NEW APPROACHES TO AROMATIC FLUORINATIONS

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CLIVE PEMBERTON

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Chemistry Department,

Imperial College,

London, SW7 2AZ.

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To My Parents

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ABSTRACT

Recent developments in nucleophilic substitutions at the annular carbon atoms of six membered carbocyclic aromatic molecules have been reviewed.

Various approaches to aromatic fluorination were investigated using fluoride ion with a view to possible ^{18}F synthetic applications. These included the use of aryne intermediates generated from tosylates, the introduction of a chromium tricarbonyl unit to activate the aromatic ring to nucleophilic attack and Pd^{0} or Pd^{II} catalysed halogen exchanges. Attempts were made to generate aryl cations by reacting aryl azidoformates with nitrosonium salts. Nickel (0) catalysed decarbonylations of aroyl fluorides were also investigated. All these proposed methods of aromatic fluorination proved unsuccessful.

Fluorobenzene was obtained in 53% yield when phenyl mercuric chloride was reacted with antimony pentafluoride. The preliminary results from the reactions with other aryl mercurials indicated that aryl fluorides were generally produced but often in low yields.

CONTENTS

NEW APPROACHES TO AROMATIC FLUORINATIONS

RECENT DEVELOPMENTS IN AROMATIC NUCLEOPHILIC SUBSTITUTION

INTRODUCTION

This review covers nucleophilic substitutions at the annular carbon atoms of six membered carbocyclic aromatic molecules. Emphasis is placed on the more interesting developments which have taken place since Zoltewicz's[1] review in 1974. Reactions which produce overall apparent nucleophilic aromatic substitution, such as oxidative addition - reductive elimination reactions,[2] are included.

The classical methods of aromatic nucleophilic substitution involving S_NAr,[3] aryne[4] and arenediazonium[5] intermediates have been discussed in detail elsewhere and are not covered in this review.

The subject matter is organised into three main sections. Reactions which involve π-bonded and σ-bonded aryl complexes are discussed in sections one and two, respectively. Other methods of substitution are covered in section three.

Technical developments (e.g., the use of crown ethers[6] and phase transfer catalysts[7]), photosubstitutions,[8] copper catalysed substitutions[9] and the ortho-alkylation of amines via their N-arylazasulphonium salts[10] are not included.

NUCLEOPHILIC ADDITION AND SUBSTITUTION REACTIONS IN η^6-ARENE COMPLEXES[11]

Nucleophilic substitutions are facilitated by the presence of electron withdrawing groups and those activating groups which can easily be removed have possible synthetic applications. Activating groups which π-bond to the aromatic ring are discussed in this section. Tricarbonyl η^5-(cyclohexadienylium)iron(0) cations are also included as they are potential aryl cation equivalents.[12]

1) TRICARBONYL η^6-(ARENE)CHROMIUM(0) COMPOUNDS [13]

Preparation

Tricarbonyl η^6-(arene)chromium(0) complexes are generally prepared by heating chromium hexacarbonyl with an excess of the aromatic substrate in an inert solvent under an atmosphere of nitrogen.[14]

An alternative method involves the use of reactive intermediates such as (tricarbonyl)tris(acetonitrile)chromium(0).[15] The advantages of this approach over the direct method of complexation are that the reactions are faster and require milder conditions.

Removal of the Chromium Tricarbonyl Group

The chromium tricarbonyl group can be removed by oxidising agents such as manganese dioxide[16] and ceric ammonium sulphate.[17] However, more selective methods of removal are available involving either irradiation in the presence of air[18] or treatment with iodine.[19]

A decomplexation method has been reported which enables the chromium tricarbonyl unit to be recovered;[20] this involved refluxing the tricarbonyl η^6-(arene)chromium(0) complex with a ten-fold excess of pyridine. (Tricarbonyl)tris(pyridine)chromium(0) was produced in high yields from these reactions and could be usefully recycled to prepare tricarbonyl η^6-(arene)chromium(0) compounds.

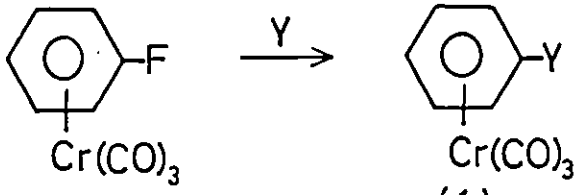
Nucleophilic Substitution and Addition Reactions

a) Displacement of Halide

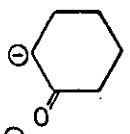
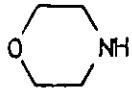
Nicholls and Whiting[16] found that the chloro group of tricarbonyl η^6-(chlorobenzene)chromium(0) could be replaced by methoxide ion to produce the η^6-(anisole) complex under conditions whereby chlorobenzene was unreactive. The aromatic ring was activated to nucleophilic substitution by the electron withdrawing power of the chromium tricarbonyl group which pK_a measurements showed to be comparable to that of a p-nitro substituent.

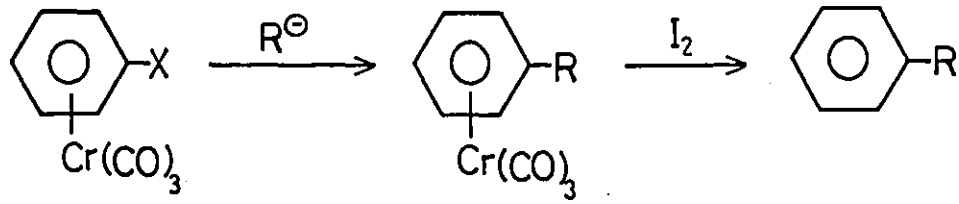
Subsequent investigations demonstrated that the halo group of tricarbonyl η^6-(haloarene)chromium(0) complexes could be substituted by various types of nucleophile (Table 1).[21,22]

TABLE 1 Reaction of tricarbonyl η^6-(fluorobenzene)chromium(0) with nucleophiles.



(1)

Y	Yield (1) (%)	Reference
$^{\ominus}O$-tBu	81	21
$^{\ominus}OCH_2Ph$	99	21
$^{\ominus}SCH_2Ph$	95	21
$^{\ominus}CH_2COCH_3$	19	21
	37	21
$^{\ominus}C{\equiv}CPh$	54	21
$PhCH_2NH_2$	87	22
	85	22



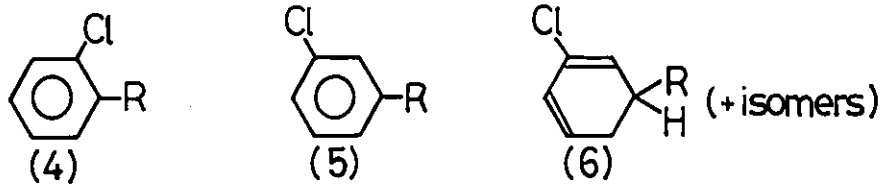
(2) (3)

SCHEME 1

Semmelhack[19] has examined the displacement of halide by carbanions (Scheme 1). Reactive tertiary carbanions and highly stabilised anions produced high yields of (3), whereas secondary and primary carbanions gave poor yields presumably because of abstraction of the relatively acidic benzylic protons in (2) by the reacting carbanion. The lithium salts of 1,3-dithiane, 2-methyl-1,3-dithiane, t-butyl acetate, acetophenone and acetonitrile all failed to give significant quantities of the desired phenylation products. The order of reactivity of the η^6-haloarene complexes with carbanion was found to be F > Cℓ >> I in accord with the normally observed rate determining step in nucleophilic aromatic substitution.

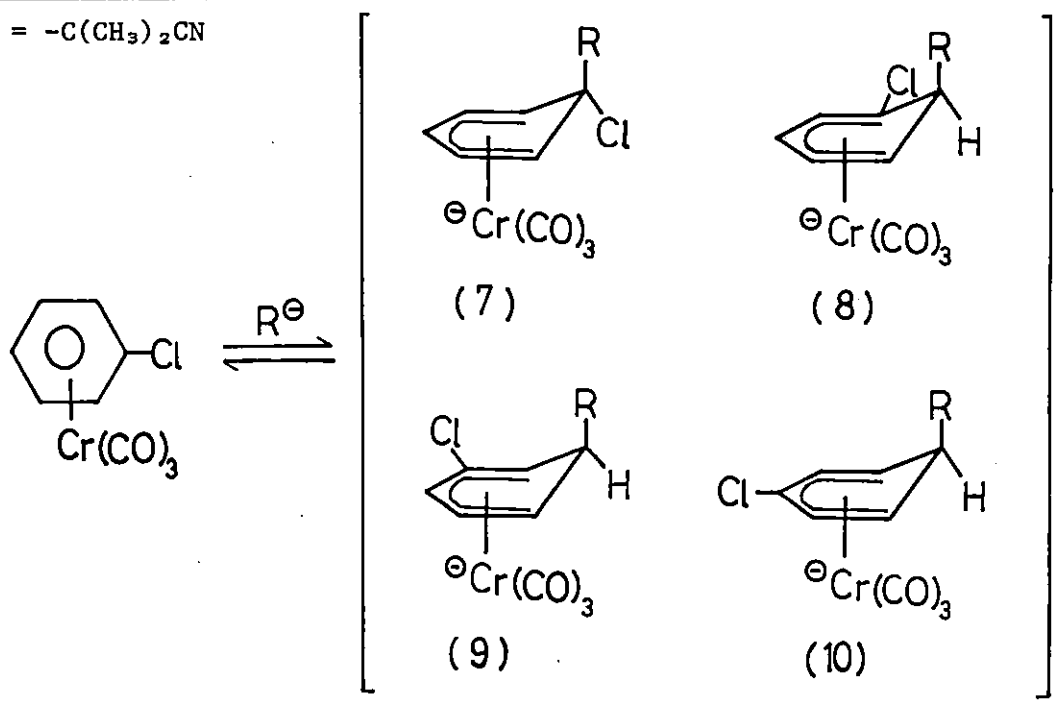
The results of quenching experiments, carried out during the course of the reaction between tricarbonyl η^6-(chlorobenzene)chromium(0) and isobutyronitrile anion (Table 2),[23] show that the reaction can not be considered to proceed by a simple S_NAr mechanism. Instead, it was postulated that the carbanion could attack all the arene sites producing intermediates (7)-(10) (Scheme 2). Nucleophilic attack at the less hindered exo-face was proposed by analogy with the findings of a crystallographic study on the addition product obtained from reaction of phenyl lithium with a cobalticinium cation.[24] X-ray analysis has subsequently confirmed the 6-exo position of the attacking nucleophile in η^5-(cyclohexadienyl)chromium(0) complexes.[25]

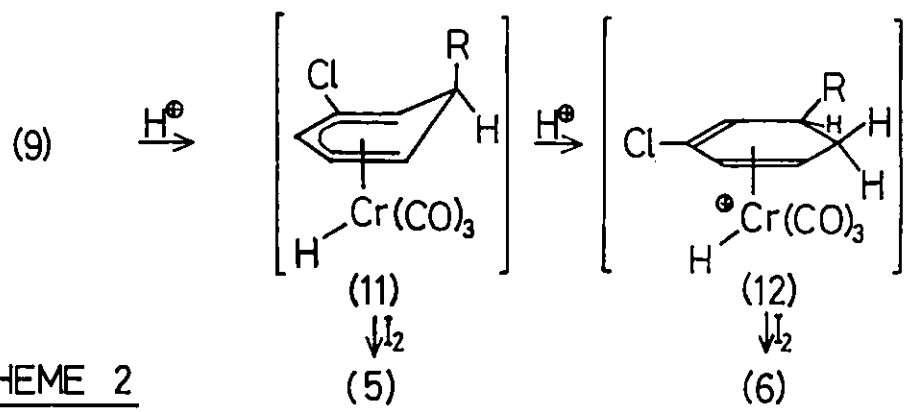
TABLE 2[23] Interruption of the reaction of tricarbonyl η^6-(chlorobenzene)-chromium(0) with isobutyronitrile anion.



