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Chemical functionalisation of polychloroarenes

A A Vasil'ev, A S Burukin, S G Zlotin

Contents

I.	Introduction	885
II.	Reactions with S- and Se-nucleophiles	886
III.	Reactions with N-nucleophiles	893
IV.	Reactions with O-nucleophiles	897
V.	Reactions with F-nucleophiles	900
VI.	Reactions with C-nucleophiles	903
VII.	Catalytic carbonylation and carboxylation	904
VIII.	Catalytic C – C cross-coupling	905
IX.	Metallation	909

Abstract. Methods for the replacement of chlorine atoms in polychloroarenes upon treatment with various reagents are surveyed. Considerable attention is given to catalytic methods and elucidation of the structure – reactivity relationships for polychloroarenes. The bibliography includes 322 references.

I. Introduction

According to the long-term environmental protection strategy of the EU countries, the production and utilisation of environmentally hazardous chemical compounds will be ceased by 2020. Polychlorinated aromatic compounds (polychloroarenes, PCA) are among such compounds. The disposal of toxic PCA produced on the industrial scale, such as first-generation insecticides polychlorobiphenyls and polychlorodioxins formed as their biodegradation products, remains an unsolved problem. Its solution requires information on the reactivity of these compounds, which would suggest promising approaches to their conversion into ecologically safe products or substances with useful properties. Catalytic hydrogenolysis of the C – Cl bond in PCA has been studied in sufficient detail.[1 – 8] However, the resulting products are, as a rule, of little practical significance because many hydrogenolysis products can be prepared according to simpler and cheaper procedures. Other reactions of PCA containing from two to six chlorine atoms in the aromatic nuclei have been documented to a lesser extent. Of these reactions, reduction-type processes, including metallation and electron-transfer reactions, as well as reactions with nucleophilic reagents, deserve notice. In addition, the development of procedures for the formation of new C – C and C – heteroatom bonds instead of poorly reactive C – Cl bonds is a good challenge for processing PCA into practically useful compounds of the aromatic series.

The chemical properties of PCA often differ from those of monochloro derivatives due to the mutual influence of the chlorine atoms. Polychloroarenes are characterised by high acidity of the aromatic protons and high electron affinity. The shift of the first half-wave reduction potential ($E_{1/2}$) to more positive values, on the average, by 0.2 – 0.3 V, upon the introduction of every next chlorine atom into the aromatic nucleus can serve as the criterion of the electron affinity.[9, 10] For example, this parameter for hexachlorobenzene is −1.44 V (relative to a saturated calomel electrode), as opposed to monochloroarenes, which are reduced at potentials equal or close to the values of supporting electrolyte discharge. At the same time, a negative charge on the chlorine atoms (for example, in hexachlorobenzene), the small C – Cl bond length (1.7 Å) and the rather large van der Waals radius of the chlorine atoms (1.8 Å) hinder the attack of nucleophiles on the electron-deficient carbon atoms in PCA.

The present review summarises the main reactions of PCA (containing from two to six carbon atoms in the aromatic core) resulting in the replacement of chlorine atoms by other elements. These include:

(1) nucleophilic substitution reactions,

(2) reactions accompanied by the C – C bond formation through metallation of PCA,

(3) transition metal-catalysed cross-coupling reactions.

The only monograph summarising the reactions of PCA was published in 1974.[11] The reactions of perchloroalkylarenes that involve the side aliphatic chains with retention of chlorine atoms in the aromatic moieties were considered in a more recent review.[12] In a chapter of a multivolume monograph [13] devoted to organic halogen-containing compounds, the properties of polyhaloarenes are not considered separately. In this connection, in our opinion, it is reasonable to discuss not only the results of studies published in the last decade, but also the earlier data. The present review includes data on low-chlorinated arenes in particular, because dioxins containing two chlorine atoms in the aromatic nuclei belong to environmentally hazardous compounds. In addition, certain reactions, which have been studied only for arenes containing two or three chlorine atoms, would be useful also for chemical

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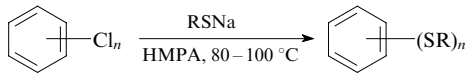
modifications of highly chlorinated PCA. Since the physicochemical properties and the structures of polychloroarenes have been covered in detail in the earlier monograph,[11] various chemical transformations of these compounds are only considered below.

II. Reactions with S- and Se-nucleophiles

Aromatic thiols, sulfides and their derivatives have found wide use as rubber vulcanisation promotors and modifiers of polymeric compositions. They also serve as intermediates in the synthesis of organic conductors, biologically active compounds and other valuable compounds. The main procedure for their synthesis is based on the nucleophilic substitution of chlorine atoms in chloroaromatic compounds under the action of sulfur-containing nucleophiles.

1. Characterisation of reactions of non-activated polychloroarenes with S- and Se-nucleophiles

Reactions of polychlorobenzenes with sodium alkanethiolates RSNa in hexamethylphosphoramide (HMPA) resulting in high yields of poly(alkylthio)benzenes were documented.[14–16]



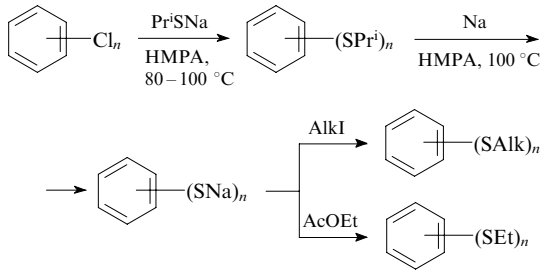
n = 2–6; R = Me, Et, Pr^i.

The course of the reactions with sodium ethanethiolate and with sodium methanethiolate especially should be thoroughly controlled [16, 17] because alkylthiobenzenes formed in the first step can undergo dealkylation induced by an excess of sodium alkenetiolate to give alkali metal arenethiolates (see the review [18]).

$$ArSR + RSNa \longrightarrow ArSNa + R_2S,$$

R = Me, Et.

It is more convenient to use Pr^{i}SNa as the sulfur-containing reagent. Under the reaction conditions, the resulting aryl isopropyl sulfides are stable. After completion of the reaction, these compounds can be transformed into benzenethiols and then into other alkyl aryl sulfides. The latter can be prepared by one-pot reactions with metallic sodium and then with alkylating agents (alkyl iodides or esters). The isopropyl groups can be removed by the reaction with sodium in HMPA or pyridine at ~100 °C.[19]



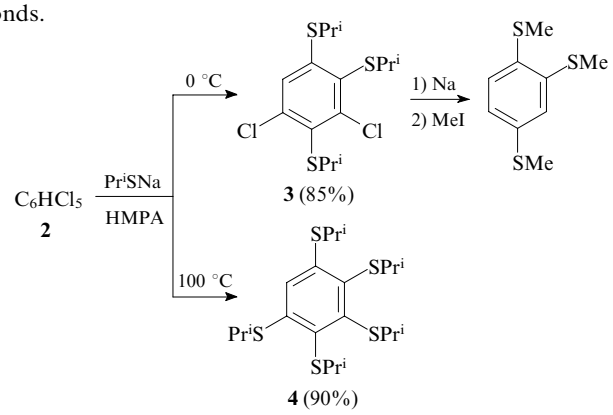
n = 2–6.

Dichlorobenzenes **1a–c**† react with sodium alkanethiolates in HMPA to form bis(alkylthio)arenes and their transformation products.[17] For example, the reactions of 1,4-dichlorobenzene (**1c**) with EtSNa and MeSNa afford 1,4-bis(ethylthio)benzene (85%) and 4-(methylthio)benzenethiol (52%), respectively, as the major products. The reactions with sodium propane-2-thiolate are not accompanied by S-dealkylation. However, these reactions afford mixtures of mono- and bis(isopropylthio)benzenes. The composition of the products depends on the amount of the reagent. The disubstitution products are the major products in the reactions of Pr^{i}SNa with 1,3- and 1,4-dichlorobenzenes (**1b,c**); for steric reasons, the reaction with 1,2 isomer **1a** gives 2-chloro(isopropylthio)benzene as the major product even in the presence of an excess of thiolate (Table 1).[15]

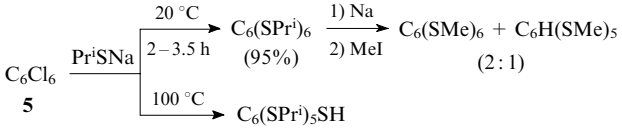
Table 1. Reactions of isomeric dichlorobenzenes **1a–c** with Pr^{i}SNa in HMPA at 80 °C.[15]

Compound	Number of equiv. of Pr^{i}SNa	Reaction time /h	Products	Yield (%)
1,2-$Cl_2C_6H_4$ (**1a**)	1	0.5	2-$ClC_6H_4SPr^i$	92
	3	36	2-$ClC_6H_4SPr^i$,	68
			1,2-$(Pr^iS)_2C_6H_4$	11
1,3-$Cl_2C_6H_4$ (**1b**)	1	0.5	3-$ClC_6H_4SPr^i$,	60
			1,3-$(Pr^iS)_2C_6H_4$	5
	3	36	1,3-$(Pr^iS)_2C_6H_4$	56
1,4-$Cl_2C_6H_4$ (**1c**)	1	0.5	4-$ClC_6H_4SPr^i$,	72
			1,4-$(Pr^iS)_2C_6H_4$	7
	3	4	1,4-$(Pr^iS)_2C_6H_4$	96

Thiolate anions react also with highly chlorinated arenes.[14, 17] For example, the reactions of isomeric tri- and tetrachlorobenzenes with an excess of Pr^{i}SNa in HMPA at 100 °C resulted in products of complete substitution of chlorine atoms in yields of up to 95%.[19] The degree of substitution in the reaction with pentachlorobenzene (**2**) can be controlled by varying the temperature. At 0 °C, three chlorine atoms are replaced to give compound **3**; at 100 °C, five chlorine atoms are replaced to form compound **4**. It should be noted that the removal of the isopropyl groups in dichloroarene **3** with metallic sodium is accompanied by reduction of the C–Cl bonds.



The product of the complete replacement of chlorine atoms in hexachlorobenzene (**5**) by Pr^{i}S groups is formed at room temperature.[17, 20] The increase in the reaction temperature to 100 °C results in the elimination of one isopropyl group and the formation of pentakis(isopropylthio)benzenethiol. The reaction of $C_6(SPr^i)_6$ with metallic sodium is accompanied by the replacement of one sulfur-containing group by hydrogen.[14]

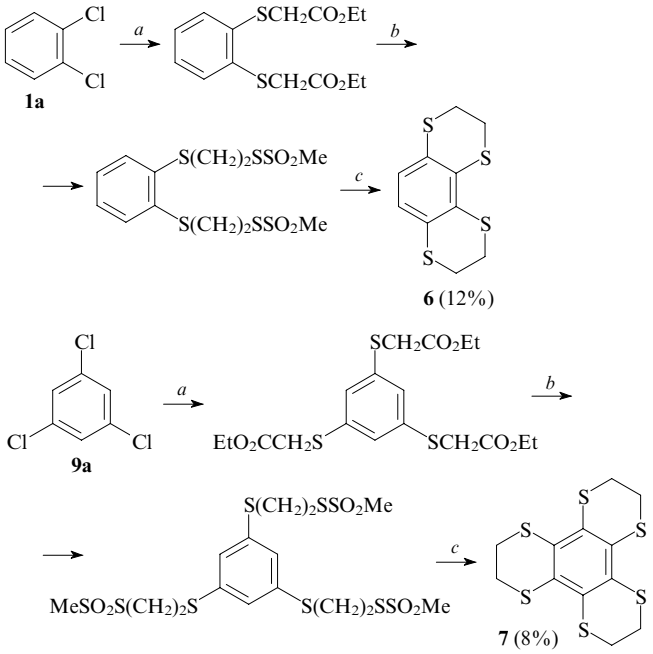


† Hereinafter, isomeric PCA have identical numbers but are denoted by different letters.

The reaction of hexachlorobenzene (**5**) with $PhCH_2SNa$ produced hexakis(benzylthio)benzene, whose benzyl groups can be removed under the action of sodium in liquid ammonia.[21]

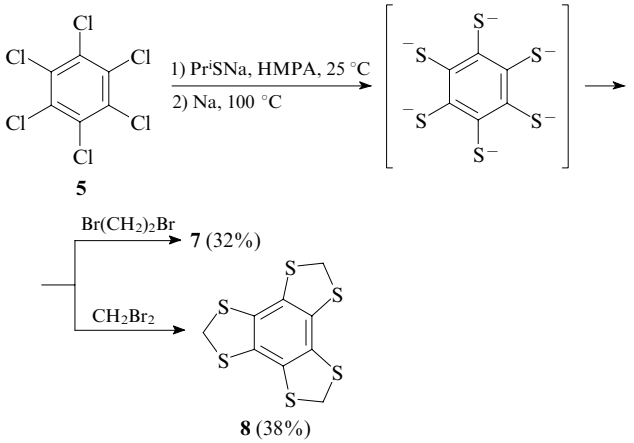
It should be noted that compounds $C_6(SAlk)_6$ are produced by nucleophilic substitution only in the case of hexachlorobenzene (**5**). Attempts to obtain this type of compounds by the reactions of copper mercaptides with tetra-, penta- or hexabromobenzenes failed.[17,22]

Polychloroarenes were used as the starting compounds for the synthesis of fused heterocycles containing the 1,4-dithiane (**6**, **7**) or 1,3-dithiolane (**8**) fragments.[20] Two approaches to the synthesis of these products were developed. One approach is based on the substitution of isopropylthio groups for chlorine atoms in 1,2-dichlorobenzene (**1a**) and 1,3,5-trichlorobenzene (**9a**) followed by the transformation of the resulting compounds into the target heterocycles in six experimental steps. Compounds **6** and **7** are formed in low yields (12% and 8%, respectively, based on the starting chloroarenes).



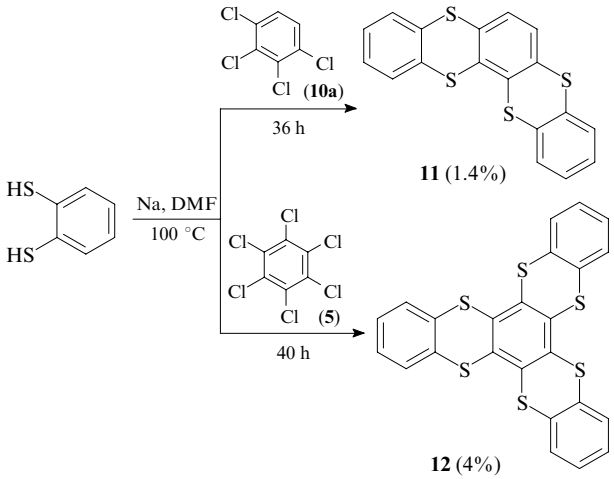
(*a*) (1) Pr^iSNa, HMPA, 25 °C, 2 h; (2) Na, 100 °C, 2 h; (3) $BrCH_2CO_2Et$, 50 °C, 2 h; (*b*) (1) $LiAlH_4$, THF; (2) $SOCl_2$, PhH, 2 h; (3) $MeSO_2SK$, EtOH, 18 h; (*c*) $AlCl_3$, $MeNO_2$.

Another, more efficient, approach is based on the treatment of the *in situ* generated benzenehexathiolate with dibromoalkanes.[20] Reaction products **7** and **8** were synthesised in two steps in satisfactory yields.

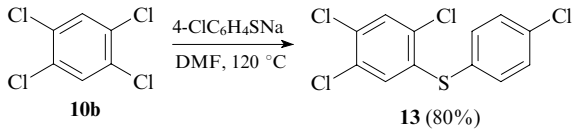


The nucleophilic substitution of sulfur for the chlorine atoms was carried out also in other solvents, for example, in DMF,[23–26] methanol,[27] *etc*. Not only alkali metal alkanethiolates, but less nucleophilic alkali metal arenethiolates were also used as the reagents. The reactions of 1,3- and 1,4-dichlorobenzenes (**1b**,**c**) with potassium benzenethiolate in DMF, dimethylacetamide (DMA), *N*-methylpyrrolidone (NMP), diglyme and ethylene glycol were investigated.[28,29] As a rule, both chlorine atoms are replaced in these reactions. The best results (high yields of products) were obtained in DMA and NMP, whereas the reactions in diglyme and ethylene glycol did not virtually take place. Such solvents as water and toluene were used primarily in combination with phase-transfer catalysts (see below).

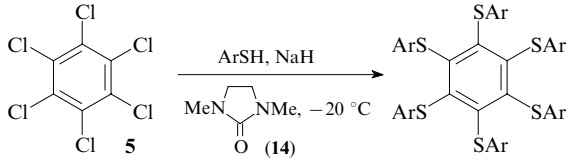
The substitution of benzene-1,2-dithiolate for the chlorine atoms in 1,2,3,4-tetrachloro- (**10a**) and hexachlorobenzene (**5**) gave polycyclic dithianes **11** and **12**, respectively; however, their yields did not exceed 4%.[24]



The reaction of 1,2,4,5-tetrachlorobenzene (**10b**) with an excess of $4\text{-}ClC_6H_4SNa$ in DMF at 120 °C affords only monsubstitution product **13** due apparently to the insufficiently high nucleophilicity of the 4-chlorobenzenethiolate anion.[30]

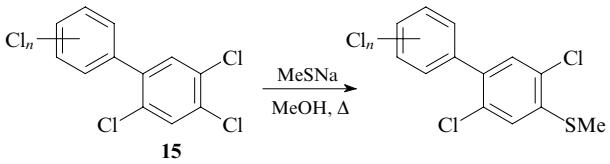


Sodium benzenethiolates (prepared from benzenethiols and NaH) react with 1,2,4-trichlorobenzene (**9b**) in 1,2-dimethoxyethane to give the complete substitution product in 94% yield.[31] Under these conditions, hexachlorobenzene (**5**) gave hexakis(phenylthio)benzene. 1,3-Dimethyimidazolidin-2-one (**14**) is a solvent of choice for such reactions. In this solvent, the reactions proceed even at room temperature to form hexakis(arylthio)benzenes in high yields.[32,33]



Ar = Ph (96%), $4\text{-}MeC_6H_4$ (91%), $4\text{-}Bu^tC_6H_4$ (76%), $4\text{-}BrC_6H_4$ (48%), 2-naphthyl (72%).

Not only mononuclear PCA, but also compounds containing several aromatic rings, react with S-nucleophiles. In polychlorobiphenyls **15**, one chlorine atom at position 4 is generally replaced.[27]

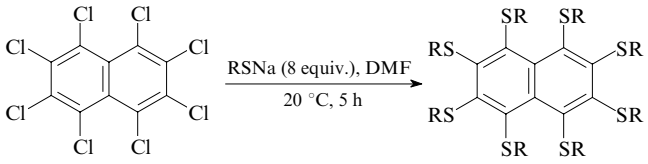


15

Cl$_n$ = 4-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 2,5-Cl$_2$C$_6$H$_3$, 2,4-Cl$_2$C$_6$H$_3$, 2,4,5-Cl$_3$C$_6$H$_2$.

The substitution product of two chlorine atoms (at positions 4 and 4′) was detected only in the case of symmetrical 2,2′,4,4′,5,5′-hexachlorobiphenyl.

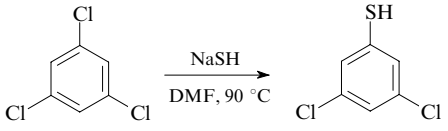
In octachloronaphthalene (**16**), all chlorine atoms can be replaced by sulfur-containing groups in DMF at room temperature.[34]



16

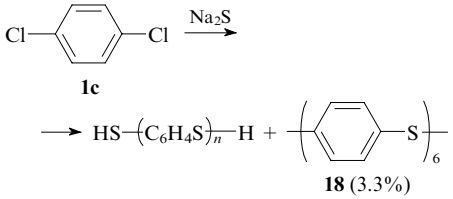
R = Et (69%), Bu^n (74%), PhCH$_2$ (Bn) (73%), cyclo-C$_6$H$_{11}$ (Cy) (48%); Ph (66%), 4-ClC$_6$H$_4$ (83%), 4-BrC$_6$H$_4$ (46%), 2-MeSC$_6$H$_4$ (66%), benzothiazol-2-yl (48%).

