Reviews

Fluorinated cyclohexadienones as versatile synthons for preparation of organofluorine compounds*

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The review summarizes the new investigation of the reactivity of polyfluorinated cyclohexadienones: nucleophilic, cycloaddition, and photochemical reactions and, furthermore, such transformations of products of these reactions as reduction, hydrolysis, and photochemical reaction. The use of polyfluorinated cyclohexadienones as highly reactive synthons opens the possibility for the synthesis of a broad variety of otherwise inaccessible fluorinated organic compounds containing functional groups, such as fluorinated derivatives of polyphenyl ethers, arylacetic acids, cyclohexenecarboxylic acids, naphthalene and anthraquinone derivatives bearing the carboxylic group, and some fluorinated heterocyclic compounds.

Key words: fluorinated cyclohexadienones, cycloaddition, bicyclo[2.2.2]octadienones, nucleophilic substitution, photolysis, reduction, hydrolysis, arylacetic acids.

1. Introduction

Preparation of functionalized organofluorine compounds is of fundamental importance because of both very limited possibilities for direct fluorination of organic compounds containing functional groups and difficulties in introduction of functional groups into fluorinated compounds.[1] Therefore, the new approach to the synthesis of such compounds using polyfluorinated cyclohexadienones as versatile synthons is very important.

The great interest in fluorine-containing and especially polyfluorinated cyclohexadienones arises from their high and diverse reactivity associated with the presence of several reaction centers in these compounds: mobile fluorine atom at the double bond, 1,3-diene system in 2,4-cyclohexadienones, carbonyl group, and reactive substituent at the sp^3-hybridized carbon atom.

Recently, much attention has been focused on a new and very promising approach to the synthesis of polyfunctional organofluorine compounds by the transformation of rather available polyfluoroaromatic compounds into very reactive polyfluorinated cyclohexadienones, which can easily be modified. It was shown that nucleophilic, cycloaddition, and photochemical reactions are the most efficient methods for the modification of polyfluorinated cyclohexadienones.

* Devoted to the blessed memory of Professor M. Hudlicky.

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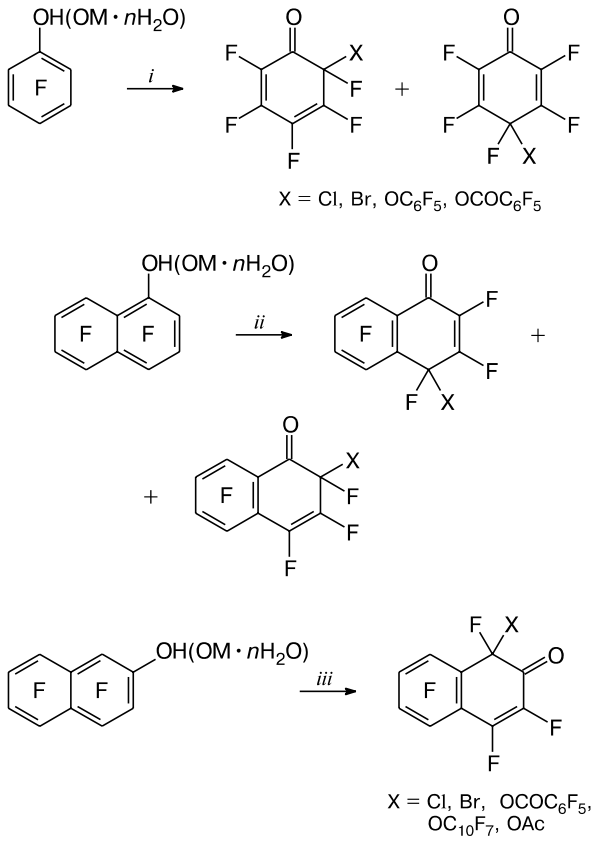
The review "*Fluorine-containing cyclohexadienones — synthesis and properties*" [2] published 15 years ago was devoted to the common methods for the synthesis of these compounds and such reactions as nucleophilic substitution and reduction. Nothing was known about the cycloaddition and reactions with participation of the carbonyl group (except of their protonation).

The review summarizes the investigations pursued in this field over the past 15 years and describes some methods for the synthesis of polyfluorinated cyclohexadienones, their nucleophilic, cycloaddition, and photochemical reactions, and some interesting transformations of the products of these reactions demonstrating the new opportunities of the directed synthesis of polyfunctional organofluorine compounds.

2. Synthesis of polyfluorinated cyclohexadienones

Scheme 1 gives the examples of the general methods for the synthesis of polyfluorinated cyclohexadienones described in the review.[2] Polyfluorinated cyclohexadienones with various substituents in the geminal position may be obtained from polyfluorinated phenols, naphthols, and their salts by halogenation[3] or oxidation.[4]

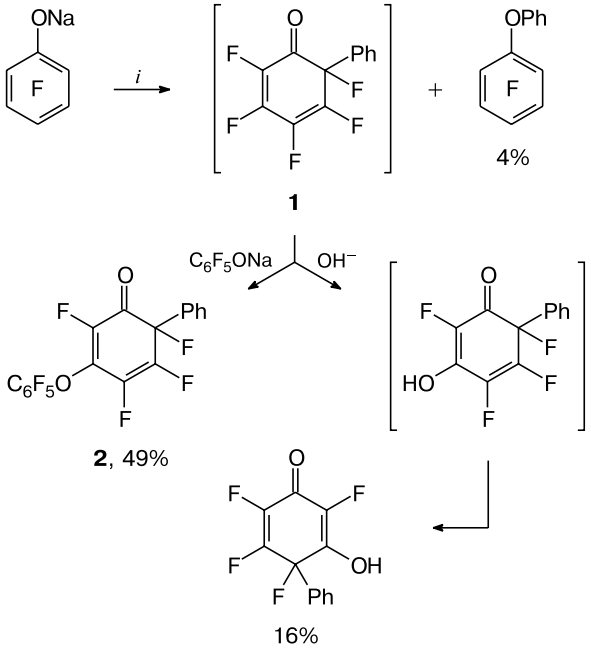
Scheme 1



Reagents: *i*. Hal_2, $(C_6F_5COO)_2$, $Pb(OAc)_4$ or PbO_2;
ii. Hal_2, $(C_6F_5COO)_2$, PbO_2 or $Pb(OAc)_4$—AcOH;
iii. Hal_2 or $(C_6F_5COO)_2$, PbO_2 or $Pb(OAc)_4$—AcOH.

A convenient procedure for the selective *ortho*-arylation of polyfluorinated phenols and naphthols leading to fluorinated cyclohexadienones with the phenyl group in the geminal position is described in Ref. 5 (Scheme 2). In the reaction of sodium pentafluorophenoxide with both $PhPb(OAc)_3$ and $Ph_2Pb(OAc)_2$,[5] at first the intermediate cyclohexadienone **1** is possibly formed. The main reaction product, 6-phenyl-3-pentafluorophenoxy-2,4,5,6-tetrafluoro-2,4-cyclohexadien-1-one (**2**), is a result of the nucleophilic replacement of the fluorine atom by the pentafluorophenoxy group in dienone **1** (Scheme 2).

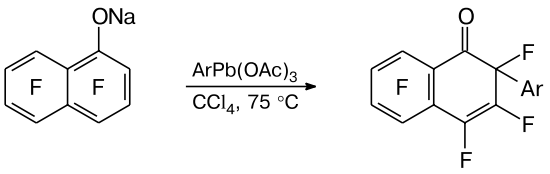
Scheme 2



i. $PhPb(OAc)_3$, CCl_4, 80 °C.

The reactions of sodium or potassium heptafluoro-1-naphthoxide with $ArPb(OAc)_3$ and $Ph_2Pb(OAc)_2$ give the respective 2-aryl-1-oxoheptafluoro-1,2-dihydronaphthalenes (Scheme 3).

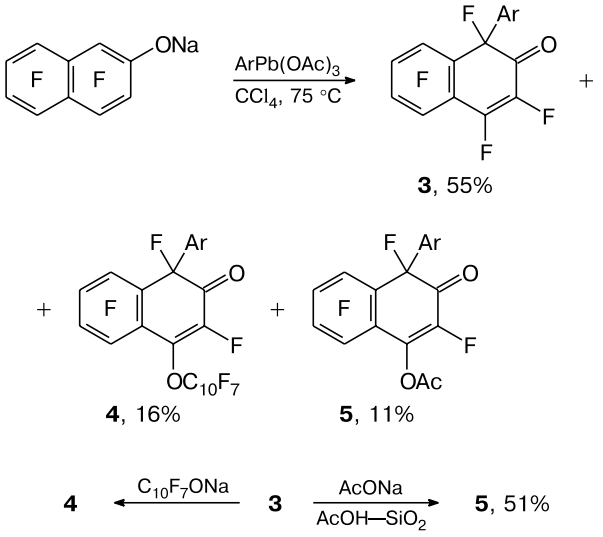
Scheme 3



Ar = Ph (83%), *p*-MeC_6H_4 (43%), *p*-$MeOC_6H_4$ (75%)

The reaction of sodium heptafluoro-2-naphthoxide with *p*-anisyllead triacetate led to the formation of a mixture, which was shown by ^{19}F NMR spectroscopy to contain 1-anisyl-2-oxoheptafluoro-1,2-dihydronaphthalene (**3**), 1-anisyl-4-(heptafluoro-2-naphthoxy)-2-oxohexafluoro-1,2-dihydronaphthalene (**4**), and 1-anisyl-4-acetoxy-2-oxohexafluoro-1,2-dihydronaphthalene (**5**). Compound **3**, which is the main reaction product, is very reactive and in the process of purification by column chromatography on silica gel deactivated by acetic acid it completely transformed into compound **5** isolated in 51% yield[5] (Scheme 4).

Scheme 4



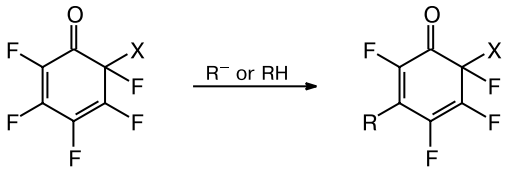
Ar = *p*-$MeOC_6H_4$

3. Nucleophilic substitution and reduction

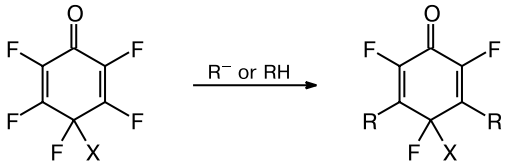
The reactions of nucleophilic reagents with cyclohexadienones containing halogen only at the saturated carbon atom generally lead to the reduction of the latter to phenols or to the substitution of halogen to form the respective substituted cyclohexadienones.[6,7]

In contrast to this, polyfluorinated cyclohexadienones readily react with nucleophilic reagents with replacement of one or two fluorine atoms at the double bonds, which is a consequence of both the high activity of compounds with fluorinated double bonds in nucleophilic reactions in general and further activation of the double bond by its conjugation with the carbonyl group.[8] Under the influence of the carbonyl group in polyfluorinated 2,4-cyclohexadienones the fluorine atom in position 3 is replaced more readily than that in position 5, which is in agreement with the data of molecular orbital studies of the charge distribution on polyhalogenated 2,4-cyclohexadienones.[9] In polyfluorinated 2,5-cyclohexadienones, the effect of the carbonyl group on the charge delocalization is such that positions 3 and 5 are more reactive in nucleophilic reactions than positions 2 and 6. Examples of such reactions are given in Scheme 5.[10,11]

Scheme 5



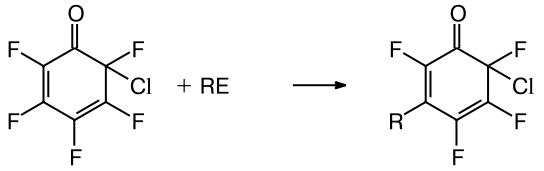
X = Cl; R = NH_2, NHC_6F_5, OPh, OC_6F_5
X = OC_6F_5; R = NHC_6F_5



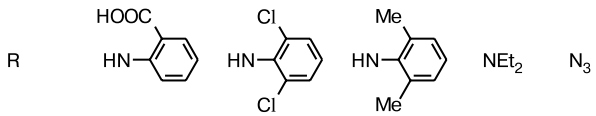
X = OC_6F_5; R = N_3, NH_2, NMe_2, NHPh, NHC_6F_5, OMe, OPh, OC_6F_5

Recently, it was shown that the fluorine atom in position 3 of 6-chloro-2,3,4,5,6-pentafluoro-2,4-cyclohexadienone can be replaced by 2,6-dichloro- or 2,6-dimethylaminophenyl, 2-carboxyaminophenyl, diethylamino, and azido groups as nucleophiles[12] (Scheme 6).