Reaction Conditions	Quenching Sequence	PhCℓ	PhR	(4)	(5)	(6)
20 hr, 25°C	a) H_2O, 25°C b) I_2	0	85	0	0	0
3 hr, 0°C	a) H_2O, 25°C b) I_2	18	40	10	2	12
3 hr, 0°C	a) CF_3CO_2H, -78°C b) I_2	0	39	19	4	22
3 hr, 0°C	a) I_2	0	19	56	12	0

R = $-C(CH_3)_2CN$

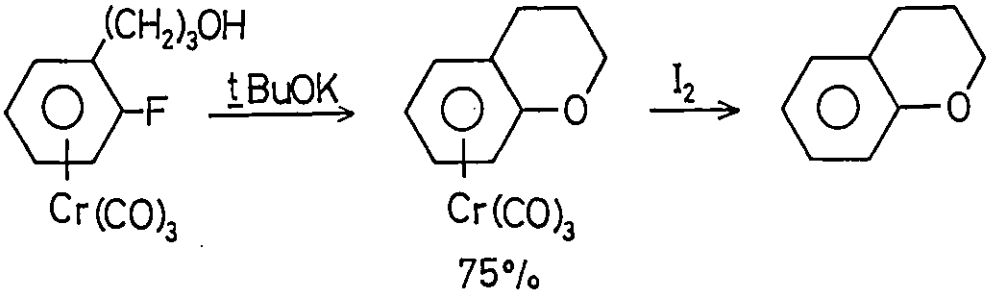




SCHEME 2

The halo substitution product (3) was formed by irreversible loss of chloride ion from (7) followed by cleavage of the chromium tricarbonyl group with iodine. Protonation of intermediate (9) would be expected to lead to the formation of (11) and (12), which upon treatment with iodine would give (5) and (6), respectively. Similarly, quenching of (8) would produce (4) and an isomer of (6). The intermediacy of (10) was discounted because no p-disubstituted chlorobenzenes were detected upon quenching.

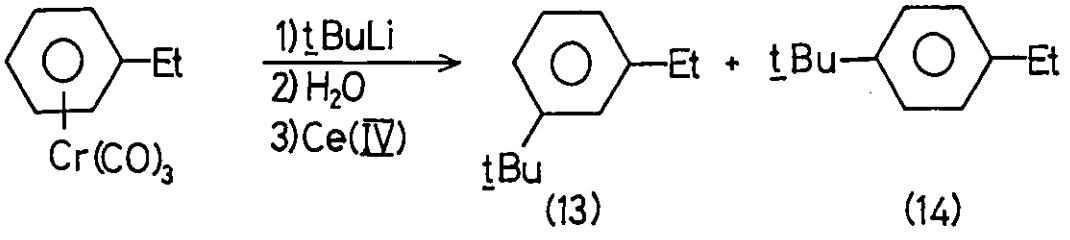
Chromans have been prepared from chromium tricarbonyl complexed aryl halides by an intramolecular nucleophilic substitution (Scheme 3).[26]



SCHEME 3

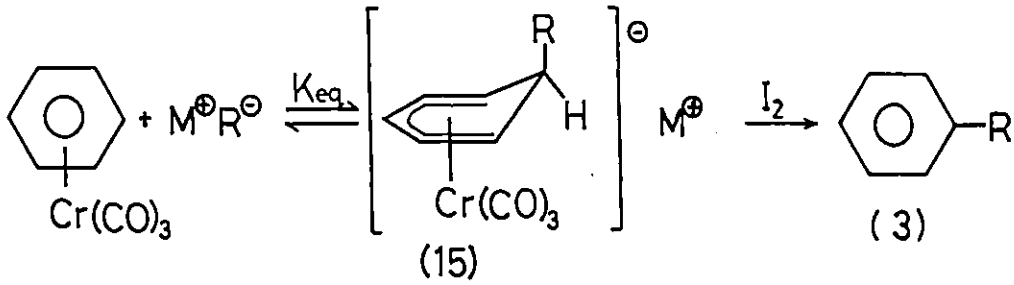
b) Displacement of Hydride

Trahanovsky and Card[17] found that nucleophilic displacement of hydride occurred when tricarbonyl η^6-(ethylbenzene)chromium(0) was reacted with t-butyl lithium; (13) and (14) were produced upon work up in yields of 32% and 9%, respectively (Scheme 4).

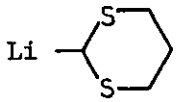
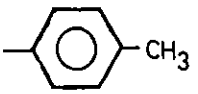


SCHEME 4

TABLE 3 [27] Reaction of tricarbonyl η^6-(benzene)chromium(0) with carbanions.



(15) (3)

MR	Yield (3) (%)
$LiC(CH_3)_2CN$	94[a]
$LiCH_2CN$	68[a]
	93[a]
$LiC(CH_3)_3$	97[a]
	71[a]
$LiC(CH_3)_2CO_2$-tBu	≃ 10[a]
$KC(CH_3)_2CO_2$-tBu	88[a]
$LiC(CH_3)_2CO_2$-tBu	91[b]
$LiCH_2CO_2$-tBu	87[b]
$LiCH(CH_3)CO_2$-tBu	88[b]
$LiCH_2\overset{O}{\overset{\|}{C}}Ph$	< 5[a]

[a] THF as reaction medium; [b] THF/HMPA 1:1 as reaction medium

Semmelhack, et al.[27-29] have studied hydride displacements from tricarbonyl η^6-(arene)chromium(0) compounds. They found that very reactive organolithium reagents produced high yields of substituted product, while poor yields were obtained with the lithium enolates of esters and ketones under mild conditions in THF (Table 3).[27] However, the use of the potassium cation or a polar, aprotic solvent (e.g., HMPA)

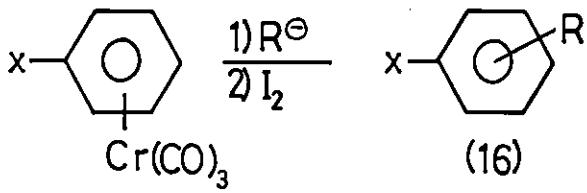
enabled significant amounts of phenylated product to be obtained with ester enolates but, unfortunately, these modifications had little effect with ketone enolates. The potassium cation and the polar, aprotic solvent are thought to have the effect of raising K_{eq} and thus providing a higher concentration of intermediate (15) prior to quenching. Primary and secondary ester enolates were found to participate as well as tertiary ester enolates under the right conditions, which is in contrast to the findings with tricarbonyl η^6-(chlorobenzene)chromium(0).[19]

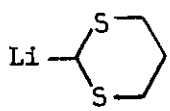
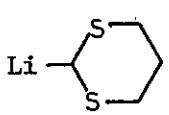
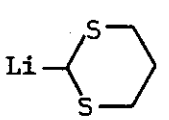
The effect of ring substituents on the regio-selectivity of hydride displacements has been investigated (Table 4).[28,29] The chromium tricarbonyl group is unlikely to influence site selectivity itself as it is more or less symmetrically disposed with respect to the arene ring atoms and therefore presumably activates each of the annular carbons equally.

The product mixtures obtained from the carbanion reactions with tricarbonyl η^6-(arene)chromium(0) complexes are the result of kinetic control. The regio-selectivity of the hydride displacement can be rationalised in most cases by charge density arguments. Strong resonance donors (e.g., -OMe, $-NMe_2$) are <u>meta</u>-directing, usually with > 90% selectivity, and powerful electron withdrawing groups (e.g., $-CF_3$) favour attack at the <u>para</u>-position.

Steric effects play an important role in determining the selectivity of hydride displacements in alkyl substituted η^6-(arene) complexes. <u>Ortho</u>- and <u>meta</u>-substitution occurred in the η^6-(toluene) complex with <u>meta</u>-substitution predominating in the case of bulky anions. The bulkier the alkyl substituent the greater was the tendency for <u>para</u>-substitution.

TABLE 4 Reaction of tricarbonyl η^6-(arene)chromium(0) with carbanions.



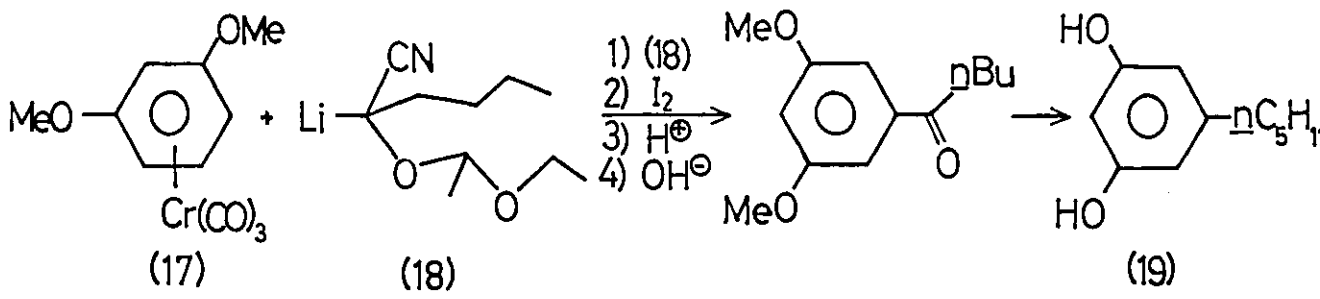
X	MR	Product Mixture o	m	p	Combined Yield (16) (%)	Reference
Me	$LiCH_2CN$	35	63	2	88	28
Me	$LiC(CH_3)_2CN$	1	97	2	86	28
Me	$LiCH_2CO_2$-tBu	28	72	0	89	28
Me		52	46	2	94	28
Et	$LiC(CN)(OR_1)CH_3$	0	94	6	89	29
tBu	$LiC(CN)(OR_1)CH_3$	0	35	65	85	29
OMe	$LiCH_2CN$	3	97	0	38	28
OMe	$LiC(CH_3)_2CN$	3	97	0	93	28
OMe	$LiCH_2CO_2$-tBu	6	94	0	86	28
OMe		10	90	0	35	28
Cl	$LiC(CH_3)_2CN$	10	89	1	84	29
Cl	$LiCH_2CO_2$-tBu	54	45	1	98	29
Cl		46	53	1	56	29
$Si(CH_3)_3$	$LiC(CH_3)_2CN$	0	2	98	65	29
$N(CH_3)_2$	$LiC(CH_3)_2CN$	1	99	0	92	29
CF_3	$LiC(CN)(OR_1)CH_3$	0	30	70	33	29

R_1 = $-CH(OEt)CH_3$

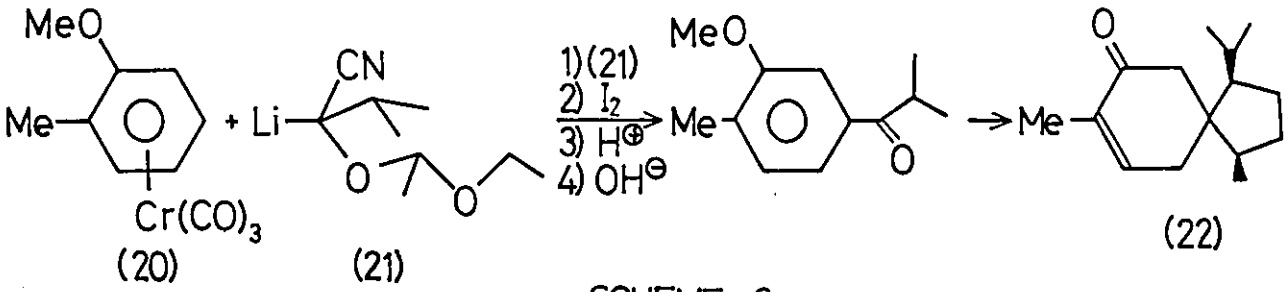
The fact that the η^6-(toluene) complex did not show similar reactivity at the ortho- and para- positions, which would be expected by the usual resonance arguments, ruled out a simple charge density explanation. It has been suggested that the regio-selectivity of attack may be influenced by the conformation of the chromium tricarbonyl unit.[30] However, it should be emphasised that a good predictive understanding of the selectivity is yet to be reported.