In addition to alkane- and arenethiolates, the reactions of PCA were carried out also with other sulfur-containing nucleophiles, including hydrogen sulfide, metal sulfides, isothiourea derivatives, heterocyclic thiones, dimethyl sulfoxide, carbon disulfide and dialkyl sulfides.[30, 35–39] For example, the reaction of 1,3,5-trichlorobenzene (**9a**) with sodium hydrosulfide produced 3,5-dichlorobenzenethiol (**17**).[30]



9a **17** (48%)

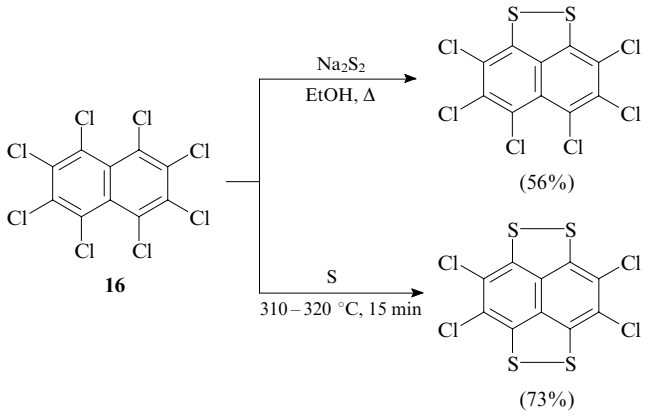
The reaction of 1,4-dichlorobenzene (**1c**) with Na_2S in NMP is of industrial significance as a procedure for the production of poly(1,4-phenylene sulfide). After the completion of the reaction in NMP, small amount of macrocyclic hexamer **18** was isolated from low-molecular-mass fractions.[39]



1c

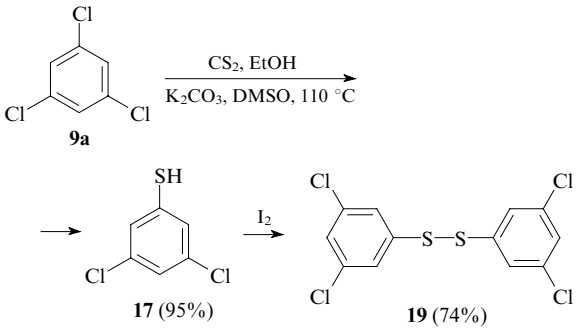
18 (3.3%)

The chlorine atoms at positions 1 and 8 in octachloronaphthalene (**16**) were replaced by the disulfide fragment upon refluxing with Na_2S_2 in ethanol.[40] Fusion of compound **16** with elemental sulfur at 310–320 °C under nitrogen allows the introduction of two disulfide bridges into the molecule.



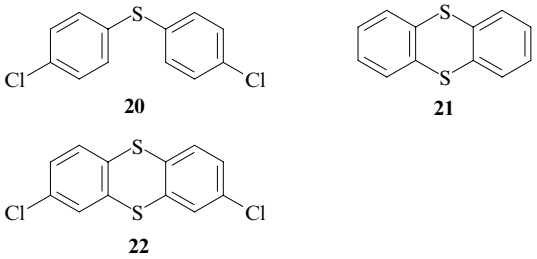
16

Carbon disulfide can be used as the S-nucleophile.[41] Oxidation of the reaction product, *viz*., 2,4-dichlorobenzenethiol (**17**), afforded the corresponding disulfide **19**. Analogously, the reaction of hexachlorobenzene (**5**) with the CS_2–Bu^{t}OK–DMSO system at 110 °C produced pentachlorobenzenethiol in 72% yield.



9a **17** (95%) **19** (74%)

The chlorine atom in chloroarenes is replaced by the sulfur atom also in the gas-phase reaction with hydrogen sulfide in a flow reactor at 500–700 °C.[35, 36] The reaction afforded a complex mixture of products consisting mainly of benzenethiols and diaryl sulfides and was accompanied by the partial dehalogenation of arenes. 1,4-Dichlorobenzene (**1c**) reacts much more easily than chlorobenzene. The yields of 4-chlorobenzenethiol and bis(4-chlorophenyl) sulfide (**20**) are 15% and 56%, respectively. Under these conditions, the reaction of 1,2-dichlorobenzene (**1a**) gives 2-chlorobenzenethiol (30%) and thianthrene **21** (61%); the reaction of 1,2,4-trichlorobenzene (**9b**) produces dichlorobenzenethiol (15%–56%) and 2,7-dichlorothianthrene **22** (26%–45%).



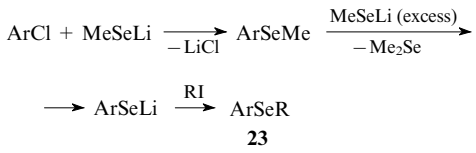
20 **21**

22

Dialkyl sulfides and dialkyl disulfides can also serve as a source of sulfur at high temperature. 1,4-Dichlorobenzene (**1c**) reacts with diethyl disulfide to form a mixture of 4-chlorobenzenethiol (55%), bis(4-chlorophenyl) sulfide (16%), benzene (9%) and thiophene (14%).[38] Presumably, the reaction involves thermal decomposition of dialkyl disulfides accompanied by elimination of hydrogen sulfide, which reacts with PCA. Dialkyl disulfides are reagents of choice for the synthesis of benzenethiols, while hydrogen sulfide, for the synthesis of diaryl sulfides.[35, 36, 38]

The replacement of chlorine atoms in PCA in the reaction with thiourea under electroreduction conditions in liquid ammonia (−40 °C, with KBr or Bu^{t}OK as the additives) was documented.[42] The reaction afforded a mixture of sulfur-containing products, *viz*., ArSH, ArSSAr and ArSAr. The ion-radical $S_{RN}1$ mechanism was proposed for this reaction.

Selenation reactions of PCA were less studied. For example, the reaction of PCA with lithium methaneselenolate produces aryl methyl selenides,[43] which readily undergo demethylation with an excess of methaneselenolate (analogously to methanethiolates). The resulting areneselenolates can be alkylated with alkyl iodides to give alkyl aryl selenides **23**.[44] Examples of such products are given in Table 2.

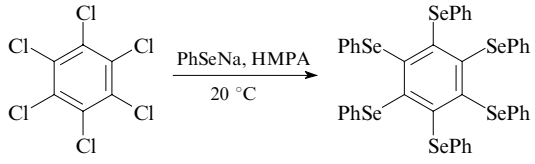


23

Table 2. Reactions of isomeric dichlorobenzenes **1a**–**c** with lithium methaneselenolate (4 equiv. MeSeLi, DMF, 120 °C) followed by alkylation with RI.[43]

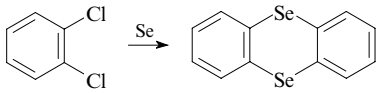
Compound	Time /h	R	Products **23**	Yield (%)
1,2-$C_6H_4Cl_2$ (**1a**)	16	Me	2-ClC_6H_4SeMe	87
1,3-$C_6H_4Cl_2$ (**1b**)	8	Me	3-ClC_6H_4SeMe	86
1,4-$C_6H_4Cl_2$ (**1c**)	8	Me	4-ClC_6H_4SeMe	72
	8	Et	4-ClC_6H_4SeEt	81
	8	Pr^i	4-$ClC_6H_4SePr^i$	76

The reaction of hexachlorobenzene (**5**) with sodium benzeneselenolate in HMPA proceeds at room temperature to give hexakis(phenylseleno)benzene.[32]



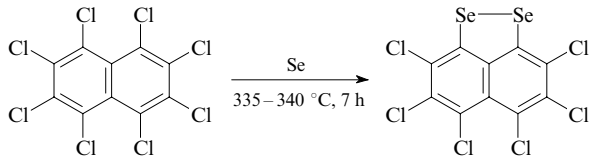
5 (51%)

The reaction of 1,2-dichlorobenzene (**1a**) with elemental selenium affords 9,10-diselena-9,10-dihydroanthracene in moderate yield.[45]



1a (26%)

A heterocycle containing the diselenide bridge between positions 1 and 8 of the naphthalene fragment was synthesised by the fusion of perchloronaphthalene (**16**) with selenium at 335–340 °C in an inert atmosphere.[40]



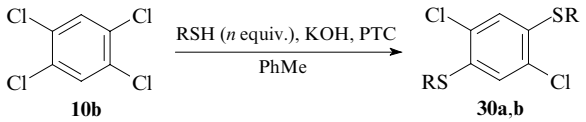
16

2. Reactions of activated polychloroarenes with S-nucleophiles

The reactions of PCA containing electron-withdrawing groups in the *ortho* or *para* positions with respect to chlorine atoms generally proceed under milder conditions, in some cases, at room or reduced temperatures. Data on the formation of the reaction products of activated PCA, including compounds **24**–**29**, with S-nucleophiles are presented in Table 3.[46–64]

3. Reactions of polychloroarenes with S-nucleophiles under conditions of phase-transfer catalysis

The reactions of PCA with S-nucleophiles can be promoted, in particular, by phase-transfer catalysts (PTC). Crown ethers, ammonium salts and phosphonium salts were used as PTC.[65,66] Under these conditions, it became possible to perform the reaction of 1,2,4,5-tetrachlorobenzene (**10b**) with an alkanethiol–KOH system in toluene, which does not proceed in the absence of catalysts (Table 4).[67] The reaction produces 1,4-dialkylthio-2,5-dichlorobenzenes (**30a**,**b**). The highest yield of the products was achieved with the use of dodecyltricyclohexylphosphonium bromide as the catalyst. The reactions of 1,3,5- and 1,2,4-trichlorobenzenes (**9a**,**b**) with alkanethiols in the presence of PTC proceed at higher temperatures.

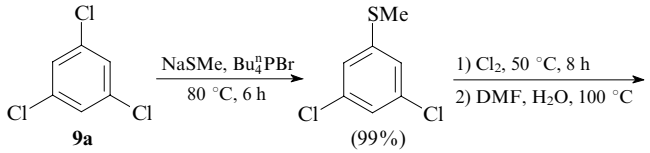


10b **30a**,**b**

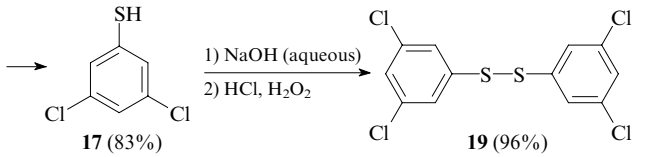
R = n-C_7H_{15} (**a**), n-$C_{12}H_{25}$ (**b**).

The reactions of dichlorobenzenes require even more drastic conditions (110 °C).[68] The reactivity of the compounds decreases in the following sequence: 1,2 isomer (**1a**) > 1,3 isomer (**1b**) > 1,4 isomer (**1c**); the reactivity of nucleophiles decreases in the following sequence: primary thiols > tertiary thiols > benzenethiols (Table 5).

The reactions of sodium methanethiolate with dichloro- and trichlorobenzenes in the presence of tetrabutylphosphonium bromide resulted in the replacement of one chlorine atom to yield (methylthio)chlorobenzenes. The latter were transformed into the corresponding disulfides by demethylation and oxidation, for example, as shown below:[65]

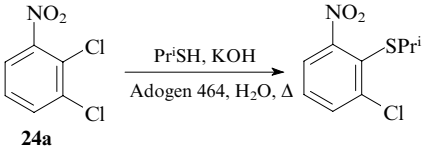


9a (99%)



17 (83%) **19** (96%)

3-Chloro-2-(isopropylthio)nitrobenzene was obtained in quantitative yield by the reaction of 2,3-dichloronitrobenzene (**24a**) with the Pr^{i}SH–KOH system in water in the presence of PTC (the quaternary ammonium salt Adogen 464).[69]



24a

Table 3. Reactions of polychloroarenes bearing electron-withdrawing groups with S-nucleophiles.

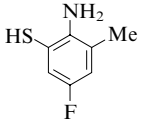
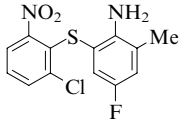
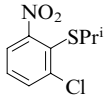
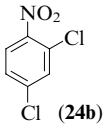
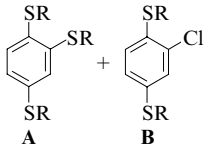
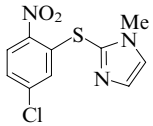
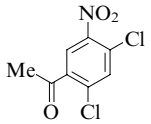
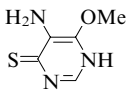
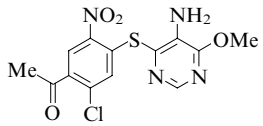
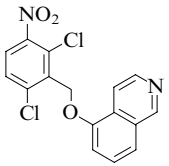
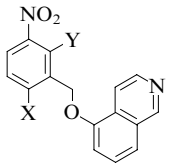
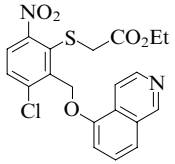
Compound	S-Nucleophile	Reaction conditions	Products	Yield (%)	Ref.
 (**24a**)		AcONa, EtOH, Δ		85	46
	Pr^iSH	H_2O – organic solvent Bu^n_4NBr, 65 °C		97	47
 (**24b**)	RSNa (R = Et, Bu^t)	HMPA, 80 °C	 **A** **B**	R = Et: **A** (65%); R = Bu^t: **A** (21%) + **B** (42%)	48
		–		99	49
		KOH, MeOH		67	50
	MeSNa	DMF, 0 °C		60 (X = Y = SMe) 24 (X = SMe, Y = Me) 7 (X = Me, Y = SMe)	51
	$HSCH_2CO_2Et$	Et_3N, DMF, 0 °C		60	51

Table 3 (continued).

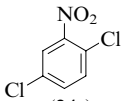
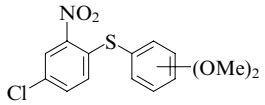
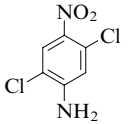
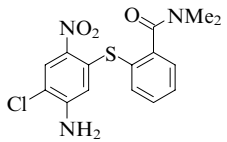
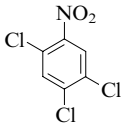
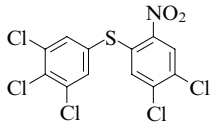
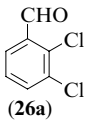
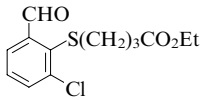
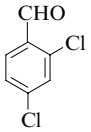
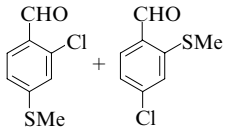
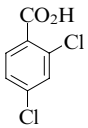
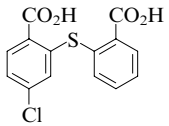
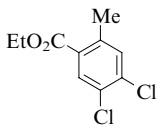
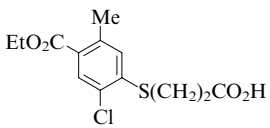
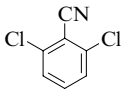
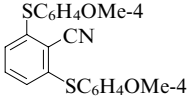
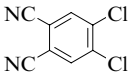
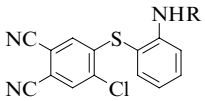
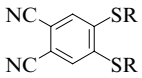
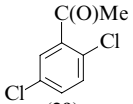
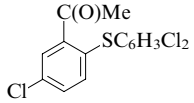
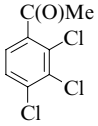
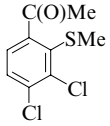
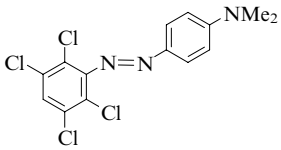
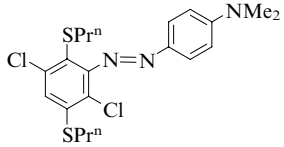
Compound	S-Nucleophile	Reaction conditions	Products	Yield (%)	Ref.
 (**24c**)	2,5-, 2,4- and 3,5-$(MeO)_2C_6H_3SH$	–		91 – 99	52
	2-$HSC_6H_4C(O)NMe_2$	K_2CO_3, DMF, Δ		75	53
 (**25a**)	1,2,3-$Cl_3C_6H_2SH$	AcONa, EtOH, Δ		6 (see [a])	54
 (**26a**)	$HS(CH_2)_3CO_2Et$	K_2CO_3, DMF, 20 °C		70	55
 (**26b**)	see [b]	KF, DMSO, sulfolane, 180 °C		71	56
 (**27a**)	2-$HSC_6H_4CO_2H$	K_2CO_3, $PhCH_2OH$, Cu, 110 °C		70	57
	$HS(CH_2)_2CO_2H$	K_2CO_3, DMF, 120 – 125 °C		60	58

Table 3 (continued).

Compound	S-Nucleophile	Reaction conditions	Products	Yield (%)	Ref.
 (**28a**)	4-$MeOC_6H_4SH$	1) Bu^tOK, DMSO 2) MeCN, Δ		9	59
	2-$RNHC_6H_4NSH$ (R = Alk)	K_2CO_3, THF		–	60
	RSH (R = Pr^n, Ph)	K_2CO_3, DMSO, 90 °C		51 (R = Pr^n), 55 (R = Ph)	61
 (**29**)	2,5- and 3,4-$Cl_2C_6H_3SH$	K_2CO_3, Cu, 125–155 °C		37–77	62
	MeSNa	THF, 25 °C		82–94	63
	Pr^nSH	NaH, DMSO, 120 °C		–	64

Note. The dash means that the reaction conditions or the yields were not reported. [a] The yield of the product of reduction to the corresponding amine is given. [b] The MeS^- ions generated *in situ* from DMSO were used as the reagent.

Table 4. Reactions of polychloroarenes **9a**,**b** and **10b** with thiols (RSH) under phase-transfer catalysis.[67]

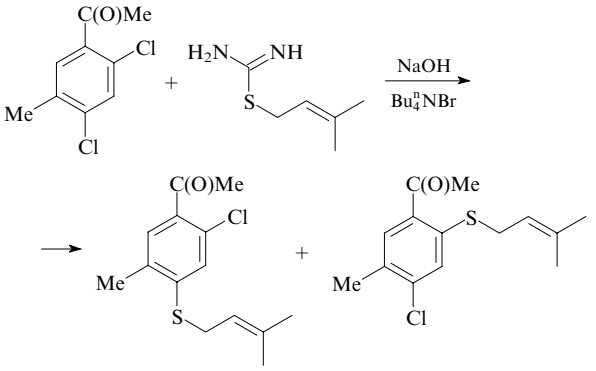
Compound	R	Equiv. of thiol, *n*	PTC	Time /h	Temperature /°C	Product	Yield (%)
1,2,4,5-$Cl_4C_6H_2$ (**10b**)	n-C_7H_{15}	3	18-Crown-6	2	25	**30a**	70
			PEG-300 [a]	2	25	**30a**	62
			n-$C_{12}H_{25}PCy_3Br$	2	25	**30a**	99
	n-$C_{12}H_{25}$	3	–	24	50	–	–
			Bu_4NBr	24	25	–	–
			Bu_4PBr	2	25	**30b**	78
1,3,5-$Cl_3C_6H_3$ (**9a**)	Pr^i	0.3	Bu_4NBr [b]	5.5	140	see [c]	85
	n-C_7H_{15}	1.5	n-$C_{12}H_{25}PCy_3Br$	3	50	see [c]	93
1,2,4-$Cl_3C_6H_3$ (**9b**)	n-C_7H_{15}	1.5	n-$C_{12}H_{25}PCy_3Br$	3	50	see [d]	92

[a] PEG is poly(ethylene glycol); [b] aqueous NaOH was used;[66] [c] 3,5-$Cl_2C_6H_3SR$ is formed; [d] 2,5-$Cl_2C_6H_3SR$ is formed.

Table 5. Reactions of isomeric dichlorobenzenes **1a**–**c** with thiols under phase-transfer catalysis (110 °C, 60% KOH, dicyclohexano-18-crown-6).[68]

Compound	Thiol	Time /h	Composition of substitution products (GLC data) (%)		Yield of the isolated monosubstitution product (%)
			mono-	di-	
1,2-$Cl_2C_6H_4$ (**1a**)	Pr^iSH	16	93	0	89
	Bu^nSH	14	92	5	88
	Bu^tSH	75	94	0	84
1,3-$Cl_2C_6H_4$ (**1b**)	Pr^iSH	24	86	6	79
	Bu^nSH	24	87	6	81
	Bu^tSH	125	86	12	73
1,4-$Cl_2C_6H_4$ (**1c**)	Pr^iSH	150	54	35	43
	Bu^nSH	90	76	14	65
	Bu^tSH	250	31	53	27

The Bu^n_4NBr-catalysed reaction of 2,4-dichloro-5-methylacetophenone with *S*-prenylisothiourea allowed the introduction of the prenylthio group into the aromatic nucleus.[70]



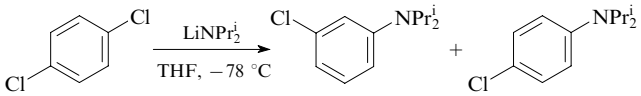
(85 : 15)

III. Reactions with N-nucleophiles

Since amines are much less reactive than S-nucleophiles, the reactions of the former with PCA are performed under more drastic conditions or in the presence of catalysts. In some cases, metal amides are used as aminating agents.

