochemicals contain a fluorinated aromatic residue as a part of their structure. The list of well-known compounds of this type includes fluoroquinolone-based antibacterial drugs (Pefloxacin, Ciprofloxacin and their analogues), tranquilizers and antidepressants belonging to fluorinated benzo-1,4-diazepines (Fludiazepam and Flunitroazepam), neuroleptics of the butyrofluorophenone series (Haloperidol, Droperidol and their analogues), the antifungal agent Fluconazole, non-steroidal antiinflammatory drugs (Flufenisal, Diflunisal and Flubiprofen).[1,2] Among agrochemicals, one should mention inhibitors of chitin biosynthesis belonging to fluorinated benzoylphenylureas (Diflubenzuron and Chlorofluazaron), efficient fluorophenyltriazole fungicides and bactericides (Flutriafol and Flusilazol), and fluorobenzamide herbicides (Barnon, Metaven and Flamprop-isopropyl).[2]

These unique properties of fluoroaromatic compounds stimulate the search and development of new methods for their preparation. Traditional methods for the synthesis of fluoroaromatic compounds are based on the direct substitution of hydrogen or functional groups attached to the aromatic ring with fluorine by treatment with various fluorinating reagents.[2,3] An alternative synthetic strategy suggests a controlled assembling of fluorinated arene structures with the use of fluorine-containing synthons capable of acting both as structural building blocks and carriers of fluorine attached to the carbon atom.

A typical example of such an approach shown in Scheme 1 includes [2 + 1]-cycloaddition of fluorohalocarbenes to cyclopentadienes to give dihalobicyclo[3.1.0]hexenes followed by the selective rearrangement *via* dehydrohalogenation and ring expansion.



X = Br, Cl, F

Scheme 1

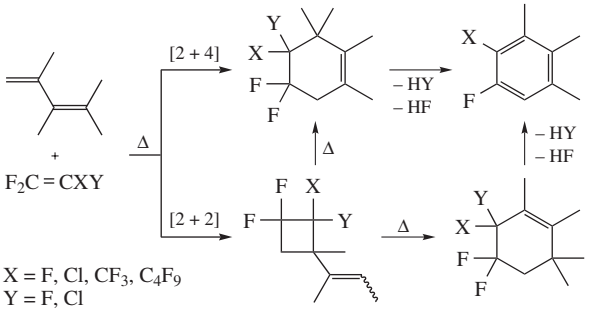
At present, the synthetic potential of this reaction, which seems to be of limited applicability initially, has been developed into a general method for the carbene-based synthesis of fluoroaromatic compounds from various types of diene substrates using various methods to generate fluorohalocarbenes.

The above strategy could also be implemented with the use of a different pathway for the construction of fluorobenzoid structures, namely, the thermal cycloaddition of fluoroolefins to 1,3-dienes followed by aromatisation of the resulting fluorinated carbocyclic adducts. In this case, the formation of the required

Oleg M. Nefedov is the head of laboratory at N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences (RAS) and the Chair (Rector) of the Higher Chemical College of the RAS. He graduated from D. I. Mendeleev Moscow Institute of Chemical Technology (1954) and received his Candidate (Ph.D.) degree in 1957. Since 1957, he is working at N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences and in 1967 he received his Doctor of Chemistry degree. He is a full member of the RAS (since 1987), Honorary Fellow of the Royal Society of Chemistry (since 1991) and the member of international and national academies. In 1988–2001, he was Vice-President of the Russian Academy of Sciences. He is awarded by various prizes in science and technology. He is the Chair of the National Committee of Russian Chemists, Member of IUPAC Bureau & the Executive Committee. His research interests include the structure and properties of carbenes and related reactive intermediates, the chemistry of strained small-ring compounds, diazo compounds and fluoroaromatic compounds.

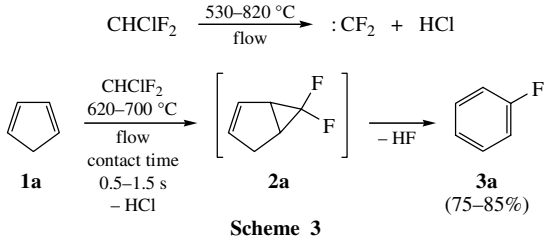
Nikolai V. Volchkov is a senior researcher at N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences. He graduated from D. I. Mendeleev Moscow Institute of Chemical Technology in 1978. Since that he is working at N. D. Zelinsky Institute of Organic Chemistry. He received his Candidate (Ph.D.) degree in organic chemistry in 1983. His research interests focus on the chemistry of fluorohalocarbenes, the reactions of fluorinated three- and four-membered carbocyclic compounds and the development and application of new methods for the preparation of fluoroaromatic compounds.

fluorinated C_6-cyclic carbon skeleton may occur either directly as [4 + 2]-cycloaddition of fluoroalkenes to dienes or *via* initial [2 + 2]-cycloaddition with the subsequent rearrangement with ring expansion typical of vinylcyclobutanes (Scheme 2).



Scheme 2

Carbene synthesis of fluoroaromatic compounds. The practical significance of the carbene method for the preparation of fluoroaromatic compounds is primarily due to the facile generation of fluorine-containing dihalocarbenes from accessible precursors, *e.g.*, fluorohalomethanes. The pyrolysis of chlorodifluoromethane, which proceeds as a selective molecular α-dehydrochlorination over a broad temperature range, is a well-known reaction of this type.[4] In the absence of difluorocarbene acceptors, the reaction ends up with the carbene recombination to give tetrafluoroethylene. However, if the pyrolysis of $CHClF_2$ is carried out in the presence of cyclopentadiene **1a**, the difluorocarbene thus formed is almost completely trapped by the diene to give fluorobenzene **3a** as a final thermally stable product.[5–12]



Scheme 3

On a preparative scale, this synthesis is carried out in one-pot transformation by passing a vapour-gas mixture of cyclopentadiene **1a** (or its dimer) and chlorodifluoromethane through a tube reactor at 620–700 °C (contact time of 0.5–1.5 s). These conditions ensure the efficiency of the initial step of $CHClF_2$ fragmentation into difluorocarbene and rearrangement of intermediate difluorobicyclo[3.1.0]hexene **2a** with HF elimination (Scheme 3).[5–12]

A number of modifications of co-pyrolysis of cyclopentadiene **1a** with $CHClF_2$ in the presence of water vapour or water–ammonia mixtures[7,10–12] or on solid alkaline packing[12,13] have been elaborated in order to decrease tar formation and increase the selectivity of the reaction.

Aside from $CHClF_2$, this process can be carried out with other industrial freons of the methane series (CHF_3, $CFCl_3$, CF_2Br_2 and CF_2Cl_2), as well as tetrafluoroethylene, hexafluoropropylene and polyfluorocarboxylic acids, which are capable of undergoing fragmentation under conditions of gas-phase pyrolysis with formation of difluoro- or chlorofluorocarbene.[6–9,12]

The reactions considered above are of general nature; they can be successfully used for one-step syntheses of fluorotoluenes **3b**,[6–9,12] difluorobenzenes **4**,[6,7,12,14–16] and binuclear aromatic fluorides **5** or **6**[5–9,12,17,18] by copyrolysis of chlorodifluoromethane with methylcyclopentadiene **1b**, 1,3-dienes **7**, indenes **8** and alkenylarenes **9** or **10** (Scheme 4).