The selectivity of methoxy substituents against para-substitution was highlighted by the reaction of tricarbonyl η^6-(1,2-dimethoxybenzene) chromium(0) with 2-lithio-2-cyanopropane, which gave the 1,2,3-isomer in 85% yield despite the sterically demanding nature of the anion.[28]

Several examples of the application of chromium tricarbonyl activation to synthetic problems have been reported. The reaction of tricarbonyl η^6-(1,3-dimethoxybenzene)chromium(0) (17) with the cyanohydrin acetal anion (18) was a key step in the synthesis of olivetol (19), addition occurring at the position meta- to the two methoxy substituents (Scheme 5).[28] Similarly, the synthesis of acorenone (22) involved the addition of the cyanohydrin acetal anion (21) to the less hindered position meta- to the methoxy group in tricarbonyl η^6-(2-methylanisole)chromium(0) (20) (Scheme 6).[31]

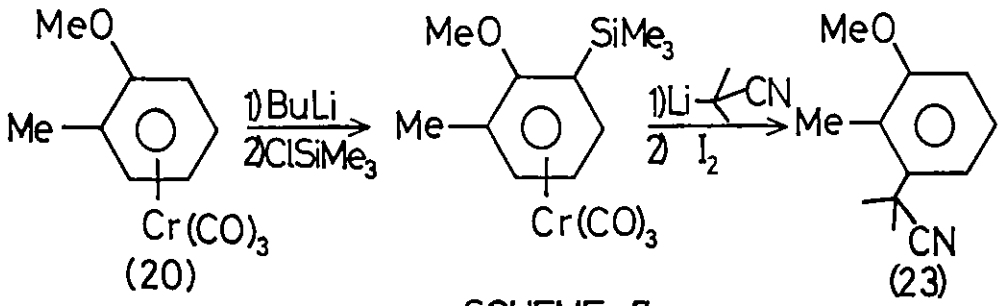


SCHEME 5



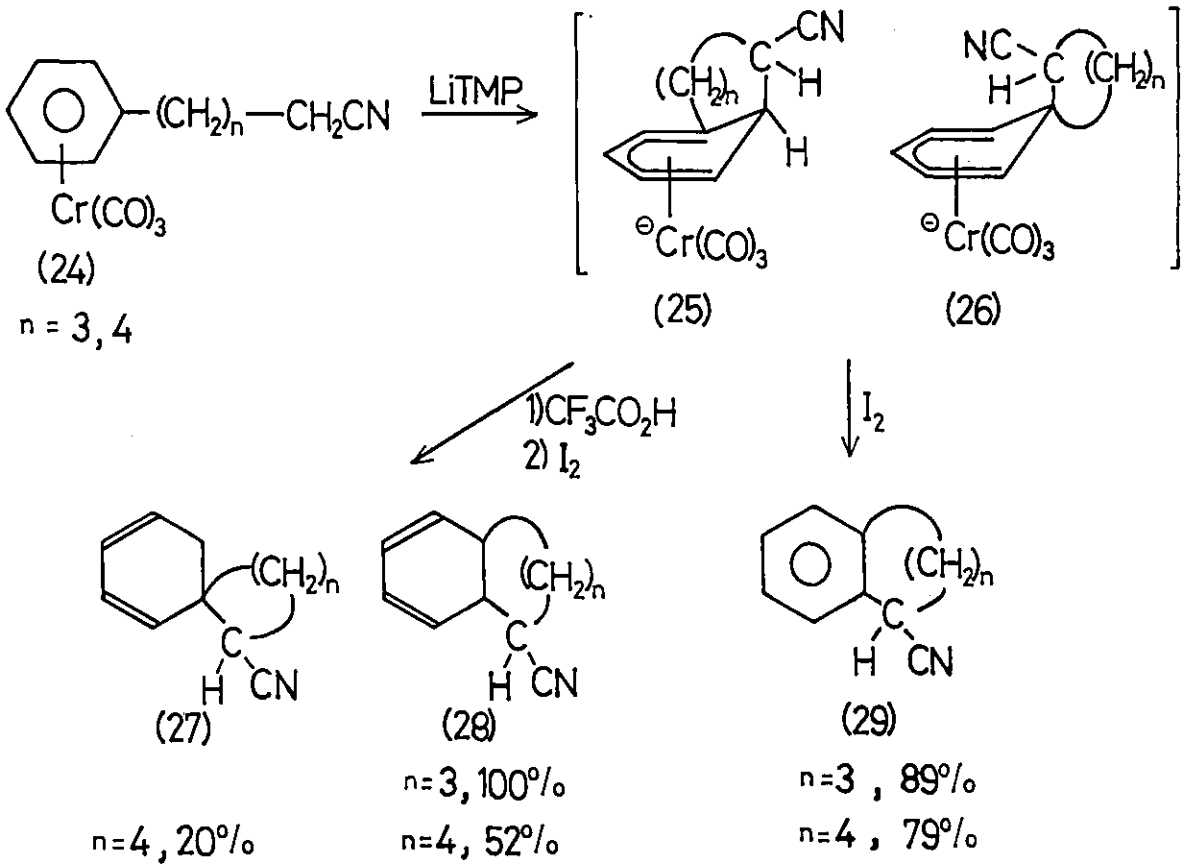
SCHEME 6

It was shown that the selectivity of attack in complex (20) could be altered through metallation, silylation and then addition (Scheme 7).[13] Proto-desilylation occurred spontaneously during the oxidation step and isomer (23) was formed in high purity due to the <u>para</u>-directing effect of the silyl substituent.



SCHEME 7

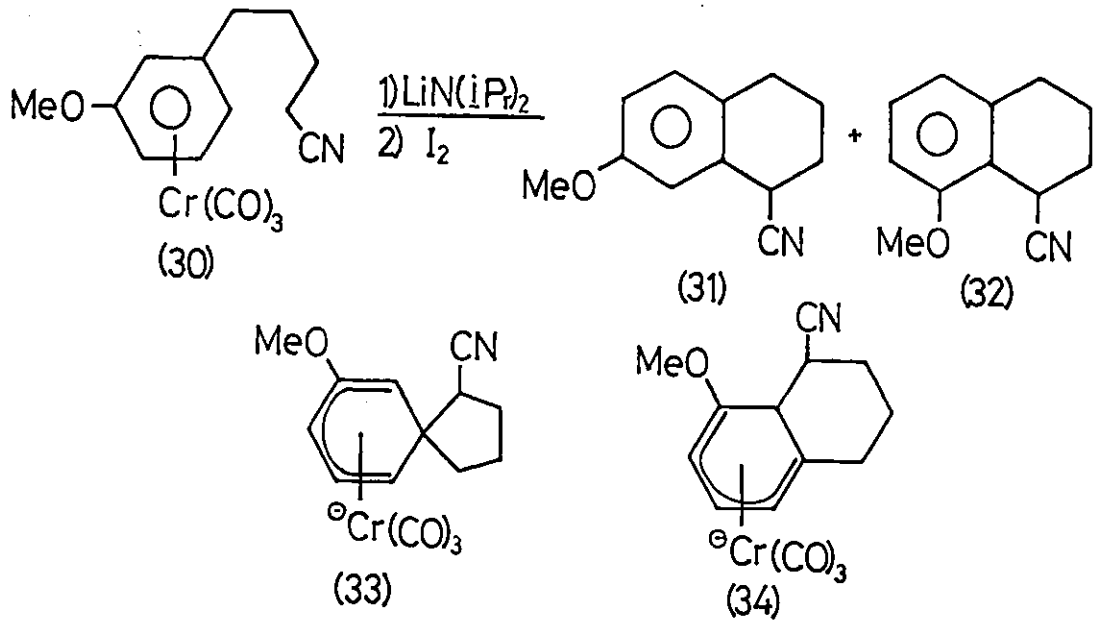
Nitrile stabilised anions produced from the tricarbonyl η^6-(arene) chromium(0) compounds (24; n = 3,4) undergo smooth intramolecular cyclisations (Scheme 8).[32] The fused (25) and spirocyclic (26) species were considered reasonable intermediates in these reactions. However, the absence of any spirocyclic product (27; n = 3) on acid quenching of the reaction of complex (24; n = 3) suggested that (25; n = 3) was the exclusive reaction intermediate for this substrate.



SCHEME 8

The site of ring closure in complex (24; n = 4) was found to depend on the mode of quenching, the reaction times and the temperatures used. The fused ring isomer (29; n = 4) was obtained in high yields when the reaction was carried out at -78°C for 30 mins. with oxidative quenching. Longer reaction times and higher temperatures gave lower yields with substantial amounts of polymeric material being formed. Acid quenching produced a mixture of the olefins (27; n = 4) and (28; n = 4) under all reaction conditions with the proportion of (27; n = 4) increasing at longer reaction times and higher temperatures. This can be explained by the intermediate (25; n = 4) being formed as the kinetic product which slowly equilibrates via a 1,2-carbon shift to the thermodynamically more favoured product (26; n = 4).

Analogues of (24), where the nitrile unit was replaced by an ester group, failed to give intramolecular addition products, reacting instead by intermolecular attack of the enolate anion on an arene ligand.



SCHEME 9

A mixture of the 1-cyanotetralin isomers (31; 54%) and (32; 36%) was obtained when complex (30) was treated with lithium diisopropylamide followed by oxidative quenching (Scheme 9). The formation of isomer (31) can be rationalised by a 1,2-alkyl shift in the spirocyclic intermediate (33). Isomer (32) could arise either from a 1,2-cyanoalkyl migration in (33) or by direct oxidative quenching of the fused ring intermediate (34).

2) π-BONDED IRON COMPLEXES

I) η^6-(Arene)-η^5-(Cyclopentadienyl)Iron(II) Cations [33]

Preparation

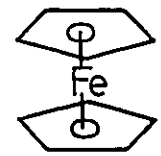
A general method for preparing η^6-(arene)-η^5-(cyclopentadienyl)iron(II) cation complexes [34] involves a Lewis acid catalysed cleavage of ferrocene in the presence of suitable aromatic substrates. In a typical reaction

ferrocene, aluminium trichloride, aluminium and arene (1:2:1: excess) are heated together at 80-165°C for 3-5 hrs, a solvent being used in the case of solid arenes. The aluminium trichloride complexes with the electron-rich cyclopentadienyl ring. The carbon-iron bond is therefore weakened and can either break unimolecularly to give an essentially free C_p-Fe^+ unit and a cyclopentadienyl anion or undergo nucleophilic attack by an aromatic substrate to form an η^6-(arene)-η^5-(cyclopentadienyl)iron(II) cation directly.

Poor yields of the η^6-(arene) complexes are often obtained because a large proportion of the ferrocene is unavailable for reaction due to bonding between aluminium trichloride and iron.

A reactivity sequence has been established for substituted ferrocenes (Scheme 10).[33]

$$FcCOR > FcR_2 \triangleq FcR > FcH \gg Fc(COR)_2$$

Fc = 

SCHEME 10

Monoacylferrocenes react with an additional mole of aluminium trichloride at the carbonyl group to form an α-ferrocenyl carbenium ion, thus strengthening the carbon to metal bond of this ligand and enhancing the cleavage of the carbon-metal bond of the unsubstituted cyclopentadienyl ring.

Cleavage of the η^6-(Arene)Iron Bond

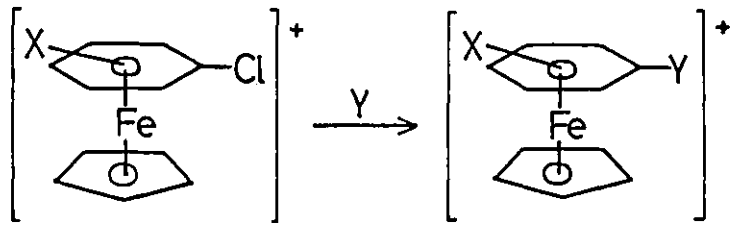
Nesmeyanov, et al.[35] observed that the decomposition of η^6-(arene)-η^5-(cyclopentadienyl)iron(II) cations in solution was accelerated by heat and light. Subsequent investigation showed that uv irradiation of the complexes in THF gave the free aromatic hydrocarbon, ferrocene and bis(tetrafluoroborate)iron(II).

Nucleophilic Substitution and Addition Reactions

a) Displacement of Halide

The chloro group in η^6-(chloroarene)-η^5-(cyclopentadienyl)iron(II) cations has been replaced by a variety of nucleophiles under mild conditions (Table 5).[36-38]

TABLE 5 Reaction of η^6-(chloroarene)-η^5-(cyclopentadienyl)iron(II) cations with nucleophiles.