Scheme 6



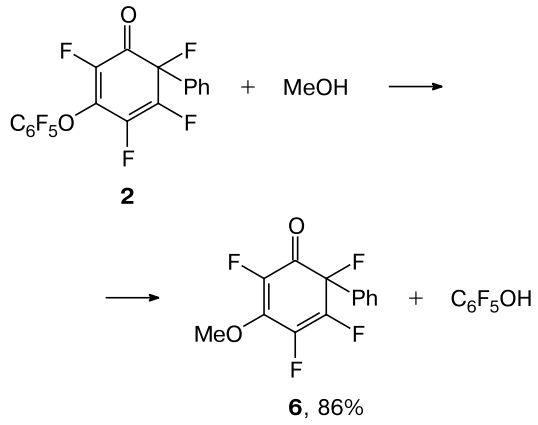
E = H, Na



The substituent in position 3 of dienone **2** is easily replaced by nucleophilic reagents under mild conditions. For example, boiling of cyclohexadienone **2** with methanol leads to the corresponding methoxy derivative **6** [12] (Scheme 7).

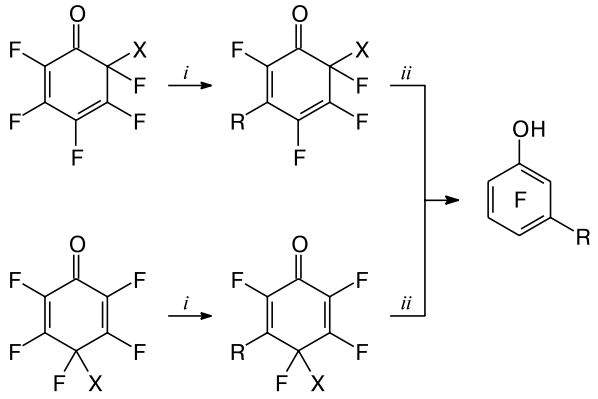
The general property of cyclohexadienones containing a halogen atom at the saturated carbon atom is the ability to be converted into phenols by reduction. When the saturated carbon atom bears fluorine and chlorine

Scheme 7



atoms as geminal substituents, reduction proceeds with elimination of the latter. Using this method for syntheses of polyfluorinated phenols is most advantageous in combination with the initial nucleophilic substitution of the fluorine atom at the double bond of cyclohexadienone[5,10,13] (Scheme 8).

Scheme 8



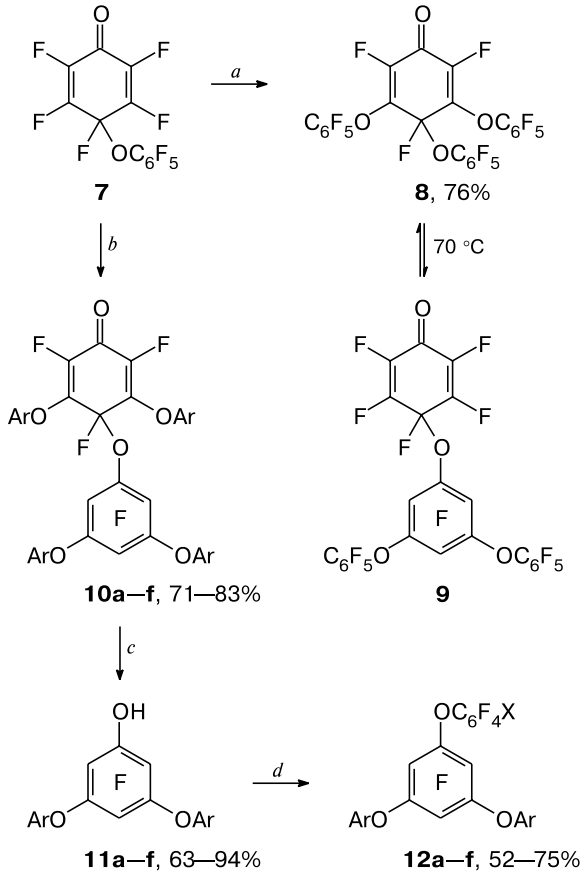
X = Cl, OC_6F_5;
R = N_3, NH_2, NMe_2, NC_5H_{10}, NHPh, NHC_6F_5, OMe, OPh, OC_6F_5

Reagents and conditions: *i*. R^- or RH; *ii*. HCl, Zn, Et_2O.

The method suggested to prepare fluorine-containing phenols by a sequence of the above reactions is an example of the general strategy of synthesis of polyfunctional aromatic compounds, which involves the transformation of the starting phenol into cyclohexadienone to facilitate the nucleophilic substitution of fluorine and the reduction of the modified cyclohexadienones to polyfluorinated phenols with various substituents.

The nucleophilic reactions of the pentafluorophenoxyl radical dimer, perfluoro-4-phenoxy-2,5-cyclohexadienone (**7**), with phenols[14] and tetrafluororesorcinol[15] were used for syntheses of some polyfluorinated polyphenyl ethers with nitro, amino, and carboxyl groups, as well as branched and linear polyfluorinated polyphenyl ethers with five and eight carbocyclic fragments in the molecule. Compound **7** reacts with two equivalents of sodium pentafluorophenoxide at room temperature, yielding 3,5-substituted cyclohexadienone **8**. The latter isomerizes at 70 °C to dienone **9**. Using four equivalents of phenol in the presence of potassium carbonate at 70 °C, one can obtain cyclohexadienones **10a—f** with the phenoxy group both in the aromatic and dienone parts of the molecule (Scheme 9).

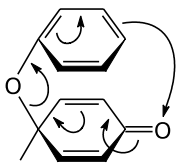
Scheme 9



X = F; Ar = C_6F_5 (**a**), Ph (**b**), 3,5-$(C_6F_5)_2C_6F_3$ (**c**);
X = CF_3; Ar = 4-$NO_2C_6H_4$ (**d**), 4-$AcOC_6H_4$ (**e**), 4-$NH_2C_6H_4$ (**f**)

Reagents and conditions: *a*. 2 C_6F_5ONa, MeCN, 20 °C; *b*. 4 ArOH, K_2CO_3, MeCN, 70 °C; *c*. $Na_2S_2O_4$, MeCN, 70 °C; *d*. C_6F_5X, K_2CO_3, DMSO, 90 °C.

For analogous isomerization of the dimers of phenoxyl radicals of different structures, two mechanisms were proposed: intramolecular mechanism *via* the transition state (TS)[16] and cage dissociation to phenoxyl radicals with their subsequent recombination.[17] The rearrangement of polyfluori-

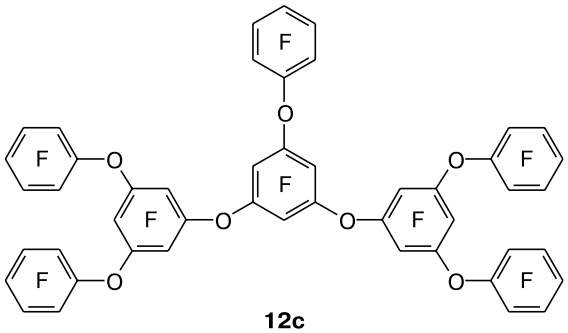


TS

nated cyclohexadienone evidently occurs by the intramolecular mechanism.

This is indicated by the absence of compounds with an *ortho*-quinoid structure among the reaction products (it is well known that these compounds are stable under reaction conditions[18]), which would arise if the mechanism of isomerization involves the dissociation—recombination of the phenoxyl radicals.

Cyclohexadienones **10a—f** can be reduced to 3,5-substituted phenols **11a—f** that form polyfluorinated polyphenyl ethers **12c** by the reactions with polyfluoroarenes, for example, **12c** with hexafluorobenzene or **12d—f** with octafluorotoluene.[15]



12c

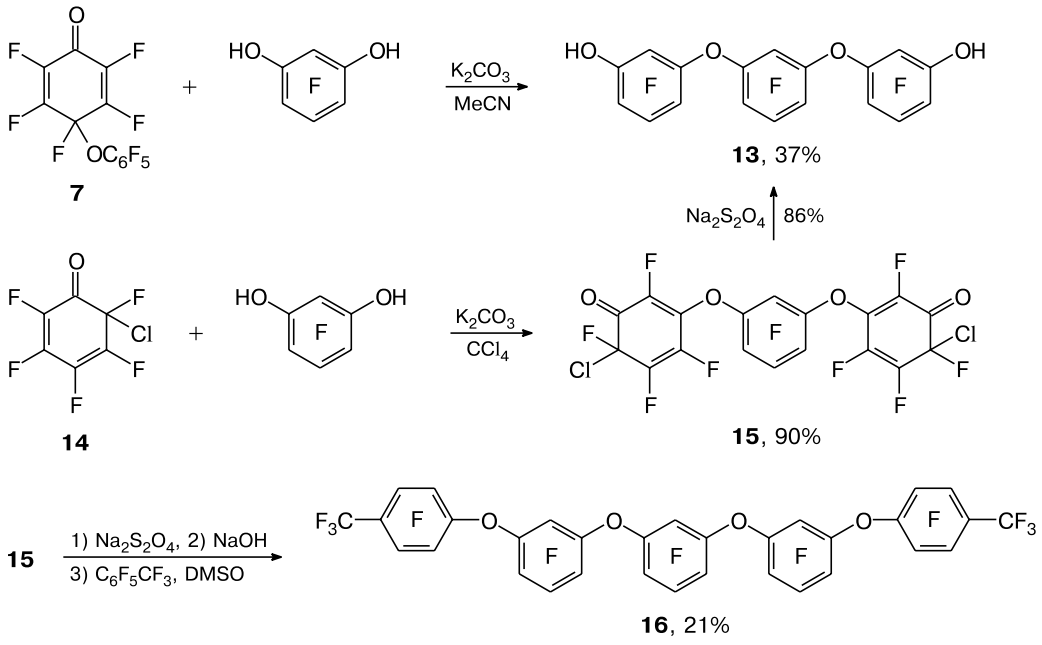
The dimer of pentafluorophenoxyl radical **7** reacts with tetrafluororesorcinol in acetonitrile in the presence of potassium carbonate at room temperature to give a mixture of substituted polyfluorinated cyclohexadienones. After reduction, tetrafluoro-1,3-bis(tetrafluoro-3-hydroxyphenoxy)benzene (**13**) was isolated from this mixture.[14]

Two equivalents of 6-chloro-2,3,4,5,6-pentafluoro-2,4-cyclohexadienone (**14**) react with tetrafluororesorcinol at room temperature to give 1,3-bis(4-chlorotetrafluoro-3-oxo-1,5-cyclohexadienyloxy)tetrafluorobenzene (**15**) in 90% yield. The reduction of this compound leads to bisphenol **13**, and the successive reduction of the disodium salt formed from **15** and the subsequent reaction with octafluorotoluene yield a mixture of polyfluorinated polyphenyl ethers, from which perfluoro{1,3-bis[3-(4-methylphenoxy)phenoxy]benzene} (**16**) was isolated (Scheme 10).

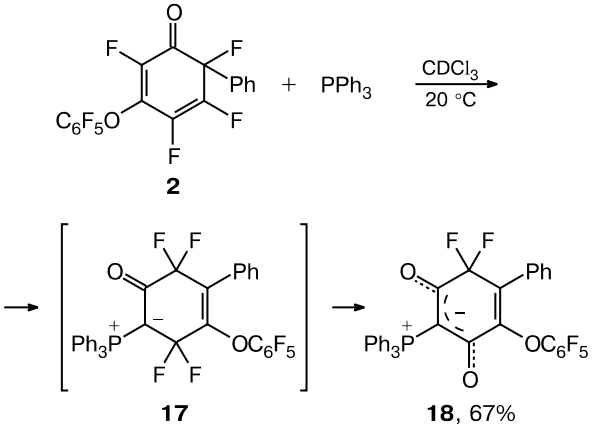
The reaction of such a nucleophile as triphenylphosphine with polyfluorinated cyclohexadienone **2** leads to a very interesting and unexpected result.[19] The ^{19}F and ^{13}C NMR spectra of intermediate **17** formed on mixing together cyclohexadienone **2** and PPh_3 in $CDCl_3$ at room temperature show the presence of two CF_2 and one carbonyl group in this compound (an attempt to isolate compound **17** has failed). However, the main product of this reaction, ylide **18**, contains only one CF_2 and two carbonyl groups (X-ray diffraction analysis data). Moreover, the phenyl and pentafluorophenoxy groups in this compound occupy the adjacent positions in contrast to the starting cyclohexadienone **2** in which these groups occupy positions 6 and 3, respectively (Scheme 11).

It is known that polyfluorinated cycloalkenes, such as perfluorocyclobutene and perfluorocyclopentene, react with PPh_3 to give stable dicarbonyl phosphorylides[20] (Scheme 12). Note that perfluorocyclohexene does not react with triphenylphosphine.