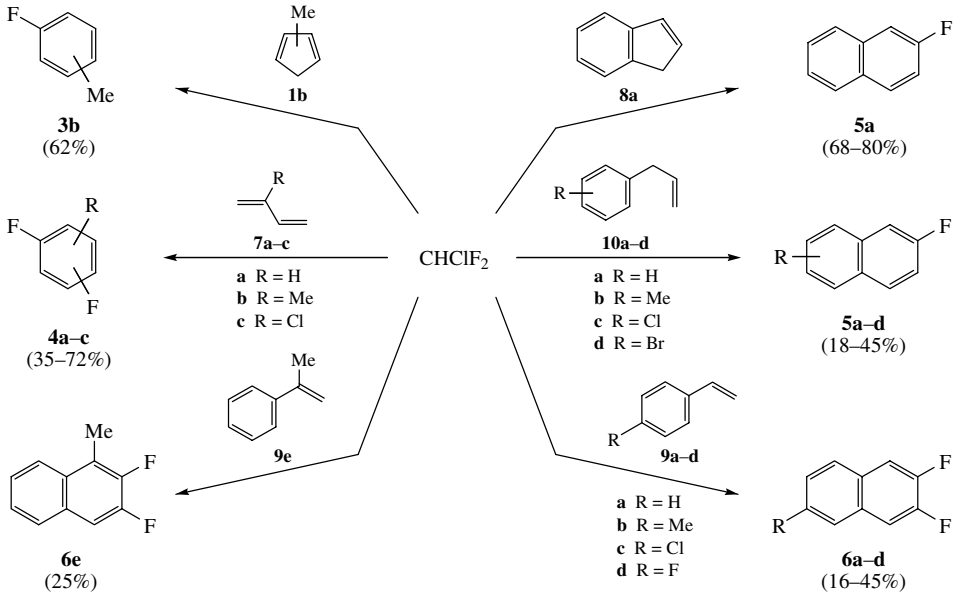
For example, the copyrolysis of $CHClF_2$ with methylcyclopentadiene **1b** (or with its dimer) at 600 °C (contact time of 2–3 s) gives a mixture of isomeric fluorotoluenes **3b** (*ortho*:*meta*:*para* = = 2:1:1) in a total yield of about 60%.[5–7,12] The copyrolysis of $CHClF_2$ with indene **8a** at 600–670 °C (contact time of 1–3 s) selectively gives 2-fluoronaphthalene **5a** (yields 68–80%)[6–9,12] (Scheme 4). In the latter case, allylbenzenes **10a–d**, which are capable of thermal cyclisation into indenes, can be used instead of an indene.[19]

Similarly, trifluoromethyl-substituted arenes **11** or **12** can be obtained[12] by the copyrolysis of cyclopentadiene or its analogues with fluorotrifluoromethylcarbene precursors (Scheme 5).

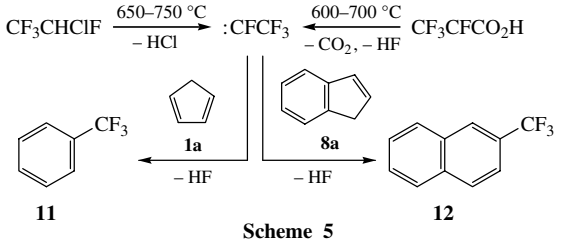
The synthetic potential of the carbene method for the preparation of fluoroaromatic compounds, which was originally carried out as a pyrolytic gas-phase processes, was substantially expanded later due to the elaboration of phase-transfer catalysis conditions[20–27] with dichlorofluoromethane as a chlorofluorocarbene precursor. Substituted cyclopentadienes, their dimers, indenes, dihalocyclopentenes, spiro-fused cyclopentadienes and fulvenes can be used in these syntheses as starting substrates to give corresponding aromatic fluorine compounds (Schemes 6–9).

The specific stereochemical feature of these reactions was established. It was found that the reaction of dichlorofluoromethane with indene **8a** in the two-phase system CH_2Cl_2–KOH_{aq}–TEBA at –5 to +5 °C results in a mixture of two isomeric cyclopropane adducts, (*Z*)-**13** and (*E*)-**13** (Scheme 6).[22,24–26]

Adduct (*Z*)-**13** with the *endo*-chlorine configuration is thermally unstable, and it is converted in a nearly quantitative yield to

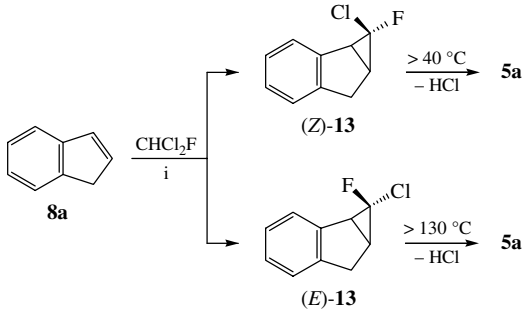


Scheme 4 *Conditions*: flow reactor, 600–680 °C, contact time: 1–3 s.



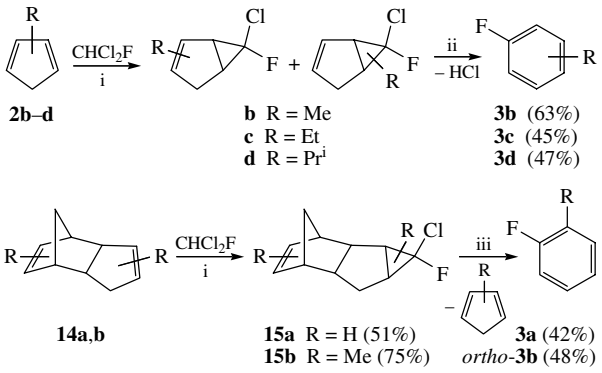
Scheme 5

2-fluoronaphthalene **5a** with HCl elimination in the temperature range 40–75 °C. Adduct (*E*)-**13** with the *endo*-fluorine configuration is more thermally stable (up to 120 °C); however, it is also converted to compound **5a** in 80–85% yield with elimination of HCl, though one could expected preferential HF elimination for (*E*)-**13**.[28] This peculiarity enables the preparative synthesis of 2-fluoronaphthalene **5a** in one step by stirring the reagents for 2–3 h followed by distillation of the reaction mixture at 100–150 °C without isolation of intermediate chlorofluorocyclopropane adducts and with complete utilization of organically bound fluorine.



Scheme 6 *Reagents and conditions*: i, KOH_{aq} (50%), TEBA (cat.), CH_2Cl_2, –5 to +5 °C.

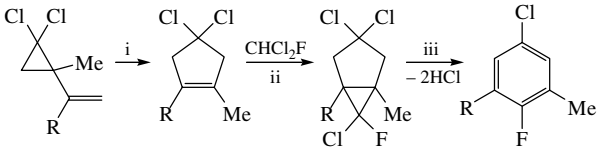
Corresponding alkylfluorobenzenes **3b** (*ortho*:*meta*:*para* = = 90:9:1), **3c** (*ortho*:*meta*:*para* = 81:15:4) or **3d** (*ortho*:*meta*:*para* = 58:32:10) were obtained in a similar way in 45–63% yields by reactions of dichlorofluoromethane with alkylcyclopentadienes **1b–d** (Scheme 7).[20–25] The isomeric composition of the resulting alkylfluorobenzenes observed for these conversions is determined by the relative rates of the competitive addition of chlorofluorocarbene to alkylated and non-substituted double bonds of starting alkylcyclopentadienes.



Scheme 7 *Reagents and conditions*: i, KOH_{aq} (50%), TEBA (cat.), CH_2Cl_2, –5 to +5 °C; ii, 120–150 °C; iii, 230 °C.

Like in the pyrolytic processes considered above, fluoroarenes can also be obtained by reactions of dichlorofluoromethane with cyclopentadiene dimers instead of cyclopentadienes. Thus, dicyclopentadienes **14a**,**b** can be efficiently chlorofluorocyclopropanated with dichlorofluoromethane under conditions of phase-transfer catalysis.[23–25] The heating of resulting adducts **15a**,**b** (220–230 °C) furnishes corresponding fluorobenzenes **3a**,**b** *via* an opening of the cyclopropane ring, dehydrochlorination and retro Diels–Alder reaction (Scheme 7). In case of methylcyclopentadiene dimers **14b**, the cycloaddition of chlorofluorocarbene occurs exclusively at the methyl-substituted double bonds of the cyclopentene fragment, thus leading ultimately to the regioselective preparation of 2-fluorotoluene (*ortho*-**3b**) in the striking contrast to the reaction with monomeric methylcyclopentadiene **1b**.