(35)

X	Y	Yield (35) (%)	Reference
H	$^{\ominus}$OEt	72	36
H	$^{\ominus}$SPh	88	36
4-CO_2H	$^{\ominus}$OEt	68	37
4-CO_2H	$^{\ominus}$SPh	51	37
4-CH_3	NH_3	60	38
4-CH_3	$^{\ominus}$OEt	47	38
4-CH_3	$^{\ominus}$CN	45	38
3-CH_3	$^{\ominus}$SPh	43	38

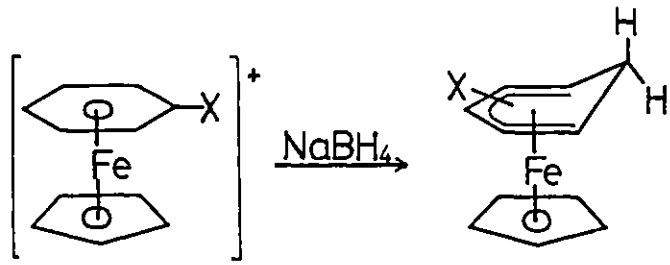
b) Displacement of Hydride

Hydride substitution in η^6-(arene)-η^5-(cyclopentadienyl)iron(II) cations occurs by a two-step process involving initial nucleophilic addition to form the 6-exo substituted η^5-(cyclohexadienyl) complex followed by abstraction of the 6-endo hydrogen.[39]

i) Nucleophilic Addition

Hydride ion was found to react with the η^6-(benzene)-η^5-(cyclopentadienyl)iron(II) cation to produce the η^5-(cyclohexadienyl)-η^5-(cyclopentadienyl)iron(II) complex.[40] The regio-selectivity of hydride attack has been investigated with various substrates (Table 6).[41]

TABLE 6 [41] Site reactivities for hydride addition reactions of η^6-(arene)-η^5-(cyclopentadienyl)iron(II) cations.



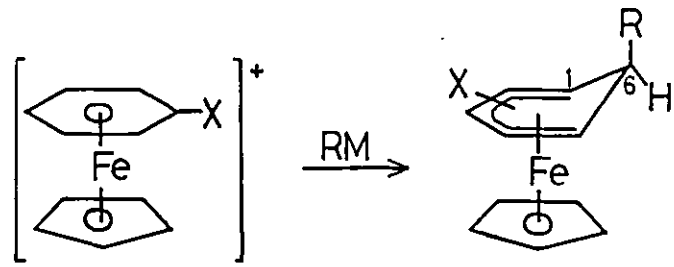
X	Electronic Effects	Relative Site Reactivity o	m	p
Cℓ	-I > + R	4	1	0
OMe	-I < + R	0.2	1	0.6
Me	+I	1	1	1
CO_2Me	-I -R	12.7	1	1.1

The variationsin the arene site reactivities towards hydride ion suggest that product distribution is controlled principally by differences in positive charge concentration at the various arene carbons, occasioned by the presence of the ring substituents and by metal ion (BH_4^-) complexation. Electron withdrawing substituents (e.g., Cℓ, CO_2Me) tend to increase the local positive charge at the ortho- relative to the meta- and para- positions and thereby favour the formation of the ortho- product. Inductive (or hyperconjugative) electron donation has no discernible influence on product formation. The meta- directing property of the methoxyl group points to the importance of a (+R) effect by which the positive charge concentration at the ortho- and para- positions are reduced through mesomeric donation from oxygen. The para- position of the methyl benzoate complex is as reactive towards hydride addition as the meta- position and this may reflect some activation of the para- carbon through the (-R) effect of the carbomethoxy group, although this effect is felt much more strongly by the ortho-carbons.

Several organometallic reagents have been shown to react with η^6-(arene)-η^5-(cyclopentadienyl)iron(II) cations (Table 7).[39,40] It was observed that methyl and phenyl lithium experienced similar directive effects to those noted for hydride addition; free ring positions were preferred and addition occurred mainly ortho- to chloro substituents.

Reactions of ethyl lithium with complex (36; X = H) were found to be both temperature and solvent dependent.[42] In ether at -25°C the electroneutral complex η^6-(C_6H_6)-η^5-(C_5H_5)Fe was formed, at 0°C the 6-exo ethyl complex (37; R = Et, X = H) was produced, while ferrocene was obtained in THF at 25°C.

TABLE 7 Reaction of η^6-(arene)-η^5-(cyclopentadienyl)iron(II) cations with nucleophiles.



(36) (37)

X in (36)	RM	(37)	Yield (37) (%)	Reference
H	PhLi	R = Ph, X = H	30	40
H	MeLi	R = Me, X = H	59	39
1,4-Me_2	PhLi	R = Ph, X = 1,4-Me_2	56	39
1-Cℓ, 4-Me	MeLi	R = Me, X = 1-Cℓ, 4-Me	40	39
		R = Me, X = 2-Cℓ, 5-Me	11	

Benzyl magnesium bromide gave the 6-exo benzyl derivative (37; R = CH_2Ph, X = H)[42] but ethyl magnesium bromide and t-butyl lithium both failed to produce the required addition product, ferrocene being formed instead.[43]

ii) Hydride Abstraction

N-Bromosuccinimide has been shown to remove the 6-endo hydrogen from complex (37) with the formation of η^6-(substituted arene)iron(II) cations.[39] However, it has been found that cleavage of the carbon-carbon bond

attaching the substituent to the ring can also occur.[44] Abstraction of the 6-exo substituent in (37) by N-bromosuccinimide or triphenylmethyl tetrafluoroborate increases along the series Me << C_5H_5 < Et < $PhCH_2$.

II) Bis-η^6-(Arene)Iron(II) Cations

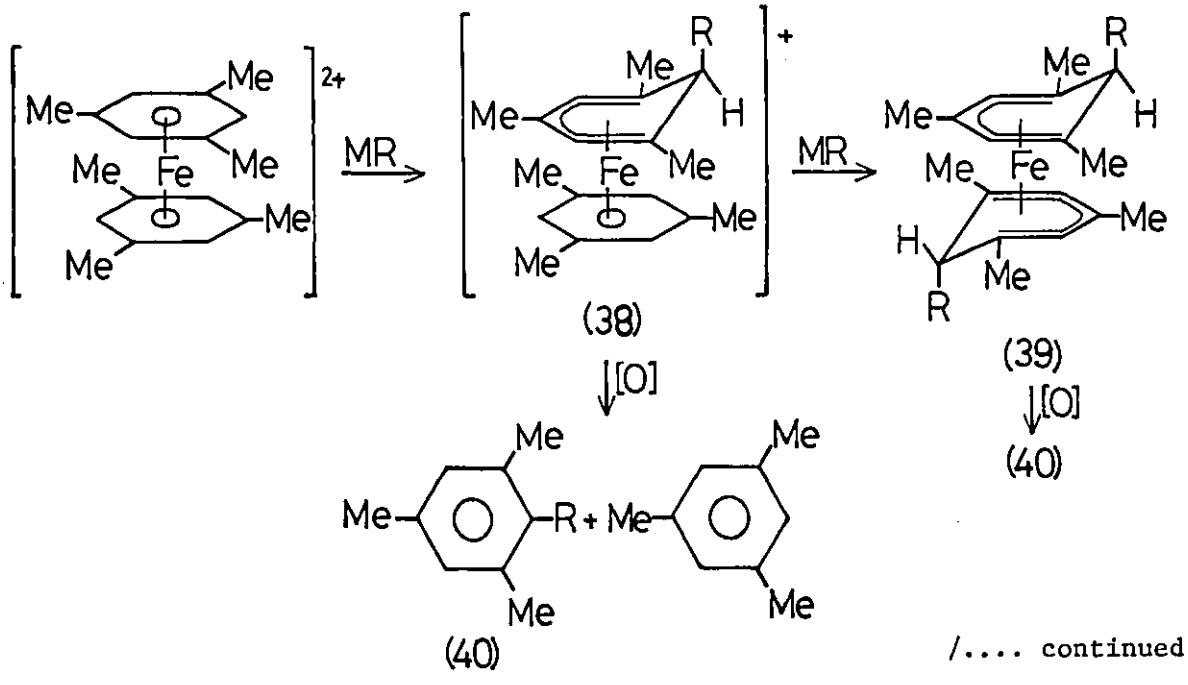
Preparation

Bis-η^6-(arene)iron(II) cations are prepared by heating together ferrous chloride, aluminium trichloride and arene (1:3.2:2.5).[45]

Nucleophilic Substitutions

Helling, et al.,[45,46] have carried out nucleophilic substitutions on bis-η^6-(arene)iron(II) cations (Table 8). Attempts to form the di-adducts (39) with KCN, $LiCH_2NO_2$, $LiCH(CH_3)NO_2$ and $LiCH_2CO_2$-tBu were unsuccessful. Nitrogen and oxygen nucleophiles were found to abstract α-protons from iron-coordinated methylated arenes and the carbanions which were thus produced reacted with unconverted substrate.

TABLE 8 Reaction of bis-η^6-(mesitylene)iron(II) cations with nucleophiles.



/.... continued

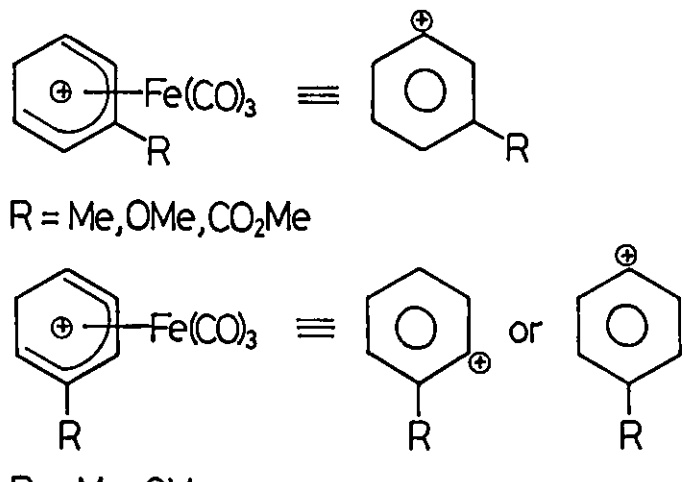
TABLE 8 (continued)

MR	Yield (38) (%)	Yield (39) (%)	[O]	Yield (40) (%)[a]	Reference
KCN	83		Ce^{IV}	53	46
$LiCH_2NO_2$	52		Ce^{IV}	45	46
$LiCH(CH_3)NO_2$	84		Ce^{IV}		46
$LiCH_2CO_2$-tBu	48		Ce^{IV}	50	46
LiPh (2 eq.)		57	$KMnO_4$	95	45
LitBu (2 eq.)		75	$KMnO_4$	18	45
LiC_2H_3 (2 eq.)		53	Ce^{IV}	82	45

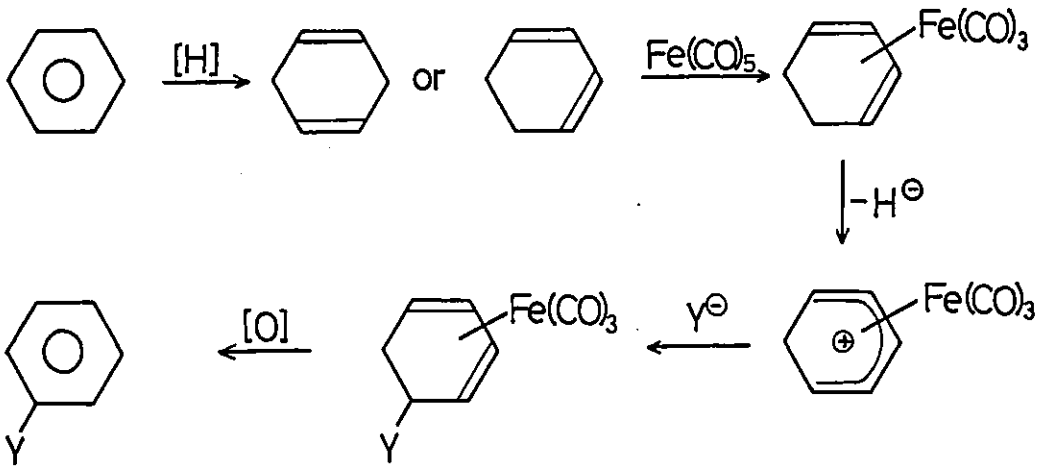
[a] Yield based on (38) or (39).

III) Tricarbonyl η^5-(Cyclohexadienylium)Iron(0) Cations [12,47]

Tricarbonyl η^5-(cyclohexadienylium)iron(0) cations are considered to be aryl cation equivalents (Scheme 11).[12] A multi-step reaction pathway involving these cationic complexes can therefore be used to bring about an apparent overall nucleophilic aromatic substitution (Scheme 12).