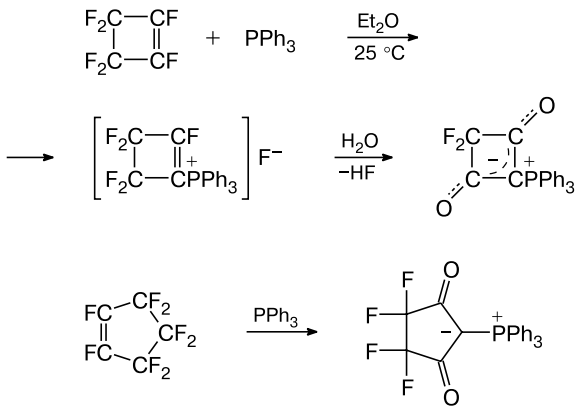
Scheme 10



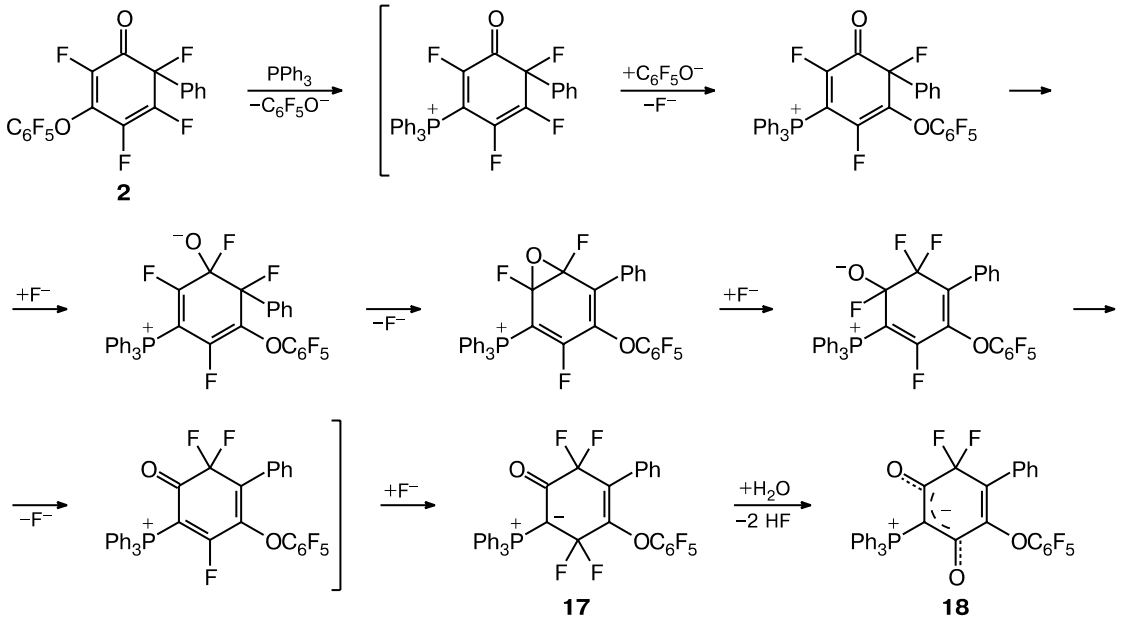
Scheme 11



Scheme 12



Scheme 13



Scheme 13 demonstrates the probable sequence of reactions leading to the formation of ylide **18**. Zwitterion **17** with two CF_2 groups is apparently unstable in contact with moisture, and after the addition of water and the elimination of HF it gives zwitterion **18** stabilized owing to the charge delocalization with participation of two carbonyl groups.

4. Reactions involving carbonyl groups

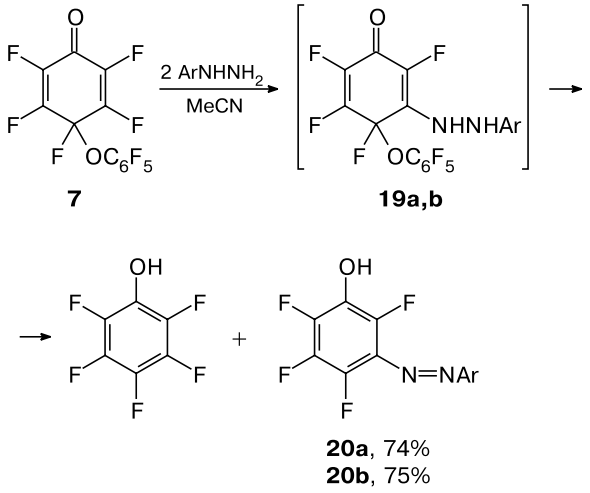
4.1. Reactions with phenylhydrazines

It is known that reactions of nonfluorinated cyclohexadienones with nucleophilic reagents involve both the double bonds and the carbonyl group.[21]

Hydrazine derivatives[22] and organometallic compounds[21,23] are most commonly used as reagents for reactions at the carbonyl group. Investigation of such reactions could give an answer to the problem of the relative reactivity of two nucleophilic centers of polyfluorinated cyclohexadienones: the fluorinated double bond and the carbonyl group.

Perfluoro-4-phenoxy-2,5-cyclohexadienone (**7**) reacts with phenyl- and pentafluorophenylhydrazine in acetonitrile to give intermediate cyclohexadienone **19**, the product of nucleophilic substitution of fluorine at the double bond in the initial dienone, which disproportionates to a mixture of 3-arylazotetrafluorophenols **20a,b** and pentafluorophenol in equal amounts (Scheme 14). Azophenol of similar structure was prepared by the oxidation of

Scheme 14



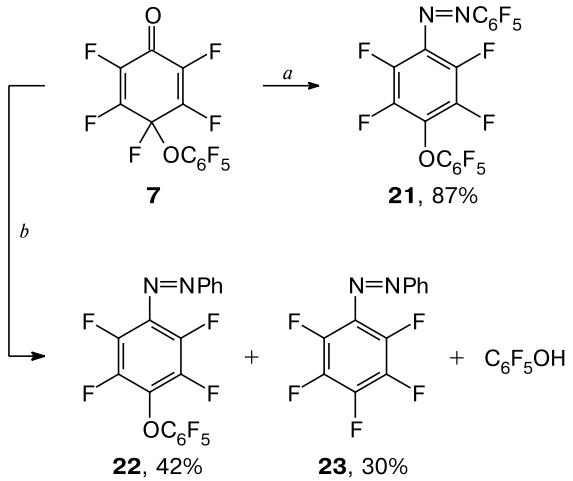
Ar = C_6F_5 (**a**), Ph (**b**)

the products of addition of phenylhydrazine to the double bond of 4-hydroxy-2,4-dimethyl-2,5-cyclohexadienone.[24]

No reaction involving the carbonyl group of polyfluorinated cyclohexadienones with phenylhydrazine takes place. The reactions of polyfluorinated cyclohexadienones with aluminum chloride complexes of phenyl- and pentafluorophenylhydrazines were investigated, as it is known that acids catalyze the reactions of arylhydrazines with the carbonyl group of cyclohexadiones.[24]

The dimer of pentafluorophenoxyl radical **7** reacts with these reagents only with participation of the carbonyl group to give the corresponding azobenzenes **21—23**.[25] Both the fluorine atom and the pentafluorophenoxyl fragment behave as leaving groups during azobenzene formation. The main product of the reaction with pentafluorophenylhydrazine—aluminum chloride complex is formed due to the elimination of the fluorine atom, while both pathways are equally probable in the case of the aluminum chloride complex of phenylhydrazine (Scheme 15).

Scheme 15

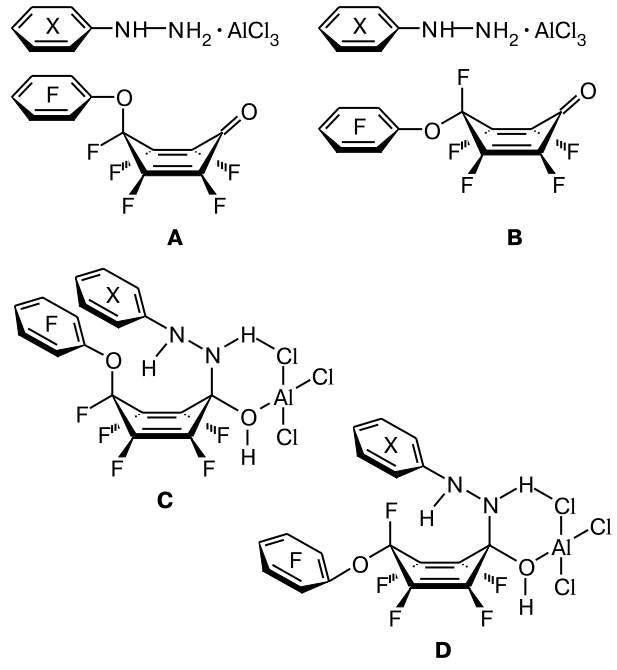


Reagents and conditions: *a*. 4 $C_6F_5NHNH_2 \cdot AlCl_3$, 36 °C; *b*. 5 $PhNHNH_2 \cdot AlCl_3$, 36 °C.

This difference in the behavior of phenyl- and pentafluorophenylhydrazine is likely to be due to the interaction between the aromatic substituent of the dienone and the aromatic ring of the hydrazine in the transition state. It was suggested[25] that the initially formed dienone—arylhydrazine—aluminum chloride complexes **A** and **B** give further intermediates of the **C** and **D** types. The leaving group is pentafluorophenoxyl in the former case and the fluorine atom in the latter.

For intermediates with nonfluorinated phenylhydrazine of the **C** type, an additional stabilization is possible owing to the π-interaction between the fluorinated and nonfluorinated aromatic rings (the formation of π-complexes between fluorinated and nonfluorinated aromatic compounds is known[26]). This will ultimately result in pentafluorophenoxyl group elimination from the geminal position of the dienone. Such type of interaction between the fluorinated aromatic rings will destabilize complex **C** and, hence, fluorine elimination will occur to a greater extent *via* transition state **D** (Scheme 16).

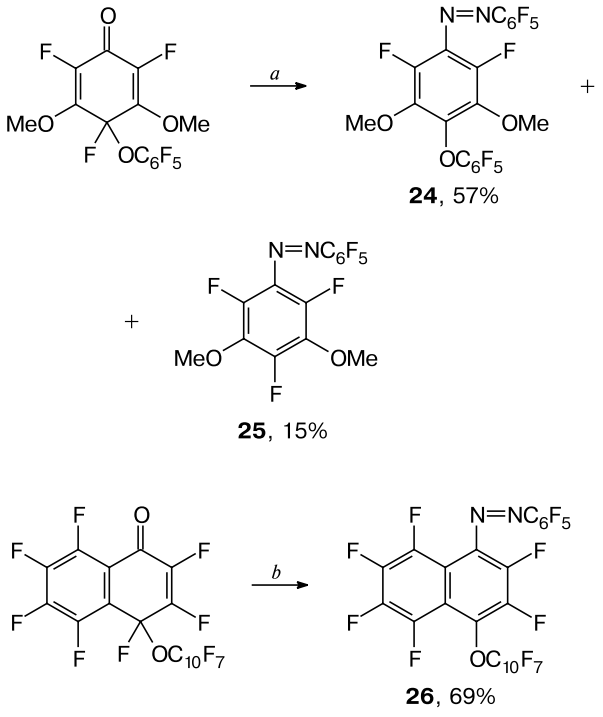
Scheme 16



X = H, F

The aluminum chloride complexes of arylhydrazines can be used for the syntheses of different fluorinated azo compounds **24—26** (Scheme 17).

Scheme 17

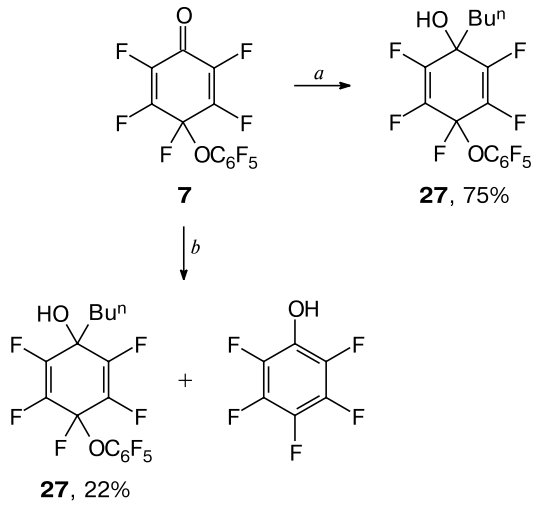


Reagent and conditions: *a*. 5 $C_6F_5NHNH_2 \cdot AlCl_3$, 20—36 °C; *b*. 5 $C_6F_5NHNH_2 \cdot AlCl_3$, 20 °C.

4.2. Reactions with organometallic compounds

The reactions of polyfluorinated cyclohexadienones with *n*-butyllithium and *n*-butylmagnesium bromide also proceed with participation of the carbonyl group to give 1-butyl-4-pentafluorophenoxy-2,3,4,5,6-pentafluorocyclohexa-2,5-dien-1-ol (**27**)[25] (Scheme 18).