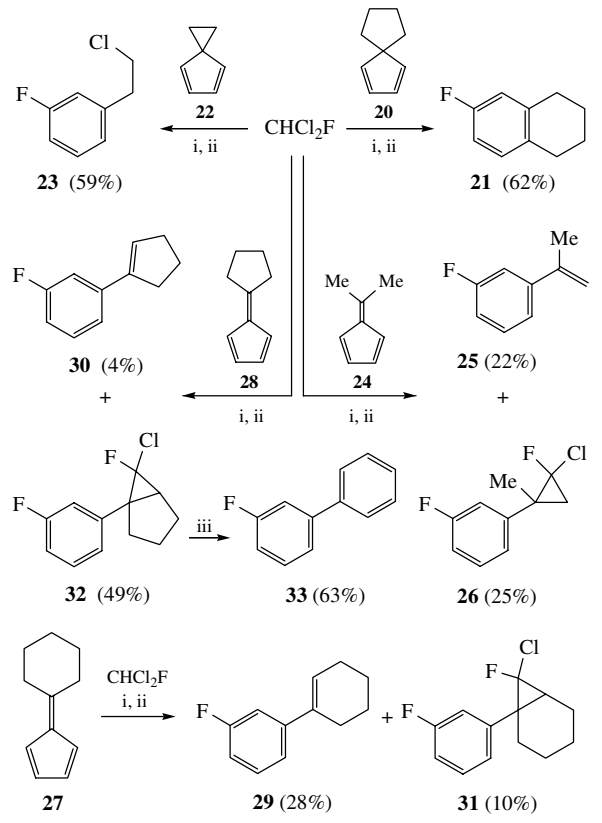
Another method for the regioselective carbene synthesis of substituted fluoroarenes[27] involves the use of dihalocyclopentenes **16**, which can be easily obtained by the thermal isomerisation of 1-vinyl-2,2-dichlorocyclopropanes **17**. In particular, this method can be employed for the regioselective syntheses of fluorinated chlorotoluenes and chloroxylenes **18a–c** *via* cycloaddition of chlorofluorocarbene, (generated from $CHCl_2F$ under conditions of phase-transfer catalysis), to 4,4-dichlorocyclopentenes **16a–c** followed by the selective thermal rearrangement of resulting bicyclo[3.1.0]hexane adducts **19a–c** with ring expansion and double dehydrochlorination[27] (Scheme 8).



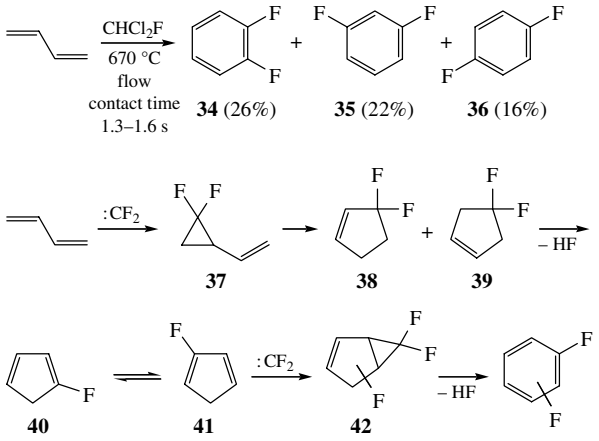
17a R = H **16a** (85%) **19a** (65%) **18a** (87%)
17b R = Me **16b** (82%) **19b** (68%) **18b** (84%)
17c R = F **16c** (83%) **19c** (34%) **18c** (85%)

Scheme 8 *Reagents and conditions*: i, flow reactor, 330–350 °C; ii, KOH_{aq}, TEBA (cat.), CH_2Cl_2, –5 to +5 °C; iii, flow reactor, 400 °C.

The mild conditions of the chlorofluorocarbene generation from $CHCl_2F$ in the presence of a phase-transfer catalyst allow us to use as the substrates comparatively labile diene compounds, which cannot be used in pyrolytic processes. This approach is applicable to the preparation of 6-fluorotetralin **21** from spiro[4.4]nona-1,3-diene **20** in 62% yield and (chloroethyl)fluorobenzene **23** from spiro[2.4]hepta-4,6-diene **22** in 59% yield[20,21,25] (Scheme 9).



Scheme 9 *Reagents and conditions*: i, KOH_{aq} (50%), TEBA (cat.), CH_2Cl_2, –5 to +5 °C; ii, 100–150 °C; iii, flow reactor, packed Al_2O_3, 300 °C.



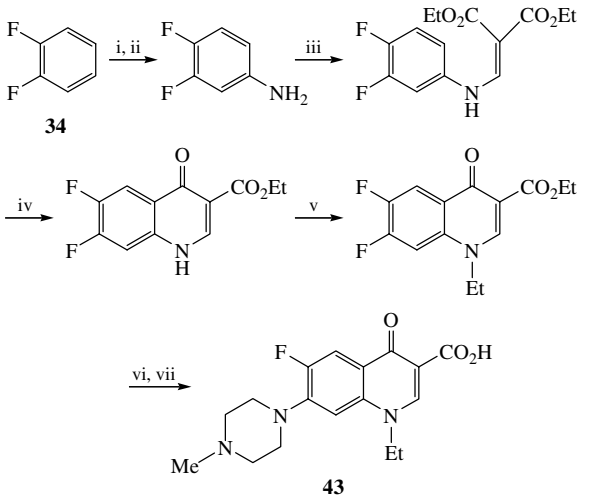
Scheme 10

Fulvenes can also be employed as starting compounds in similar syntheses[23–25] (Scheme 9). For example, the reaction of 6,6-dimethylfulvene **24** with $CHCl_2F$ in the presence of aqueous KOH and TEBA results in a mixture of 3-fluoro-α-methylstyrene **25** (yield 22%) and its chlorofluorocarbene cycloadduct **26** (yield 25%). Similar reactions of penta- and tetramethylenefulvenes **27** and **28** give[23–25] corresponding cycloalkenylfluorobenzenes **29** or **30** and products **31** or **32** of their subsequent chlorofluorocyclopropanation. Chlorofluorocyclopropane **32** formed in the latter case can be subjected to a thermal rearrangement with ring expansion and dehydrohalogenation to give 3-fluorobiphenyl **33** (Scheme 9).

The above carbene method is convenient for the preparation of difluoroaromatic compounds. One of the most interesting and practically important examples is the one-step synthesis of difluorobenzenes **34**–**36** in a total yield of 65–72% by copyrolysis of a mixture of chlorodifluoromethane and buta-1,3-diene in a flow reactor at 620–700 °C (Scheme 10).[6,7,12,14–16,25]

This process involves[6,12,25] a complex sequence of reactions, namely, addition of difluorocarbene, which is generated from $CHClF_2$, to buta-1,3-diene; thermal isomerisation of resulting vinyldifluorocyclopropane **37** to difluorocyclopentenes **38** and **39**; the subsequent dehydrofluorination of the latter to fluorocyclopentadienes **40** and **41**, which are further converted into difluorobenzenes *via* formation and thermal rearrangement of trifluorobicyclo[3.1.0]hexenes **42** (Scheme 10).

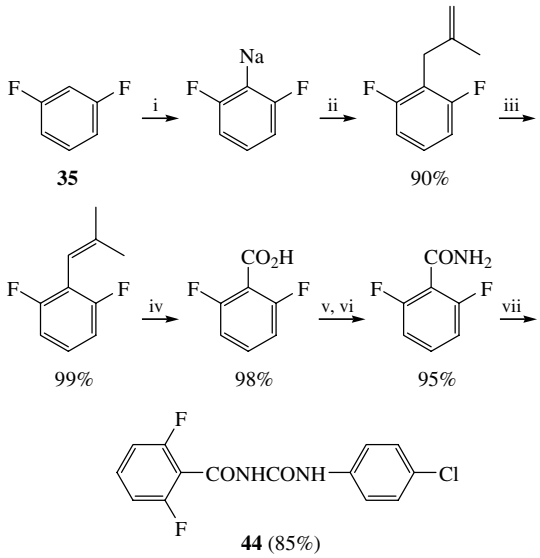
Based on this process, we have elaborated a new semi-industrial technology for the preparation of difluorobenzenes, involving a one-step synthesis of mixtures of isomeric difluorobenzenes followed by their separation by fractional and extractive distillation[29] giving individual isomers with 98–99% purity.



Scheme 11 *Reagents and conditions*: i, HNO_3, H_2SO_4, 10–35 °C; ii, H_2, Pd/C; iii, $EtOCH{=}C(CO_2Et)_2$, 105–110 °C; iv, 225–235 °C; v, EtBr, K_2CO_3, DMFA; vi, AcOH, H_2SO_4; vii, *N*-methylpiperazine, DMSO, 105–110 °C.