SCHEME 11



SCHEME 12

Preparation of Tricarbonyl η^4-(Cyclohexa-1,3-diene)Iron(0) Complexes [47]

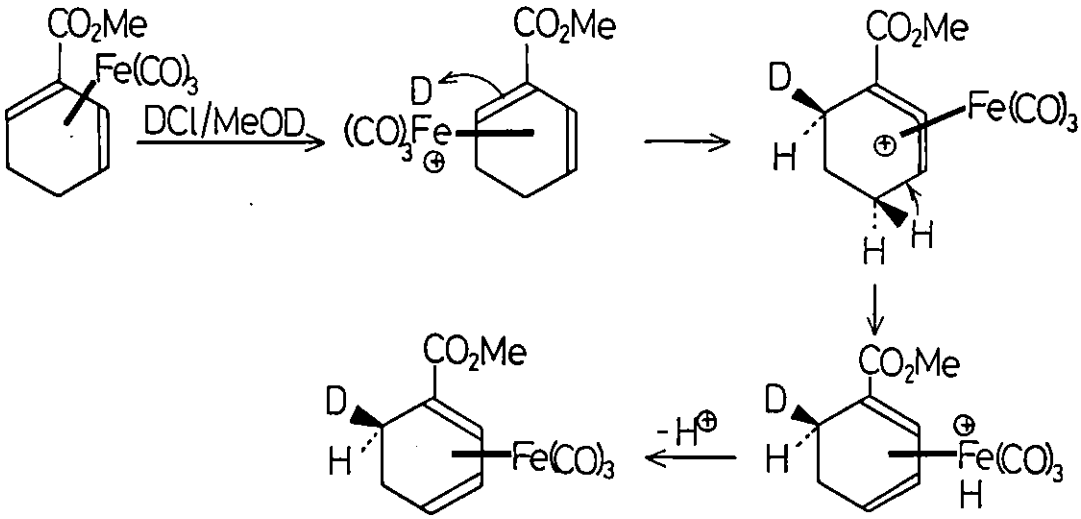
Tricarbonyl η^4-(cyclohexa-1,3-diene)iron(0) complexes are prepared by reacting cyclohexadienes with iron pentacarbonyl in refluxing n-butyl ether.[48] Conjugated dienes react under mild conditions without rearrangement. Cyclohexa-1,4-dienes are generally more readily available than the 1,3-dienes, being produced by Birch reduction of aromatic rings,[49] but their complexation reactions are slower and give rise to mixtures whose compositions are probably mainly kinetically controlled. However, prior catalytic equilibration of cyclohexa-1,4-dienes with the 1,3-dienes can enable selective complexation to occur if only one dominant 1,3-diene is produced.

The process of pre-conjugation was found to be a key step in the formation of tricarbonyl η^4-(1,3-dimethoxycyclohexa-1,3-diene)iron(0) as the complexation reaction with the 1,4-diene resulted in a poor yield mixed with the products of methoxy loss.[50]

Acid catalysed isomerisation of complexes occurs to give the thermodynamically more stable isomer , characterised by 1-CO_2Me or 1-$COCH_3$ or

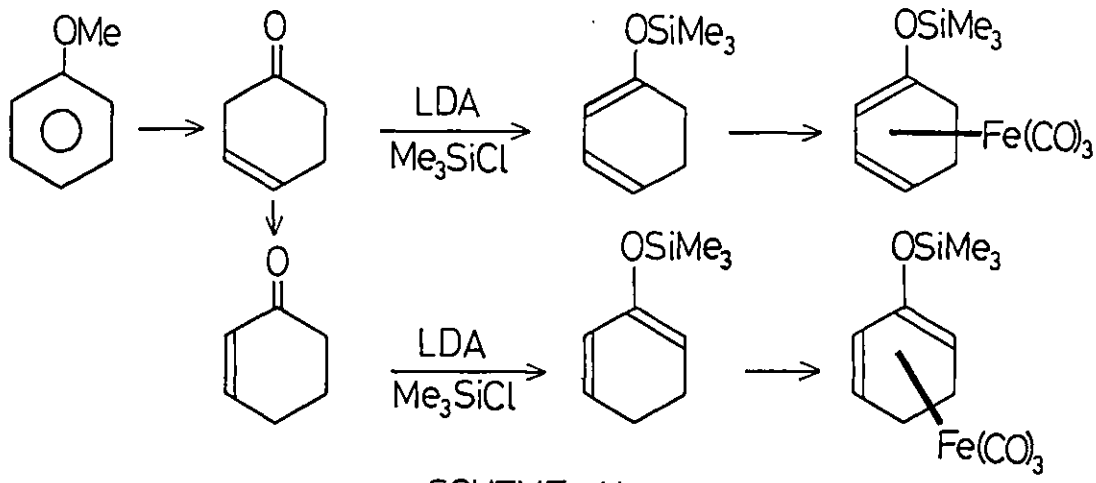
2-alkyl. Thermodynamic stability may relate to the ability of $Fe(CO)_3$ to supply electrons in the 1-position to withdrawing groups, such as carbomethoxy, or to avoid interaction with alkyl groups in the 2-position.

The isomerisation mechanism, elucidated by deuteriation, seems to involve initial protonation (or deuteriation) on $Fe(CO)_3$ and stereospecific transfer to one or the other end of the complexed system. The cationic intermediate then loses a proton (or deuteron) by an equally stereospecific process *via* $Fe(CO)_3$ to yield a new complex. The process continues until an equilibrium mixture is obtained. An example of such a conversion is the isomerisation of tricarbonyl η^4-(2-methoxycarbonylcyclohexa-1,3-diene)iron(0) to its 1-methoxycarbonyl complex (Scheme 13).[51]



SCHEME 13

A method has been developed, based on the kinetic or thermodynamic enolisation of cyclohexenones, which enables the preparation of tricarbonyl η^4-(cyclohexa-1,3-diene)iron(0) complexes with an -OR group (R = $SiMe_3$) at the 1- or 2- position (Scheme 14).[47]



SCHEME 14

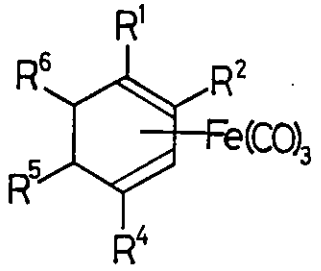
Formation of Tricarbonyl η^5-(Cyclohexadienylium)Iron(0) Cations [47]

The most widely used method for preparing tricarbonyl η^5-(cyclohexadienylium)iron(0) cations involves hydride abstraction from neutral tricarbonyl η^4-(cyclohexa-1,3-diene)iron(0) complexes. Triphenylmethyl tetrafluoroborate or hexafluorophosphate are the reagents generally used having advantages in selectivity but disadvantages in lack of reactivity. Attack occurs entirely on the exo-side.

The selectivity of hydride abstraction in substituted cyclohexa-1,3-diene complexes has been investigated (Table 9)[51-53] and was found to be controlled by steric and electronic effects. Hydride loss generally occurred from the position remote from terminal substituents. In the monosubstituted series, hydride abstraction from 2-OMe and 2-CO_2Me substituted complexes was predominantly at the C-5 and C-6 positions, respectively.

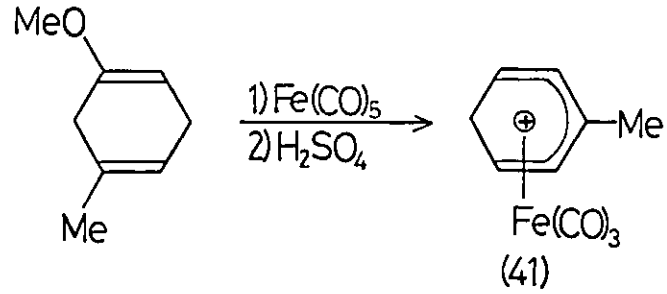
Tricarbonyl η^5-(cyclohexadienylium)iron(0) cations have also been prepared by an acid promoted demethoxylation of the appropriate methoxy substituted complex. This method has enabled pure salts to be produced which are unobtainable by hydride removal. A good example of such a case

TABLE 9 Hydride Abstraction from Substituted Tricarbonyl η^4-(cyclohexa-1,3-diene)iron(0) Complexes.



R^1	R^2	R^4	R^5	R^6	% Abstraction C-5	% Abstraction C-6	Total Yield of Salt (%)	Ref.
H	OMe	H	H	H	100	0	95	52
H	OMe	Me	H	H	0	100	98	52
H	OMe	Me	H	endo-Me	0	100	98	52
H	OMe	Me	H	exo-Me	0	0	0	52
OMe	H	H	H	H	80	20	98	52
OMe	H	Me	H	H	10	90	90	52
H	Me	H	H	H	60	40	94	52
H	Me	Me	H	H	0	100	96	52
H	Me	H	iPr	H	0	0	0	52
iPr	H	Me	H	H	100	0	100	52
CO_2Me	H	H	H	H	100	0	94	51
H	CO_2Me	H	H	H	10	90	90	53

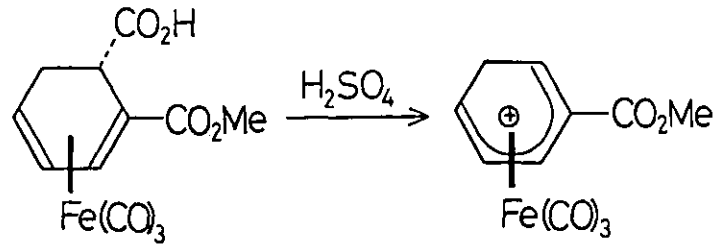
is the formation of tricarbonyl η^5-(3-methylcyclohexadienylium)iron(0) (41) from 1-methoxy-5-methylcyclohexa-1,4-diene (Scheme 15).[54] The initial complexation produced a mixture of isomeric diene iron complexes but subsequent demethoxylation resulted in the formation of the cyclohexadienylium cation (41) in 72% yield. In contrast, complexation of 1-methylcyclohexa-1,4-diene followed by hydride abstraction gave a mixture of (41) and its 1- and 2-methyl isomers.



(41)

SCHEME 15

Another method of forming cyclohexadienylium cations involves acid catalysed decarboxylation of an allylic exo-carboxyl group (Scheme 16).[55]

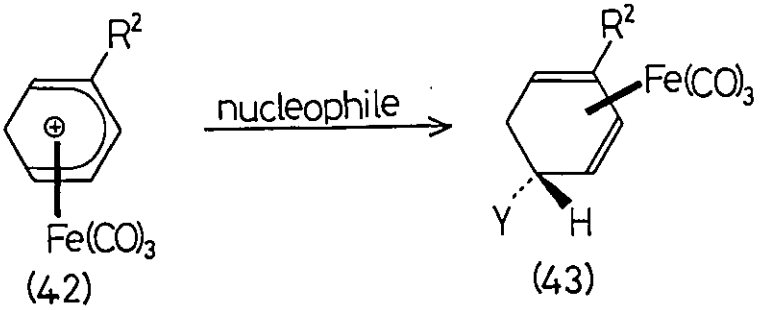


SCHEME 16

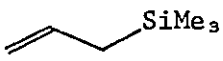
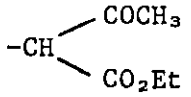
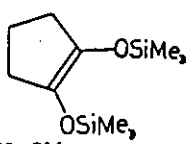
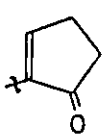
Nucleophilic Addition Reactions

Tricarbonyl η^5-(cyclohexadienylium)iron(0) cations react with a variety of nucleophiles (Tables 10 and 11).[52,56-66] The nucleophile generally attacks from the exo- face at its least hindered terminus. The more reactive the anion the lower is the selectivity of the addition; lithium alkyls add to both the 1- and 5- positions[57] whereas the less nucleophilic zinc and cadmium reagents give regio-selective alkylation at the 5-position.[56]

TABLE 10 Reaction of Tricarbonyl η^5-(cyclohexadienylium)Iron(0) Cations with Nucleophiles.