1. Amination of non-activated polychloroarenes

The reaction of 1,4-dichlorobenzene (**1c**) with lithium diisopropylamide at −78 °C affords a mixture of isomeric amination products,[71] with 3-chloro-*N*,*N*-diisopropylaniline predominating. This can be attributed to the fact that the reaction proceeds *via* 4-chlorobenzyne.

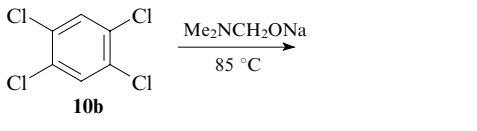


1c

(64 : 36)

The reaction of an excess of 1,2-dichlorobenzene (**1a**) with diphenylamine and KOH in the presence of polyethylene glycol dimethyl ether at 160–165°C produced *N*-(3-chlorophenyl)-*N*,*N*-diphenylamine in 53% yield,[72] which is also evidence for the intermediate formation of 3-chlorobenzyne. The reaction of 1,3,5-trichlorobenzene (**9a**) with hydrazine hydrate at 180–200 °C in pyridine produced 3,5-dichlorophenylhydrazine in 60%–82% yield.[73]

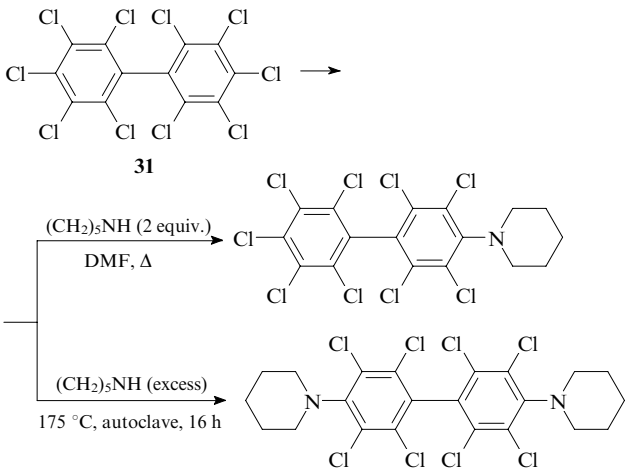
1,2,4,5-Tetrachlorobenzene (**10b**) reacts with a strong reducing agent, Me_2NCH_2ONa, which is prepared from $NaBH_4$ and DMF in the presence of Cp_2TiCl_2 (Cp = η-C_5H_5). The complete conversion of the starting compound (GLC data) affords 2,4,5-trichloro-*N*,*N*-dimethylaniline along with the reduction product.[74]



10b

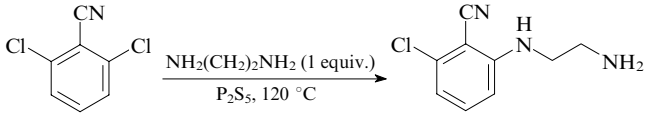
(1 : 1.2)

In the reaction of piperidine with decachlorobiphenyl (**31**), one or two chlorine atoms are replaced.[75] The degree of conversion depends on the reaction conditions. Thus the monosubstitution at position 4 is achieved upon refluxing in DMF, whereas prolonged heating with an excess of piperidine in an autoclave gives the 4,4′-disubstituted product.

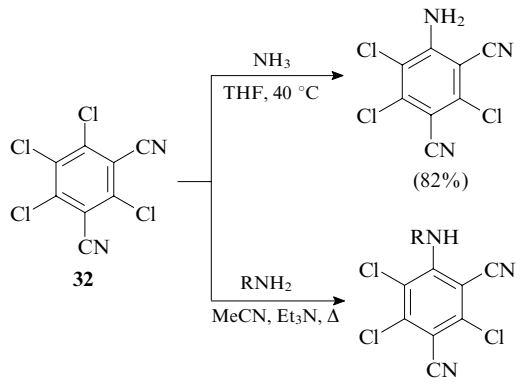


2. Substituent effect on the reactivity and regioselectivity of amination of polychloroarenes

The reactivity of PCA and the pathway of amination depend on the nature and position of the substituent. For example, 2,6-dichlorobenzonitrile (**28a**) reacts with ethylenediamine at 120 °C resulting in the replacement of one chlorine atom.[76] The reaction was performed in the presence of catalytic amounts of P_2S_5 to ensure the attack of ethylenediamine at the nitrile group with the aim of providing the route to the corresponding imidazolidine; however, the electrophilicity of the aromatic C–Cl fragment proved to be higher.

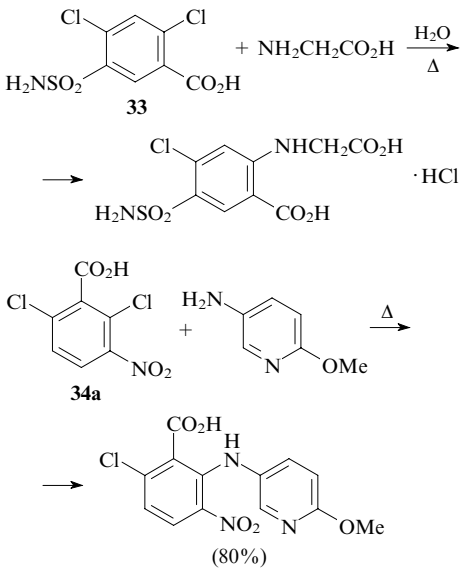


The reaction of perchloroisophthalonitrile (**32**) with ammonia proceeds under milder conditions[77] to give 3,5,6-trichloro-2,4-dicyanoaniline. In the reaction of compound **32** with an oligopeptide, it is the amino group of the lysine fragment that is involved in the replacement.[78]

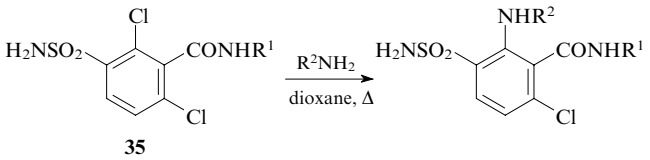


R = (P)–O2C–Glu(Lys–Gly–NHBoc)–Lys–Gly–NHBoc ((P) is solid support).

In the reactions of dichlorobenzoic acid derivatives **33** and **34a** with amines, one chlorine atom in the *ortho* position with respect to the carboxy group is replaced.[79–82]

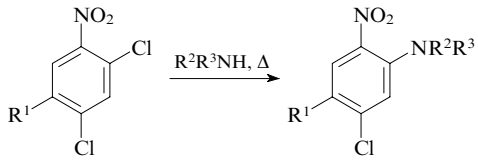


The reactions of polychlorobenzoic esters or amides with amines and hydrazines proceed analogously.[82] For example, methyl 2,6-dichloro-3-nitrobenzoate reacts with 1 equiv. of alkylamine or hydrazine in aqueous ethanol resulting in the replacement of the chlorine atom at position 2 (82%–97% yields). In the presence of an excess of amine, both chlorine atoms are replaced to give the corresponding products in virtually quantitative yield. In the reactions of 3-aminosulfonyl-2,6-dichlorobenzamides **35** with alkyl- and benzylamines in EtOH, also one or two chlorine atoms are replaced depending on the conditions; in dioxane, the major products result from the replacement of the chlorine atom at position 2.[83]



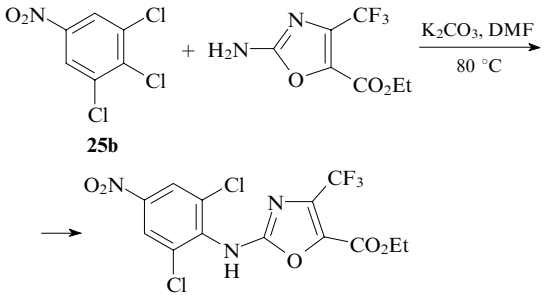
R^1	R^2	Yield (%)
H	Bn	62
	Bu^n	86
2-MeC_6H_4	Bn	67
	Bu^n	82
$Ph(CH_2)_2$	$EtO(CH_2)_2$	88

The nitro group is a good activating substituent in the nucleophilic substitution reactions involving PCA.[84–93] In 2,4-dichloronitrobenzene derivatives **24b**, **25a** and **36**, the chlorine atom in the *ortho* position with respect to the nitro group is replaced.[85, 86, 88]



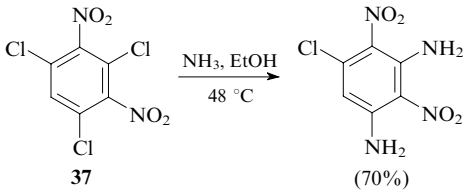
R^1 = H (**24b**), Me (**36**), Cl (**25a**);
R^2R^3N = AlkNH, NH_2, $N(CH_2)_4$, N O.

In the reaction of 3,4,5-trichloronitrobenzene (**25b**) with a heterocyclic amine, the replacement occurs primarily at the chlorine atom in the *para* position with respect to the nitro group.[94]

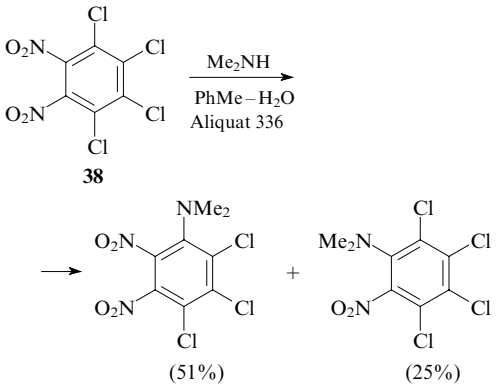


The reactions of PCA with amines proceed more rapidly at high pressure (0.6–1.0 GPa).[95] For example, 2,3,5,6-tetrachloronitrobenzene reacts with primary amines under these conditions to form the substitution product of the nitro group; in the reactions with secondary amines, the chlorine atom in the *ortho* position with respect to the nitro group is replaced. In some cases, the reactions afford mixtures of isomeric mono- and diamines. The reactions with diamines produce annelated compounds.

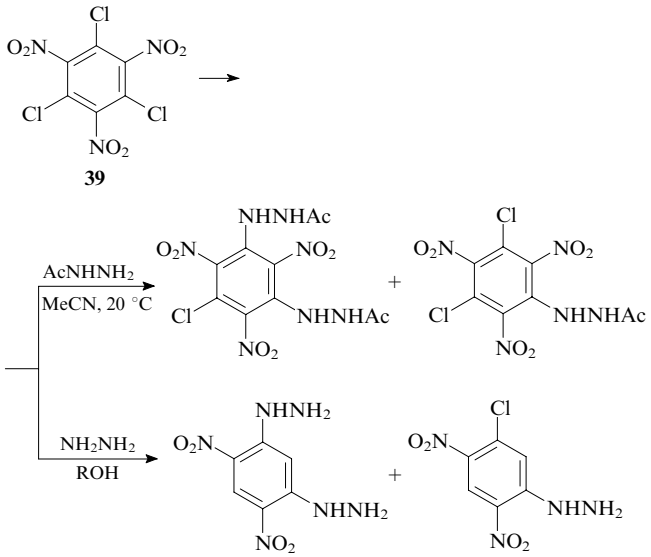
Polychloroarenes containing two nitro groups react at substantially lower temperatures. For example, ammonolysis of 2,4,6-trichloro-1,3-dinitrobenzene (**37**) proceeds at 48 °C and results in the replacement of two chlorine atoms.[96]



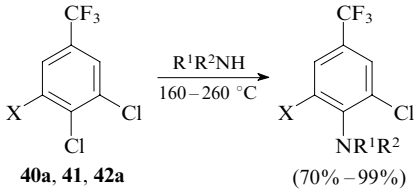
In the reactions of 1,2,3,4-tetrachlorodinitrobenzene (**38**) with amines, not only chlorine atoms, but also nitro groups are replaced.[97] As a rule, primary amines replace one of the nitro groups, whereas secondary amines replace the chlorine atom in the *ortho* position with respect to the nitro group. High yields of the substitution products were achieved in the reactions performed in the two-phase toluene–water system in the presence of tetraalkylammonium salts (for example, Aliquat 336).



Trichlorotrinitrobenzene **39** reacts with hydrazine derivatives at room temperature.[98] The reaction with acetylhydrazine affords a mixture of monosubstitution products. The reaction with unsubstituted hydrazine is accompanied by dehalogenation and denitration.

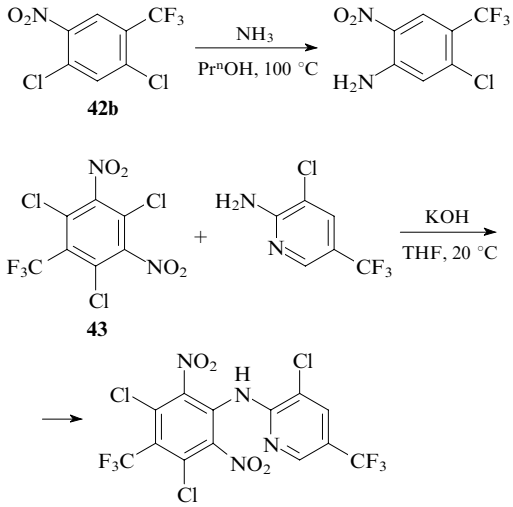


The trifluoromethyl group having a strong $-I$ effect also facilitates the replacement of the chlorine atom in PCA. However, its activating effect is weaker than the effect of $-M$ groups. The reactions of trifluoromethyl derivatives of PCA **40a**, **41** and **42a** with amines proceed, as a rule, only at high temperature.[99–104]



X = H (**40a**), Cl (**41**), NO_2 (**42a**).

Due to the simultaneous presence of the CF_3 and NO_2 groups in chloroarenes **42b** and **43**, the reactions can be performed under milder conditions.[105, 106]

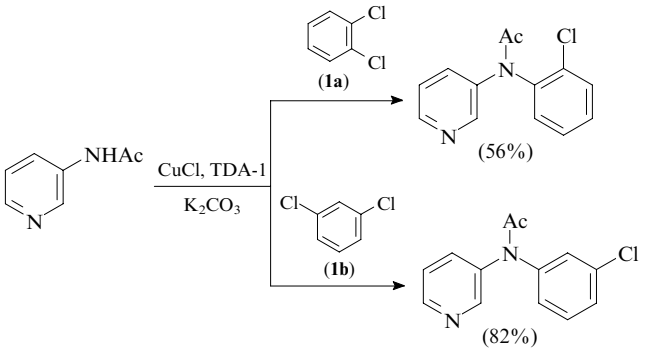


The relative reactivity of chlorine atoms in PCA depends not only on the activating substituents, but also on the polarisability of the nucleophile.[107] For example, 2,4,6-trichloro-3,5-bis(trifluoromethylsulfonyl)nitrobenzene reacts with sodium azide (a soft nucleophile) in methanol at −80 °C to form a mixture of substitution products. However, harder nucleophiles, such as piperidine and 4-acetylaminoaniline, selectively replace one chlorine atom in the *ortho* position with respect to the nitro group.

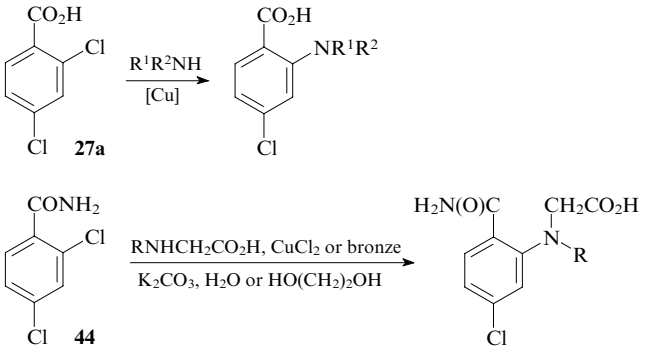
3. Catalytic amination of polychloroarenes

Copper salts and oxides catalyse amination of non-activated PCA. The reactions of 1,3-dichloro-substituted tetrafluoro- and 2,4,6-trifluorobenzenes with aqueous ammonia in the presence of CuCl in an autoclave at 140 °C were found to proceed non-selectively to give mixtures of amination and hydrodechlorination products.[108] The reactions of 1,2- and 1,4-dichlorobenzenes (**1a**,**c**) with ammonia in the presence of copper oxide at 180–240 °C produce the corresponding phenylenediamines.[109]

Ultradispersed (nanosized) copper, which is formed *in situ* by the reaction of tris(3,6-dioxaheptyl)amine (TDA-1) with copper salts, proved to be an efficient catalyst for the reaction of *N*-(3-pyridyl)acetamide with dichlorobenzenes **1a**,**b**.[110] The solvent-free reaction was carried out by refluxing the reactants with azeotropic distillation of water.

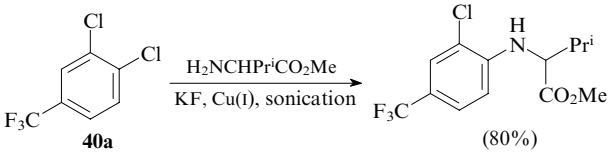


In some cases, it is reasonable to perform the amination of PCA bearing electron-withdrawing substituents in the presence of copper or its salts as the catalyst. For example, 2,4-dichlorobenzoic acid (**27a**) and its amide (**44**) react with amines in the presence of copper or its salts resulting in the replacement of the *ortho*-chlorine atom with respect to the electron-withdrawing group.[111–119]

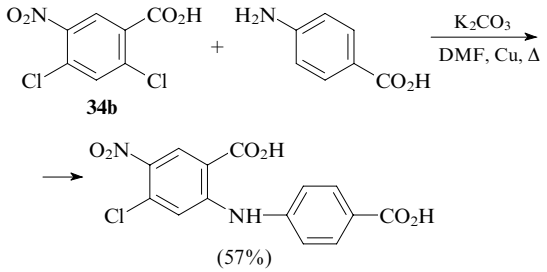


R = H (55%), 4-FC_6H_4 (80%).

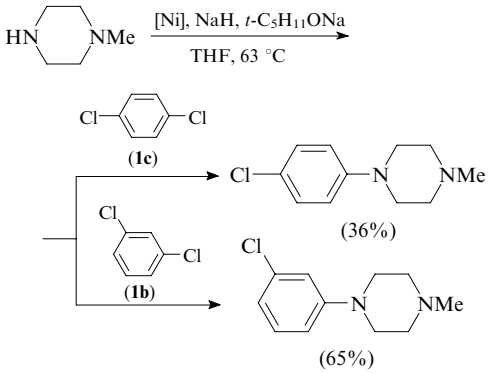
In the reaction of valine methyl ester with 3,4-dichloro(trifluoromethyl)benzene (**40a**) catalysed by Cu(I) salts using sonication, the chlorine atom in the *para* position with respect to the CF_3 group is replaced to give the corresponding substitution product in high yield.[120] Without sonication, the yield is as low as 10%.



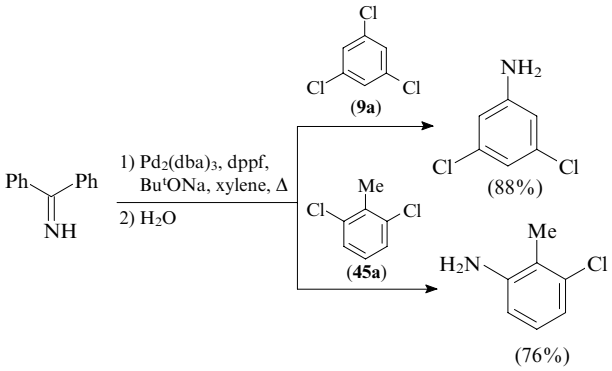
4-Aminobenzoic acid in which the nucleophilicity of the amino group is lower than that in aniline reacts with 2,4-dichloro-5-nitrobenzoic acid (**34b**) in boiling DMF in the presence of copper powder to give 2-(4-carboxyanilino)-4-chloro-5-nitrobenzoic acid.[121]



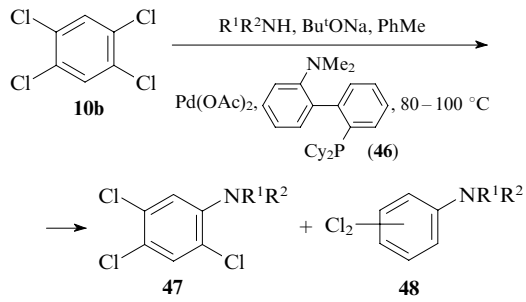
Nickel complexes with the 1,1′-bis(diphenylphosphino)ferrocene (dppf), 1,10-phenanthroline (phen) and 2,2′-bipyridyl (bipy) ligands were examined as catalysts for amination of PCA.[122] Under these conditions, 1-methylpiperazine reacts with 1,3- and 1,4-dichlorobenzenes (**1b**,**c**), resulting in the replacement of only one chlorine atom.