Scheme 18



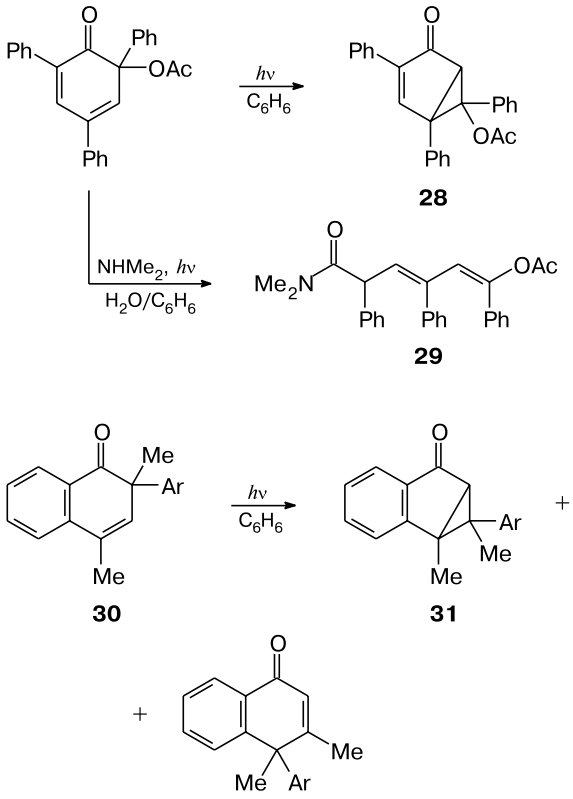
Reagents and conditions: *a*. Bu^nLi, −5 °C; *b*. Bu^nMgBr, 36 °C.

Thus, polyfluorinated 2,5-cyclohexadienones can react with nucleophilic reagents *via* 1,2-addition to the carbonyl group exclusively in spite of the availability of nucleophilically mobile fluorine atoms at the double bond of the cyclohexadienone.

4.3. Photochemical transformations

The photochemical behavior of nonfluorinated 2,4-cyclohexadienones is well known. Cyclopropane derivatives **28** or ring-cleavage products **29** are formed depending on the solvent and the structure of the starting dienone.[27] The photolysis of substituted 1-oxo-1,2-dihydronaphthalenes **30** mainly leads to cyclopropane derivatives **31** [28] (Scheme 19). 2-Oxo-1,2-dihydronaphthalenes are virtually inactive in photochemical reactions. Only one example of cyclodimerization of these compounds is known.[29]

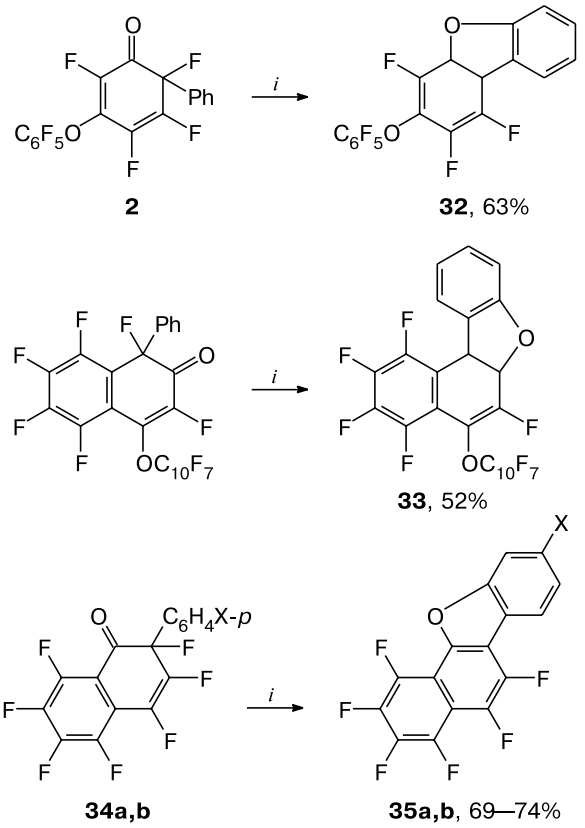
Scheme 19



In contrast to the photolysis of nonfluorinated cyclohexadienones, the photochemical reactions of polyfluorinated cyclohexadienones in a hexane solution proceed with participation of the carbonyl group and of the phenyl group in the geminal position leading to polyfluorinated furan derivatives: dibenzofurans **32** and benzonaphthofurans **33** and **35** [30] (Scheme 20).

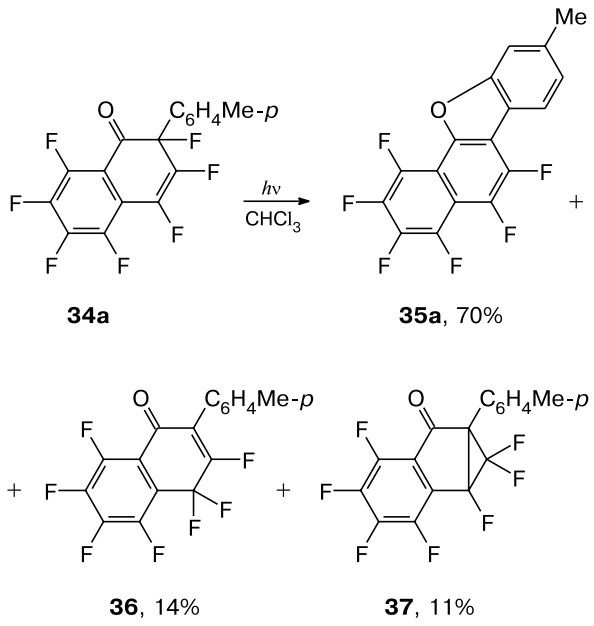
The photolysis of a chloroform solution of heptafluoro-1-oxo-2-(*p*-tolyl)-1,2-dihydronaphthalene (**34a**) gives the

Scheme 20



fluorinated naphthobenzofuran derivative **35a** as the main product along with a small amount of product resulting from fluorine atom migration: heptafluoro-1-oxo-2-(*p*-tolyl)-1,4-dihydronaphthalene (**36**). In addition, it is the only reaction of polyfluorocyclohexadienones studied in which the formation of a cyclopropane derivative characteristics of hydrocarbon analogs, *viz.*, heptafluoro-6a-(*p*-tolyl)-1,1a-dihydrocyclopropa[*a*]indenone (**37**), was marked (Scheme 21).

Scheme 21



5. Cycloaddition reactions of polyfluorinated cyclohexadienones

5.1. 1,3-Cycloaddition reactions of diazomethane and its derivatives

It is known that alkyl-substituted 2,4-cyclohexadienones react with diazomethane and alkyl- or phenyldiazomethanes only at carbon-carbon double bonds.[31—34] In the case of acetoxyalkylcyclohexadienones, the cycloadducts formed in these reactions can easily be transformed into 7-hydroxyindazoles[32] or into methyl-substituted 2,4-cyclohexadienones.[33,35] The influence of the position of the substituent on the regioselectivity of cycloaddition is well studied. Cycloaddition occurs generally at the C(2)=C(3) bond.[31,33,34] The alkyl groups (except the *tert*-butyl group) in position 2 do not hinder such cycloaddition.[31,33]

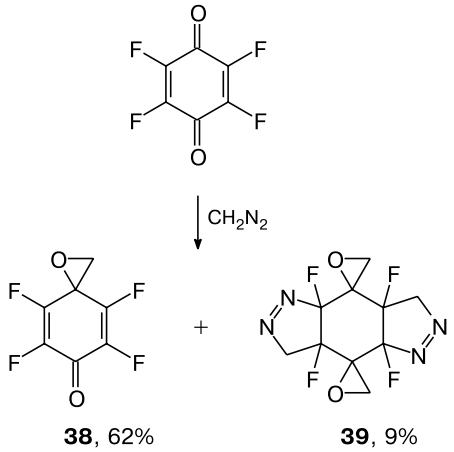
On the contrary, the alkyl group in position 3 directs the reaction to the C(4)=C(5) bond.[31] If the geminal substituents in position 6 of 2,4-cyclohexadienones are relatively small (*e.g.*, methyl groups or one hydroxyl and one methyl group), bis-adducts to both double bonds can be formed.[32,34,36] Some more inter- and intramolecular cycloadditions of 2,4-cyclohexadienones with specific diazo compounds giving polycyclic pyrazoles and cyclopropanes in several steps were described.[37,38]

Recently,[39] it was shown that diazomethane reacts with tetrafluoro-*p*-benzoquinone to give 2′,3′,5′,6′-tetrafluorospiro[oxirane-2,1′-cyclohexa-2,5-dien]-4′-one (**38**) as the main product, formed due to the reaction at the carbonyl group, along with a small amount of pentacyclic compound **39**, which is the product of the reaction involving both double bonds and the carbonyl groups of tetrafluoro-*p*-benzoquinone (Scheme 22).

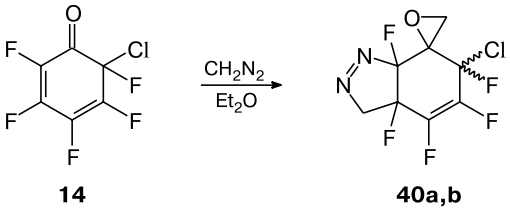
6-Chloro-2,3,4,5,6-pentafluoro-2,4-cyclohexadienone (**14**) reacts with diazomethane in ether at 0 °C with participation of both the carbonyl groups and the double bond to give a 58 : 42 mixture of two isomers of 6-chloro-3a,4,5,6,7a-pentafluoro-3a,6,7,7a-tetrahydrospiro[3*H*-indazolo-7,2′-oxirane] (**40a,b**) in a 52% overall yield[40] (Scheme 23).

The structures of compounds **40a** and **40b** were attributed on the basis of the analysis of the ^{19}F NMR spectrum of the isomeric mixture in which one of the isomers has

Scheme 22



Scheme 23

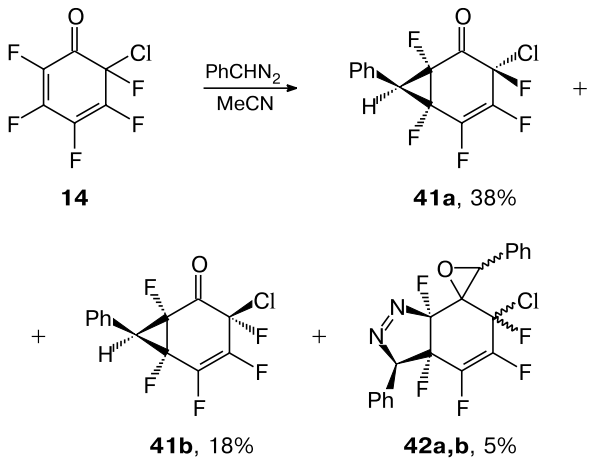


the splitting constants $J_{F(3a),F(6)} = J_{F(6),F(3a)} = 7$ and $J_{F(6),F(7a)} = J_{F(7a),F(6)} = 12.5$ Hz, while for the other isomer these constants are <2 Hz.

The main products of the reaction of 6-chloro-2,3,4,5,6-pentafluoro-2,4-cyclohexadienone (**14**) with phenyldiazomethane in acetonitrile (the addition of a solution of phenyldiazomethane to a solution of dienone **14**) are isomeric 3-chloro-1,3,4,5,6-pentafluoro-7-phenylbicyclo[4.1.0]hept-4-en-2-ones (**41a** and **41b**, 62 : 38) formed with participation of only the fluorinated double bond. Isomeric 6-chloro-3a,4,5,6,7a-pentafluoro-3,3′-diphenyl-3a,6,7,7a-tetrahydrospiro[3*H*-indazole-7,2′-oxiranes] (**42a** and **42b**, 67 : 33) were also obtained but in a low yield (5%) (Scheme 24). Compounds **41a,b** can be regarded as latent σ-homo-*o*-benzoquinones[41] opening an approach to fluorinated tropolones. The ^{1}H and ^{19}F NMR spectra of the isomeric compounds **42a** and **42b** are similar to those of **40a** and **40b**. However, the signals of F(3a), which is adjacent to the phenyl group in the pyrazoline ring of compounds **42a** and **42b**, exhibit a downfield shift of about 10 ppm.

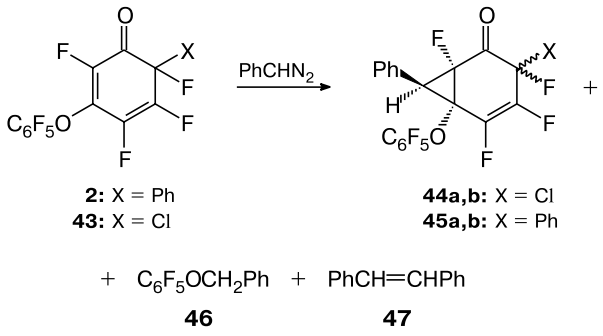
Bicycloheptenones **41a** and **41b** were isolated in the pure form, and their structures were determined by X-ray diffraction analysis. The X-ray structures show that the cycloaddition of cyclohexadienone **14** and phenyldiazomethane occurs with high selectivity: both isomers, **41a** and **41b**, have an *endo*-configuration.