1,2-Difluorobenzene **34** obtained by this procedure was used for the commercial production of 3,4-difluoroaniline[30] and for the development of a technology for the preparation of highly efficient antibacterial agent Pefloxacin **43** (Scheme 11).[31–33]

Another example refers to the development of a process[34,35] for the preparation of an inhibitor of chitin biosynthesis, *viz.*, diflubenzuron (Dimilin) **44** from 1,3-difluorobenzene **35** (Scheme 12).



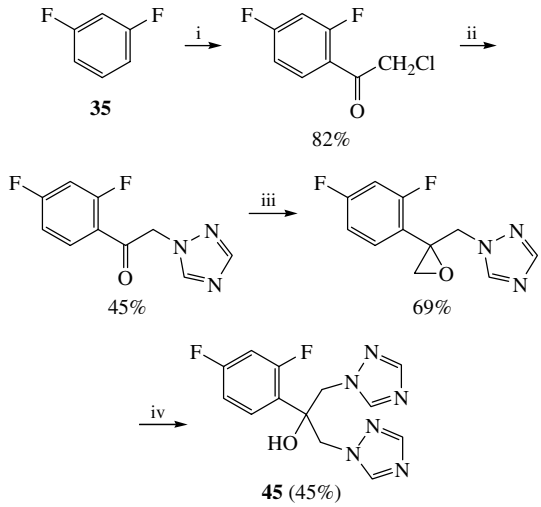
Scheme 12 *Reagents and conditions*: i, Na, NH_3, $FeCl_3$, –33 °C; ii, $ClCH_2(Me)C{=}CH_2$, –33 °C; iii, TsOH, benzene, 80 °C; iv, O_3, O_2, H_2O_2, Ac_2O, SeO_2; v, $SOCl_2$; vi, NH_3; vii, 4-ClC_6H_4NCO, xylene, 140–142 °C.

One more example of the targets directed utilization of 1,3-difluorobenzene is the synthesis of highly efficient antifungal compound Fluconazole **45** (Scheme 13).

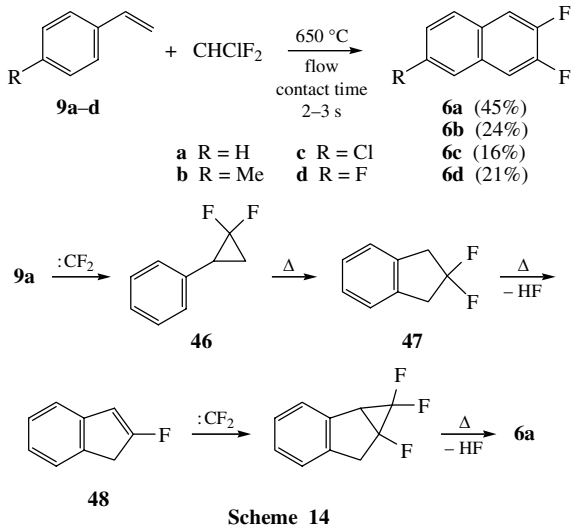
Using a carbene-based method, namely, the copyrolysis of chlorofluoromethane with styrenes **9a**–**e**, we succeeded in preparation of 2,3-difluoronaphthalene **6a** and its derivatives **6b**–**e**, a hitherto unknown class of fluoroaromatic compounds[6,12,18,25] (Schemes 4, 14).

The mechanism of the process experimentally proven[6] for the synthesis of compound **6a** involves the consecutive cycloaddition of difluorocarbene to original styrene **9a** and to intermediate fluoroindene **48** (Scheme 14).

Resulting 2,3-difluoronaphthalene **6a** can be selectively converted into various functional derivatives **49**–**56** by electrophilic substitution reactions proceeding at the 5-position or by metallation with BuLi that occurs selectively at the 1- or 4-positions (Scheme 15).[36]

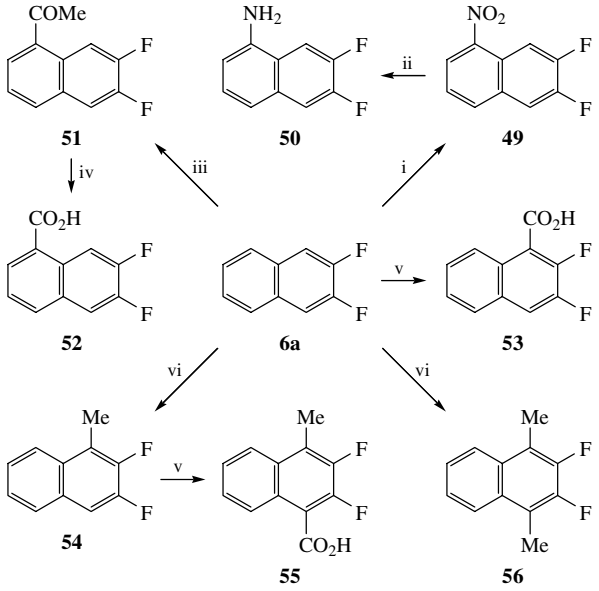


Scheme 13 *Reagents and conditions*: i, $CH_2ClCOCl$, $AlCl_3$, 40–43 °C; ii, 1,2,4-triazole, NEt_3, $MeCO_2Et$, 75–78 °C; iii, $Me_3S^+OI^-$, Me_4NBr, toluene, NaOH, 60 °C; iv, 1,2,4-triazole, K_2CO_3, DMSO, 90 °C.



Scheme 14

Difluoronaphthalenes **49**–**56**, which are practically inaccessible by other synthetic methods, are of considerable interest for the syntheses of new compounds with potentially high biological activity. For example, according to our *in vitro* studies, 2,3-difluoro-5-nitronaphthalene **49** has a high mycostatic activity against a number of pathogenic agents of surface and deep mycoses, such as *Candida albicans*, *Trichophyton gypseum* and *Microsporon lanosum*.

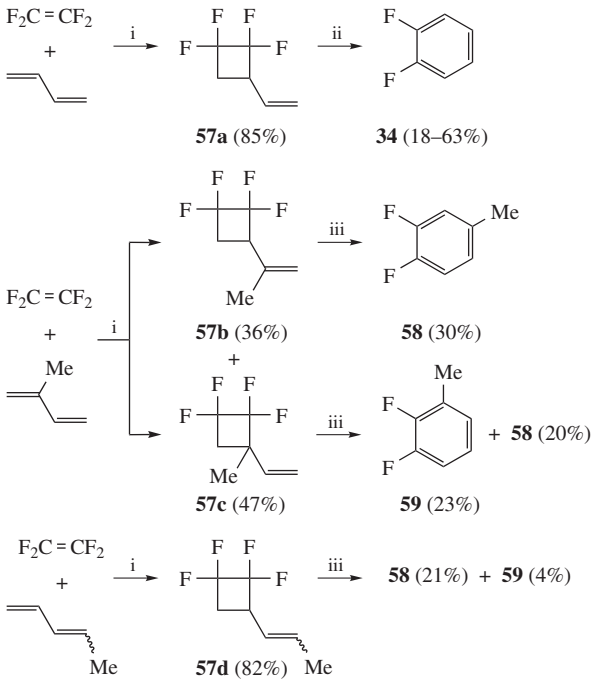


Scheme 15 *Reagents and conditions*: i, HNO_3, H_2SO_4, 20–50 °C; ii, NH_2NH_2, H_2O, Ni, EtOH, 30–40 °C; iii, MeCOCl, $AlCl_3$, CH_2Cl_2, 25 °C; iv, $NaOH_{aq}$, Br_2, 0–10 °C; v, BuLi, THF, –75 °C, CO_2, HCl; vi, BuLi, THF, –75 °C, MeI.