Amination of PCA (for example, of compounds **9a** and **45a**) with benzophenone imine can be performed with the use of the catalytic $Pd_2(dba)_3$–dppf system (dba is dibenzylideneacetone).[123] After hydrolysis in the final step, the corresponding aniline derivatives are obtained in good yields.



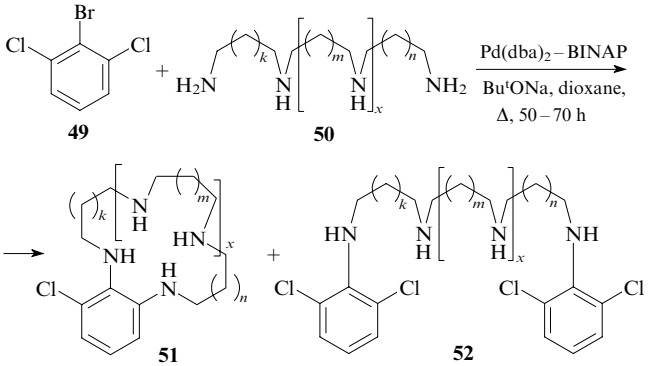
Cross-coupling of 1,2,4,5-tetrachlorobenzene (**10b**) with primary and secondary amines in the presence of $Pd(OAc)_2$ and ligand **46** according to a developed procedure[124] afford compounds **47** as a result of the replacement of one chlorine atom.[125,126] The reaction is accompanied by reductive dechlorination to dichloroaniline derivatives **48**. Hexachlorobenzene (**5**) does not react with amines under the above-mentioned conditions.



R^1R^2N	Yield (%)	
	47	**48**
$(CH_2)_4N$	26	10
$O(CH_2CH_2)_2N$	25	41
Bu^nNH	72	4

Amination of chloroarenes with *trans*-di(μ-acetato)bis{2-[di(*tert*-butyl)phosphino]-2-methylpropyl-C,P}dipalladium (which was prepared by heating $Pd(OAc)_2$ with Bu^t_3P in toluene) was covered by the patent.[127] This method was used for the synthesis of *N*-(4-chlorophenyl)piperidine (59% yield) and 1,4-bis(dibutylamino)benzene (77% yield) by the reactions of 1,4-dichlorobenzene (**1c**) with piperidine or dibutylamine, respectively.

Cross-coupling of 1-bromo-2,6-dichlorobenzene (**49**) with polyamines **50** catalysed by the $Pd(dba)_2$–BINAP system [BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] proceeds slowly.[128] However, cyclisation products **51** were prepared by refluxing the reactants in dioxane over a long period of time (50–70 h), the yields being dependent on the length and conformational flexibility of the polyamine chain. The structures of linear by-products **52** provide evidence that the bromine atom is replaced in the first step of the reaction. No cyclisation products are formed in the reaction with the diamino ether $H_2N(CH_2CH_2O)_2CH_2CH_2NH_2$.



k	*m*	*n*	*x*	Yield (%)	
				51	**52**
1	0	1	1	47	–
0	0	0	1	27	–
0	1	0	1	17	–
0	0	0	2	12	17
0	0	0	3	10	21

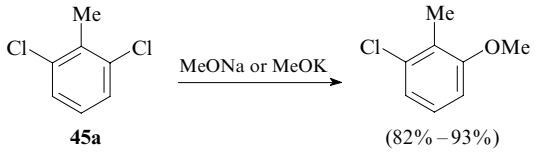
The results of studies on the reactions of mono- and polynuclear chloroarenes in the presence of catalytic systems containing a source of palladium combined with BINAP,[129–131] 1-diphenylphosphino-2-(1-methoxyethyl)ferrocene[132] or tri(*tert*-butyl)phosphine[133] may be useful for performing the C–N cross-coupling reactions of PCA.

IV. Reactions with O-nucleophiles

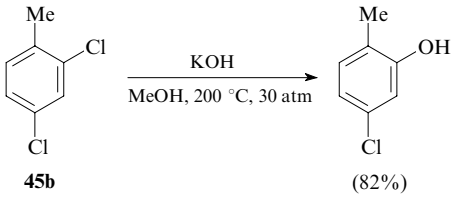
Chlorine atoms in PCA can be replaced by O-nucleophiles to form phenols or their ethers.

1. Reactivity of polychloroarenes towards O-nucleophiles in the presence of bases

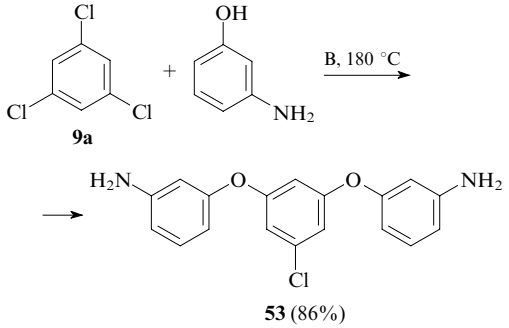
Isomeric dichlorobenzenes react with NaOMe in HMPA to form the corresponding chloroanisoles.[134] In the reactions of 2,6-dichlorotoluene (**45a**) with potassium or sodium methoxides in aprotic solvents, one chlorine atom is replaced.[135–138] The reaction rate can be increased by addition of copper compounds; however, the resulting aryl methyl ether undergoes partial demethylation.



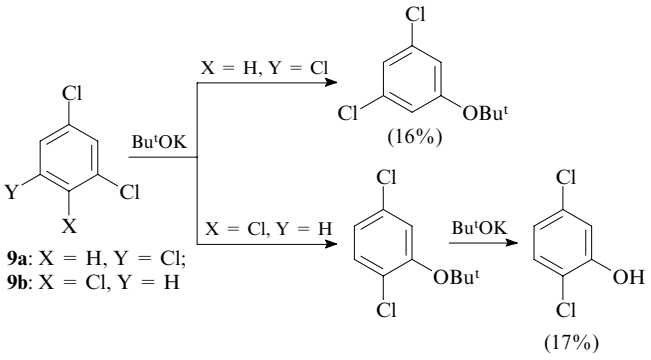
The reaction of 2,4-dichlorotoluene (**45b**) with KOH in methanol at 200 °C and 30 atm produced 5-chloro-2-methylphenol.[139] At lower pressure (12 atm), the product was obtained in substantially lower yield (12%).



3-Aminophenol reacts with 1,3,5-trichlorobenzene (**9a**) as the O-nucleophile to give diether **53**.[140] In this reaction, K_2CO_3 or NaOMe was used as the base (B) and HMPA or NMP as the solvent.

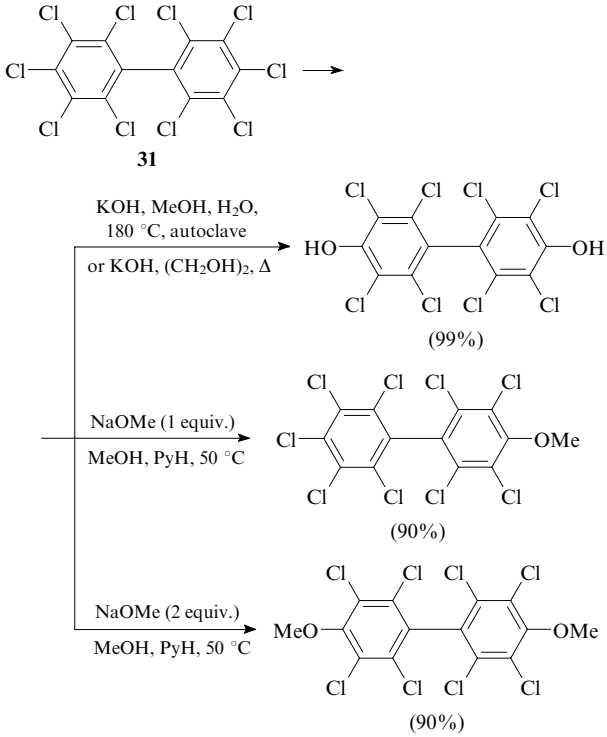


The reactions of 1,3,5- (**9a**) and 1,2,4-trichlorobenzenes (**9b**) with Bu^tOK in HMPA[141] resulted in the replacement of one chlorine atom to give the corresponding substitution products in low yields. In the case of isomer **9b**, the initially formed ether undergoes dealkylation to give 2,5-dichlorophenol.



Unlike compounds **9a**,**b**, 1,2,3,5-tetrachlorobenzene (**10c**) undergoes disproportionation under these conditions to form a mixture of 1,2,4,5-tetrachlorobenzene (**10b**), pentachlorobenzene (**2**) and isomeric trichlorobenzenes.[141]

Hexachlorobenzene (**5**) reacts with potassium *tert*-butoxide in THF [142] or with the Pr^{i}OH – NaOH system [143] to give the corresponding alkyl pentachlorophenyl ethers in 67% and 92% yields, respectively. The reaction of decachlorobiphenyl (**31**) with KOH in aqueous methanol (autoclave, 180 °C) or in boiling ethylene glycol produces 4,4′-dihydroxyoctachlorobiphenyl in quantitative yield.[144] In the reaction of decachlorobiphenyl (**31**) with sodium methoxide in a MeOH – pyridine mixture (PyH), one or two chlorine atoms at positions 4 and 4′ are replaced depending on the amount of the nucleophile.[75]



The reactions of octachloronaphthalene (**16**) with alkali metal hydroxides and alkoxides were investigated.[142, 145] Although the reaction conditions are substantially different, it should be noted that the attack of the alkoxide ion occurs predominantly on position 1 of the naphthalene ring; the attack of the hydroxide ion, on position 2. These reactions produce compounds **54a** and **54b**, respectively (Table 6).

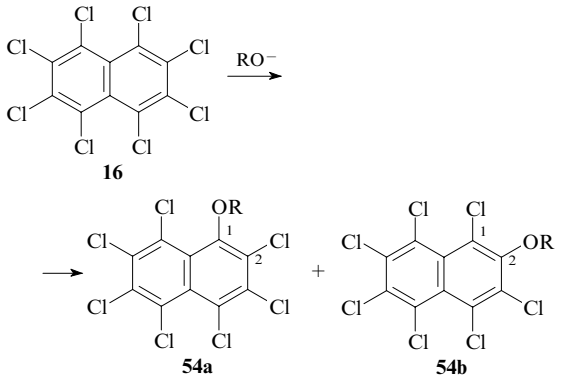
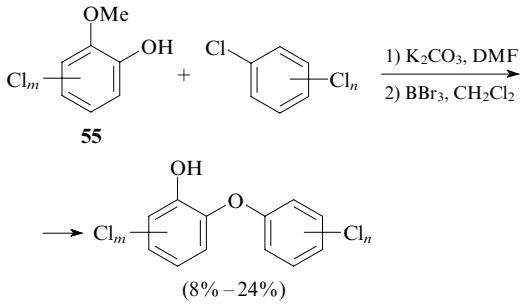


Table 6. Reactions of octachloronaphthalene (**16**) with alkali metal derivatives.[142, 145]

R	Reagent	Solvent	Temperature /°C	Yield (%)	**54a** : **54b**
Me	MeONa	pyridine	115	25 [a]	90 : 10
Me	MeOH, NaOH		~100	63	99 : 1
Bu^t	Bu^{t}OK	THF	20	82	85 : 15
H	KOH	DMSO	120	90	30 : 70

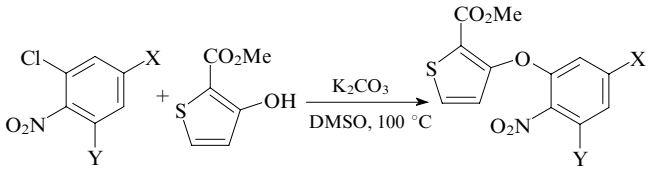
[a] Disubstituted (25% yield) and trisubstituted (20%) products were also isolated.

Polychlorinated *o*-hydroxylated diphenyl oxides were synthesised by the reactions of polychlorobenzenes with (poly)chloroguaiacols **55** in the K_2CO_3 – DMF system followed by demethylation of the substitution products with boron tribromide.[146]



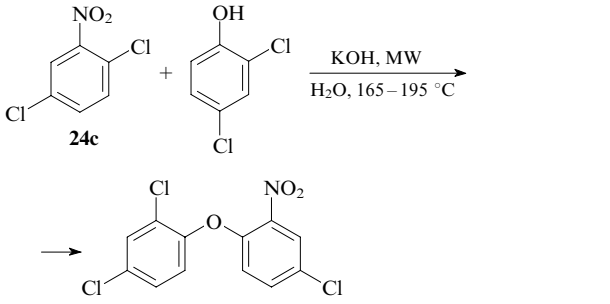
$m = 0-4$; $n = 2-5$.

As mentioned above, the presence of an electron-withdrawing substituent in the aromatic ring increases the reactivity of PCA, due to which the reactions with O-nucleophiles can be performed under milder conditions. In these reactions, it is the chlorine atom in the *ortho* position with respect to the electron-withdrawing group that, as a rule, undergoes replacement. For example, the reaction of 2,4-dichlorobenzoic acid (**27a**) with chlorophenols in pyridine in the presence of K_2CO_3 afforded *ortho*-substitution products (in approximately 70% yields).[147] In the reactions of 2,4- (**24b**) and 2,6-dichloronitrobenzenes (**24d**) with hydroxythiophene derivatives in DMSO at 100 °C, the chlorine atom in the *ortho* position with respect to the nitro group is replaced to give the products in 57% and 84% yields, respectively.[148]

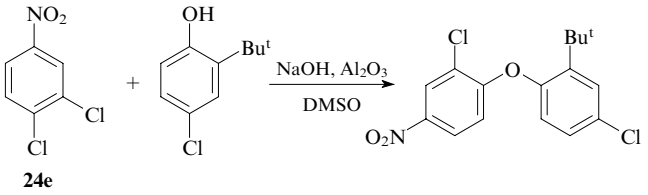


24b: X = Cl, Y = H;
24d: X = H, Y = Cl

The reactions of 2,5-dichloronitrobenzene (**24c**) with substituted phenols,[149,150] including the microwave (MW)-promoted reactions, are characterised by analogous regioselectivity.[151]

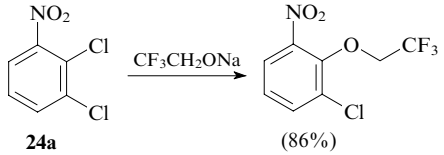


In the reactions of 3,4-dichloronitrobenzene (**24e**)[152,153] and 3,4-dichloro-1-trifluoromethylbenzene (**40a**)[154] containing no chlorine atoms in the *ortho* position with respect to the electron-withdrawing group, the attack of O-nucleophiles occurs on the *para* position; for example:



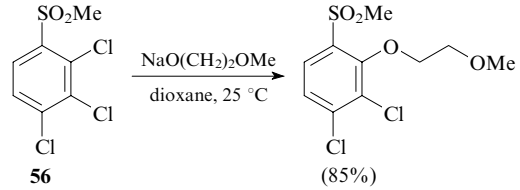
The *para* position in the aromatic ring is more active in hydrolysis of 1-substituted 3,4-dichlorobenzenes. For example, hydrolysis of 3,4-dichloronitrobenzene (**24e**) (15% NaOH in MeOH, 72 °C) affords 2-chloro-4-nitrophenol with the regioselectivity of >99%.[155] The reaction of 3,4-dichlorotrifluoromethylbenzene (**40a**) with the $Bu^tOH-KOH$ system in DMSO at 75 °C produces 2-chloro-4-trifluoromethylphenol in 27% yield.[156] Interestingly, the hydroxy group replaces the Cl atom in the *meta* position with respect to the nitro group in 2,5-dichloronitrobenzene (**24c**) upon hydrolysis of the latter with aqueous NaOH.[157]

The reactions of dichloronitrobenzenes **24** with sodium 2,2,2-trifluoroethoxide proceed under more drastic conditions (in DMF or HMPA at 150 °C under N_2).[158] The reactivity of the chlorine atoms increases in the following sequence: *ortho* position > *para* position > *meta* position. For example, under these reaction conditions, the chlorine atom in the *ortho* position with respect to the nitro group is replaced in 2,3- and 2,5-dichloronitrobenzenes (**24a**,**c**), the reaction of 2,4 isomer **24b** affords a mixture of the *ortho*- and *para*-substituted products in a ratio of 3 : 1, and 3,4 isomer **24e** gives the *para*-substituted product.

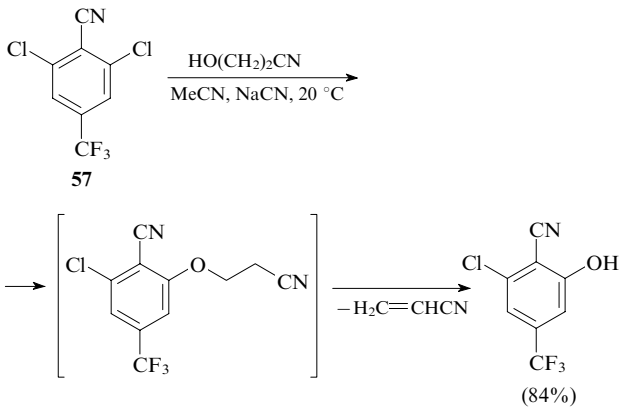


The reactions of sodium 2,2,2-trifluoroethoxide with dichlorobenzonitriles proceed analogously to form products in higher yields.

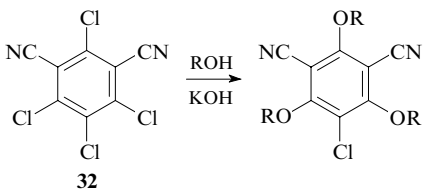
The reactions of trichloroarenes containing electron-withdrawing substituents proceed analogously. For example, the replacement of the chlorine atom in sulfone **56** in the reaction with sodium 2-methoxyethoxide also occurs at the *ortho* position.[159,160]



The reactions of dichlorobenzenes containing two or more electron-withdrawing groups with O-nucleophiles were documented.[161,162] The product of the replacement at the *para* position with respect to the trifluoromethyl group was prepared in 75% yield by refluxing 3,4-dichloro-2-nitro-6-trifluoromethylbenzene (**42c**) with 3-hydroxybenzoate in acetone in the presence of potassium carbonate. In the reaction of 2,4-dichloro-3,5-dinitrotrifluoromethylbenzene (**43**) with ethyl 3-hydroxybenzoate in acetone at room temperature, the chlorine atom at position 4 is also replaced,[161] and the subsequent nitration affords ethyl 5-(3-chloro-2,6-dinitro-4-trifluoromethylphenoxy)-2-nitrobenzoate in a total yield of 83%. 2,6-Dichloro-4-trifluoromethylbenzonitrile (**57**) reacts with $HOCH_2CH_2CN$ and NaCN in acetonitrile at room temperature. In this case, acrylonitrile is eliminated from the initially formed β-cyanoethyl ether to give the corresponding phenol.[162]



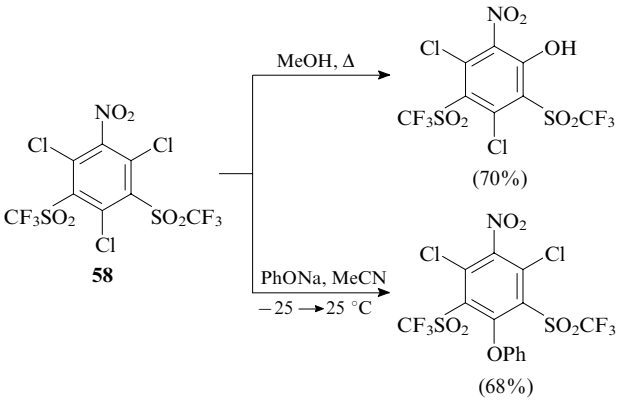
Three chlorine atoms are replaced in perchloroisophthalonitrile (**32**) by refluxing it in alcoholic solutions of KOH.[163]



R = Me (79% yield), Et (58%).

Due to high electrophilicity, the chlorine atom at position 2 in 2,4,6-trichloro-1-nitro-3,5-bis(trifluoromethylsulfonyl)benzene (**58**) is replaced by the hydroxy group upon refluxing in methanol even in the absence of bases (apparently, due to the presence of water in methanol).[107] In the reaction of compound

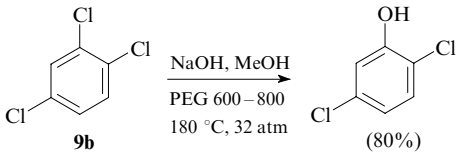
58 with sodium phenoxide in acetonitrile, it is the chlorine atom at position 4 that is replaced.