Scheme 24



The reactions of 6-chloro-3-(pentafluorophenoxy)-2,4,5,6-tetrafluoro-2,4-cyclohexadienone (**43**) and cyclohexadienone **2** with phenyldiazomethane in acetonitrile afford mixtures of isomeric cyclopropane derivatives **44a** and **44b** (67 : 33) or **45a** and **45b** (83 : 17), respectively, as the main products in rather low yields (36 and 13%) along with benzyl pentafluorophenyl ether **46** (~10%). Considerable amounts of (*Z*)- and (*E*)-stilbenes **47** as products of competitive reactions are also formed. Spirotetrahydroindazoles of the types **40** and **42** were not detected (Scheme 25).

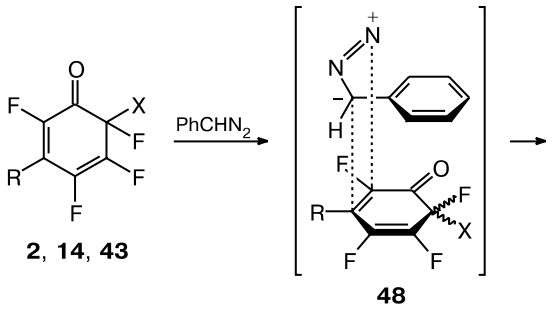
Scheme 25

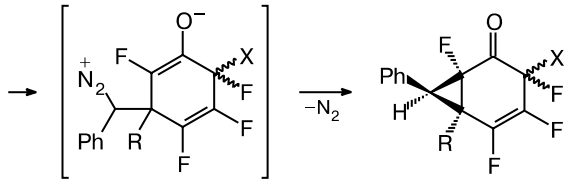


The following mechanism was proposed for the formation of norcarene derivatives in the reactions of polyfluorinated cyclohexadienones **2**, **14**, and **43** with phenyldiazomethane (Scheme 26).

Zwitterion **49**, which formed in the first step from dienones **2**, **14**, or **43** through a transition state similar to **48**, is stabilized either due to the elimination of nitrogen followed by cyclization resulting in the formation of norcarene derivatives **41**, **44**, and **45** as mixtures of isomers different in stereochemistry of the CXF fragment, or in the result of the elimination of pentafluorophenol,

Scheme 26





$C_6F_5OH + PhCHN_2 \xrightarrow{-N_2} C_6F_5OCH_2Ph$ (**46**)

	2, **45**	**14**, **41**	**43**, **44**
X	Ph	Cl	Cl
R	OC_6F_5	F	OC_6F_5

whose interaction with phenyldiazomethane affords benzyl pentafluorophenyl ether **46**. The probability of the latter reaction was verified in an independent experiment. In addition, it is known that the pentafluorophenoxy group in position 3 of polyfluorinated cyclohexadienones can easily be replaced by various nucleophilic reagents.[19]

The scheme proposed is corroborated by the *endo*-configuration of norcarene derivatives **41a,b** found by X-ray diffraction analysis, the known high reactivity of position 3 of polyfluorinated cyclohexadienones in the reactions with nucleophiles,[2] and the data that the orientation in the reactions of diazomethane with polyfluorinated alkenes is the same as that in nucleophilic reactions.[42]

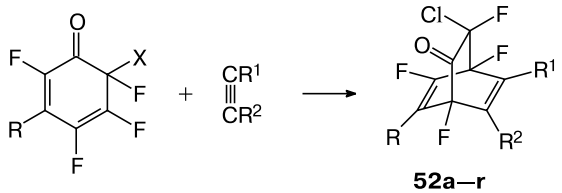
Thus, polyfluorinated 2,4-cyclohexadienones, unlike nonfluorinated cyclohexadienes, react with diazomethane at both the double bonds and the carbonyl group to form isomeric fluorine-containing tetrahydrospiro[indazol-oxiranes], which differ in steric arrangement of the halogen atoms of the CFCl group. Polyfluorinated 2,4-cyclohexadienones react with phenyldiazomethane predominantly at the fluorinated double bond to give with high stereoselectivity isomeric fluorine-containing phenylbicyclo[4.1.0]heptenones having *endo*-configuration.

5.2. [4+2] Cycloaddition reactions

5.2.1. Reactions with acetylene derivatives

Polyfluorinated cyclohexadienones **2**, **6**, **14**, **43**, **50**, and **51** easily undergo [4+2] cycloaddition reactions with such dienophiles as acetylene derivatives containing the aryl, alkyl, and hydroxyalkyl groups to give stable adducts in high yields (75—96%).[12,43—45] The reactions generally occur under mild conditions, at the boiling temperature of the corresponding solvent (benzene, toluene, or carbon tetrachloride). The structures of bicyclo[2.2.2]octadienones **52a—r** was proposed on the basis of analysis of their ^{19}F NMR spectra. Cycloaddition proceeds regio- and stereospecifically to form only isomers **52** (R^1 = H) (Scheme 27).

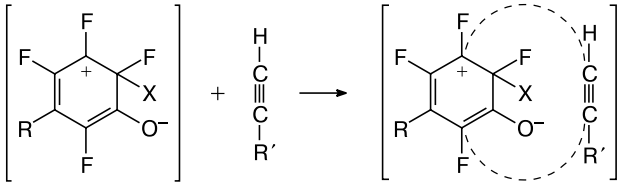
Scheme 27



Compound **52**	Initial compound	X	R	R^1	R^2
a	**14**	Cl	F	H	Ph
b	**14**	Cl	F	Ph	Ph
c	**14**	Cl	F	H	Bu
d	**14**	Cl	F	Et	Et
e	**14**	Cl	F	H	CH_2OH
f	**14**	Cl	F	H	CMe_2OH
g	**43**	Cl	OC_6F_5	H	Ph
h	**43**	Cl	OC_6F_5	Ph	Ph
i	**43**	Cl	OC_6F_5	H	Bu
j	**43**	Cl	OC_6F_5	Et	Et
k	**43**	Cl	OC_6F_5	H	CH_2OH
l	**43**	Cl	OC_6F_5	H	CMe_2OH
m	**50**	Cl	OMe	H	Bu
n	**50**	Cl	OMe	H	CH_2OH
o	**2**	Ph	OC_6F_5	H	Ph
p	**6**	Ph	OMe	H	Bu
r	**51**	OC_6F_5	F	H	Ph

The observed orientation is consistent with the electron density distribution in the diene and dienophile. Polyfluorinated cyclohexadienone can be presented as a bipolar molecule in which the positive charge is localized on the C(5) atom. For this reason, it reacts with a dienophile in accordance with the Markovnikov rule attacking the unsubstituted position of asymmetric acetylene (Scheme 28).

Scheme 28



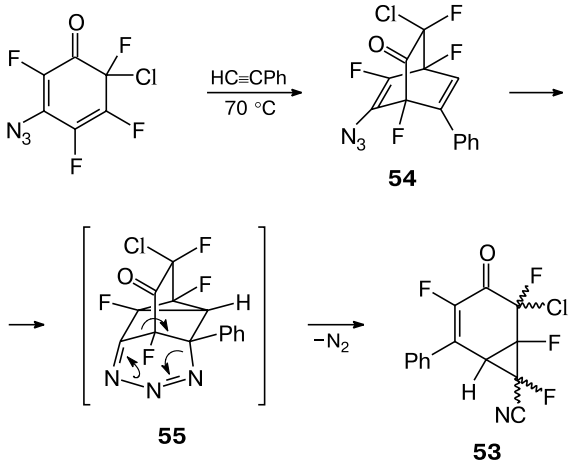
The X-ray diffraction data show[45] that the Diels—Alder reactions of polyfluorinated cyclohexadienones with acetylene occur with high stereoselectivity. The configuration of the sp^3-hybridized carbon atom bearing the fluorine atom and substituent X, is independent of the nature of this substituent: the fluorine atom is always oriented toward the bond formed due to dienophile addition.

The calculations performed by the molecular mechanics (MM) method[45] for two epimeric adducts with different arrangements of the fluorine and chlorine atoms at the sp^3-hybridized carbon atom, for example, adducts obtained in the cycloaddition reactions of dienone **14** with phenylacetylene and of dienone **43** with hex-1-yne, showed that these epimeric pairs had almost the same stability: 0.2 kcal mol^{-1} for **52a** and −0.5 kcal mol^{-1} for **52i**. This implies the absence of a correlation between the stereoselectivity of cycloaddition and the thermodynamic stability of the reaction products. The stereoselectivity of the reactions is a result, perhaps, of a less hindered attack of cyclohexadienone by the dienophile on the side of the fluorine atom than on the side of other geminal substituents, such as the chlorine, phenyl, or pentafluorophenoxyl group.[45]

An unexpected result was obtained in the cycloaddition reaction of 3-azidotetrafluoro-6-chloro-2,4-cyclohexadien-1-one. Heating of this dienone with phenylacetylene in CCl_4 at 70 °C gives 4-oxo-2-phenyl-3,5,6,7-tetrafluoro-5-chlorobicyclo[4.1.0]hept-2-ene-7-carbonitrile (**53**) as the main product[12] (Scheme 29).

Scheme 29 presents a possible formation of cyclopropane derivative **53**. Cycloadduct **54** was identified among the reaction products by the ^{19}F NMR method.

Scheme 29

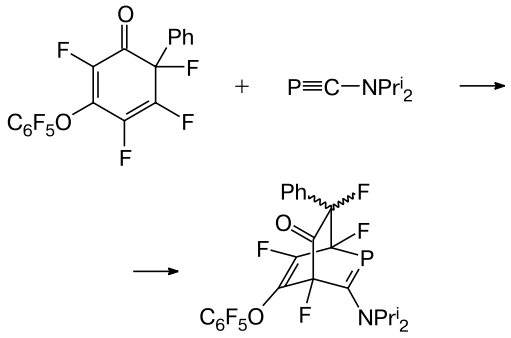


54 **55** **53**

Phosphaalkynes, being heteroanalogs of acetylene, also enter into [4+2] cycloaddition reactions with polyfluorinated cyclohexadienones.[46] The reactions of [4+2] cycloaddition of phosphaalkynes with cyclic 1,3-dienes were earlier used for syntheses of cyclic phosphaalkenes, in particular, phosphaaromatic compounds.[47,48] The stability of the bicyclic adducts depends on the structure of the 1,3-diene system. For example, the bicyclic adduct of the Diels—Alder reaction of cyclopentadiene and phosphaalkyne bearing the *tert*-butyl group was characterized only spectroscopically in a solution.[49] The expected bicyclic adduct was not found in the reaction of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene with the same phosphaalkyne.[50] Only the reactions of cyclohexadiene[49,51] and 9-substituted anthracenes[52] with *tert*-butylphosphaethyne afford the respective stable 2-phosphabicyclo[2.2.2]octa-2,5-dienes.

Heating of bis(isopropyl)aminophosphaethyne with cyclohexadienone **2** in a dichloromethane solution from −196 °C to ~20 °C gives only one isomeric bicyclic adduct **56** in ~100% yield[46] (Scheme 30).

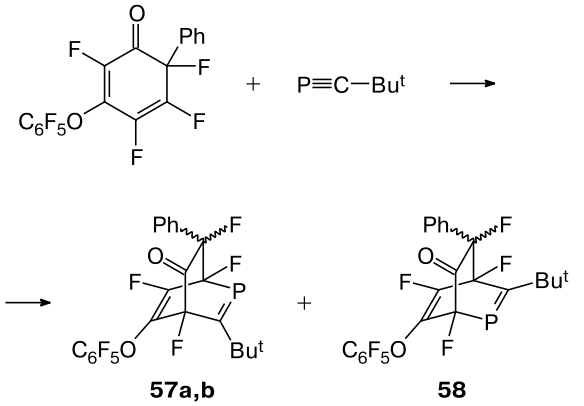
Scheme 30



56

The chemical composition and structure of adduct **56** were determined by elemental analysis and spectroscopic studies (mass spectrometry, ^1H, ^{19}F, ^{31}P, and ^{13}C NMR spectroscopy). Adduct **56** is stable at room temperature in the solid state and in standard solvents. Unlike 2-phosphabicyclo[2.2.2]octa-2,5-diene, fluorine-containing adduct **56** in an excess of phosphaalkyne does not undergo the homo Diels—Alder reaction.[49] It is of interest that, unlike the reaction of bis(isopropyl)aminophosphaethyne with cyclohexadienone **2**, the reaction with *tert*-butylphosphaethyne, according to the mass spectrometric and NMR spectroscopic data, affords a mixture of three compounds **57a,b** and **58** in a ratio of 90 : 4 : 6. The ^{31}P NMR spectroscopic data suggest that in a mixture of the products regioisomer **57** exists as a mixture of two isomers, whereas regioisomer **58** exists as one isomer. Researchers could not determine stereochemistry of either minor isomers **57b** and **58** or isomer **57a** isolated in the individual form. The reaction with *tert*-butylphosphaethyne occurs with a much lower rate because the complete conversion of cyclohexadienone **2** is achieved by heating of the reactants mixture for 2 days at 60 °C (Scheme 31).