Synthesis of fluoroaromatic compounds by thermal cycloaddition of polyfluoroolefins to 1,3-dienes. A general approach to the synthesis of aromatic fluorine compounds is based on the ability of fluoroolefins to undergo thermally induced addition to 1,3-dienes by [2 + 4]- and [2 + 2]-cycloaddition types.[37] In this case, terminal polyfluoroolefins typically undergo preferential or exclusive [2 + 2]-cycloaddition. The resulting vinylcyclobutane adducts can be converted to fluoroaromatic compounds *via* the step of vinylcyclobutane–cyclohexene rearrangement.[25,38–52]

For example, 1-vinyl-2,2,3,3-tetrafluorocyclobutane **57a** obtained by thermal addition of tetrafluoroethylene to buta-1,3-diene is converted to 1,2-difluorobenzene **34** in a flow reactor packed with pieces of quartz or other solid materials (activated carbon, Al_2O_3, Cu, MgO, *etc.*) at 400–800 °C (Scheme 16).[38,39]

The pyrolysis of methyl-substituted tetrafluoro(vinyl)cyclobutanes **57b**–**d** obtained by thermal cycloaddition of tetrafluoroethylene to isoprene or penta-1,3-diene under similar conditions results[38,39] in 3,4-difluorotoluene **58** or its mixtures with 2,3-difluorotoluene **59** (Scheme 16).



Scheme 16 *Conditions*: i, flow reactor, 470 °C, contact time 4–6 s; ii, flow reactor, 600–800 °C, contact time 4–8 s; iii, flow reactor, 650 °C, contact time 6–8 s.

Similar results were obtained by Weigert,[50,51] who reported a synthesis of 1,2-difluorobenzene **34** (yield 20–67%) from **57a**, as well as mixtures of 2,3- and 3,4-difluorotoluenes **58** and **59** (overall yield 7–27%) from compounds **57b**–**d** at 400–600 °C in a flow reactor packed with various solid materials (SiC, NaF, Al_2O_3, 0.5% Pd/Al_2O_3, *etc.*).

The observed conversions of compounds **57a**–**d** to difluoroarenes **34**, **58** or **59** are explained by the established[39–43] ability of tetrafluoro(vinyl)cyclobutanes **57a**–**d** to undergo a thermal rearrangement with ring expansion due to competitive opening of the cyclobutane ring at the C(1)–C(4) (pathway A) or C(1)–C(2) bond (pathway B) to give tetrafluorocyclohexenes **62a**–**d** or **63a**–**d**, respectively, as a result of the 1,6-cyclisation of corresponding intermediate biradicals **60a**–**d** or **61a**–**d** (see Scheme 17).†

Note that all tetrafluoro(vinyl)cyclobutanes **57a**–**d** undergo preferential isomerisation *via* cleavage of the C(1)–C(4) bond (pathway A) to give corresponding cyclohexenes **62a**–**d** as major isomerisation products (see Table 1).[39,40]

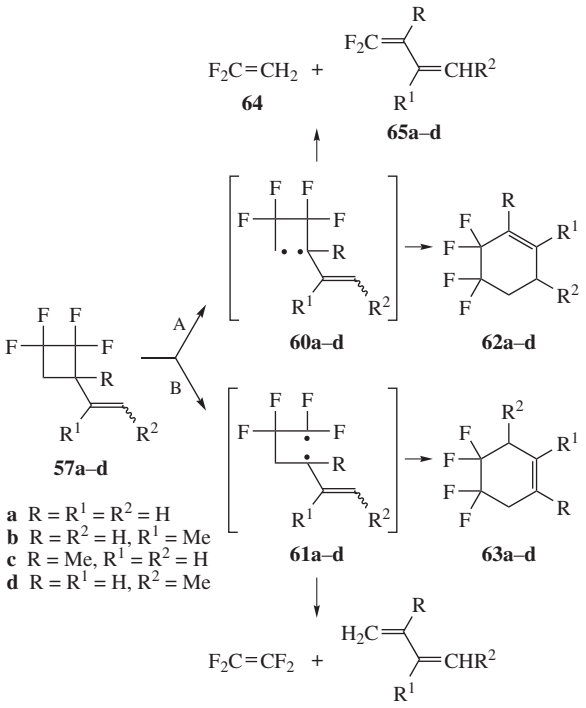
The comparatively low yields of tetrafluorocyclohexenes **62a**–**d** and **63a**–**d** (total yields 50–60%) are due to the fact that

Table 1 Yields of products of thermally induced isomerisation of tetrafluoro(vinyl)cyclobutanes **57a**–**d** under conditions of gas-phase pyrolysis at 490–500 °C (contact time, 8–10 s).[39,40]

Original tetrafluoro(vinyl)cyclobutane					Yield[a] (%)	
Compound	R	R^1	R^2	Conversion of **57a**–**d** (%)	**62**	**63**
57a	H	H	H	78	45	8
57b	H	Me	H	85	40	17
57c	Me	H	H	83	38	18
57d	H	H	Me	63	36	7

[a] With respect to compound **57** that has been consumed in the reaction.

† The communication by Weigert and Davis[51] that only tetrafluorocyclohexene products **63a**,**d** rather than tetrafluorocyclohexenes **62a**,**d** are formed under conditions of pyrolysis of **57a** and **57d** at 350–600 °C is likely to be wrong.



Scheme 17

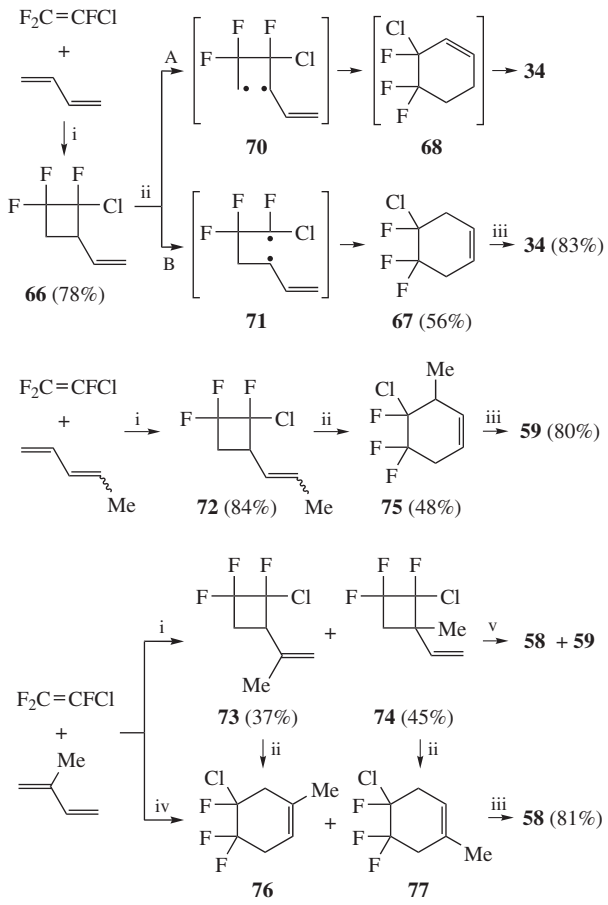
pyrolysis of tetrafluoro(vinyl)cyclobutanes **57a–d** is accompanied by a competing fragmentation reaction to give 1,1-difluoroethylene **64** and corresponding 1,1-difluorobuta-1,3-dienes **65a–d** (total yields 30–35%), as well as small amounts (3–5%) of the initial reactants, tetrafluoroethylene and dienes.[39–42]

The reactions considered above are also typical of the vinylcyclobutane adducts of 1,3-dienes with chlorotrifluoroethylene (Scheme 18).

Thus, 1-vinyl-2-chloro-2,3,3-trifluorocyclobutane **66** is converted[40,42] into a mixture of 4-chloro-4,5,5-trifluorocyclohexene **67** (yield 49–56%) and 1,2-difluorobenzene **34** (yield 3–8%) under conditions of gas-phase pyrolysis at 440–550 °C (contact time of 0.2–10 s). The process is accompanied by the formation of retrocyclisation products, *i.e.*, chlorotrifluoroethylene and butadiene (total yield 32–35%). In addition, 1,1-difluoroethylene **64** and 1-chloro-1-fluorobuta-1,3-diene were identified as minor products. The data obtained allow us to conclude that the thermolysis of compound **66**, unlike that of tetrafluorocyclobutanes **57a–d**, preferentially occurs by opening of the cyclobutane ring at the C(1)–C(2) bond and intermediate formation of biradical **71** (pathway B). Judging from the composition of the products, the relative contribution of alternative processes with ring opening at the C(1)–C(4) bond (pathway A) does not exceed 10–15%. Note that chlorotrifluorocyclohexene **68**, whose formation might be expected if the isomerisation of compound **66** occurred by pathway A, was not found among the reaction products. However, the formation of 1,2-difluorobenzene **34** in amounts correlating with the yields of difluoroethylene **64** and 1-chloro-1-fluorobuta-1,3-diene, detected even at small conversions of compound **66**, allows us to assume that compound **68** is possibly formed and completely converted to **34** under the conditions used.