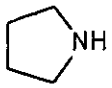
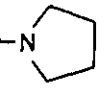
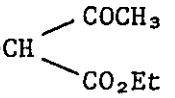
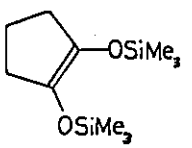
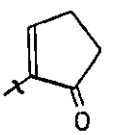
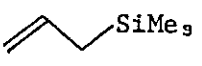
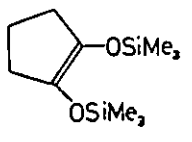
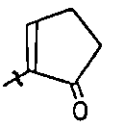


(42) (43)

R^2	Nucleophilic Reagent	Yield (43)		Ref.
		Y	%	
H	$(Me_2CH)_2Cd$	$-CHMe_2$	52	56
H	Ph_2Cd	-Ph	83	56
H	$(MeCH=CH)_2Cd$	-CH=CHMe	40	56
H	$(Me_2CH)_2Zn$	$-CHMe_2$	35	56
H	Ph_2Zn	-Ph	67	56
H	MeLi	-Me	87	57
H	t-BuLi	-t-Bu	79	57
H		$-CH_2-CH=CH_2$	52	58
H	KCN	-CN	59	59
H	$NaCH(CO_2Et)_2$	$-CH(CO_2Et)_2$	82	59
H	$CH_3COCH_3/EtOH$	$-CH_2COCH_3$	77	52
H	$CH_2(COCH_3)_2/H_2O$	$-CH(COCH_3)_2$	93	60
H	$CH_3COCH_2CO_2Et/EtOH$		70	61
H			76	62
H	NaOMe	-OMe	53	59
H	$H_2O/NaHCO_3$	-OH	75	60

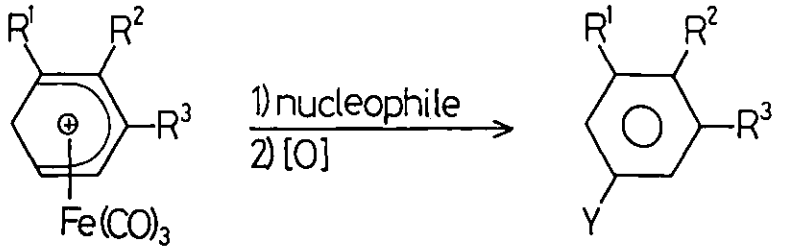
/.... continued

TABLE 10 (continued).

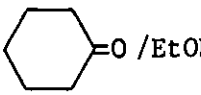
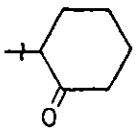
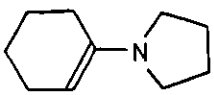
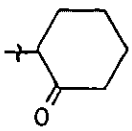
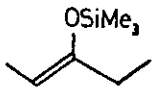
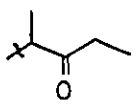
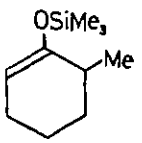
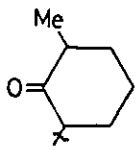
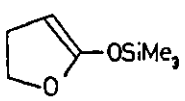
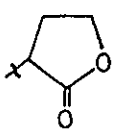
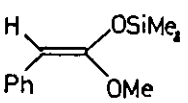
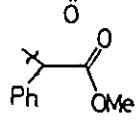
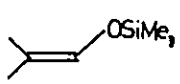
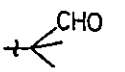
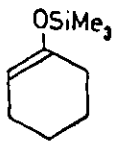
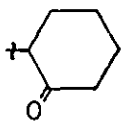
R^2	Nucleophilic Reagent	Yield (43)		Ref.
		Y	%	
H			82	60
H	KF/18-crown-6	-F	70	63
OMe	$(Me_2CH)_2Zn$	$-CHMe_2$	10	56
OMe	MeLi	-Me (100:0)[a]	94	57
OMe	i-PrLi	-i-Pr (90:10)[a]	94	57
OMe	t-BuLi	-t-Bu (60:40)[a]	87	57
OMe	$CH_2(COCH_3)_2$/aq.EtOH	$-CH(COCH_3)_2$	81	61
OMe	$CH_3COCH_2CO_2Et$/aq.EtOH		71	61
OMe			56	62
OH	NaCN	-CN	61	64
OH	$CH_2(COCH_3)_2/NEt_3$	$-CH(COCH_3)_2$	40	64
Me	$(Me_2CH)_2Zn$	$-CHMe_2$	50	56
Me	MeLi	-Me (75:25)[a]	96	57
Me	i-PrLi	-i-Pr (90:10)[a]	94	57
Me	t-BuLi	-t-Bu (80:20)[a]	87	57
Me		$-CH_2-CH=CH_2$	64	58
Me			78	62

[a] the ratio of the 5-substituted η^4-cyclohexadiene iron(0) complex (43) to its isomer formed by attack at C-1 in (42). A combined yield is quoted.

TABLE 11 Reaction of Tricarbonyl η^5-(cyclohexadienylium)Iron(0) Cations with Nucleophiles and Subsequent Oxidative Cleavage of the Iron Tricarbonyl Group.



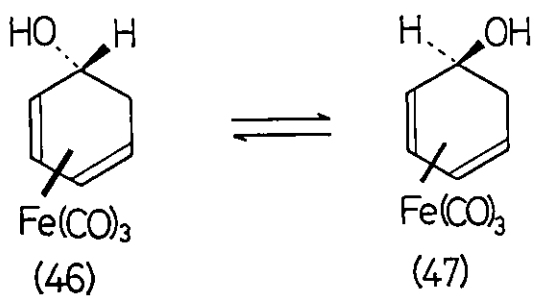
(44) (45)

R^1	R^2	R^3	Nucleophilic Reagent	[O]	Overall Yield		Ref.
					Y	%	
H	H	H	CH_3COCH_3/EtOH	$Pb(OAc)_4$	$-CH_2COCH_3$	42	52
H	H	H	 /EtOH	i) $FeCl_3/HCl$ ii) Pd/C		47	52
H	OMe	H		i) Ce(IV) ii) DDQ		29	65
H	OMe	H	KCN	Pd/C	-CN	38	60
CO_2Me	Me	H		i) $Me_3NO.2H_2O$ ii) DDQ		52	66
CO_2Me	Me	H		i) $Me_3NO.2H_2O$ ii) DDQ		59	66
CO_2Me	Me	H		i) $Me_3NO.2H_2O$ ii) DDQ		34	66
H	$-(CH_2)_4-$			i) $Me_3NO.2H_2O$ ii) DDQ		60	66
H	$-(CH_2)_4-$			i) $Me_3NO.2H_2O$ ii) DDQ		74	66
H	$-(CH_2)_4-$			i) $Me_3NO.2H_2O$ ii) DDQ		68	66

Regio-control is influenced by the electronic and steric effects of substituents. The cations (42; R^2 = OMe) and (44; R^1 = CO_2Me, R^2 = R^3 = H) gave the 5-product except when very reactive anions were used. The selectivity in the reactions of cations having a weakly directive group, such as 2-Me (42; R^2 = Me), was dependent on the nature of the reagent.

The rates of the addition reactions can be qualitatively explained in terms of the probable electronic effects of substituents; electron withdrawal increases reaction rates while electron donation stabilises the cation and slows rates. The donating properties of a 2-OMe group effects the 1-position more than the 5-position.

Carbon nucleophiles normally add irreversibly but oxygen or nitrogen nucleophiles may add reversibly or irreversibly according to structure and conditions.[47] In reversible cases, the products are thermodynamically determined structurally and sterically and the effect of substituents probably involve similar considerations to those discussed for acid catalysed equilibria. One steric example is the hydroxydiene (46), obtainable by the action of mild base in water on the cation, and the diastereoisomer (47), obtainable by borohydride reduction of the dienone (Scheme 17). These can be equilibrated in water to the same mixture from either direction.[56]



(46) (47)

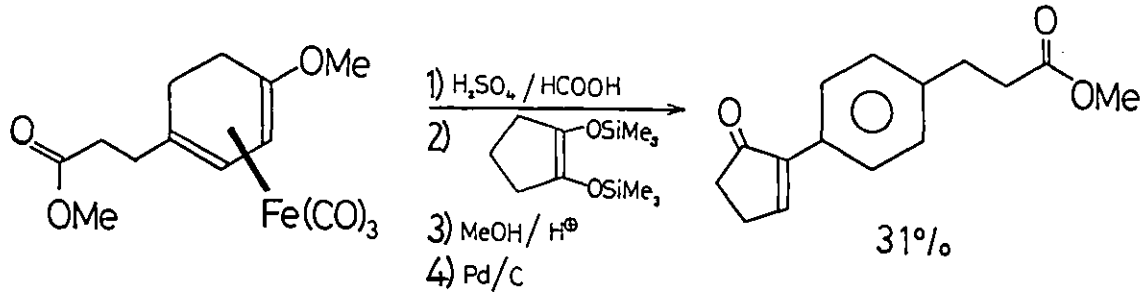
SCHEME 17

The reaction of oxyanions with cation (42; R^2 = H) have been investigated[67] and the success of the nucleophilic additions were found to be dramatically dependent upon the choice of solvent, temperature and nucleophile. The reaction with sodium methoxide in acetonitrile at room temperature gave (43; R^2 = H, Y = OMe) in 1% yield (cf. NaOMe/MeOH → 53% [59]) and substantial amounts of dimer. A reduction in the basicity of the oxyanion enabled the addition process to become competitive with dimer formation, e.g., potassium phenoxide produced the cyclohexadiene complex (43; R^2 = H, Y = OPh) in 64% yield. Lower reaction temperatures resulted in a decrease in dimer formation.

Tricarbonyl η^5-(cyclcohexadienylium)iron(0) cations react with thermodynamic enols[52,60,61] and O-silylated enolates.[62,66] O-Silylated enolates can result from either kinetic or thermodynamic enolisation and the regiospecificity is retained in the reactions.

Oxidative cleavage of the iron tricarbonyl group in tricarbonyl η^4-(cyclohexa-1,3-diene)iron(0) complexes can lead to the formation of aromatic products (Table 11).

Birch, et al.,[68] have used a tricarbonyl iron stabilised cation in the first step towards the synthesis of a prostaglandin analogue (Scheme 18).



SCHEME 18

3) TRICARBONYL η^6-(ARENE)MANGANESE(I) CATIONS

Preparation

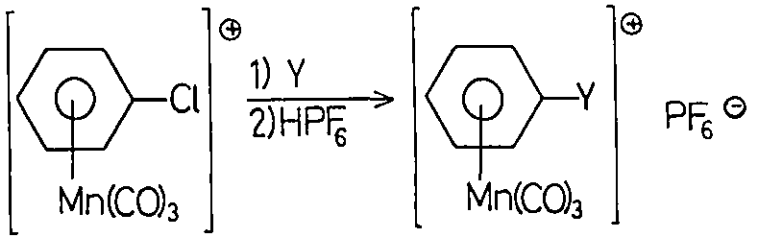
Tricarbonyl η^6-(arene)manganese(I) cations are prepared by heating the appropriate arene with either pentacarbonyl manganese(I) bromide and aluminium trichloride[69] or tricarbonyl η^5-(methylcyclopentadienyl)-manganese(I) and aluminium tribromide.[70]

Nucleophilic Substitution and Addition Reactions

a) Displacement of Halide

Nucleophilic substitution of the chloro group in tricarbonyl η^6-(chlorobenzene)manganese(I) cation proceeded readily with several types of nucleophile (Table 12).[71] Reactions with hydroxide, cyanide, cyanate and thiocyanate were attempted but complex mixtures were obtained, possibly due to competing displacement of the arene by nucleophilic attack on the metal.

TABLE 12[71] Reaction of Tricarbonyl η^6-(chlorobenzene)manganese(I) Cation with Nucleophiles.



(48)

/..... continued.

TABLE 12 (continued)

Y	Yield (48) (%)
$^{\ominus}OMe$	45
$^{\ominus}OPh$	66
$^{\ominus}SPh$	33
$^{\ominus}N_3$	66
NH_3	66
$PhNH_2$	91
Et_2NH	87

It was found that N,N-diethylaniline could be displaced from (48, Y = NEt_2) by heating the complex in acetonitrile, the tris(acetonitrile) cation $[Mn(CO)_3(NCMe)_3]^+$ being produced.

b) Displacement of Hydride

Tricarbonyl η^6-(arene)manganese(I) cations undergo nucleophilic additions with hydride, phenide,[40] cyanide,[72] diethyl malonate anion, azide, methoxide and thiocyanate[73] to form the corresponding 6-exo substituted η^5-(cyclohexadienyl) complexes.