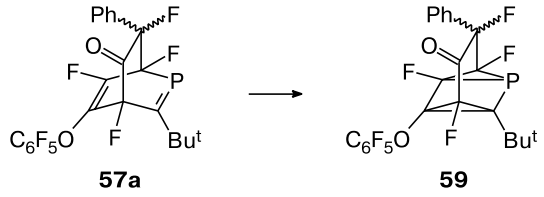
Scheme 31



57a,b **58**

Bicyclic adducts **57a,b** and **58** also do not undergo a homo Diels—Alder reaction with an excess of *tert*-butylphosphaethyne at 60 °C. However, for isomer **57a** in chloroform, intramolecular [2+2] cycloaddition was observed, which was probably initiated by diffuse daylight. When a solution of adduct **57a** was stored at room temperature for 20 h, compound **59** was detected by NMR, and after storage for 7 days its yield increased to 60% (Scheme 32).

Scheme 32



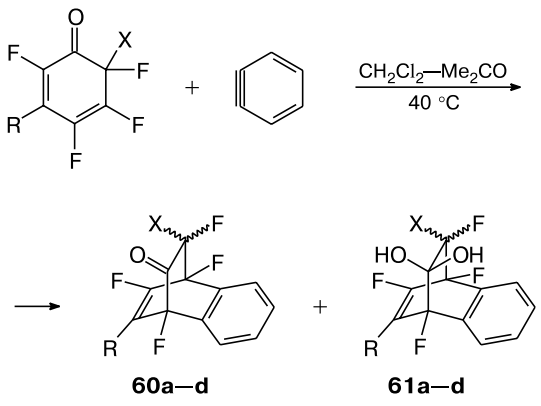
57a **59**

Heating of adduct **57a** to 60 °C does not accelerate the formation of compound **59** but results in the remarkable decomposition of both the initial adduct **57a** and compound **59**. The formation of tetracyclic product **59** is likely a result of valence isomerization due to intramolecular [2+2] cycloaddition under the action of diffuse daylight.

The tetracyclic structure of compound **59** was proposed on the basis of analysis of the NMR spectroscopic data. The observed considerable upfield shift of the signal from ^{31}P ($\Delta\delta_P$ 304.1 ppm) caused by the valence isomerization of compound **57a** (δ_P = 217.7 ppm) to **59** (δ_P = −86.4 ppm) is consistent with the shift $\Delta\delta_P$ 445 ppm observed for the photochemical transformation of 2-Dewar phosphine into the corresponding phosphoprismane derivative.[53] Like for adduct **57a**, the stereochemistry of phosphoprismane **59** was not determined.

Polyfluorinated cyclohexadienones enter into [4+2] cycloaddition reactions with such dienophile as dehydrobenzene.[54] The latter was obtained *in situ* from *o*-aminobenzoic acid and isoamyl nitrite[55] (Scheme 33).

Scheme 33



60a—d **61a—d**

	a	b	c	d
R	F	OC_6F_5	OMe	F
X	Cl	Cl	Cl	OC_6F_5

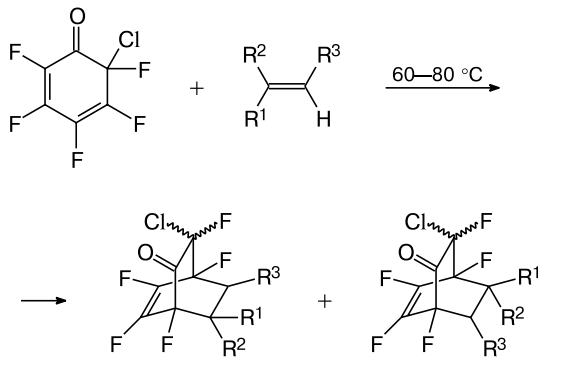
The reaction products obtained in low yields (26—37%) are mixtures of two compounds **60a—d** and **61a—d**, whose chemical shifts in the ^{19}F NMR spectra are close and typical of cycloadducts formed in the reactions of polyfluorinated 2,4-cyclohexadienones with acetylene derivatives. When an isolated mixture of the reaction products was dissolved in hexane, the ^{19}F NMR spectra of the solution exhibited only adducts **60a—d**, which were transformed into compounds **61a—d** on replacing hexane by acetone (several days of storage at room temperature). Analysis of the ^{13}C NMR spectra of these compounds[45] suggests that compounds **61a—d** are hydrated forms of adducts **60a—d**, whose formation involves, most likely, water present in the solvents. In the ^{13}C NMR spectrum of the hydrated forms of cycloadducts **61a—d**, the signal from the carbon atom of the carbonyl group in adducts **60a—d** (~180—181 ppm) disappears, and a signal with the chemical shift typical of acetals (~145—146 ppm) appears.[56]

5.2.2. Reactions with alkenes

The reactions of polyfluorinated cyclohexadienones with alkenes[57] (hex-1-ene, allylbenzene, styrene, α-methylstyrene, indene, acrylic acid, and butyl methacrylate) afford bicyclic adducts **62a—g** in high yields (84—97%). For most alkenes, these reactions occur with high regioselectivity similarly to the reactions with acetylenes,[45] except for the reactions with hex-1-ene and allylbenzene yielding a mixture of equal amounts of two isomeric cycloadducts **62a,b** and **63a,b**, which were isolated by chromatography on silica gel (Scheme 34).

The absence of regioselectivity in the reactions with hex-1-ene and allylbenzene seems to be the result of only weak polarization of the double bond in each of these compounds.

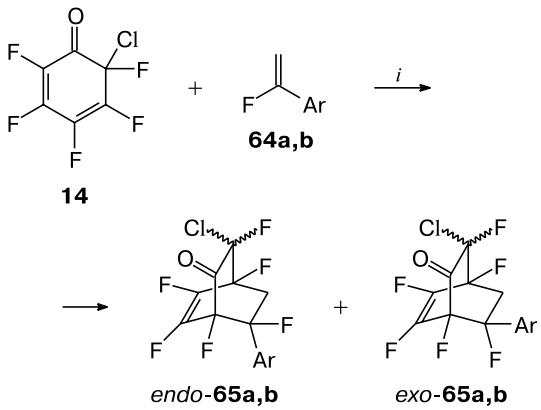
Scheme 34



	a	b	c	d	e	f	g
R^1	H	H	H	Me	Me	H	H
R^2	Bu	CH_2Ph	*o*-$C_6H_4CH_2$	COOBu	Ph	COOH	Ph
R^3	H	H		H	H	H	H

The reactions of cyclohexadienone **14** with α-fluorostyrene (**64a**) and α-fluoro-4-chlorostyrene (**64b**) in boiling benzene afford [4+2] cycloaddition products as a mixture of two isomers (*endo*-**65a,b** and *exo*-**65a,b**)[58] (Scheme 35).

Scheme 35



a: Ar = Ph (70%), *endo* : *exo* = 53 : 47
b: Ar = *p*-ClC_6H_4 (78%), *endo* : *exo* = 42 : 58

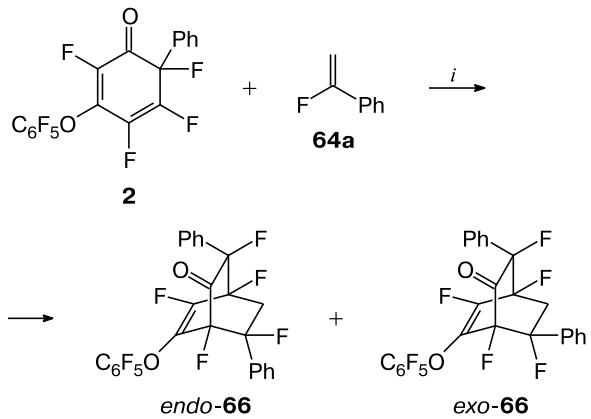
i. C_6H_6, 80 °C, 20 h.

The structures of bicyclo[2.2.2]octenones **65a,b** (see Scheme 35) were proposed on the basis of the ^{19}F NMR spectroscopic data.

The *endo*- and *exo*-configurations of isomeric bicyclic adducts **65** were confirmed by the correlation of their spectra and the NMR spectra of the cycloadducts obtained in the reactions of α-fluorostyrenes and 1,3-diphenylisobenzofuran.[59] The structure of one of the isomeric bicyclo[2.2.2]octenones (**65a,b**) was confirmed by the X-ray diffraction data.

The reaction of cyclohexadienone **2** and α-fluorostyrene **64a** occurs similarly but under more drastic conditions to give two isomeric bicyclic adducts (*endo*-**66** and *exo*-**66**) (Scheme 36). Regio- and stereochemistry for the isomers of 3-(pentafluorophenoxy)-5,6-bisphenyl-1,2,4,5,7-pentafluorobicyclo[2.2.2]hex-2-en-8-one *endo*-**66** and *exo*-**66** was confirmed by the X-ray diffraction data.[58]

Scheme 36



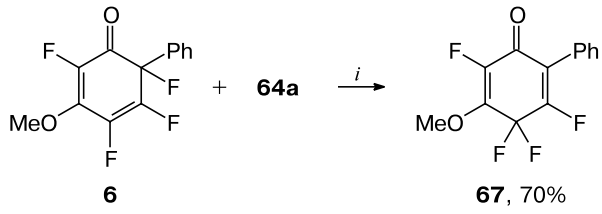
Yield 90%, *endo*-**60** : *exo*-**60** ratio 43 : 57

i. $PhCH_3$, 110 °C, 20 h.

Like the reactions with acetylenes, the reactions of cyclohexadienones **2** and **14** with α-fluorostyrenes **64a,b** are characterized by high regioselectivity: the fluorine atom of the CFX group in bicyclo[2.2.2]octenones **65** and **66** is oriented to the side of a new bond formed upon the addition of α-fluorostyrene **64a** (X-ray diffraction data for *endo*-**65a**, *endo*- and *exo*-**66**).[58]

An attempt to perform the reaction of 3-methoxy-6-phenyl-2,4,5,6-tetrafluoro-2,4-cyclohexadienone (**6**) with α-fluorostyrene **64a** was unsuccessful, which is associated, most likely, with the orbital coefficients and orbital energies of the atoms involved in the reaction (Table 1). Only the product of allyl migration of the fluorine atom,

Scheme 37



i. $PhCH_3$, 110 °C, 30 h.

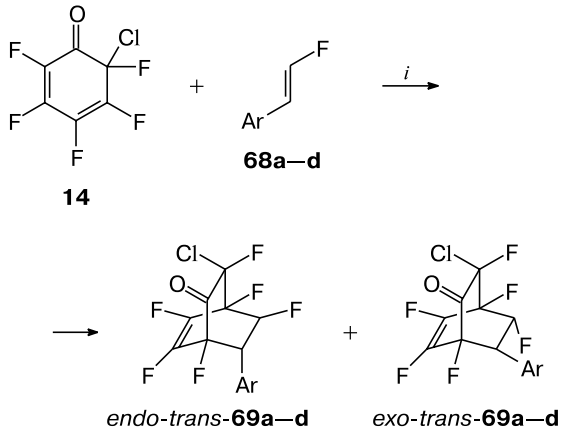
Table 1. Orbital coefficients and orbital energies of fluorinated 2,4-dienones **2**, **6**, and **14** and styrenes **64a** and **68a**

Compound	Orbital coefficients (Orbital energies/eV)			
	HOMO		LUMO	
	C(2)	C(5)	C(2)	C(5)
2	−0.01 (−10.36)	+0.02	−0.44 (−2.08)	−0.50
6	+0.49 (−10.18)	−0.08	−0.48 (−1.78)	−0.46
14	−0.50 (−10.73)	+0.50	+0.45 (−2.44)	+0.45
	C(1)	C(2)	C(1)	C(2)
64a	+0.33 (−9.38)	+0.51	+0.33 (−0.40)	−0.45
68a	−0.36 (−9.20)	−0.46	−0.34 (−0.40)	+0.49

viz. 3-methoxy-6-phenyl-2,4,4,5-tetrafluoro-2,5-cyclohexadienone (**67**), is formed instead of bicyclic adducts (Scheme 37).

β-Fluorostyrene is known to behave in the reaction with 1,3-diphenylisobenzofuran as a less reactive dienophile than α-fluorostyrene.[59] The reactions of polyfluorinated 2,4-cyclohexadienones with *trans*-β-fluorostyrenes **68a—d** also occur more slowly than the reactions with α-fluorostyrenes. However, boiling of cyclohexadienone **14** with *trans*-β-fluorostyrenes **68a—d** in toluene affords two bicyclic adducts in 75—79% yields. They are *endo-trans*- and *exo-trans*-isomers of **69** with prevailing of the *endo-trans*-isomers in all cases (Table 2, Scheme 38).

Scheme 38



Ar = Ph (**a**), *p*-ClC_6H_4 (**b**), *p*-FC_6H_4 (**c**), *m*-MeC_6H_4 (**d**)

i. $PhCH_3$, 110 °C, 30 h.