The main product of thermolysis of **66**, *viz.*, chlorotrifluorocyclohexene **67**, can be easily converted to 1,2-difluorobenzene **34** by pyrolysis at 620 °C (yield 63%) or by alkaline dehydrohalogenation under conditions of phase-transfer catalysis (yield 83%).[25,48,49]

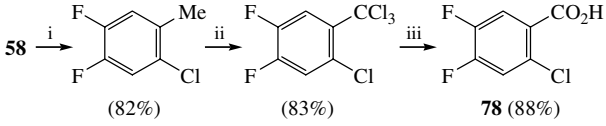
The above specific features of reactions of compound **66** are also characteristic of methyl-substituted chlorotrifluoro(vinyl)cyclobutanes **72–74**, which were obtained by cycloaddition of chlorotrifluoroethylene to penta-1,3-diene or isoprene at 390–410 °C. They undergo rearrangement[40] to corresponding chlorotrifluorocyclohexenes **75**, **76** or **77** at 425–490 °C due to ring opening at the C(1)–C(2) bond (Scheme 18). The aromatisation



Scheme 18 *Reagents and conditions*: i, flow reactor, 390–410 °C, contact time, 7–8 s; ii, flow reactor, 420–550 °C, contact time, 0.2–8 s; iii, KOH_{aq} (50%), TEBA (cat.), 85–95 °C, 2–4 h; iv, flow reactor, 435–500 °C, contact time, 5–15 s; v, flow reactor, 600–650 °C, contact time, 5–15 s.

of cyclohexenes **76** and **77**, isolated by fractional distillation from mixtures of pyrolysis products of compounds **73** and **74**, under conditions of alkaline dehydrohalogenation results in 3,4-difluorotoluene **58** in 81% yield.[25,48,49] Under the same conditions,[25,48,49] cyclohexene **75** obtained by pyrolysis of compound **72** gives 2,3-difluorotoluene **59** in 80% yield. Thus, the thermal cyclisation of chlorotrifluoroethylene with isoprene or penta-1,3-diene can be used for the preparation of 3,4-difluorotoluene **58** or 2,3-difluorotoluene **59**, respectively. In this case, it is possible[25,48,49] to use a simplified two-step version of such syntheses. This version involves the copyrolysis of chlorotrifluoroethylene with isoprene or penta-1,3-diene at 435–500 °C (contact time of 5–15 s) followed by isolation and alkaline dehydrohalogenation of chlorotrifluorocyclohexenes **75** or **76** and **77** formed as major products. Note that the direct aromatisation of cyclobutanes **72–74** at 600–650 °C under conditions of combined formation and thermally induced dehydrohalogenation of chlorotrifluorocyclohexenes **75–77** without preliminary isolation of the latter results[50,52] in practically inseparable mixtures of isomeric difluorotoluenes **58** and **59**, presumably due to side processes of isomerisation of compounds **72–74** by alternative pathway A.

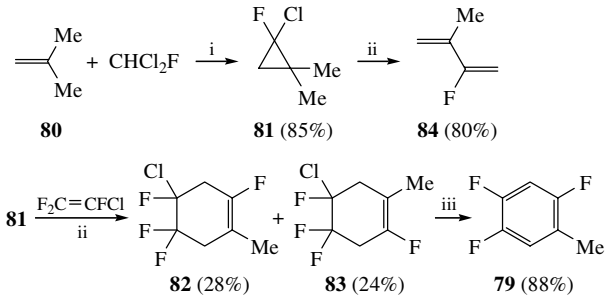
We have applied the above synthesis of 3,4-difluorotoluene **58** from isoprene and chlorotrifluoroethylene[48,49] to the preparation of 2-chloro-4,5-difluorobenzoic acid **78**, a key starting



Scheme 19 *Reagents and conditions*: i, Cl_2, $FeCl_3$, 10–35 °C; ii, Cl_2, *hv*, 80–140 °C; iii, 85% H_2SO_4 (H_2O), 50–80 °C.

compound for the production of main fluoroquinolone antibacterial compounds (Norfloxacin, Pefloxacin, Ciprofloxacin and their analogues) (Scheme 19).

Within the framework of the general methodology for synthesising fluoroarenes by thermally induced cyclisation of polyfluoroolefins, we have developed an original three-step method for the synthesis of 2,4,5-trifluorotoluene **79** from isobutene **80**, dichlorofluoromethane and chlorotrifluoroethylene (Scheme 20).[25]

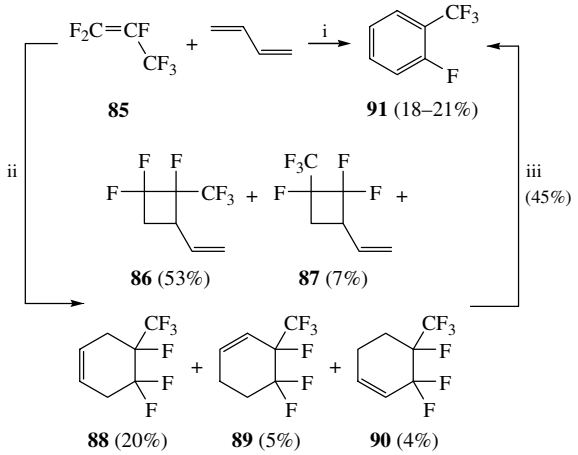


Scheme 20 *Reagents and conditions*: i, KOH_{aq} (50%), TEBA (cat.), –10 to +5 °C, 4–6 h; ii, flow reactor, 460–480 °C, contact time, 7–8 s; iii, KOH_{aq} (50%), TEBA (cat.), 85–95 °C, 3–4 h.

The process involves a thermally induced reaction of chlorotrifluoroethylene with 2-chloro-2-fluoro-1,1-dimethylcyclopropane **81** at 460–480 °C to give a mixture of isomeric chlorotetrafluorocyclohexanes **82** and **83**, which are readily converted to trifluorotoluene **79** in 88% yield by alkaline dehydrohalogenation under conditions of phase-transfer catalysis. The synthesis is based on the ability of chlorofluorocyclopropane **81**, which is easily prepared from isobutene **80** and dichlorofluoromethane under conditions of phase-transfer catalysis, to undergo selective rearrangement with ring opening and dehydrochlorination to give 3-fluoro-2-methylbuta-1,3-diene **84** at elevated temperatures.[25,53]

Perfluoroalkylated benzenes can be obtained if polyfluoroolefins with longer carbon chains are used instead of tetrafluoroethylene and chlorotrifluoroethylene in the reactions with 1,3-butadiene. For example, copyrolysis of compound **85** with buta-1,3-diene in a flow reactor at 650–700 °C (contact time of 10–15 s) results[39,46,47] in 2-fluoro-1-(trifluoromethyl)benzene **91** in 18–21% yield (Scheme 21). The yield of compound **91** can be increased to 35–40% if the process is carried out in two stages[39] *via* an intermediate preparation of cycloadducts **86–89** by copyrolysis of buta-1,3-diene and compound **85** at 450–550 °C followed by thermal aromatisation of compounds **86–89** by pyrolysis at 670–700 °C.

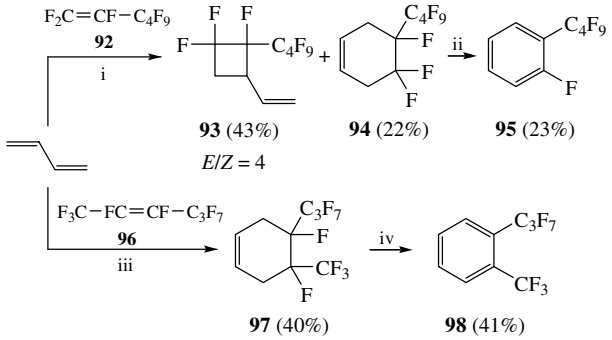
Thermal reactions of buta-1,3-diene with perfluorohex-1-ene **92** under conditions of gas-phase pyrolysis at 475 °C (contact time of 25 s) furnish[39,46] a mixture of [2 + 2]- and [2 + 4]-cross-



Scheme 21 *Reagents and conditions*: i, flow reactor, 650–700 °C; contact time, 10–18 s; ii, flow reactor, 460 °C, contact time, 8–10 s, the conversion of compound **85** is about 20%; iii, flow reactor, 700 °C, contact time, 10–15 s. The yields of compounds **86–90** are given with respect to the amount of compound **85** that underwent the reaction.