The selectivity of nucleophilic addition has been investigated and it was found that addition occurred ortho- to chloro and meta- to methoxy and N,N-dimethyl groups.[74] The inductive effect predominates over the mesomeric effect for halogen atoms, while the reverse is true with methoxy and N,N-dimethyl groups. These findings were similar to those obtained with the η^6-(arene)-η^5-(cyclopentadienyl)iron(II) cations.[41]

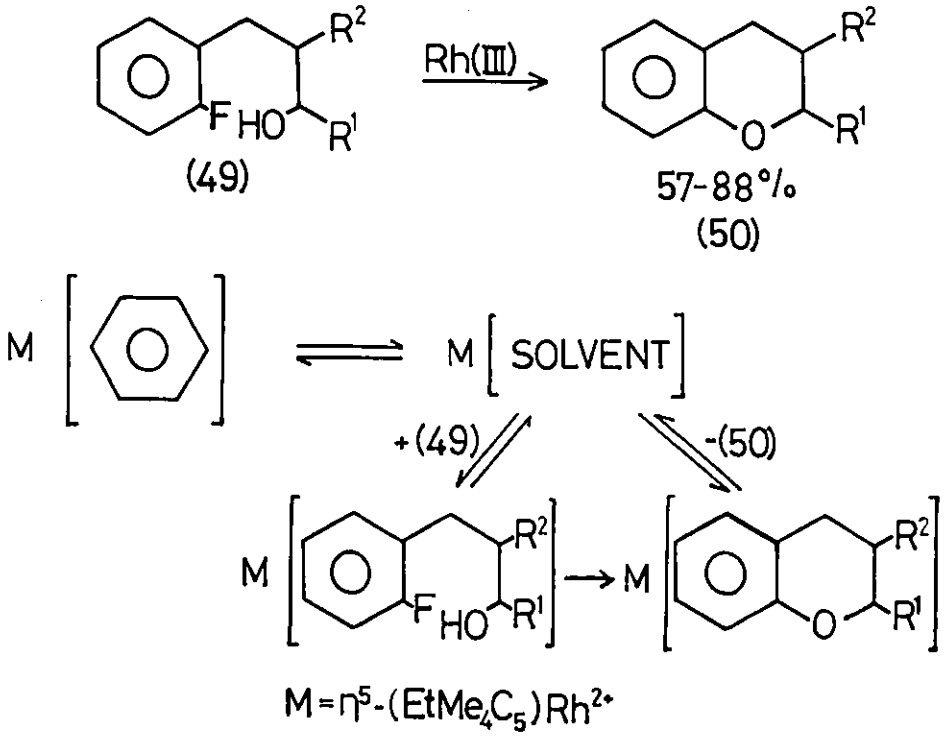
Some of the 6-exo substituted η^5-(cyclohexadienyl) complexes have very low stability and reaction with conventional hydride abstracting agents (e.g., Ph_3C^+, NBS) can result in the removal of the 6-exo substituent. However, free arene nitriles have been liberated from the corresponding cyano complexes in high yields (70-80%) using cerium(IV) sulphate in sulphuric acid at room temperature.[73]

4) OTHER η^6-(ARENE) METAL COMPLEXES

Nucleophilic Addition and Substitution Reactions

η^6-(Arene)-η^5-$(Me_5C_5)M^{2+}$ (M = Rh, Ir) underwent nucleophilic additions with $NaBH_4$ and MeLi to produce the corresponding 6-substituted η^5-(cyclohexadienyl) complex.[75]

η^6-(C_6H_6)-η^5-$(EtMe_4C_5)Rh^{2+}$ has been found to act as a metal catalyst in the formation of chromans (50) from aryl fluorides (49) (Scheme 19).[26] The mechanism proposed for these reactions involved the reversible displacement

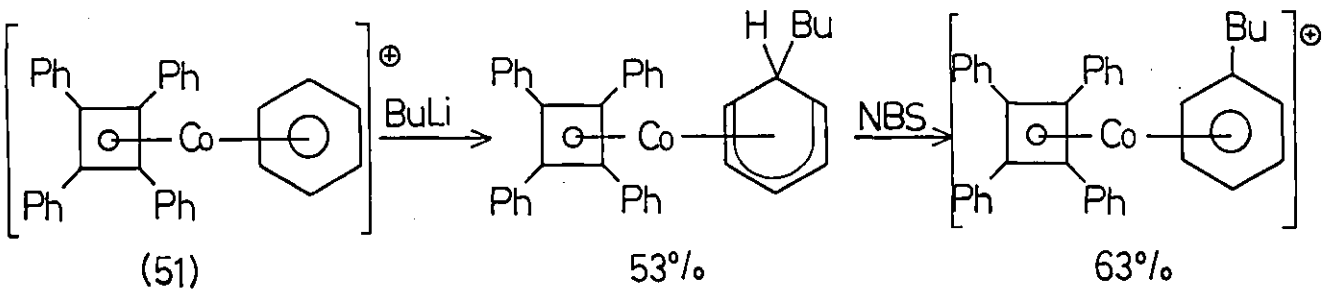


SCHEME 19

of the coordinated benzene in the catalyst by other arenes *via* an intermediate solvated species. A metal facilitated intramolecular nucleophilic substitution would then be followed by a similar displacement of the cyclised product (50) by the starting arene (49).

Stable η^5-(cyclohexadienyl) complexes were obtained from the reaction of $[\eta^6\text{-}(C_6H_6)PR_3(N\text{-}N)Ru]^{2+}$ (PR_3 = PMe_2Ph, PMe_3; N-N = 1,10-phenanthroline, 2,2'-bipyridyl) with hydride, cyanide and hydroxide anions.[76] However, similar reactions with $[\eta^6\text{-}(C_6H_6)C\ell(PR_3)Ru]^+$ or $[\eta^6\text{-}(C_6H_6)C\ell(N\text{-}N)Ru]^+$ led to facile decomposition due probably to competing attack on the metal. Ring attack is favoured in $[\eta^6\text{-}(C_6H_6)PR_3(N\text{-}N)Ru]^{2+}$ because of the presence of strong metal-ligand bonds which minimise the possibility of alternative reaction pathways and the high formal positive charge. The π-acceptor ligands PR_3 and N-N also render the coordinated arene more susceptible to attack.

The η^6-(benzene)-η^4-(tetraphenylcyclobutadiene)cobalt(I) cation (51) was found to react with butyl lithium (Scheme 20) but was resistant to nucleophilic attack by alkoxide and Grignard reagents.[77]



(51) 53% 63%

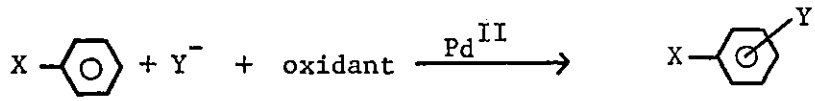
SCHEME 20

$[\eta^6\text{-}(C_6H_6)\text{-}\eta^3\text{-}(C_3H_5)L_2Mo]^+$ (L_2 = $Me_2PCH_2CH_2PMe_2$, $Ph_2PCH_2CH_2PPh_2$) reacted with hydride, cyanide and butyl lithium to form the neutral 6-substituted η^5-(cyclohexadienyl) derivatives.[78]

NUCLEOPHILIC SUBSTITUTION REACTIONS IN σ-ARYL COMPLEXES.

1) PALLADIUM AND NICKEL COMPLEXES

Henry[79] found that Pd^{II} salts could catalyse direct aromatic substitutions (Scheme 21). The reactions gave substitution patterns consistent with an electrophilic substitution and control experiments showed that biphenyls were produced in the absence of oxidant.

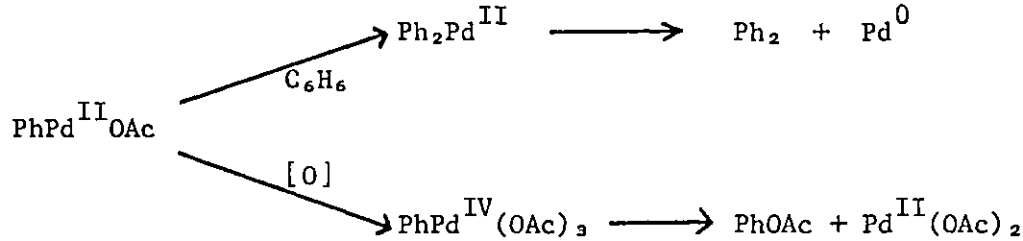


Y = OAc, N_3, Cℓ, NO_2, CN, SCN, Br

oxidant = $K_2Cr_2O_7$, $Pb(OAc)_4$, $KMnO_4$

SCHEME 21

The results of rate studies on palladium(II) acetate catalysed benzene substitutions strongly suggest that phenyl Pd^{II} acetate is the intermediate in the formation of substituted product and biphenyl (Scheme 22).[80]

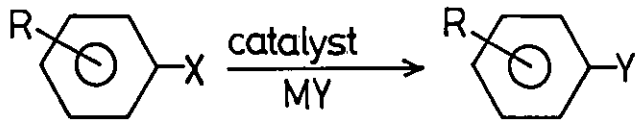


SCHEME 22

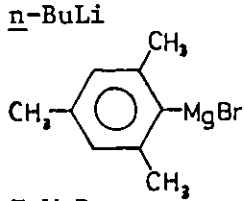
Ni^0 and Pd^0 complexes have been used to bring about the selective replacement of the halo group of aryl halides by various nucleophiles (Talbe 13).[2,81-92] These reactions involve initial oxidative addition of the aryl halide to the Pd^0 or Ni^0 species followed by metathetical exchange of the halo group by nucleophile and subsequent

reductive elimination of the metal catalyst. Aryl Ni^{II} and aryl Pd^{II} complexes can also act as catalysts in these replacement reactions.

TABLE 13 Reaction of Aryl Halides with Nucleophiles Catalysed by Nickel or Palladium Complexes.



(52)

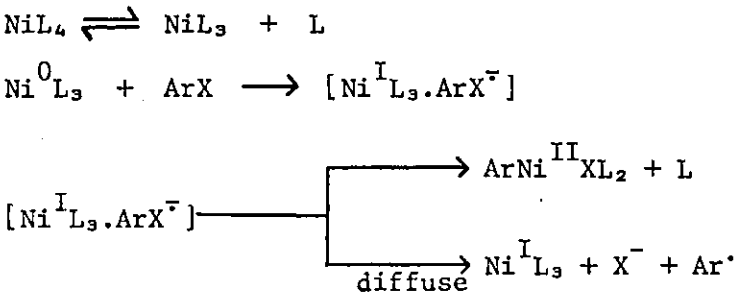
R	X	Catalyst	MY	Yield (52) (%)	Ref.
H	I	$PhPd^{II}I(PPh_3)_2$	EtMgBr	32	81
H	I	$PhPd^{II}I(PPh_3)_2$	n-BuLi	45	81
H	I	$PhPd^{II}I(PPh_3)_2$		64	81
H	Cℓ	$Ni^{II}Cℓ_2(dppe)$	EtMgBr	98	2
H	Cℓ	$Ni^{II}Cℓ_2(dppe)$	n-BuMgBr	76	2
H	Br	$Pd^{II}Cℓ_2(dppf)$	n-BuMgCℓ	92	82
H	Br	$Pd^{II}Cℓ_2(dppf)$	s-BuMgCℓ	95	82
4-CN	Br	$Ni^0(PPh_3)_4$	$PhCH_2ZnBr$	92	83
4-CO_2Me	Br	$Ni^0(PPh_3)_4$	$PhCH_2ZnBr$	85	83
H	I	$Pd^0(PPh_3)_4$	PhC≡CNa	95	84
H	I	$Pd^0(PPh_3)_4$	$C_3H_7C{\equiv}CNa$	97	84
2-CN	Br	$Pd^0(PPh_3)_4$	PhC≡CNa	93	84
4-OMe	Br	$Pd^{II}Cℓ_2(PPh_3)_2$	PhC≡CNa	77	84
H	I	$Pd^0(PPh_3)_4$	HC≡CZnCℓ	67	85
H	I	$Pd^0(PPh_3)_4$	PhC≡CZnCℓ	93	85
2-CH_3	I	$Pd^0(PPh_3)_4$	HC≡CZnCℓ	71	85
H	Br	$Ni^0(PPh_3)_4$	$PhCOCH_2Li$	65	86
H	I	$Pd^0(PPh_3)_4$	$BrZnCH_2CO_2Et$	47	87
H	Br	$Pd^0(PPh_3)_4$	$BrZnCH_2CO_2Et$	15	87
4-CO_2H	I	$Pd^0(PPh_3)_4$	$BrZnCH_2CO_2Et$	85	87

/.... continued.