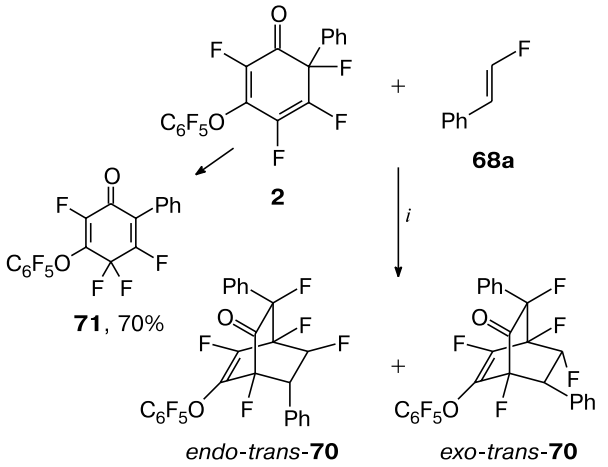
Table 2. Products of the Diels—Alder reactions of dienone **14** and *trans*-β-fluorostyrenes **68a—d**

Adduct	Ar in **68**	Yield (%)	Ratio *endo* : *exo*
69a	Ph	77	74 : 26
69b	*p*-ClC_6H_4	78	65 : 35
69c	*p*-FC_6H_4	75	67 : 33
69d	*m*-MeC_6H_4	79	63 : 37

Diastereoisomers of *trans*-isomers **69a,b** were separated chromatographically, and their structures were confirmed by the NMR spectroscopic data. Owing to an admixture of the *cis*-isomers (13—25%) in the initial *trans*-β-fluorostyrenes **69a—d**, the mixture of cycloaddition products also contains bicyclic adducts (to 10%), which can be the products of cycloaddition of *cis*-β-fluorostyrenes to polyfluorinated 2,4-cyclohexadienones (*endo-cis*-isomers).

Cyclohexadienone **2** demonstrates a low reactivity in the reaction with *trans*-β-fluorostyrene **68a**, being isomerized predominantly to 3-(pentafluorophenoxy)-6-phenyl-2,4,4,5-tetrafluoro-2,5-cyclohexadienone (**71**): the cycloaddition products (*endo-trans*-**70** and *exo-trans*-**70**) were obtained in low yields (Scheme 39).

Scheme 39



Reagents, conditions, and yield: *i*. $PhCH_3$, 110 °C, 30 h, 21% yield, *endo*-**70** : *exo*-**70** ratio 55 : 45.

Under the same conditions cyclohexadienone **6** gives only isomerization product **67**, as in the reaction with α-fluorostyrene (see Scheme 37).

The orbital coefficients and orbital energies of the centers (see Table 1) involved in the formation of the cyclic systems were calculated[58] at the PM3 level.[60] A comparison of the HOMO and LUMO energies of **14**

and **64a** shows that their interaction includes, most likely, a concerted Diels—Alder process with an inverse electron demand (Δ = 6.94 eV). In addition, the orbital coefficients of the reacting centers shows a very efficient overlapping of the orbitals. For the reaction of **14** with **68a**, the difference between the $HOMO_{styrene}$ and $LUMO_{dienone}$ energies (6.76 eV) is much lower than that for the $LUMO_{styrene}$ and $HOMO_{dienone}$ pair (10.33 eV). However, the coefficients of the orbitals involved in the reaction point to a much lower overlapping.

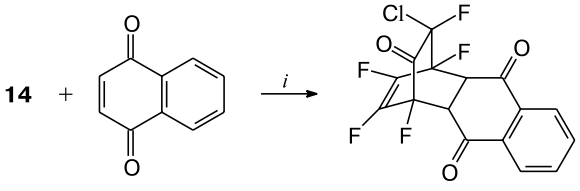
For the reactions of **2** with **64a** and **68a**, the standard Diels—Alder reactions are less probable. However, the differences in the $HOMO_{styrene}$ and $LUMO_{dienone}$ energies become greater (7.30 eV or 7.12 eV, respectively) and, in addition, the overlapping of the participating orbitals becomes smaller in the reaction of **2** with **64a** and still smaller for the reaction of **2** with **68a**. This can possibly be explained by the partial thermal isomerization of **2** to **71** (see Scheme 39).

Finally, in the cycloaddition of methoxy-substituted cyclohexadienone **6** with **64a** and **68a**, the energy differences for the participating orbitals become the largest (7.60 eV or 7.42 eV, respectively). Thus, the isomerization of **6** to **67** becomes preferential under thermal conditions (see Scheme 37).

Attempts to introduce α-fluoro-α,β-unsaturated ketones, for example, 4-fluoroct-4-en-3-one, into the Diels—Alder reactions with polyfluorinated 2,4-cyclohexadienones were unsuccessful. Even a prolonged treatment of the reactants in boiling toluene or in the presence of the florisil sorbent, which is known to catalyze cycloaddition reactions of this type,[61] did not give any cycloadducts.

At the same time, cyclohexadienone **14** easily undergoes the dienone synthesis with such dienophile as naphthoquinone to give adduct **72** in a high yield[62] (Scheme 40).

Scheme 40



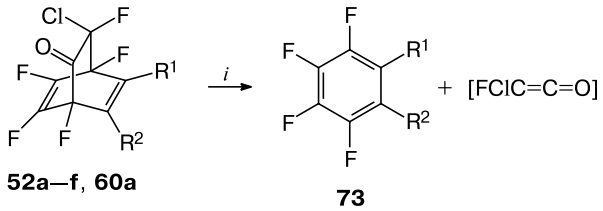
i. $PhCH_3$, 110 °C.

5.3. Transformations of fluorinated bicyclo[2.2.2]octadienones

5.3.1. Photochemical reactions

The photochemical transformations of fluorinated bicyclo[2.2.2]octadienones **52a—f** and **60a** bearing the CFCl group in the vicinal position to the carbonyl group at room temperature in chloroform afford tetrafluoroaromatic compounds **73a—g** as major products, possibly due to chlorofluoroketene FClC=C=O elimination.[63] For the 75—100% conversion of bicyclo[2.2.2]octadienones, the yields of fluoroaromatic compounds range from 50 to 86% per reacted bicyclo[2.2.2]octadienone (Scheme 41).

Scheme 41



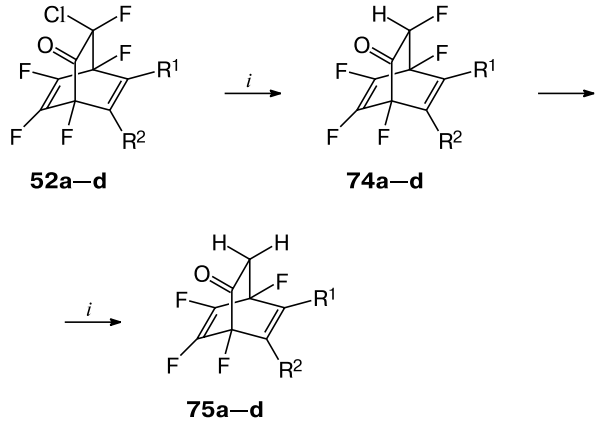
i. *h*ν, 250—400 nm, $CHCl_3$, 18—20 °C.

It is known that photolysis of (tetrafluorobenzo)bicyclo[2.2.2]octa-2,5-dienone[64] and nonfluorinated bicyclo[2.2.2]octadienones in an ether or acetone solution[65,66] leads to a loss of a bridge having the carbonyl group.

5.3.2. Selective reductive dehalogenation of halogen atoms at sp^3-hybridized carbon atom

The reactions of bicyclic adducts, 8-chloro-1,2,3,4,8-pentafluorobicyclo[2.2.2]octa-2,5-dienones **52a—d** with Zn in acetic acid lead to successive replacements of halogen atoms at the sp^3-hybridized carbon atom by hydrogen.[67] The structures of new bicyclic adducts **74a—d** and **75a—d** were confirmed by a comparison of their spectral characteristics with those of the starting cyclic adducts,

Scheme 42



R^1 = H, R^2 = Ph (**a**); R^1 = R^2 = Ph (**b**); R^1 = H, R^2 = Bu (**c**); R^1 = R^2 = Et (**d**)

i. Zn, AcOH, reflux.

Table 3. Reduction of bicyclooctadienones **52a—d** with Zn/AcOH

Compound	Molar ratio Zn : **52**	τ/h	Yield of products (%)
52a	3	2	**74a** (77)
	6	8	**75a** (73)
52b	2.5	4	**74b** (86)
	6	12	**75b** (81)
52c	6	6	**74c** (72)
	12	16	**75c** (65)
52d	6	8	**74d** (70)
	15	10	**75d** (68)

and the ^{1}H NMR spectra indicate the appearance of signals from the CHF and CH_2 groups. The fluorine atoms in other positions remain unaffected (Scheme 42).

It should be noted that the substitution of hydrogen for chlorine at the α-position to the carbonyl group, particularly in cyclic ketones, is well known,[68] but a similar substitution for fluorine atoms has not been found in the literature.[69]

The reaction conditions and yields are presented in Table 3.

5.3.3. Hydrolysis of bicyclic adducts in the presence of different alcohols and amines

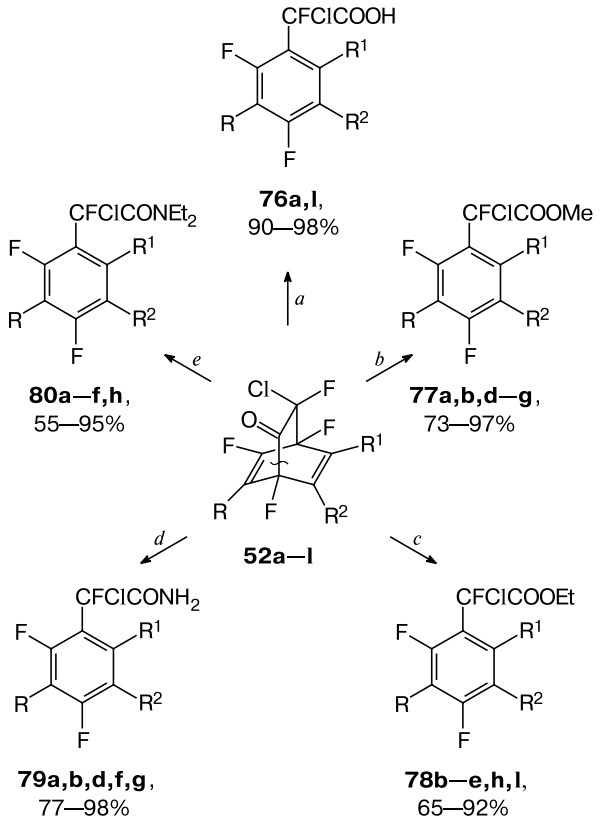
A remarkable property of the Diels—Alder adducts obtained in the reactions of polyfluorinated cyclohexadienones with acetylene derivatives is their easy cleavage by nucleophilic reagents to form aromatic compounds. A specific feature of these reactions is the preservation in the final aromatic compounds of the structural elements of the bridge containing the CFCl and carbonyl groups[45] (Scheme 43).

The bicyclic adducts obtained by the replacement of the geminal chlorine and fluorine atoms by hydrogen[67] undergo easy aromatization to give the corresponding fluorinated arylacetic acids in high yields (85—95%) (Scheme 44).

Unlike these hydrolysis reactions, adducts **85** and **86** obtained in analogous reactions of polyfluorinated cyclohexadienes[70] and nonfluorinated cyclohexadienones[71] loose the structural elements of the bridge upon hydrolysis or thermolysis (Scheme 45).

The treatment of cyclic adducts **60a—d** obtained from polyfluorinated cyclohexadienones **14**, **43**, **50**, and **51** and dehydrobenzene with an alkali in an aqueous solution of dioxane or with aqueous ammonia in dioxane at room temperature affords fluorine-containing naphthylacetic acids **87a—d** or their amides **88a—d** in high yields.[54] Notably, aromatization occurs with preservation of the structural elements of the bridge containing the carbonyl group (Scheme 46).

Scheme 43



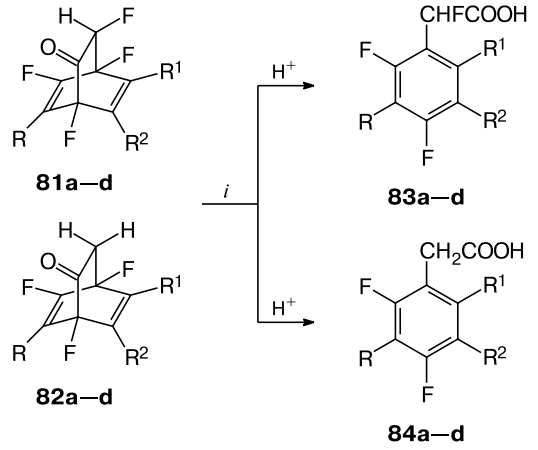
	X	R	R^1	R^2
a	Cl	F	H	Ph
b	Cl	F	Ph	Ph
c	Cl	F	H	Bu
d	Cl	F	Et	Et
e	Cl	F	H	CH_2OH
f	Cl	F	H	CMe_2OH
g	Cl	OC_6F_5	H	Ph
h	Cl	OC_6F_5	Ph	Ph
i	Cl	OC_6F_5	H	Bu
j	Cl	OC_6F_5	Et	Et
k	Cl	OC_6F_5	H	CH_2OH
l	Cl	OC_6F_5	H	CMe_2OH

Reagents: *a*. 1) NaOH, aqueous dioxane; 2) H^+; *b*. MeOH, K_2CO_3; *c*. EtOH, K_2CO_3; *d*. aqueous NH_3, dioxane; *e*. Et_2NH, benzene.