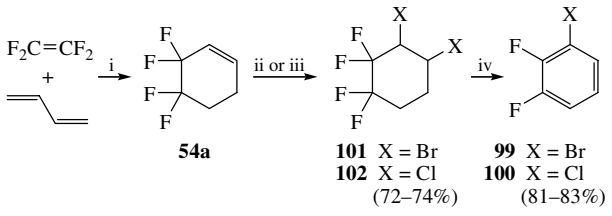
cycloaddition products of **93** and **94**, which give[39] 1-fluoro-2-nonafluorobutylbenzene **95** in 23% yield at 700°C. Alkaline dehydrofluorination of compound **94** results[39] in compound **95** in 53% yield (Scheme 22).

The copyrolysis of *trans*-perfluorohex-2-ene **96** with buta-1,3-diene at 520–540 °C results in [2 + 4]-cycloadduct **97** but no noticeable amounts of [2+2]-cycloaddition products are detected.[39,46] Resulting cyclohexene **97** was converted into 1-(trifluoromethyl)-2-(heptafluoropropyl)benzene **98** by alkaline dehydrobluorination in 41% yield[39] (Scheme 22).



Scheme 22 *Reagents and conditions*: i, flow reactor, 475 °C, contact time, 25 s, the conversion of compound **92** is about 23%; ii, flow reactor, 700 °C, contact time, 8–10 s; iii, flow reactor, 540 °C, contact time, 25 s, the conversion of compound **96** is about 15%; iv, Bu^tOK, Bu^tOH, 80–85 °C. The yields of compounds **93**, **94** and **97** are given with respect to the amount of compound **92** or **96** that has undergone the reaction.

In the considered preparation of fluoro- and perfluoroalkyl-substituted arenes, fluorine and other substituents (alkyl and perfluoroalkyl groups) are introduced in the final benzoid structure directly with the starting olefin or diene fragment. However, a modified variant is also possible, which involves a combination of synthetic construction of a fluorinated six-membered carbocycle from fluoroalkene and diene blocks with the introduction of an additional functional substituent in intermediate cyclohexene structures. We have shown the principal possibility of such a modification of the method[44,45] for the regioselective synthesis of 2,3-difluorohalobenzenes **99** and **100** starting from tetrafluoroethylene and butadiene and involving intermediate steps of halogenation of tetrafluorocyclohexene **62a** followed by triple dehydrohalogenation of the resulting tetrafluorodihalocyclohexenes **101** or **102** (Scheme 23).



Scheme 23 *Reagents and conditions*: i, flow reactor, 490–500 °C, contact time, 8–10 s; ii, Br_2, $CHCl_3$, Fe (cat.), 20–25 °C; iii, Cl_2, $CHCl_3$, Fe (cat.), 20–35 °C; iv, KOH_{aq} (50%), TEBA (cat.), benzene, 85–95 °C.

This modification of the method should be of a general character, and it may be a promising method for the synthesis of fluoroarenes with various functional substituents that are introduced into intermediate fluorocyclohexene structures by addition to the double bond.

To summarise, the above strategy of the synthesis of aromatic fluorine compounds using fluorohalocarbenes and fluoroolefins as building blocks offers new convenient routes to diverse mono-, di- and polyfluorinated arenes. Simple diene substrates and commercially available fluorohalomethanes and polyfluoroolefins can be used as starting materials in this synthesis. In some cases, the methods developed have real prospects of practical applications not only for preparative purposes but also for the commercial production of practically useful fluoroarenes.

References

1 (*a*) *Organofluorine Compounds in Medical Chemistry and Biomedical Application*, eds. R. Filler, Y. Kobayashi and L. M. Yagupolskii, Elsevier, Amsterdam, 1993, p. 48; (*b*) *Organofluorine Chemistry: Principles and Commercial Applications*, eds. R. E. Banks, B. E. Smart and J. C. Talow, Plenum Press, New York, 1994; (*c*) *Novoe v tekhnologii soedinenii ftora* (*Fluorine Compounds. Modern Technology and Application*), ed. N. Ishikawa, Mir, Moscow, 1984 (in Russian); (*d*) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell Publishing, Oxford, 2004.

2 (*a*) N. Ishikawa and E. Kobayashi, *Fluorine Compounds. Chemistry and Application*, Kodansha Scientific, 1979 (Mir, Moscow, 1982); (*b*) *Soedineniya ftora. Sintez i primenenie* (*Fluorine Compounds. Synthesis and Application*), ed. N. Ishikawa, Mir, Moscow, 1990 (in Russian).

3 (*a*) W. A. Sheppard and C. M. Sharts, *Organic Fluorine Chemistry*, W. A. Benjamin, New York, 1969; (*b*) *Chemistry of Organic Fluorine Compounds*, eds. M. Hudlicky and A. E. Pavlath, American Chemical Society, Washington, DC, 1995; (*c*) *Aromatic Fluorination*, eds. J. N. Clarc, D. Wails and T. W. Bastock, CRC Press, Boca Raton, FL, 1996; (*d*) G. G. Furin and A. A. Fainzilberg, *Sovremennye metody ftorirovaniya organicheskikh soedinenii* (*Modern Methods for Fluorination of Organic Compounds*), Nauka, Moscow, 2000 (in Russian).

4 (*a*) F. W. Dalby, *J. Chem. Phys.*, 1964, **41**, 2297; (*b*) J. P. Edvards, *Nature*, 1964, **202**, 1329.

5 O. M. Nefedov and A. A. Ivashenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1968, 446 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1968, **17**, 445).

6 O. M. Nefedov and A. A. Ivashenko, *Novoe v knimii karbenov* (*Advances in the Chemistry of Carbenes*), Nauka, Moscow, 1973, pp. 145–149 (in Russian).

7 (*a*) O. M. Nefedov and A. A. Ivashenko, *British Patent 1,130,268*, 1967; (*b*) O. M. Nefedov and A. A. Ivashenko, *French Patent 1,526,638*, 1967; (*c*) O. M. Nefedov and A. A. Ivashenko, *U.S. Patent 3,499,942*, 1970.

8 O. M. Nefedov and A. A. Ivashenko, *USSR Inventor's Certificate, no. 277,759*, 1967.

9 O. M. Nefedov and A. A. Ivashenko, *USSR Inventor's Certificate, no. 279,608*, 1967.

10 I. D. Kushina, S. F. Politanskii, V. U. Shevchuk, I. M. Gutor, A. A. Ivashenko and O. M. Nefedov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1974, 946 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1974, **23**, 918).

11 O. M. Nefedov, A. A. Ivashenko, S. F. Politanskii, I. D. Kushina, V. M. Yakovlev and A. V. Strashnenko, *USSR Inventor's Certificate, No. 572,446*, 1977.

12 O. M. Nefedov and N. V. Volchkov, in *Chemistry of Carbenes and Small-Sized Cyclic Compounds*, Mir, Moscow, 1989, p. 69.

13 S. F. Politanskii, A. A. Ivashenko and M. B. Lipkind, *Abstracts of the 3rd Conference on the Chemistry of Carbenes*, Moscow, 1982, p. 68 (in Russian).

14 O. M. Nefedov and A. A. Ivashenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1968, 1417 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1968, **17**, 1346).

15 O. M. Nefedov and A. A. Ivashenko, *USSR Inventor's Certificate, No. 214,530*, 1968.

16 A. I. Shipilov, V. F. Zabolotskikh, V. S. Shaidurov, N. V. Volchkov, S. F. Politanskii and O. M. Nefedov, *USSR Inventor's Certificate, No. 1,148,274*, 1984.

17 O. M. Nefedov and A. A. Ivashenko, *USSR Inventor's Certificate, No. 339,535*, 1971.

18 O. M. Nefedov and A. A. Ivashenko, *USSR Inventor's Certificate, No. 290,900*, 1970.

19 O. M. Nefedov and A. A. Ivashenko, *USSR Inventor's Certificate, No. 406,820*, 1972.

20 N. V. Volchkov, A. V. Zabolotskikh, M. B. Lipkind and O. M. Nefedov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 1935 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 1782).