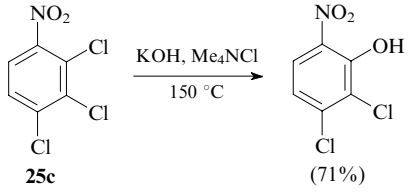
2. Reactions of polychloroarenes with O-nucleophiles in the presence of catalysts

In some cases, the reactions of PCA with O-nucleophiles are notably promoted by phase-transfer catalysts, metal complex catalysts or enzymes. Let us consider several reactions performed in the presence of phase-transfer catalysts. The reaction of 1,2-dichlorobenzene (**1a**) with the KOH – MeOH system in the presence of 18-crown-6 at 0 °C afforded 2-chloroanisole in 60% yield.[164] 2,4-Dichlorotoluene (**45b**) reacts with KOH in ethylene glycol at 200 °C and 30 atm in the presence of dibenzo-18-crown-6 to give 5-chloro-2-methylphenol in 78% yield.[139] The reaction of 1,2,3-trichlorobenzene (**9c**) with methanolic KOH at 140 °C in the presence of TDA-1 as the PTC affords a mixture of dichloroanisoles in a total yield of 97%;[164] in the absence of PTC, the yields of the products decrease to 8%.

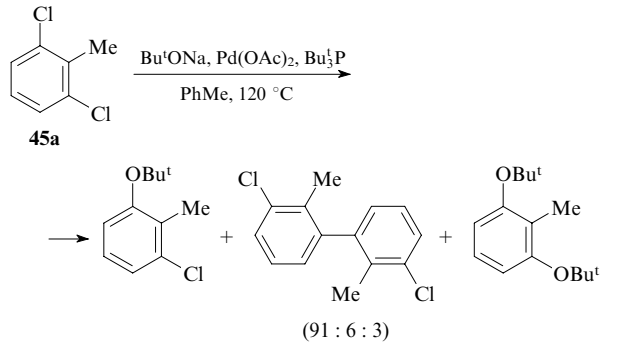
Hydrolysis of 1,2,4-trichlorobenzene (**9b**) with methanolic NaOH in the presence of poly(ethylene glycol) (PEG 600 – 800) gives 2,5-dichlorophenol.[165]



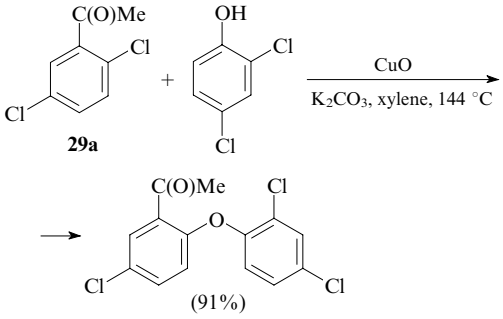
The replacement of the chlorine atom mainly in the *ortho* position with respect to an electron-withdrawing group is observed also in catalytic reactions. 2,3,4-Trichloronitrobenzene (**25c**) reacts with KOH in DMSO in the presence of tetramethylammonium chloride at 150 °C in an autoclave to form 2,3-dichloro-6-nitrophenol.[166]



In addition to PTC, the C – O bond formation in the reactions of PCA is promoted by transition metal compounds. For example, 2,6-dichlorotoluene (**45a**), which is poorly reactive in the absence of catalysts, reacts with sodium *tert*-butoxide in toluene in the presence of the $Pd(OAc)_2 - Bu^t_3P$ system[167] to form 2-(*tert*-butoxy)-6-chlorotoluene. In this reaction, the homodimerisation product of PCA and 2,6-bis(*tert*-butoxy)toluene were isolated as the by-products. The use of the PCy_3 and dppf ligands combined with a palladium salt proved to be less efficient.

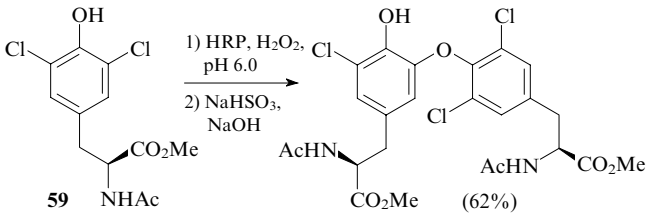


Copper compounds are used as catalysts for the C – O cross-coupling involving dichlorobenzenes with electron-withdrawing groups. For example, the reaction of 2,5-dichloroacetophenone (**29a**) with 2,4-dichlorophenol in the presence of CuO resulted in the replacement of the chlorine atom in the *ortho* position of the benzene ring of ketone.[168] In the absence of catalysts (heating of compound **29a** with KOH in xylene), the yield of the product decreases to 82%.[169]



In the reactions of 2,5-dichlorobenzoic acid with 3- and 4-chlorophenols (Cu, CuI, NaOMe, MeOH, 200 °C), the chlorine atom at position 2 was replaced to give the products in 78% – 82% yield.[170]

Enzymatic dimerisation of dichlorotyrosine (**59**) catalysed by horseradish peroxidase (HRP) formally proceeds as the nucleophilic substitution of one chlorine atom to yield an isodityrosine derivative.[171 – 173]



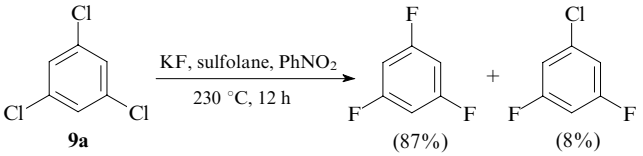
V. Reactions with F-nucleophiles

A convenient procedure for the synthesis of fluorine-containing aromatic compounds is based on the replacement of chlorine atoms in PCA under the action of metal fluorides. Considerable data on fluorodechlorination reactions of arenes were covered by patents, which is evidence that this approach is of practical importance. Data on this problem were summarised in the review[174] and monographs.[175, 176]

1. Reactivity of polychloroarenes in fluorodechlorination

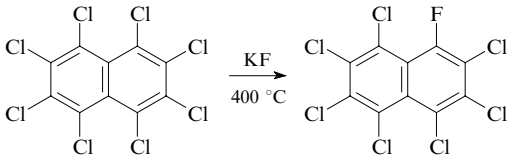
The fact that it is possible, in principle, to transform PCA into polyfluoroarenes was demonstrated for the first time in 1947.[177] The reaction of hexachlorobenzene (**5**) with BrF_3 followed by the successive treatment of the resulting mixture of perhalocyclohexanes $C_6Br_2Cl_4F_6$ with SbF_5 and zinc dust produced a mixture of chlorofluorobenzenes $C_6Cl_nF_{6-n}$ ($n = 0-6$). Individual reaction products, including hexafluorobenzene (**60**, ~10% yield), were isolated by rectification.

Later, available alkali and alkaline-earth fluorides have been used as fluorination agents. The reactions of non-activated PCA, for example, of 1,3,5-trichlorobenzene (**9a**), with metal fluorides are performed in polar aprotic solvents (sulfolane, DMF, *etc.*) under rather drastic conditions.[178,179] The necessity of using high temperatures is determined by low solubility of inorganic fluorides in organic solvents and their ability to form stable weakly nucleophilic hydrates.

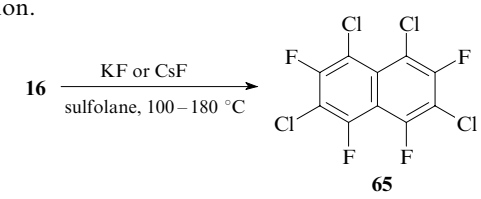


The reaction of hexachlorobenzene (**5**) with KF in an autoclave at 460–470 °C for 20 h and then at 490–510 °C for 10 h produced a mixture containing hexafluorobenzene (**60**) and chloropentafluorobenzene (**61**).[180,181] At lower temperatures (400–480 °C, 19–35 h), the yield of hexafluorobenzene (**60**) was at most 6%.[182] In the presence of water vapour,[183] fluorodechlorination is accompanied by the replacement of one chlorine atom with hydrogen to form a large set of polyhalobenzenes, including compounds **60**–**63** (Scheme 1).

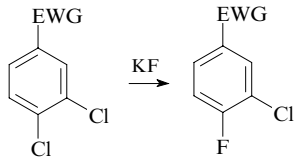
Heating of octachloronaphthalene (**16**) with KF in an autoclave (300–330 °C, 25 h) gave a mixture of products, from which octafluoronaphthalene (24%) was isolated by rectification.[184] According to the data of another study,[185] this reaction at 400 °C, even in the presence of a tenfold excess of KF, afforded heptachloro-1-fluoronaphthalene (**64**) as the major product.



The increase in the temperature to 420 °C resulted in the formation of a mixture of higher fluorodechlorinated products from which 1- and 2-chloro-substituted heptafluoronaphthalenes were isolated in 14.5% and 9.5% yields, respectively. The reaction of octachloride **16** in sulfolane affords a mixture of fluorodechlorination products containing from 1 to 4 fluorine atoms.[186] Individual 2,4,5,7-tetrachloro-1,3,6,8-tetrafluoronaphthalene (**65**) was isolated from the mixture by sublimation.

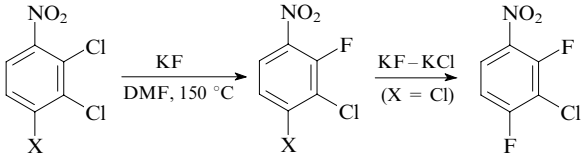


Polychloroarenes containing additional electron-withdrawing substituents in the aromatic nucleus are more reactive in fluorodechlorination compared to polychlorobenzenes, the reaction often being regioselective. For example, fluorodechlorination of *o*-dichlorobenzenes **24e** and **40a** containing electron-withdrawing groups at position 1 gives 4-fluoro derivatives.[187–189] The reactions with KF are carried out in aprotic solvents (DMSO, DMF, NMP, sulfolane or DMAA) at 190–250 °C; the products are formed in yields of up to 90%.



EWG = NO_2 (**24e**), CF_3 (**40a**).

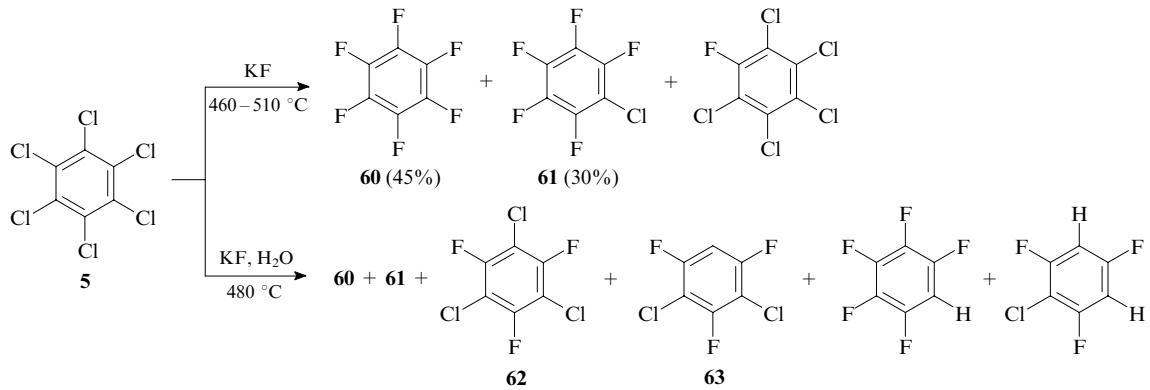
The chlorine atom in the *ortho* position with respect to the electron-withdrawing substituent is, as a rule, replaced in 1-nitro-substituted chlorobenzenes **24a**[190–192] and **25c**.[193] However, it has been possible to replace the chlorine atoms in the *ortho* and *para* positions by refluxing compound **25c** in DMF in the presence of a mixture of KF and KCl.[194]



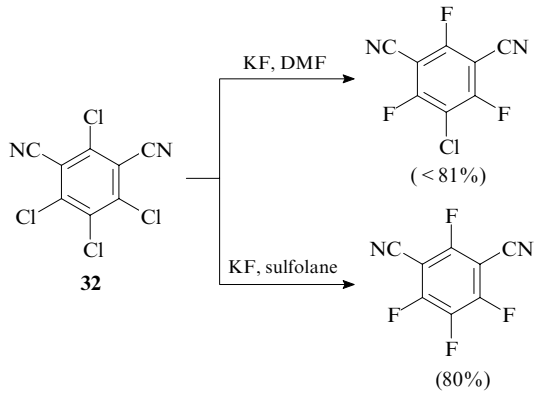
24a: X = H;
25c: X = Cl

The cyano group serves as a good activating substituent in polychloroarenes. For example, fluorodechlorination of pentachlorobenzonitrile with KF at 350 °C in an autoclave results in pentafluorobenzonitrile in 70% yield.[195] An analogous

Scheme 1

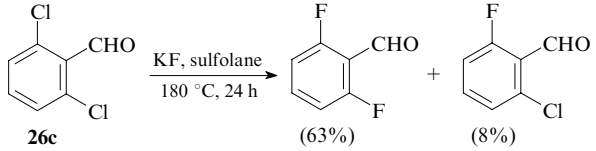


reaction of tetrachlorophthalonitrile proceeds at 300 °C (the yield of the tetrafluoro derivative is 74%).[196] The reaction of 2,3,4,5-tetrachlorobenzonitrile with KF in sulfolane affords a mixture of fluorodechlorination products, including 2,3,4,5-tetrafluorobenzonitrile.[197] The reaction of tetrachloroisophthalonitrile (**32**) with KF in DMF resulted in the replacement of three chlorine atoms in the *ortho* positions with respect to the cyano groups.[198–201] All four chlorine atoms in compound **32** can be replaced by performing the reaction in sulfolane.[202]



It should be noted that the reaction of 2,4-dichloro-5-fluorobenzoyl fluoride with KF in aprotic solvents gives 2,4,5-trifluorobenzoyl fluoride as the major product.[203]

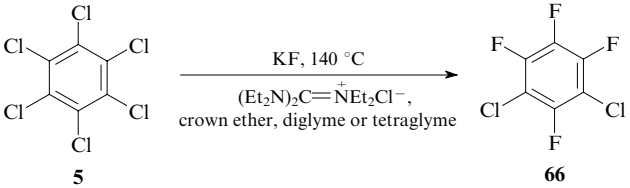
In spite of drastic conditions, PCA containing the labile aldehyde group undergo fluorodechlorination. For example, the reaction of 2,6-dichlorobenzaldehyde (**26c**) with KF in sulfolane at 180 °C affords 2,6-difluorobenzaldehyde in good yield, while the monofluoro derivative is formed as a by-product.[179]



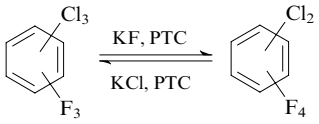
2. The means for activation of fluorodechlorination

The use of PTC (quaternary ammonium or phosphonium salts) facilitating the transfer of fluoride anions to an organic phase is one of ways of promoting fluorodechlorination of PCA.[204] The use of salts of HF with organic bases, for example, $Ph_4P^+(HF_3)^-$,[205] or fluorides with organic cations, such as Me_4NF, as fluorination agents was documented.[206]

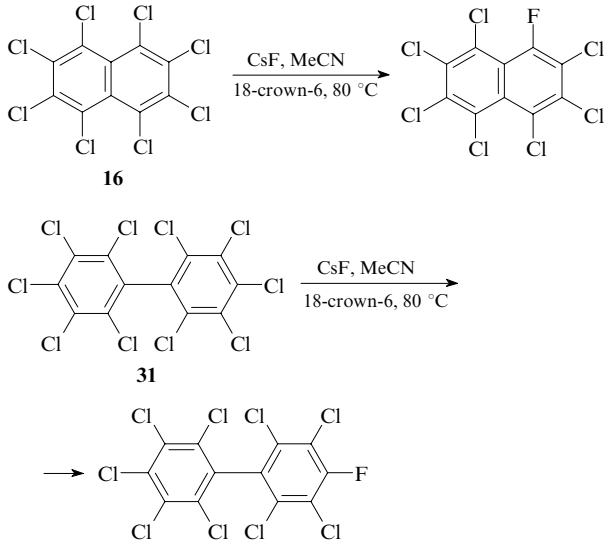
Fluorodechlorination of hexachlorobenzene (**5**) with KF supported on CaF_2 or BaF_2 in the presence of $(Et_2N)_4PBr$ as the catalyst at 230 °C in an autoclave affords a mixture of arenes C_6ClF_5 (**61**, 25% yield), $C_6Cl_2F_4$ (45%) and $C_6Cl_3F_3$ (**62**, 30%).[207] Under the above-mentioned conditions, no reaction proceeds in the absence of catalysts. Hexaethylguanidinium chloride in combination with crown ethers, diglyme or tetraglyme can be used as PTCs.[208] The reaction of hexachlorobenzene (**5**) in the presence of this catalytic system gave a mixture of isomeric products, resulting from the substitution of four chlorine atoms, 1,2,3,5-tetrafluoro derivative **66** being the major product (>90%).



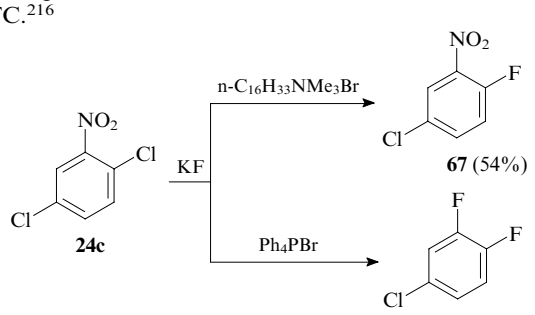
The inhibition of the subsequent fluorodechlorination of compound **66** is, apparently, attributed to an increase in the concentration of chloride ions with rather high nucleophilicity. The suggestion that the fluorodechlorination is reversible was confirmed in the study,[209] where the possibility of transforming $C_6Cl_2F_4$ into trichlorotrifluorobenzene was demonstrated.



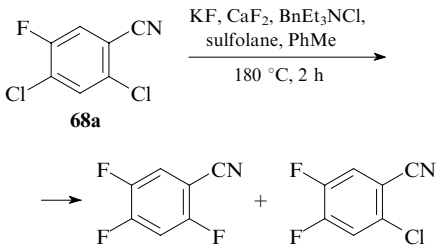
The 18-crown-6-catalysed fluorodechlorination of binuclear PCA **16** and **31** with CsF under mild conditions (MeCN, 80 °C)[210] allows the selective introduction of one fluorine atom at positions 1 and 4, respectively.