This specific feature of aromatization is opposite to transformations of some analogs of the above-mentioned adducts. For example, adduct **89** obtained in the reaction of dehydrobenzene and hexamethylcyclohexa-2,4-dienone does not change on treatment with an aqueous alkali[72,73,74] and gives aromatization product **90** only in the reaction with very strong bases or on heating at an elevated temperature (450—550 °C) due to the elimination of the bridge containing the carbonyl group[74] (Scheme 47).

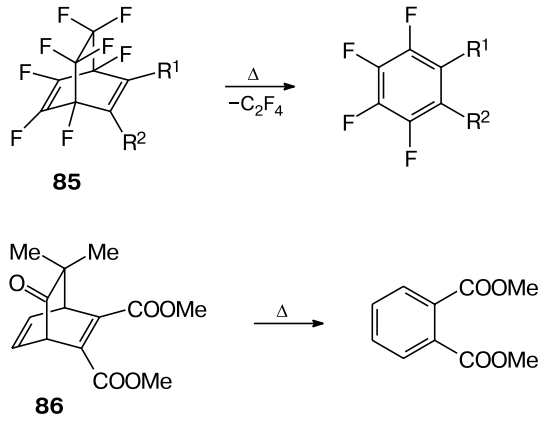
The reactions of fluorobenzobarrelene **91** with sodium hydroxide in water at room temperature or on boil-

Scheme 44

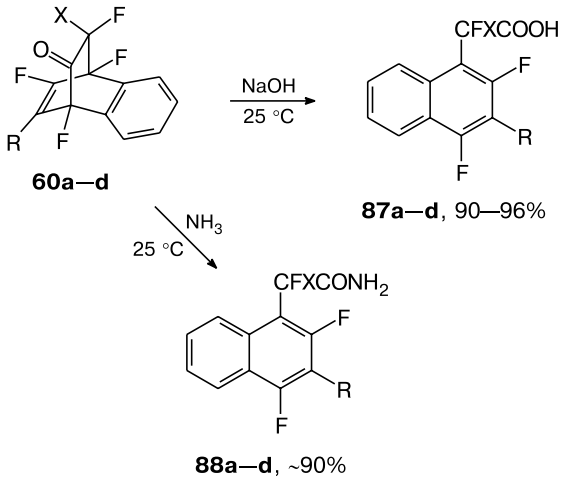


i. NaOH, aqueous dioxane.

Scheme 45

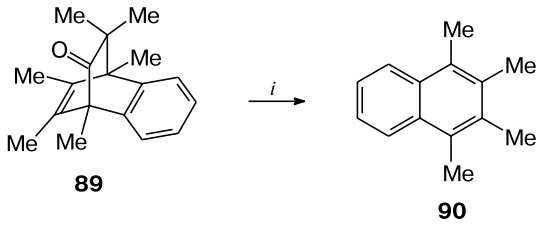


Scheme 46



X = Cl; R = F (**a**), OC_6F_5 (**b**), OMe (**c**);
X = OC_6F_5; R = F (**d**)

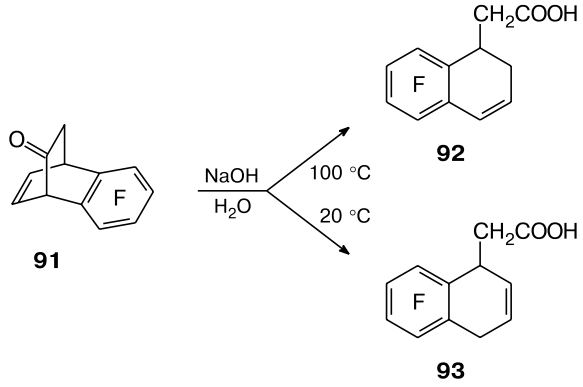
Scheme 47



i. 450—550 °C or a strong base.

ing afford products in which the carbonyl group remains intact, but these are nonaromatic compounds, such as 1,2- (**92**) and 1,4-dihydronaphthalenes (**93**)[75] (Scheme 48).

Scheme 48

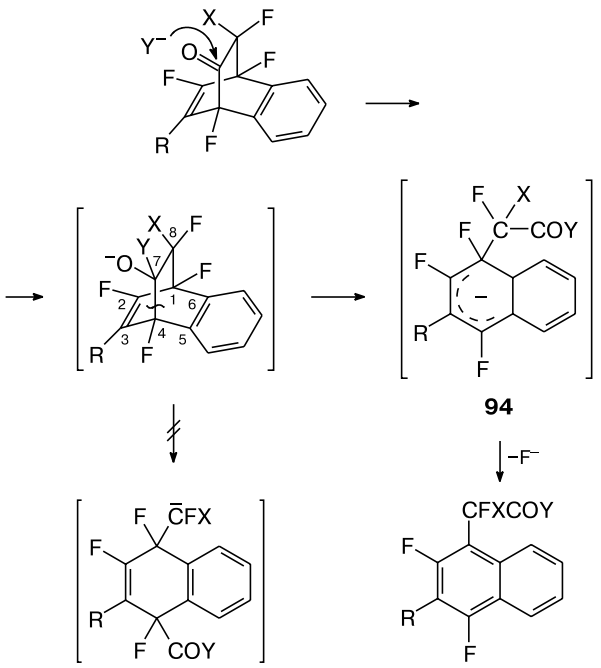


The mechanism of aromatization of the polyfluorinated Diels—Alder adducts evidently includes the C(4)—C(7) bond cleavage by a nucleophile with the formation of stable anionic σ-complex **94**, which undergoes aromatization through the elimination of the fluoride ion from the geminal node of the cycle (Scheme 49).

The alkaline cleavage of bicyclic adducts obtained in the Diels—Alder reactions of polyfluorinated cyclohexadienones and acetylenes is a convenient method for the synthesis of fluorine-substituted phenylacetic acids. Changing substituents in acetylene, as well as in the geminal position and in position 3 of polyfluorinated 2,4-cyclohexadienone, and using different alcohols and amines in the step of adduct aromatization, one can obtain different derivatives of phenylacetic acid containing functional groups along with fluorine atoms. It is difficult to obtain this type of potentially biologically active compounds by other methods.

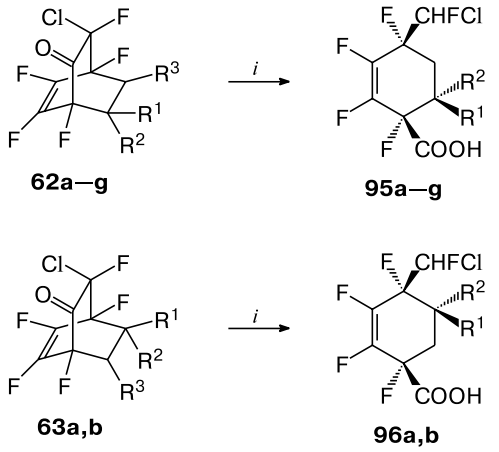
The cycloadducts obtained in the reactions of polyfluorinated cyclohexadienones with alkenes also readily undergo alkaline cleavage in aqueous dioxane to form fluorine-containing cyclohexenecarboxylic acids **95a—g** and **96a,b** in high yields (65—95%).[57] The configurations

Scheme 49



of these compounds were confirmed by the X-ray diffraction data for cyclohexenecarboxylic acids **95g** and **96a**, which are the cleavage products of the adducts obtained in the Diels—Alder reactions of *n*-butyl methacrylate and hex-1-ene with polyfluorinated cyclohexadienones (Scheme 50).

Scheme 50

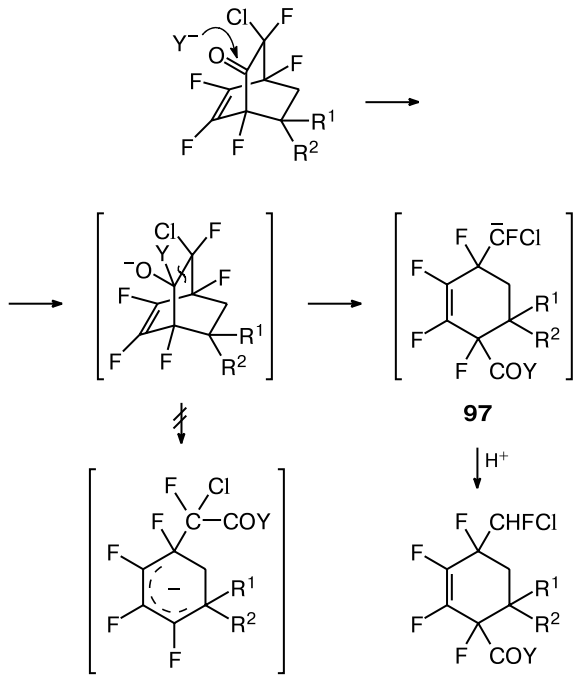


	a	**b**	**c**	**d**	**e**	**f**	**g**
R^1	H	H	H	Me	Me	H	H
R^2	Bu	CH_2Ph	*	COOBu	Ph	COOH	Ph
R^3	H	H	*	H	H	H	H

i. NaOH, H^+, aqueous dioxane. * R^2R^3 = *o*-$C_6H_4CH_2$.

The most interesting feature of this reaction is that the action of nucleophiles on the adducts obtained in the reactions of polyfluorinated cyclohexadienones with alkene cleaves the C(7)—C(8) bond instead of the C(4)—C(7) bond, as it takes place for bicyclic adducts obtained in the reactions of polyfluorinated cyclohexadienones with acetylenes and dehydrobenzene (Scheme 51).

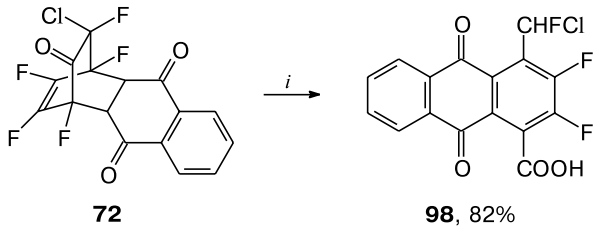
Scheme 51



The intermediate anions with a negative charge on the carbon atom bound to fluorine and chlorine are stabilized by proton addition to form cyclohexenecarboxylic acids.[57]

Cycloadduct **72** formed in the reaction of polyfluorinated cyclohexadienone **14** with 1,4-naphthoquinone reacts with sodium hydroxide at room temperature with simultaneous splitting of the C—C bond in the O=C—CFCl fragment and hydrogen fluoride elimination to form fluorinated anthraquinonecarboxylic acid **98**. This

Scheme 52



i. NaOH, aqueous dioxane.

new method is a convenient way to the functional derivatives of fluorinated anthraquinones[62] (Scheme 52).

6. Conclusion

The synthetic transformations considered in this review based on the use of polyfluorinated cyclohexadienones as synthons allow the preparation of a wide variety of fluorinated compounds by photolysis, nucleophilic reactions, cycloaddition, and simple transformations of products of these reactions: derivatives of polyphenyl ethers, arylacetic acids, naphthalene and anthraquinone derivatives containing the carboxyl group, cyclohexenecarboxylic acids, fluorinated heterocyclic compounds, cyclopropane derivatives, and bicyclic phosphorus-containing compounds. The further transformation and modification of products of these reactions provide access to the earlier unavailable organofluorine compounds of different structural types.

The new approach is especially important for syntheses of fluorinated derivatives of aryl- and diarylacetic acids because representatives of these classes of compounds are a basis of many drugs (propanidid, diclophenac, spasmolytin, paphencil, aprofene). It is well known that fluorine atoms strengthen the activity of pharmaceutical preparations, enhance the metabolic stability, prolong their action, and often reduce their toxicity.[76—78]

The approach in which polyfluorinated cyclohexadienones can be used as highly reactive synthons provide diverse challenges for syntheses of unavailable physiologically active fluorinated arylacetic acids containing functional groups. Such syntheses are possible due to the introduction of required functional groups at all stages of synthesis of these acids: nucleophilic substitution of the fluorine atom in position 3 of polyfluorinated cyclohexadienones; using of different substituted acetylenes in cycloaddition reactions; selective replacement of the halogen atoms at the sp^3-hybridized carbon atom of bicyclic adducts by the hydrogen atom; hydrolysis of bicyclic adducts in the presence of different alcohols and amines to form derivatives of arylacetic acids.

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