21 O. M. Nefedov, N. V. Volchkov and A. V. Zabolotskikh, *J. Fluorine Chem.*, 1991, **54**, 86.

22 N. V. Volchkov, A. V. Zabolotskikh, A. V. Ignatenko and O. M. Nefedov, *Izv. Akad. Nauk, Ser. Khim.*, 1990, 1609 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 1458).

23 A. V. Zabolotskikh, N. V. Volchkov and O. M. Nefedov, *Abstracts of the 6th All-Union Conference on the Chemistry of Organofluorine Compounds*, Novosibirsk, 1990, p. 26 (in Russian).

24 A. V. Zabolotskikh, N. V. Volchkov and O. M. Nefedov, *Abstracts of the 5th Conference on the Chemistry of Carbenes*, Moscow, 1992, p. 48 (in Russian).

25 O. M. Nefedov and N. V. Volchkov, *Zh. Org. Khim.*, 1994, **30**, 1123 (*Russ. J. Org. Chem.*, 1994, **30**, 1181).

26 N. V. Volchkov, A. V. Ignatenko and O. M. Nevedov, *Abstracts of the 6th International Conference on the Chemistry of Carbenes and Related Intermediates*, St. Petersburg, 1998, p. 34 (in Russian).

27 N. V. Volchkov, M. B. Lipkind and O. M. Nefedov, *Abstracts of the 8th Conference on the Chemistry of Carbenes and Related Intermediates*, Kazan, 2003, p. 97 (in Russian).

28 (*a*) R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970; (*b*) C. H. DePuy, L. G. Schnack, J. W. Hausser and W. Wiedemann, *J. Am. Chem. Soc.*, 1965, **87**, 4006; (*c*) P. v. R. Schleyer, G. W. Van Dine, U. Schollkopf and J. Paust, *J. Am. Chem. Soc.*, 1966, **88**, 2868; (*d*) D. T. Clark and D. P. Armstrong, *Theor. Chim. Acta. (Berlin)*, 1969, 605; (*e*) A. I. Ioffe and O. M. Nefedov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1974, 1536 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1974, **23**, 1455).

29 M. I. Zaretskii, R. E. Serebryakov, E. M. Chartov, S. Z. Taits, O. M. Nefedov, A. S. Mozzhukhin, L. A. Pershina, N. V. Volchkov, A. I. Shipilov and A. V. Ignatenko, *USSR Inventor's Certificate, No. 1,608,181*, 1990.

30 A. I. Shipilov, V. F. Zabolotskikh, O. M. Nefedov, N. V. Volchkov, O. N. Chupakhin, V. N. Charushin, A. S. Kochanov, A. V. Tiunov and E. V. Abramenko, *USSR Inventor's Certificate, No. 1,792,936*, 1993.

31 O. N. Chupakhin, V. N. Charushin, G. A. Mokrushina, S. K. Kotovskaya, I. V. Kaplenko, I. V. Karpin, G. M. Petrova, E. O. Sidorov, O. M. Nefedov, N. V. Volchkov, M. B. Lipkind, V. S. Shaidurov, V. F. Zabolotskikh, A. I. Shipilov, G. A. Tolstikov, V. A. Gruzdev, S. M. Navashin and I. P. Fomina, *USSR Inventor's Certificate, No. 1,766,921*, 1993.

32 U. M. Dzemelev, O. M. Nefedov, G. A. Tolstikov, O. N. Chupakhin, V. N. Charushin, S. M. Navashin, V. A. Dokichev, S. Z. Sultanov, V. A. Gruzdev and V. N. Zverev, *USSR Inventor's Certificate, No. 1,796,623*, 1993.

33 U. M. Dzemelev, G. A. Tolstikov, O. M. Nefedov, O. N. Chupakhin, V. N. Charushin, S. M. Navashin, V. A. Dokichev, S. Z. Sultanov, V. A. Gruzdev and V. N. Zverev, *USSR Inventor's Certificate, No. 1,786,028*, 1993.

34 V. N. Odinokov, G. Yu. Ishmuratov, R. Ya. Kharisov, L. P. Botsman, G. A. Tolstikov, V. F. Zabolotskikh, N. V. Volchkov and O. M. Nefedov, *USSR Inventor's Certificate, No. 1,469,795*, 1988.

35 G. A. Tolstikov, G. V. Leplyanin, V. N. Odinokov, L. F. Antonova, O. S. Kukovinets, E. A. Lozhkina, V. Zh. Bikulova, O. M. Nefedov, N. V. Volchkov, V. F. Zabolotskikh, V. N. Burov, E. P. Mokrousova, E. A. Stepanycheva and N. S. Nazarenko, *USSR Inventor's Certificate, No. 1,803,988*, 1992.

36 O. M. Nefedov, N. V. Volchkov, M. B. Lipkind, M. C. Oshepkov and A. A. Tonkikh, *Izv. Akad. Nauk, Ser. Khim.*, 2006, in press.

37 W. H. Sharkey, in *Fluorine Chemistry Reviews*, ed. P. Tarrant, Marcel Dekker, New York, 1968, vol. 2, pp. 1–54.

38 O. M. Nefedov, S. F. Politansky, A. A. Ivashenko, M. B. Lipkind, A. V. Strashnenko and V. N. Veremiy, *USSR Inventor's Certificate, No. 869,242*, 1980.

39 M. B. Lipkind, *PhD Thesis*, N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, 1987.

40 M. B. Lipkind, N. V. Volchkov, A. I. Shipilov and V. F. Zabolotskikh, *Abstracts of the 6th All-Union Conference on the Chemistry of Organofluorine Compounds*, Novosibirsk, 1990, p. 26 (in Russian).

41 A. I. Shipilov, V. F. Zabolotskikh, V. S. Shaidurov, N. V. Volchkov, S. F. Politansky and O. M. Nefedov, *Abstracts of the 5th All-Union Conference on the Chemistry of Organofluorine Compounds*, Moscow, 1986, p. 142 (in Russian).

42 A. I. Shipilov, *PhD Thesis*, N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, 1989.

43 A. I. Shipilov, V. F. Zabolotskikh and O. M. Nefedov, *Zh. Prikl. Khim.*, 1994, **67**, 84 (*Russ. J. Appl. Chem.*, 1994, **67**, 77).

44 N. V. Volchkov, M. B. Lipkind and O. M. Nefedov, *Abstracts of the 2th International Conference 'Chemistry, Technology and Application of Fluorocompounds'*, St. Petersburg, 1997, p. 62 (in Russian).

45 N. V. Volchkov, M. B. Lipkind and O. M. Nefedov, *Abstracts of the 16th International Symposium on Fluorine Chemistry*, University of Durham, 2000, vol. 2, p. 70.

46 N. V. Volchkov, M. B. Lipkind, S. F. Politansky, A. I. Ignatenko, O. M. Nefedov, V. S. Shaidurov, V. F. Zabolotskikh and A. I. Shipilov, *USSR Inventor's Certificate, No. 1,380,189*, 1987.

47 N. V. Volchkov, M. B. Lipkind, S. F. Politansky, A. I. Ignatenko, O. M. Nefedov, V. S. Shaidurov, V. F. Zabolotskikh and A. I. Shipilov, *USSR Inventor's Certificate, No. 1,354,643*, 1987.

48 O. M. Nefedov, N. V. Volchkov, M. B. Lipkind, H. S. Lee, Y. J. Park and M. H. Kim, *U.S. Patent No. 6,008,407*, 1998.

49 O. M. Nefedov, N. V. Volchkov, M. B. Lipkind, H. S. Lee, Y. J. Park and M. H. Kim, *Korean Patent Application No. 98-38405*, 1998.

50 F. J. Weigert, *U.S. Patent No. 4,754,084*, 1988.

51 F. J. Weigert and R. F. Davis, *J. Fluorine Chem.*, 1993, **63**, 69.

52 F. J. Weigert and R. F. Davis, *J. Fluorine Chem.*, 1993, **63**, 59.

53 E. V. Guseva, N. V. Volchkov, Yu. V. Tomilov and O. M. Nefedov, *Eur. J. Org. Chem.*, 2004, **14**, 3136.

Received: 27th March 2006; Com. 06/2707