Phase-transfer catalysts are successfully used for fluorodechlorination of PCA containing additional electron-withdrawing substituents. In these reactions, the chlorine atoms in the *ortho* and *para* positions with respect to these substituents are generally replaced. For example, the reaction of 2,3-dichloronitrobenzene (**24a**) with KF in xylene in the presence of trimethyl(ethoxypolyoxypropyl)ammonium chloride produced 3-chloro-2-fluoronitrobenzene in 72% yield.[211] Under these conditions, both chlorine atoms are replaced in 2,6-dichlorobenzonitrile (**28a**)[212] and 2,4-dichloronitrobenzene (**24b**).[213] The fluorodechlorination of 2,5-dichloronitrobenzene (**24c**) in the presence of trimethylcetylammonium bromide at 140–150 °C affords product **67**.[214, 215] The nitro group is also replaced in the reaction with the use of Ph_4PBr as the PTC.[216]



The reaction of 2,4-dichloro-5-fluorobenzonitrile (**68a**) with KF supported on CaF_2 in the presence of $BnEt_3NCl$ produces a mixture of 2,4,5-trifluoro- and 2-chloro-4,5-difluorobenzonitriles in a total yield of 82 %.[198, 217]



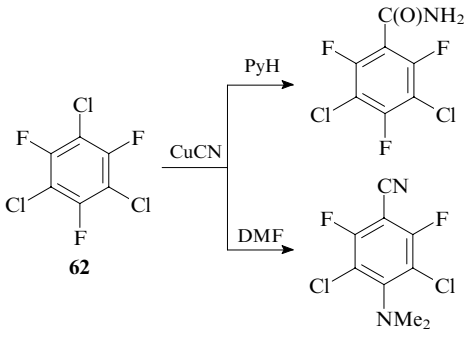
Fluorodechlorination of 3,4-dichlorobenzonitrile (**28b**) with KF in DMSO in the presence of PTCs of the iminium series, such as $(R^1_2N)_2C{=}N^+{=}C(NR^2_2)_2Hal^-$, $(R^1_2N)_2C{=}N^+{=}P(NR^2_2)_3Hal^-$ or $(R^1_2N)_3P{=}N^+{=}P(NR^2_2)_3Hal^-$ (R^1, R^2 = Alk), occurs exclusively at position 4 (the yield of the product is 81% – 92%).[218] Polychloroarenes containing chlorine atoms in the *meta* position with respect to an electron-withdrawing substituent are much less reactive. For example, only one chlorine atom is replaced in 3,5-dichloro-4-fluorobenzonitrile (**68b**) or 3,5-dichloro-4-fluoro-1-trifluoromethylbenzene in the reaction with KF in sulfolane in the presence of PTC.[219]

Fluorodechlorination of PCA is promoted by sonication.[187, 220] For example, the reaction of 3,4-dichloronitrobenzene (**24e**) with KF and *N*-(2-ethylhexyl)-4-(*N*,*N*-dimethylamino)pyridinium bromide on polystyrene in DMSO promoted by sonication produced 3-chloro-4-fluoronitrobenzene in 95% yield.[220]

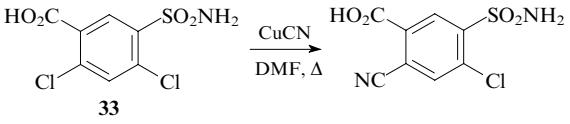
VI. Reactions with C-nucleophiles

1. Cyanation reactions

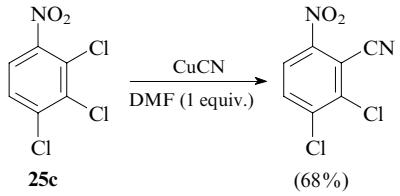
The reactions of PCA with copper cyanide produce the corresponding chlorobenzonitriles generally in low yields. For example, the yield of pentachlorobenzonitrile in the reaction of hexachlorobenzene (**5**) with CuCN was only 4%.[221] 3,5-Dichloro-2,4,6-trifluorobenzamide and 3,5-dichloro-2,6-difluoro-4-dimethylaminobenzonitrile were synthesised by the reaction of 2,4,6-trichloro-1,3,5-trifluorobenzene (**62**) with CuCN in pyridine and DMF, respectively.[222]



In 5-aminosulfonyl-2,4-dichlorobenzoic acid (**33**), the chlorine atom at position 2 is replaced upon heating with CuCN in DMF to give the derivative of phthalic acid mononitrile.[223]



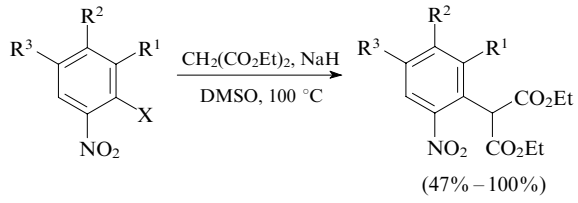
2,3,4-Trichloronitrobenzene (**25c**) is transformed into 5,6-dichloro-2-nitrobenzonitrile in the reaction with CuCN in the presence of 1 equiv. of DMF.[224]



The yield of the cyanation product can be increased in the presence of transition metal complexes as catalysts. For example, the reaction of 1,4-dichlorobenzene (**1c**) with KCN catalysed by Pd or Ni complexes at 100 – 250 °C produces terephthalonitrile in 87% yield.[225]

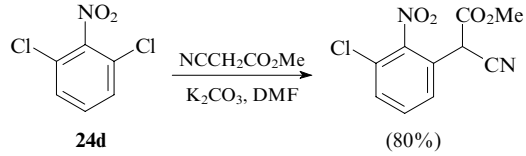
2. Reactions of polychloroarenes with carbanions

Polychloroarenes activated by the nitro group readily react with anions of CH acids (malonic and cyanoacetic esters, *etc.*) on heating in aprotic solvents. As a rule, it is the halogen atom in the *ortho* position with respect to an electron-withdrawing substituent that is replaced.[226 – 228] The reaction with diethyl malonate can serve as an example:



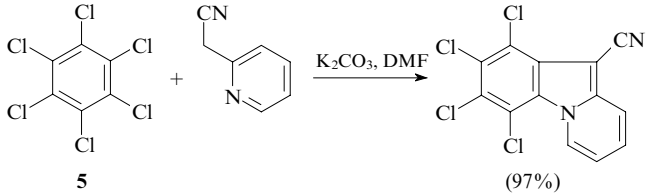
X = Cl, F; R^1, R^2 = Cl, H; R^3 = Cl, H, ArC(O).

Methyl (3-chloro-2-nitrophenyl)cyanoacetate was prepared by the reaction of 2,6-dichloronitrobenzene (**24d**) with methyl cyanoacetate in DMF in the presence of K_2CO_3.[229, 230]

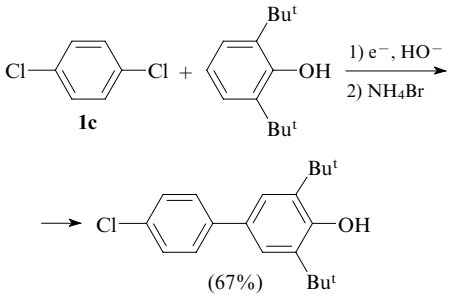


If a PCA contains no chlorine atoms in the *ortho* position with respect to the activating group, the chlorine atom in the *para* position is replaced. For example, *para*-substitution products were obtained in 80% – 85% yields from 3,4-dichloronitrobenzene (**24e**) and 3,4,5-trichloronitrobenzene (**25b**).[228]

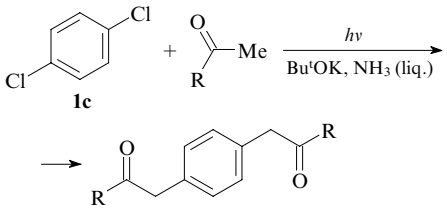
The reaction of the 2-(cyanomethyl)pyridine anion with hexachlorobenzene (**5**) affords the pyrido[1,2-*a*]indole derivative in nearly quantitative yield.[231]



The electrochemically generated 2,6-di(*tert*-butyl)-phenolate anion reacts with 1,4-dichlorobenzene (**1c**) as the C-nucleophile.[232]



The reactions of methyl ketone enolates with 1,4-dichlorobenzene (**1c**) in liquid ammonia were studied.[233] Under photochemical conditions, the ion-radical mechanism operates.



R = Me, Bu^t.

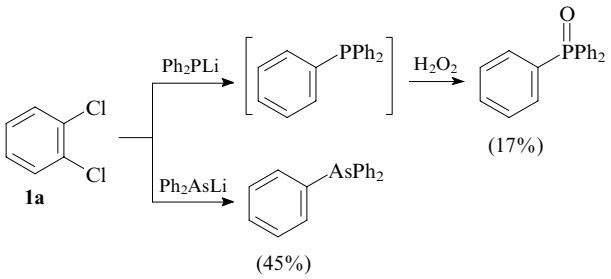
Irradiation of PCA with the light from a mercury lamp (254- or 185-nm) in benzene for 40 h at 25 °C under nitrogen resulted in the replacement of chlorine atoms by phenyl groups, the solvent serving as the source of the latter (Table 7).[234] The reaction, which proceeds apparently by the radical mechanism, is accompanied by partial hydrodechlorination of both the starting arenes and products, particularly, of highly chlorinated compounds.

Table 7. Photochemical transformations of polychloroarenes in benzene.[234]

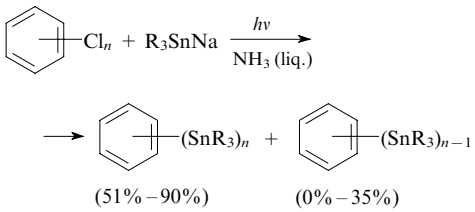
Compounds	Products (yield, %)
1,2-$Cl_2C_6H_4$ (**1a**)	2-ClC_6H_4Ph (43) + Ph_2 (14) + 1,2-$Ph_2C_6H_4$ (1)
1,3-$Cl_2C_6H_4$ (**1b**)	3-ClC_6H_4Ph (41) + Ph_2 (1)
1,4-$Cl_2C_6H_4$ (**1c**)	4-ClC_6H_4Ph (26) + Ph_2 (1)
1,3,5-$Cl_3C_6H_3$ (**9a**)	3,5-$Cl_2C_6H_3Ph$ (31) + 1,3-$Cl_2C_6H_4$ (1)
1,2,3-$Cl_3C_6H_3$ (**9c**)	2,5-$Cl_2C_6H_3Ph$ (22) + 3-ClC_6H_4Ph (3) + + 4-ClC_6H_4Ph (1) + 1,4-$Cl_2C_6H_4$ (1)
1,2,3,4-$Cl_4C_6H_2$ (**10a**)	2,3,6-$Cl_3C_6H_2Ph$ (21) + 1,2,4-$Cl_3C_6H_3$ (3) + + 4-Cl-1,2-$Ph_2C_6H_3$ (2) + 2,5-$Cl_2C_6H_3Ph$ (1) + + 3,6-Cl_2-1,2-$Ph_2C_6H_2$ (1) + Ph_2 (1)
1,2,4,5-$Cl_4C_6H_2$ (**10b**)	2,4,5-$Cl_3C_6H_2Ph$ (9) + 3,4-$Cl_2C_6H_3Ph$ (9) + + 1,2,4-$Cl_3C_6H_3$ (2)
1,2,3,5-$Cl_4C_6H_2$ (**10c**)	2,4,6-$Cl_3C_6H_2Ph$ (7) + 2,3,5-$Cl_3C_6H_2Ph$ (5) + + 1,3,5-$Cl_3C_6H_3$ (2)

3. Reactions with anions of heteroorganic compounds

In the reactions of 1,2-dichlorobenzene (**1a**) with lithium diphenylphosphide and diphenylarsenide, one of the chlorine atoms is replaced by a heteroorganic substituent and another chlorine atom is replaced by hydrogen to give the corresponding products in low yields.[235] The hypothesis that this reaction proceeds *via* benzyne was not confirmed, since experiments with furan as a scavenger were unsuccessful.



UV irradiation (λ = 350 nm) of some PCA in the presence of Me_3SnNa [236, 237] or Ph_3SnNa [238] in liquid ammonia affords substitution products. The reaction proceeds by the anion-radical mechanism and only under irradiation.



n = 2, 3; R = Me, Ph.

1,4-Bis(triphenylstannyl)benzene was obtained in 90% yield by the reaction of 1,4-dichlorobenzene (**1c**) with $SnPh_4$ in DMSO or acetonitrile under photochemical conditions.[239]

VII. Catalytic carbonylation and carboxylation

Catalytic carbonylation of polychloroarenes in the CO – $Co_2(CO)_8$ – NaOH – H_2O system proceeds under UV irradiation (Table 8).[240] In some cases, the reaction is accompanied by partial dechlorination (see, for example, the transformation of compound **69**). The selectivity of the reaction is determined by the number and arrangement of substituents in the starting arene.

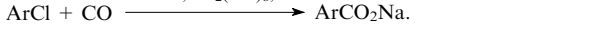
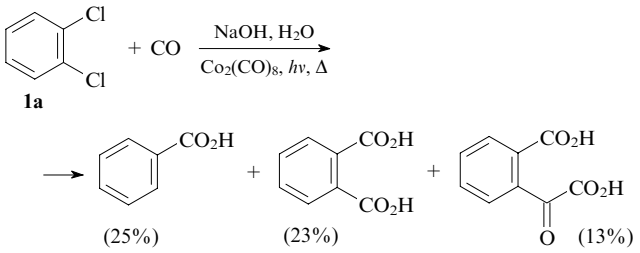


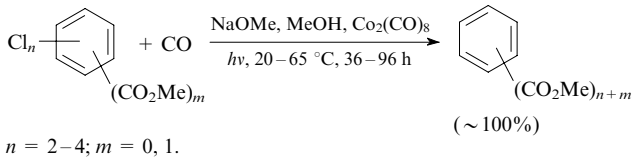
Table 8. Carbonylation of PCA [conditions: 1) *hv*, CO, $Co_2(CO)_8$, NaOH, H_2O; 2) H^+] with the 100% conversion of the substrate.[240]

Compound	Time /h	Products	Yield (%)
1,2-$Cl_2C_6H_4$ (**1a**)	24	$PhCO_2H$	24
		2-$ClC_6H_4CO_2H$	40
		1,2-$(HO_2C)_2C_6H_4$	2
		PhCl	7
1,3-$Cl_2C_6H_4$ (**1b**)	20	1,3-$(HO_2C)_2C_6H_4$	92
1,4-$Cl_2C_6H_4$ (**1c**)	20	1,4-$(HO_2C)_2C_6H_4$	88
1,3,5-$Cl_3C_6H_3$ (**9a**)	20	1,3,5-$(HO_2C)_3C_6H_3$	86
3,5-$Cl_2C_6H_3CO_2H$ (**27b**)	20	1,3,5-$(HO_2C)_3C_6H_3$	89
3,4-$Cl_2C_6H_3CO_2H$ (**27c**)	6	4-$ClC_6H_4CO_2H$	15
		1,4-$(HO_2C)_2C_6H_4$	14
		2-Cl-$C_6H_3(CO_2H)_2$-1,4	57
		1,2,4-$(HO_2C)_3C_6H_3$	11
4,5-$Cl_2C_6H_2(CO_2H)_2$-1,2 (**69**)	24	1,2,4-$(HO_2C)_3C_6H_3$	53
		1,2,4,5-$(HO_2C)_4C_6H_2$	30

Carbonylation of 1,2-dichlorobenzene (**1a**) affords, along with benzoic and phthalic acids, 2-carboxyphenylglyoxalic acid.[241]



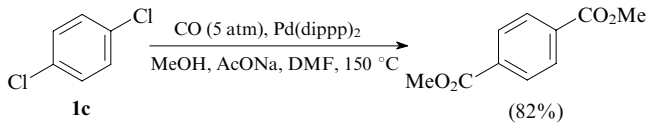
The reaction of polychloroarenes with carbon monoxide in methanol in the presence of MeONa produces methyl arenepolycarboxylates.[242] The reaction time varies from 36 to 95 h. Compounds containing vicinal chlorine atoms react much more slowly.



$n = 2-4$; $m = 0, 1$.

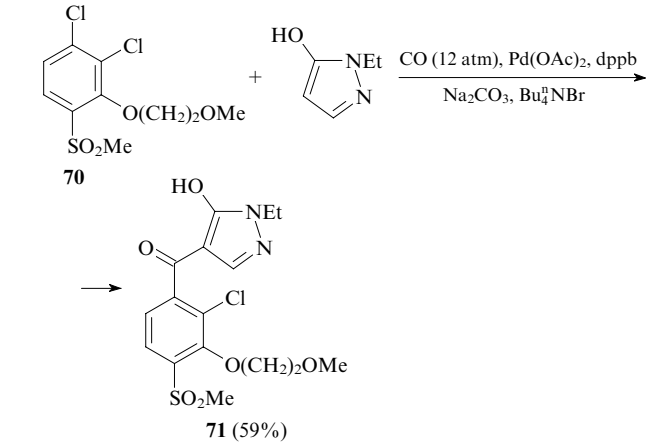
Carbonylation of 1,4-dichloro- (**1c**) and 1,3,5-trichlorobenzenes (**9a**) in EtOH affords ethyl benzenedi- and tricarboxylates.[243]

Palladium(0) complexes can be used as catalysts for these reactions.[244]



dippp is 1,3-bis(diisopropylphosphino)propane.

The use of Pd catalysts in combination with PTC allowed the carbonylation of dichloroarene **70** in the presence of 1-ethyl-5-hydroxypyrazole giving rise to aryl pyrazolyl ketone derivative **71**.[160]



dppb is 1,4-bis(diphenylphosphino)butane.

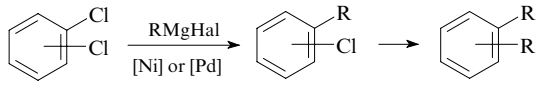
The reactions of PCA with CO_2 proceed less selectively. Electrochemical carboxylation of 3,4-dichloro-1-trifluoromethylbenzene (**40a**) in aprotic polar solvents (Bu_4NBr as the supporting electrolyte, 15 °C, the current density $j = 5-50$ mA cm^{-2}) affords 2-chloro-4-trifluoromethylbenzoic acid as the major product.[245] Electrochemical carboxylation of 1,2,4,5-tetrachlorobenzene (**10b**) and hexachlorobenzene (**5**) is accompanied by reductive hydrodechlorination.[246]

VIII. Catalytic C – C cross-coupling

Aryl chlorides are, as a rule, less reactive than the corresponding bromides and iodides in cross-coupling reactions catalysed by Pd or Ni complexes. The following approaches are used to accelerate these reactions: (1) the introduction of electron-withdrawing groups into the aromatic nucleus, (2) an increase in the nucleophilicity of the cross-counterpart or (3) the use of efficient catalytic systems. In recent years, considerable progress has been achieved in the design of new catalysts, particularly, in combination with sterically hindered phosphine[247–257] and *N*-heterocyclic[258–266] ligands. Data on some other types of ligands were reported elsewhere.[267–272]

1. Reactions of polychloroarenes with organometallic compounds (M = Mg, Al or Zn)

Cross-coupling of PCA, unlike the analogous reactions with monochloroarenes, have been little studied. Most attention was focused on the transition metal complex-catalysed reactions of dichlorobenzenes **1a–c** with the Grignard reagents containing primary or secondary alkyl substituents (the Kumada reaction).[273–277]



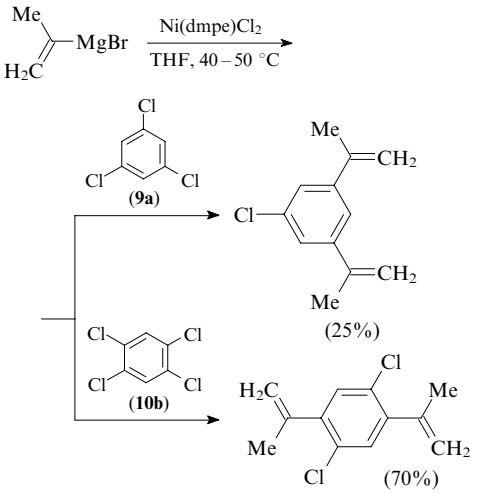
R = Alk, Ph.

The nickel complexes $Ni(dppp)Cl_2$ [dppp is 1,3-bis(diphenylphosphino)propane] and $Ni(dppe)Cl_2$ [dppe is 1,2-bis(diphenylphosphino)ethane] are the catalysts of choice allowing the replacement of both chlorine atoms.[273] The high activity of these complexes is attributed to the fact that, after the replacement of the first chlorine atom, the catalyst tends to migrate intramolecularly to the second chlorine atom rather than to escape into solution. This reaction catalysed by the complex $Ni(PPh_3)_2Cl_2$ with the monodentate phosphine ligand affords products in much lower yields.

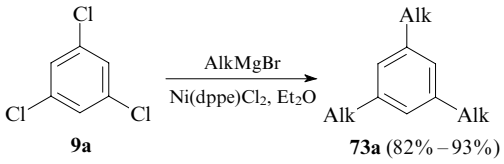
The reaction can be terminated after the replacement of one chlorine atom in the case of the complex $Ni(triphos)ClPF_6$ [triphos is the tridentate ligand *P*,*P*-bis(2-diphenylphosphinoethyl)phenylphosphine].[277] In the cross-coupling reactions of 2,5-dichloro-1-trifluoromethylbenzene (**40b**) and 2,3-dichloroanisole (**72a**) with EtMgBr, the chlorine atom in the *meta* position with respect to the electron-withdrawing substituent is predominantly replaced.[277] The selectivity is particularly high in the reaction with compound **72a** (the yields of 2-chloro-3-ethyl- and 3-chloro-2-ethylanisoles are 70% and 4%, respectively).

The reaction can be terminated at the monoalkylation step also in the presence of palladium catalysts [the complex $Pd(dppf)Cl_2$ is the catalyst of choice] in the dichlorobenzene : Grignard reagent molar ratio of ~2 : 1.[276] In some cases, it is advantageous to add 0.5–1 equiv. (with respect to the catalyst) of the corresponding free ligand. The reactions efficiently proceed in THF at 85–105 °C. The $Pd(PPh_3)_4$-catalysed reaction of 1,4-dichlorobenzene (**1c**) with MeMgBr affords 4-chlorotoluene as the major product (92%).[278]

Several cross-coupling reactions of higher chlorinated PCA with the Grignard reagents were documented. The reactions of 1,3,5-trichlorobenzene (**9a**) and 1,2,4,5-tetrachlorobenzene (**10b**) with isopropenylmagnesium bromide in THF in the presence of $Ni(dmpe)Cl_2$ [dmpe is bis(dimethylphosphino)-ethane] resulted in the replacement of two chlorine atoms.[273]

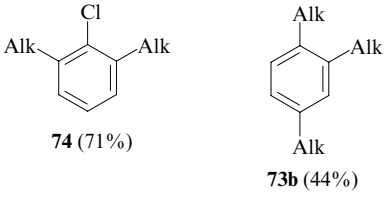


The use of the complex $Ni(dppe)Cl_2$ allowed the replacement of all chlorine atoms in 1,3,5-trichlorobenzene (**9a**),[279] 1,3,5-trialkylbenzenes **73a** being produced in yields of up to 93%.

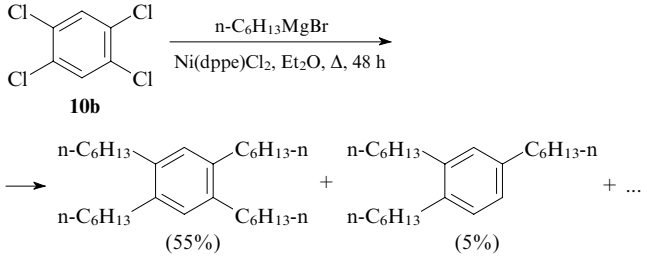


Alk = n-C_nH_{2n+1} (n = 6 – 10).

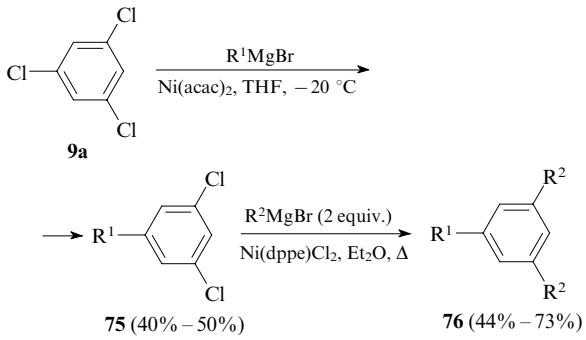
Polychloroarenes containing vicinal chlorine atoms are less reactive towords alkylmagnesium bromides. For example, only 'lateral' chlorine atoms are replaced in 1,2,3-trichlorobenzene (**9c**) to give monochlorides **74**. The reaction of 1,2,4-trichlorobenzene (**9b**) affords a mixture of complete substitution products, *viz*., compounds **73b** (44%), along with dialkylchlorobenzene (22%), the positions of the substituents in the latter remaining unknown.



The reaction of 1,2,4,5-tetrachlorobenzene (**10b**) with n-hexylmagnesium bromide in the presence of $Ni(dppe)Cl_2$ affords tetrahexylbenzene along with by-products, one of which was identified as 1,2,4-tri(n-hexyl)benzene.[279]

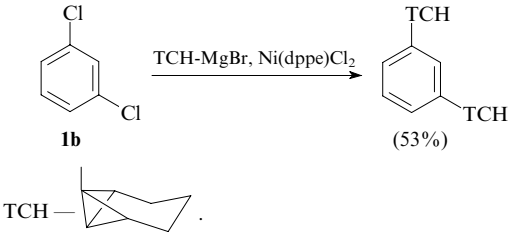


The use of various catalysts allowed the synthesis of 1,3,5-trialkylbenzenes containing different alkyl substituents starting from 1,3,5-trichlorobenzene (**9a**).[279] The reaction in THF at −20 °C in the presence of $Ni(acac)_2$ as the catalyst afforded compounds **75** as a result of the replacement of the first chlorine atom by the group R^1. The latter compounds were used in the $Ni(dppe)Cl_2$-catalysed reaction with an excess of another alkylmagnesium bromide R^2MgBr. The preparative yields of trialkylbenzenes **76** were achieved only after refluxing in diethyl ether for 7 – 10 days.

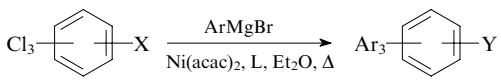


R^1, R^2 = Alk.

The reactions of di- (**1a**,**b**) and trichlorobenzenes (**9a**) with the tricyclic Grignard reagent, *viz*., tricyclo[4.1.0.0.^{2,7}]hept-1-ylmagnesium bromide (TCH-MgBr), in the presence of $Ni(dppe)Cl_2$ were documented.[280] The satisfactory yield of the substitution product (53%) was achieved only in the reaction with 1,3-dichlorobenzene (**1b**).



Cross-coupling of tri- and tetrachloroarenes with aromatic Grignard reagents (Table 9) were performed with the use of the catalytic system $Ni(acac)_2$ – diphenyl[2-(1-hydroxyethyl)phenyl]phosphine (L).[281] Under these conditions, complete substitution of trichlorobenzenes **9a**,**b**,**d** and **77** occured to give the corresponding products in high yields. In the case of 1,2,4,5-tetrachlorobenzene (**10b**), incomplete conversion is accompanied by partial dechlorination.



X = H, Cl, OMe; Y = H, Ar, OMe; Ar = Ph, 4-MeC_6H_4 (Tol);

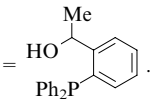
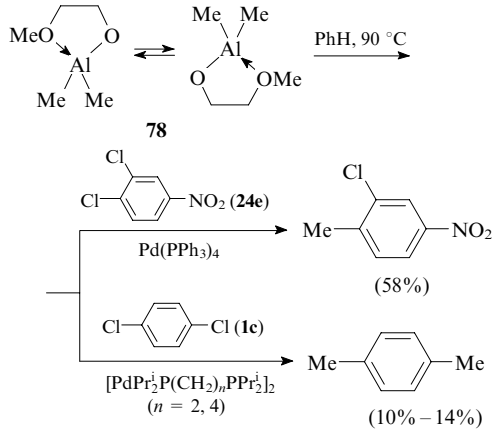


Table 9. Cross-coupling of tri- and tetrachlorobenzenes with ArMgBr.[281]

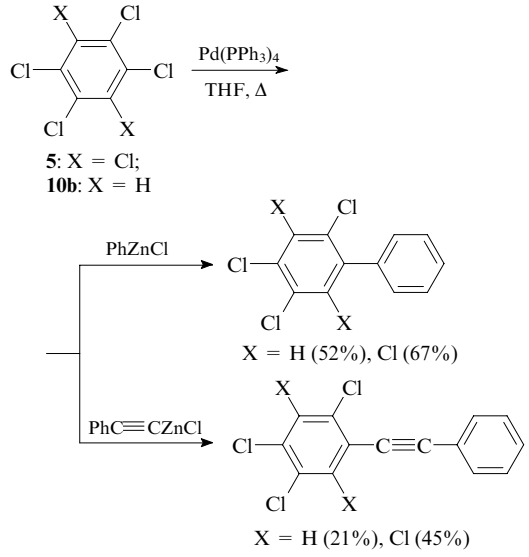
Compound	Ar	Time /h	Product	Yield (%)
1,3,5-$Cl_3C_6H_3$ (**9a**)	Tol	2	1,3,5- $Tol_3C_6H_3$	91
1,2,4-$Cl_3C_6H_3$ (**9b**)	Ph	48	1,2,4-$Ph_3C_6H_3$	89
1,2,3-$Cl_3C_6H_3$ (**9d**)	Tol	24	2,6-$Tol_2C_6H_4$	85
1,2,4,5-$Cl_4C_6H_2$ (**10b**)	Ph	96	1,2,4,5-$Ph_4C_6H_2$	58 [a]
2,4,6-$Cl_3C_6H_2OMe$ (**77**)	Tol	20	2,4,6-$Tol_3C_6H_2OMe$	80

[a] By-products: 1-Cl-2,4,5-$Ph_3C_6H_2$ and 1,2,4-$Ph_3C_6H_3$ (2 : 3).

Reactions of PCA with complex organoaluminium compounds were documented.[282] For example, compound **24e** containing the nitro group reacts with derivative **78** in the presence of $Pd(PPh_3)_4$. The reaction with non-reactive 1,4-dichlorobenzene (**1c**) required the use of a Pd complex with electron-rich phosphine ligands; however, the yield of *p*-xylene was at most 14%.

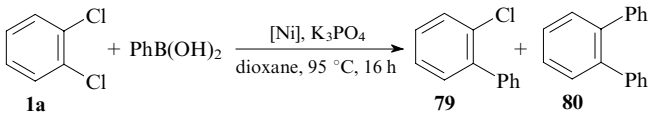


In the $Pd(PPh_3)_4$-catalysed reactions of 1,2,4,5-tetrachlorobenzene (**10b**) and hexachlorobenzene (**5**) with organozinc compounds (1.6 mol per mole of arene) in boiling THF, one chlorine atom is replaced to give the corresponding products in moderate yields.[283] The conversion of PCA varies from 58% to 89% and is accompanied by side processes, such as homocoupling of the nucleophilic and electrophilic components and reductive dechlorination.



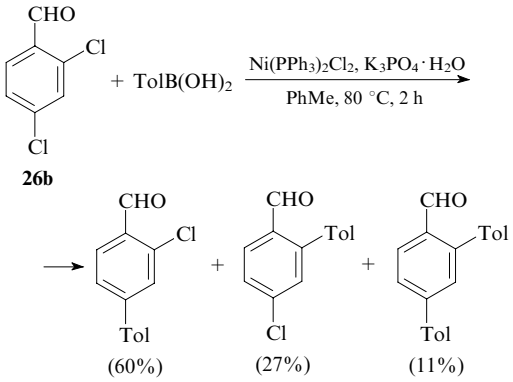
2. Reactions of polychloroarenes with arylboronic acids

Transition metal-catalysed cross-coupling reaction of PCA with arylboronic acids (the Suzuki reaction) can serve as a convenient one-pot procedure for the synthesis of polyarylbenzenes. However, this reaction is far from being always selective. For example, the reaction of 1,2-dichlorobenzene (**1a**) with 4.4 equiv. of $PhB(OH)_2$ in the presence of the nickel complexes $Ni(dppf)Cl_2$ or $Ni(PPh_3)_2Cl_2$ affords a mixture of 2-chlorobiphenyl (**79**) and *o*-terphenyl (**80**).[284]



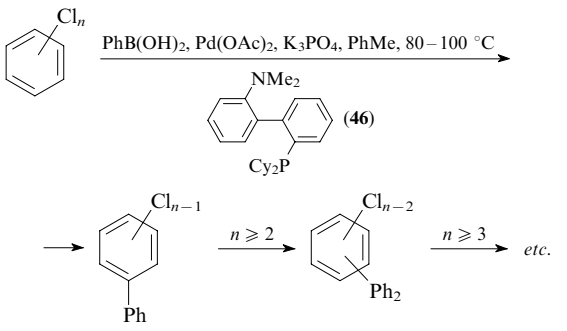
[Ni]	Yield (%)	
	79	**80**
$Ni(dppf)Cl_2$	4	69
$Ni(PPh_3)_2Cl_2$	34	28

Cross-coupling of 2,4-dichlorobenzaldehyde (**26b**) with *p*-tolylboronic acid with a nickel catalyst also affords a mixture of compounds, with the *para*-substitution product predominating (the *para* isomer : *ortho* isomer ratio ~2 : 1).[285] On the contrary, the *ortho* isomer is formed in higher yield with the palladium catalyst $Pd(dba)_2 - L$ (L = PPh_3, PCy_3, dppb or dppf).



The reaction of 1,2-dichlorobenzene (**1a**) with $PhB(OH)_2$ on a heterogeneous nanocluster catalyst with the composition Cu/Pd/Ru in DMF at 110 °C in the presence of K_2CO_3 as a base affords the monoarylated product in 25% yield.[286] In the reaction of 1,4-dichlorobenzene (**1c**) with 4-tolylboronic acid in the presence of the catalytic system $PdCl_2 - PCy_3 - Na_2CO_3$ in NMP at 150 °C, also only one chlorine atom is replaced.[287]

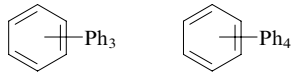
We demonstrated [283] that highly chlorinated PCA, such as C_6Cl_6 (**5**) and C_6Cl_5Ac, do not react with phenylboronic acid in the presence of $Pd(PPh_3)_4$ under the conditions typical of the reaction of aryl bromides. Unexpectedly, pentachloroiodobenzene also appeared to be inert under these conditions due apparently to steric hindrance of the reactive C—I bond by the adjacent chlorine atoms. The target products were synthesised with the use of modern catalytic systems designed in recent years for the cross-coupling of monochloroarenes, including deactivated compounds. For example, the cross-coupling of $PhB(OH)_2$ with equimolar amounts of 1,2,4,5-tetrachlorobenzene (**10b**) and hexachlorobenzene (**5**) in the presence of the system $Pd(dba)_2 - Bu^t_3P - K_3PO_4 - PhMe$ (Ref. 248) gave the



n = 2–6.

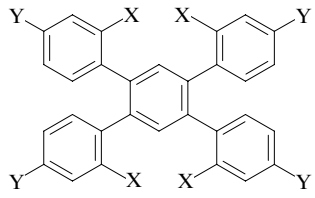
products in 82% and 37% yields, respectively.[283] The Buchwald ligands containing the 2-phosphinobiphenyl fragment, particularly, 2-dicyclohexylphosphino-2′-dimethylaminobiphenyl (**46**),[125,126] proved to be very efficient in these reactions.[247,252,253]

The cross-coupling of tri- and tetrachlorobenzenes with arylboronic acids $ArB(OH)_2$ (Ar = Ph, 4-$MeOC_6H_4$ or 4-FC_6H_4) under Buchwald conditions resulted in the complete replacement of the chlorine atoms to give compounds **81**–**84** in high yields.



81a–c **82a,b**

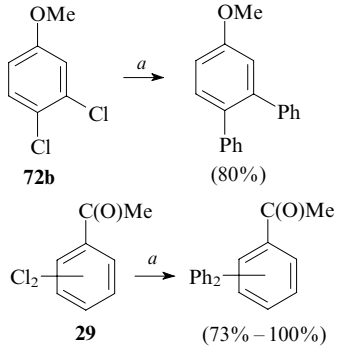
Isomers: 1,2,3 (**81a**, 94%); 1,2,4 (**81b**, ~ 100%); 1,3,5 (**81c**, ~ 100%); 1,2,3,4 (**82a**, 88%); 1,2,4,5 (**82b**, 94%).



83: X = H, Y = OMe (100%);
84: X = Y = F (81%).

Attempts to use this procedure for the synthesis of pentaphenylbenzene from C_6HCl_5 (**2**) and for the synthesis of hexaphenylbenzene from C_6Cl_6 (**5**) failed although the target products were detected by GLC-mass spectrometry in amounts up to 10%. After the introduction of four phenyl groups, the replacement of the chlorine atoms by hydrogen in the intermediates Ph_4C_6HCl and $Ph_4C_6Cl_2$ became the major reaction.

Polychloroarenes containing both electron-donating and electron-withdrawing substituents in the aromatic ring react with phenylboronic acid in the presence of the catalytic system $Pd(OAc)_2$–ligand **46**. Under these conditions, all chlorine atoms were replaced in 3,4-dichloroanisole (**72b**) and isomeric dichloroacetophenones **29**.[125]

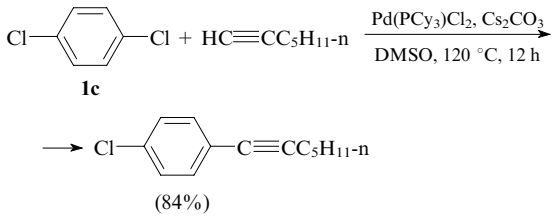


(*a*) $PhB(OH)_2$ (2.5 mol), $Pd(OAc)_2$, **46**, K_3PO_4, PhMe, 90 °C.

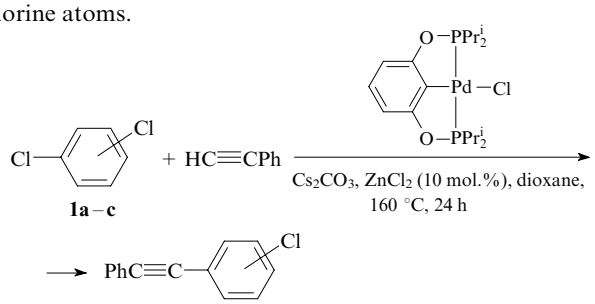
The use of palladium *N*-heterocyclic carbene complexes [prepared *in situ* from $Pd(OAc)_2$ and imidazolium salts][283,288] and the ligand-free method [289] for the cross-coupling of 1,2,4,5-tetrachlorobenzene (**10b**) and hexachlorobenzene (**5**) proved to be less efficient.

3. Reactions of polychloroarenes with terminal acetylenes

The reactions of di- and trichlorobenzenes with terminal acetylenes were carried out.[290–293] The cross-coupling reaction of 1,4-dichlorobenzene (**1c**) with hept-1-yne in the presence of $Pd(PCy_3)_2Cl_2$ affords the monosubstitution product in high yield.[290]

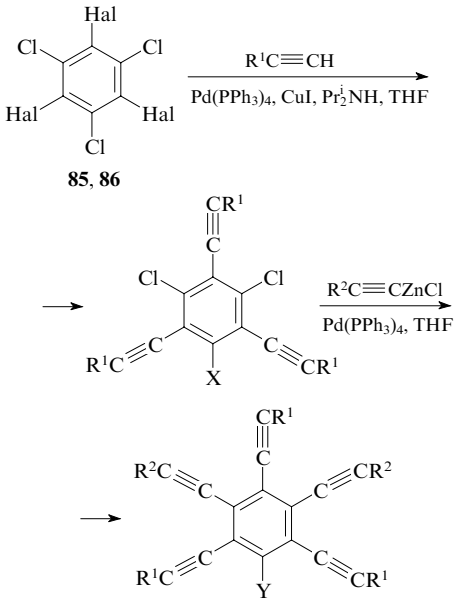


The reaction of isomeric dichlorobenzenes **1a–c** with phenylacetylene in the presence of a pincer palladium complex with additives of $ZnCl_2$ also gives monosubstitution products.[291] Their yields depend on the mutual arrangement of the chlorine atoms.



Isomers: 1,2 (36%), 1,3 (19%), 1,4 (80%).

Unexpected results were obtained in the reactions of alkynes with symmetrical tribromotrichloro- (**85**) and trichlorotriiodobenzenes (**86**).[292,293] For example, only bromine atoms are replaced in the Sonogashira reaction (75 °C, 30 h) of 1,3,5-tribromo-2,4,6-trichlorobenzene (**85**) with trimethylsilylacetylene. It has become possible to introduce six acetylene groups into the aromatic core only with the use of more reactive alkyne zinc derivatives.



Hal = Br (**85**): R^1 = Me_3Si, X = Cl (62%); R^2 = Ph, Y = $C{\equiv}CR^2$ (69%); Hal = I (**86**): R^1 = Ph (33%), R^2 = Me_3Si (51%), X = Y = $C{\equiv}CR^1$.

2,4,6-Trichloro-1,3,5-triiodobenzene (**86**) reacts with phenylacetylene to form 4,6-dichloro-1,2,3,5-tetrakis(phenylethynyl)benzene. To replace the remaining chlorine atoms, the

reaction with trimethylsilylethynylzinc was carried out at high temperature (90 °C) .

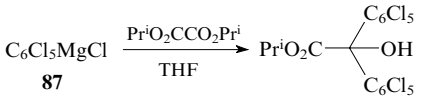
IX. Metallation

1. Grignard reagents based on polychloroarenes: synthesis and reactions with electrophiles

Polychloroarenes react with magnesium to form organomagnesium derivatives. The nature of the solvent is of considerable importance in the synthesis of polychloroarylmagnesium halides. Tetrahydrofuran and other cyclic ethers, such as tetrahydropyran, ethyl tetrahydrofurfuryl ether, 2-ethoxytetrahydropyran and dihydropyran are convenient solvents for this purpose. In these solvents, isomeric 1,3- and 1,4-dichlorobenzenes (**1b**,**c**) form the Grignard reagents in good yields.[294, 295] The reaction of 1,2-dichlorobenzene (**1a**) and highly chlorinated PCA give the target products in low yields because of oligomerisation as the side process. An exception is hexachlorobenzene (**5**), which gives C_6Cl_5MgCl in THF in 77% yield.[294] In diethyl ether, C_6Cl_5MgCl was prepared by slow (over 2 days) addition of 1,2-dibromoethane to a suspension of an excess of magnesium and hexachlorobenzene (**5**) in diethyl ether (the latter compound is very poorly soluble in diethyl ether).[296, 297]

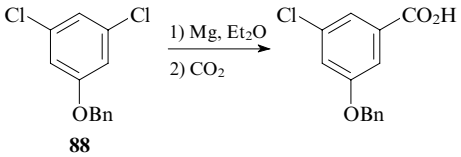
The reactions of these organomagnesium derivatives with a series of electrophiles were studied. For example, the reaction of the Grignard reagent prepared from C_6Cl_6 (**5**) with gaseous CO_2 affords pentachlorobenzoic acid in 77% yield,[296] whereas the treatment of this Grignard reagent with acetic anhydride affords pentachloroacetophenone in 31% yield. These results are in contradiction with the data of the study,[294] where it was noted that C_6Cl_5MgCl does not react with carbon dioxide in THF but reacts with more reactive $SiCl_4$ under analogous conditions.

An α-hydroxy ester was synthesised by the reaction of C_6Cl_5MgCl (**87**) with diisopropyl oxalate in THF (the yield was not reported).[298]



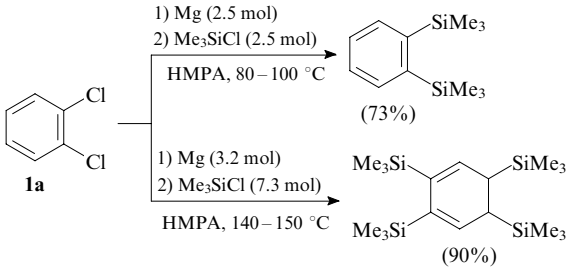
Decachlorobiphenyl (**31**), like hexachlorobenzene (**5**), forms the Grignard reagents in the reactions carried out in the presence of 1,2-dibromoethane.[75] The chlorine atoms at positions 4 and 4′ are only involved in the reaction giving rise to mono- and dimetallated derivatives, and the latter can be transformed into nona- and octachlorobiphenyls by quenching with water (Scheme 2).

The one-pot synthesis of 3-benzyloxy-5-chlorobenzoic acid from 5-benzyloxy-1,3-dichlorobenzene (**88**) *via* the Grignard reagent was documented (the conditions and yields were not reported in detail).[299]

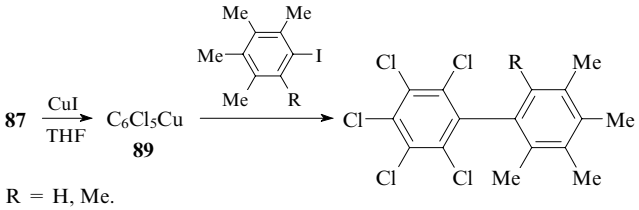


88

Slow (over 50 h) addition of 1,2-dichlorobenzene (**1a**) to a mixture of metallic magnesium and Me_3SiCl in HMPA at 80 – 100 °C resulted in 1,2-bis(trimethylsilyl)benzene as the major product.[300] The reactions of other PCA containing from two to four chlorine atoms proceed analogously. 2,3,5,6-Tetrakis(trimethylsilyl)cyclohexa-1,3-diene was prepared from compound **1a** in high yield with the use of an excess of reagents at higher temperatures (140 – 150 °C).[301]



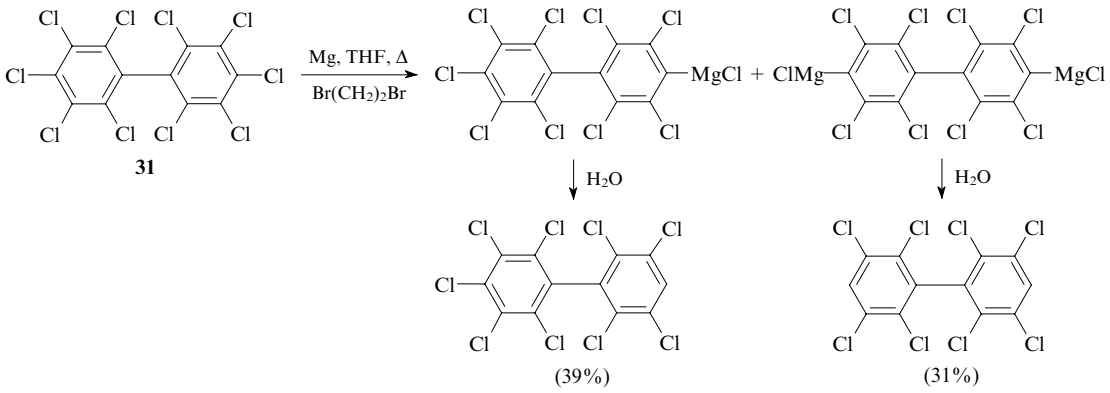
Transmetallation of compound **87** with CuI in THF produces organocopper compound **89**.[302] The corresponding biaryls were obtained in moderate yields (~25%) by the cross-coupling of compound **89** with tetra- and pentamethylphenyl iodides.

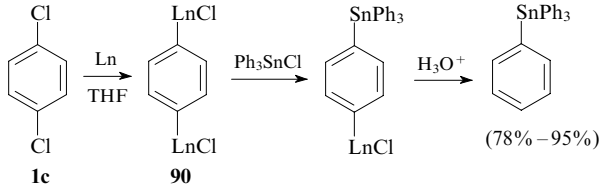


R = H, Me.

Organometallic reagents **90** analogous to the Grignard reagents were prepared by the reaction of 1,4-dichlorobenzene (**1c**) with ytterbium and samarium.[303] Their subsequent treatment with triphenyltin chloride and water in an acidic medium afforded tetraphenyltin in high yield.

Scheme 2



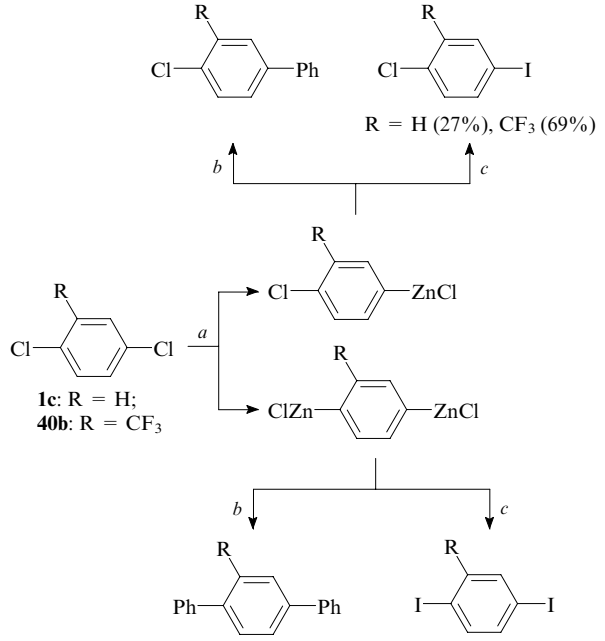


1c **90**

Ln = Yb, Sm.

Organozinc derivatives of PCA were synthesised by electrolysis of 1,4-dichlorobenzene (**1c**) and 2,5-dichloro-1-trifluoromethylbenzenes (**40b**). The reactions were carried out in an undivided cell with a sacrificial zinc anode in a MeCN–pyridine mixture (9 : 1) in the presence of $CoCl_2$ and $ZnBr_2$ as the catalysts.[304] The resulting organometallic compounds were transformed into the corresponding iodobenzenes or cross-coupling products with PhI in the presence of $Pd(PPh_3)_2Cl_2$ (Scheme 3).

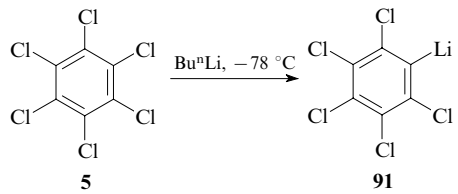
Scheme 3



(*a*) e^- (2 F mol^{-1}); $CoCl_2$ (cat), $ZnBr_2$ (cat), Zn anode, MeCN–PyH (9 : 1); (*b*) PhI, $Pd(PPh_3)_4Cl_2$; (*c*) I_2.

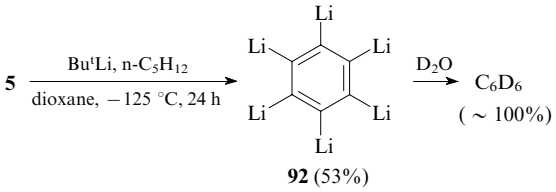
2. Synthesis and reactions of organolithium derivatives of polychloroarenes

Unlike aryl bromides and iodides, monochloroarenes do not, as a rule, react with alkyllithium reagents. However, the mutual activation of chlorine atoms in PCA favours the reactions with these organometallic compounds. For example, hexachlorobenzene (**5**) reacts with Bu^nLi in a THF–hexane mixture at −78 °C to form pentachlorophenyllithium (**91**).[305] In diethyl ether, this reaction proceeds at −10 °C.[306]



5 **91**

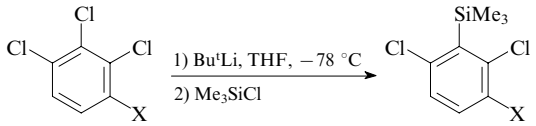
The reaction of hexachlorobenzene (**5**) with an excess of Bu^nLi gives a product, in which two Cl atoms in the *para* positions are replaced.[307] Lithiation with *tert*-butyllithium at −125 °C allows the replacement of all six Cl atoms. Upon treatment with D_2O, the resulting hexalithium derivative **92** gives benzene-d_6 in quantitative yield.[308]



92 (53%)

In polychloroarenes containing aromatic C—H bonds, the hydrogen atom can selectively be replaced by lithium. For example, the reaction of 1,3,5-trichlorobenzene (**9a**) with Bu^nLi produces symmetrical trilithiotrichlorobenzene,[307] whereas the reaction of 1,2,4,5-tetrachlorobenzene (**10b**) results in the replacement of one or two hydrogen atoms depending on the amount of the lithiating reagent.[309] The reaction of pentachlorobenzene (**2**) with Bu^nLi also results in the replacement of the H atom by Li.[307, 309]

Under the lithiation conditions, 1,2,3-trichloro- (**9c**) and 1,2,3,4-tetrachlorobenzenes (**10a**) give mixtures of dechlorination and deprotonation products.[307] High chemoselectivity was observed in the reaction with Bu^tLi. Thus treatment of the lithiation products with chlorotrimethylsilane affords the corresponding trimethylsilylarenes containing one less chlorine atom.

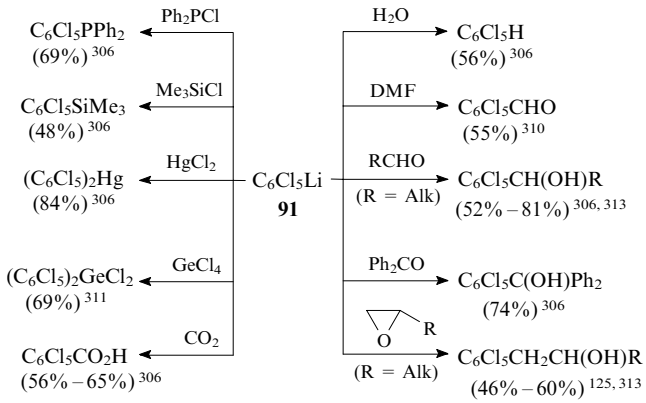


9c, **10a**

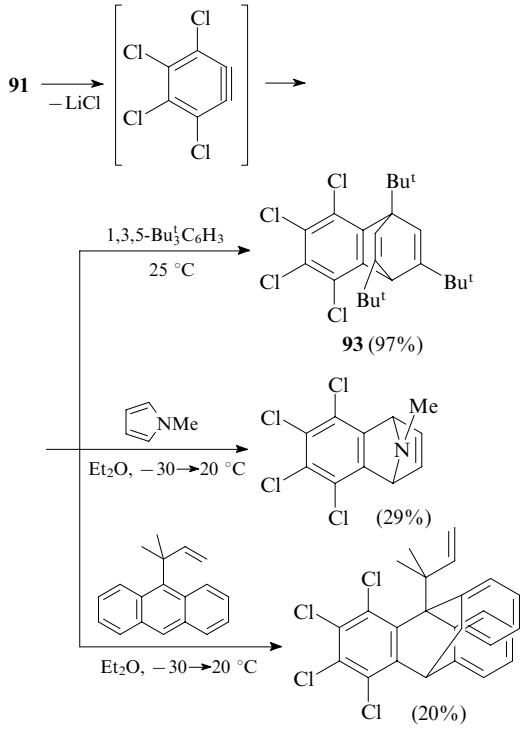
X = H (**9c**), Cl (**10a**).

The lithiation of decachlorobiphenyl (**31**), like the reaction with Mg, proceeds regioselectively at positions 4 and 4′.[75] Quenching of the lithiation products with water affords nona- and octachlorobiphenyls, and their reactions with dimethyl sulfate produce the corresponding 4-methyl- and 4,4′-dimethylperchlorobiphenyls.

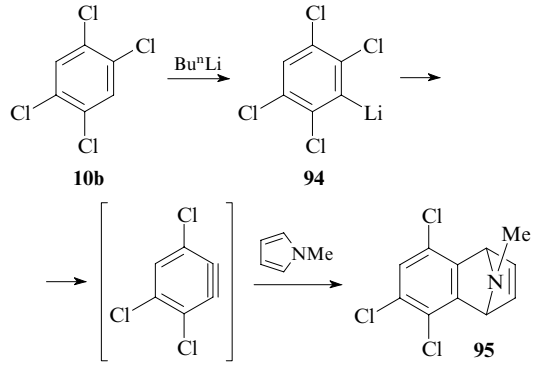
Lithium derivatives of PCA are valuable intermediates in the synthesis of various heteroorganic and functionalised arene derivatives.[125, 306, 310–313] Selected reactions of pentachlorophenyllithium (**91**) with electrophiles with references to the original papers are given below.



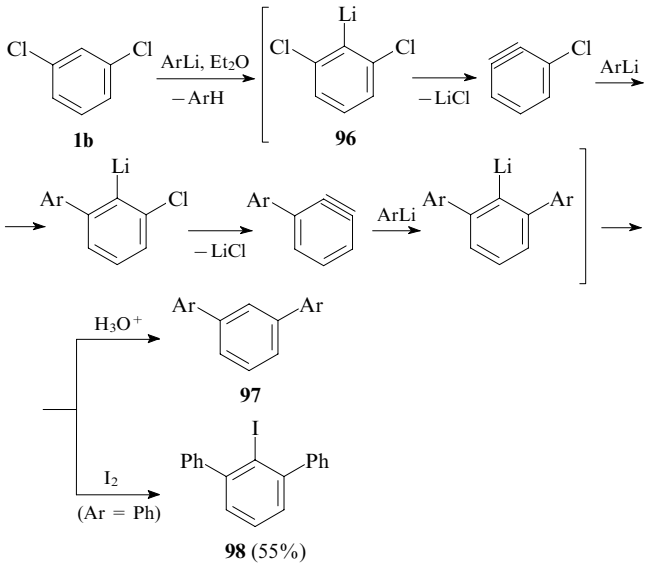
Although polychlorophenyllithium derivatives are rather stable (compound **91** is stable in diethyl ether at −10 °C), in some cases these compounds eliminate LiCl to form the corresponding dehydrobenzenes.[314] For example, the reaction of compound **91** with 1,3,5-tri(*tert*-butyl)benzene affords the cycloaddition product **93**.[305] The reactions of C_6Cl_5Li (**91**) with *N*-methylpyrrole[315] and substituted anthracene proceed[316] analogously.



2,3,5,6-Tetrachlorophenyllithium (**94**) derived from 1,2,4,5-tetrachlorobenzene (**10b**) can be transformed into 3,4,6-trichlorobenzyne, which was detected judging from the formation of the cycloaddition product with *N*-methylpyrrole, *viz*., compound **95**.[315]

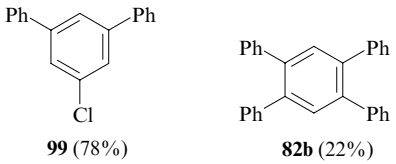


The reactions of 1,3-dichlorobenzene (**1b**) with an excess of ArLi were found[317] to proceed *via* 3-chlorobenzyne, 1,3-dichloro-2-lithiobenzene (**96**) being a precursor of the latter. These reactions afford ultimately *m*-terphenyls **97**. The reaction of compound **1b** with phenyllithium followed by quenching of the reaction mixture with molecular iodine affords the iodo derivative of *m*-terphenyl **98**.

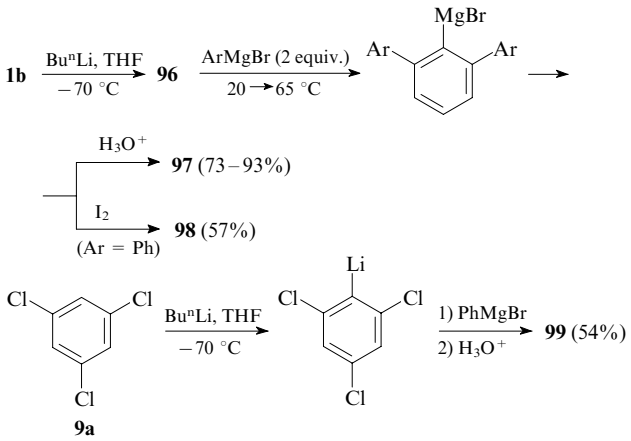


Ar = Ph (73%), 4-PhC_6H_4 (65%), 2-$MeOC_6H_4$ (93%), 4-$MeOC_6H_4$ (80%).

Compounds **99** and **82b** were prepared analogously from 1,3,5-trichloro- (**9a**) and 1,2,4,5-tetrachlorobenzenes (**10b**), respectively, by the reactions with PhLi.[317]

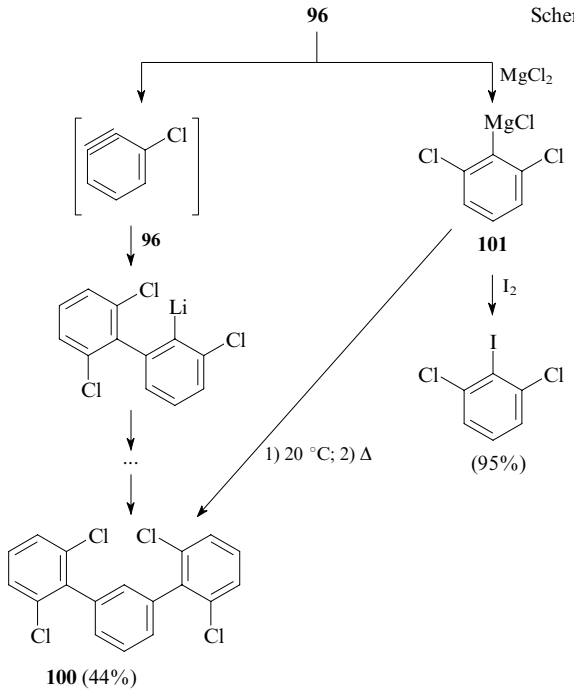


An efficient procedure for the synthesis of *m*-terphenyls is based on the lithiation of polychlorobenzenes **1b** or **9a** with n-butyllithium followed by treatment with ArMgBr. The mechanism of these transformations is analogous to that of the above-described reactions.[317]

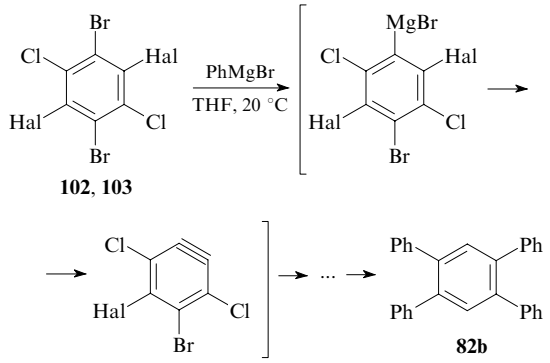


1,3-Dichloro-2-lithiobenzene (**96**) gives biphenyl and *m*-terphenyl derivatives as a result of the reaction with 3-chlorobenzyne generated *in situ*.[318] The yield of 2,2′,6,6′-tetrachloro-*m*-terphenyl (**100**) was increased to 44% by transforming the lithium derivative into organomagnesium compound **101**, which reacts more smoothly (Scheme 4).[317]

Scheme 4



The reactions of 1,2,4,5-tertrabromodichloro- (**102**) and 1,4-dibromotetrachlorobenzenes (**103**) with an excess of PhMgBr also proceed *via* the dihydrobenzene derivative to give 1,2,4,5-tetraphenylbenzene (**82b**).[319]



Hal = Br (**102**, 65%); Cl (**103**, 36%).

* * *

As can be seen from the above data, polychloroarenes can serve as multifunctional synthons for the preparation of various classes of organic and heteroorganic compounds. Nucleophilic aromatic substitution and metallation reactions of PCA have been studied in sufficient detail, whereas transition metal-catalysed cross-coupling reactions have received less attention. A serious progress in the metal complex catalysis achieved in the past years allows the expectation of the development of new efficient methods for transformations of PCA into valuable aromatic compounds. Some of new catalytic systems have been successfully tested in the cross-coupling reactions of dichlorobenzenes and highly chlorinated arenes.

Investigations of the reactivity of PCA are of applied importance. The results of these investigations can substantially contribute to the solution of the problem of chemical utilisation of toxic organochlorine compounds, such as pesticides, waste transformer oil (see, for example, Refs 320–322), dioxins, *etc.*, including the processing of these compounds into new products and materials with practically useful properties.

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