TABLE 13 (continued)

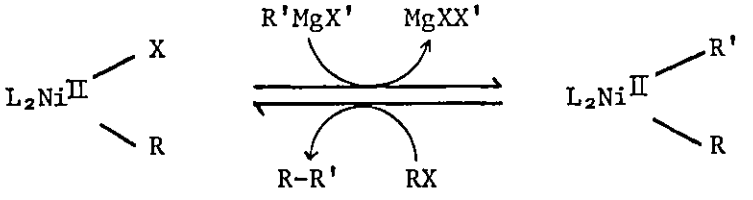
R	X	Catalyst	MY	Yield (52) (%)	Ref.
H	I	$Ni^0(PPh_3)_4$	$BrZnCH_2CO_2Et$	55	87
H	Br	$Ni^0(PPh_3)_4$	$BrZnCH_2CO_2Et$	67	87
H	Cℓ	$Ni^0(PPh_3)_4$	$BrZnCH_2CO_2Et$	65	87
H	I	$Ni^{II}Br_2$/n-BuLi	$LiCH_2CO_2$-t-Bu	73	88
H	I	$Ni^{II}Br_2$/n-BuLi	$LiCH(C_6H_5)CO_2Et$	46	88
H	I	$Ni^{II}Br_2$/n-BuLi	$LiCH_2CH{=}CHCO_2Et$	60	88
H	Br	(1-naphthyl)$Ni^{II}Cℓ(PPh_3)_2$	NaCN	97	89
2-CH_3	Br	(2-tolyl)$Ni^{II}Br(PPh_3)_2$	NaCN	90	89
H	Br	$Ni^{II}Br_2$/Zn	KI	77	90
H	Br	$Ni^{II}Br_2/PBu_3$	KI	89	90
4-OMe	Br	$Ni^{II}Br_2$/Zn	KI	78	90
4-Cℓ	Br	$Ni^{II}Br_2$/Zn	KI	81	90
H	I	(2-tolyl)$Ni^{II}Br(PEt_3)_2$	$Bu_4N^+Br^-$	74	91
2-Me	I	(2-tolyl)$Ni^{II}Br(PEt_3)_2$	$Bu_4N^+Br^-$	74	91
4-OMe	I	(2-tolyl)$Ni^{II}Br(PEt_3)_2$	$Bu_4N^+Br^-$	72	91
H	Br	(2-tolyl)$Ni^{II}Br(PEt_3)_2$	$Bu_4N^+I^-$	14	91
H	Br	$Ni^{II}Cℓ_2$	LiCℓ	68	92
H	Br	$Ni^0(CO)_2(PPh_3)_2$	PhONa	33	92
H	Br	$Ni^0(CO)_2$(dppe)	CH_3NH_2	15	92
H	Br	$Ni^0(CO)_2(PPh_3)_2$	$(CH_3)_2NH$	57	92

Kochi, et al.[93] have investigated the oxidative addition of aryl halides to Ni^0 complexes. Two principal products were obtained from the reactions, one being the Ni^{II} oxidative adduct and the other a paramagnetic Ni^I species. The experimental results suggested that the products were formed via a common intermediate. It was proposed that the electron deficient aryl halide reacted with the Ni^0 electron donor to form a tight ion pair which could then either collapse to produce the oxidative adduct or release an aryl radical by diffusion out of the solvent cage to give the Ni^I species (Scheme 23).



SCHEME 23

Two independent facts concerning σ-organonickel complexes led Kumada[2] to the discovery that Grignard reagents and aryl halides could be catalytically cross-coupled using nickel phosphine complexes. The first piece of information involved the well established replacement of the halo group of (halo)(organo) Ni^{II} complexes by Grignards[94] and, the second, the release with coupling of two organogroups on a nickel complex by the action of an organic halide.[95] Combination of these two reactions enabled a selective method of carbon-carbon cross-coupling to be developed (Scheme 24).



SCHEME 24

The fact that the reductive elimination is intramolecular demands that it proceeds in a concerted fashion <u>via</u> a transition state in which the two organo groups are juxtaposed. Analysis of orbital correlation diagrams has shown that concerted eliminations from <u>cis</u>-square planar, trigonal bipyramidal and tetrahedral complexes are symmetry allowed.[96]

1,1-Reductive eliminations from trigonal three coordinate species are symmetry forbidden.

Mechanistic studies on the release of cross-coupled product from trans-(methyl)(phenyl)bis(triethylphosphine)Ni^{II} by direct thermolysis[97] failed to provide any conclusive evidence for isomerisation to the cis-square planar or tetrahedral species. However, the observation that the reductive elimination was inhibited by added triphenylphosphine suggested that the reaction proceeded by prior dissociation since no five coordinate nickel complexes could be detected by ^{31}P NMR.

The recent investigations into the reductive elimination of ethane from di(methyl)bis(phosphine)Pd^{II} complexes showed that trans complexes could easily be isomerised to their corresponding cis compounds in polar coordinating solvents and that elimination only occurred when the methyl groups were in a cis configuration.[96] The isomerisation process was thought to involve a five coordinate transition state produced by coordination of the solvent to the square planar Pd^{II} complex. It was not clear whether the function of the solvent in the reductive elimination step was to aid phosphine dissociation by solution or by occupying the coordination site vacated by phosphine.

The probable importance of the cis configuration in reductive elimination is further emphasised by the remarkable catalytic activity shown by bidentate diphosphine ligands in cross-coupling reactions.[2]

The reductive elimination of methylarene from trans-(methyl)(aryl) bis(triethylphosphine)Ni^{II} can be induced by aryl halide.[98] The reaction is thought to involve a radical chain process and can lead to extensive

scrambling of aryl groups (Scheme 25). The induced reductive elimination is a significantly more facile process than direct thermolysis.

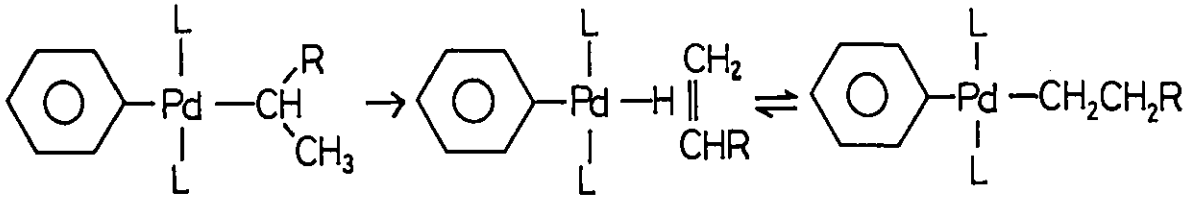
$$ArNi^{I} + ArX \longrightarrow Ar_2Ni^{III}X$$

$$Ar_2Ni^{III}X + ArNi^{II}Me \longrightarrow ArNi^{II}X + Ar_2Ni^{III}Me$$

$$Ar_2Ni^{III}Me \longrightarrow ArMe + ArNi^{I}$$

SCHEME 25

Secondary alkyl Grignard reagents have been cross-coupled with aryl halides in high yields using dichloro[1,1'-bis(diphenylphosphino)ferrocene]-Pd^{II} as catalyst.[82] These coupling reactions generally suffer from competing isomerisation and reduction processes which involve σ-π interconversions of σ-alkylated intermediates and hydrido-olefin metal intermediates by β-hydride elimination and readdition (Scheme 26). The [1,1'-bis(diphenylphosphino)ferrocene] ligand must retard the β-hydride elimination and/or accelerate the reductive elimination of coupling products from the diorganopalladium complex. Other bidentate ligands fail to completely suppress the side reactions and it is suggested that the delicate steric and electronic changes in the phosphine ligands bring about marked differences in catalytic activity.



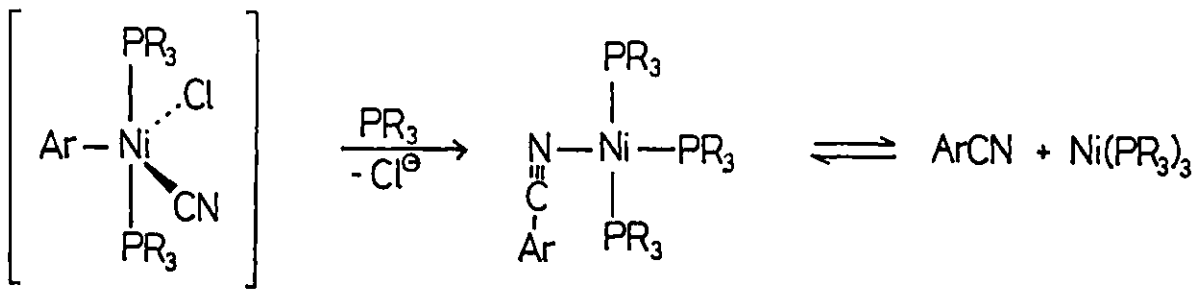
SCHEME 26

Organozinc reagents were found to be better than the corresponding magnesium and aluminium reagents in their nickel and palladium catalysed reactions with aryl halides.[83] This was because less biaryl by-product was produced during their use.

Palladium complexes have been used as catalysts in the synthesis of aryl acetylene derivatives.[84] The acetylenic compounds were also prepared using nickel complexes but these reactions were no longer catalytic because coordination of the acetylene group on to the nickel lowered its ability to undergo oxidative addition.

The mechanism involved in the nickel catalysed arylations of lithium ester enolates is unclear.[88] The addition of triphenylphosphine or tributylphosphine to suspensions of nickel(II)bromide/n-butyl lithium resulted in the formation of totally inactive material. Therefore, if the reactions do proceed through a Ni^0 species then its ligands can not be strongly coordinating.

The nickel catalysed cyanation of chlorobenzene has been studied by infra red spectroscopy.[89] It was proposed that a five coordinate nickel intermediate (53) was produced which underwent reductive elimination by migration of the aryl group on to the cyano group with subsequent elimination of aryl nitrile (Scheme 27). An analogous mechanism was previously suggested for carbon monoxide insertions.[99]



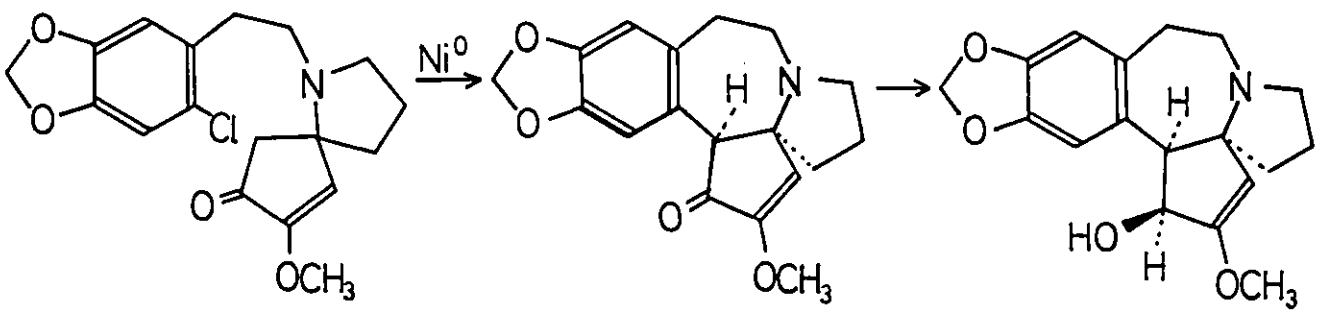
(53)

SCHEME 27

The rate of the cyanation reaction was influenced by substituents on the aryl halide.[89] It was found that o-substituted aryls were less reactive than the analogous m-and p-substituted compounds and that the reaction rates decreased on passing from electron releasing to electron withdrawing groups. These findings can possibly be explained in terms of the relative stabilities of the intermediate Ni^{II} complexes, an increase in stability causing a decrease in the rate of cyanation. Electron releasing groups will obviously assist the reductive elimination process.

Trialkylphosphines were found to be less suitable than triarylphosphinesas ligands in the nickel catalysed cyanations because they formed more stable Ni^{II} complexes.

A Ni^{0} complex has been used to bring about the ring closure step in the synthesis of cephalotaxine (54) (Scheme 28).[86]

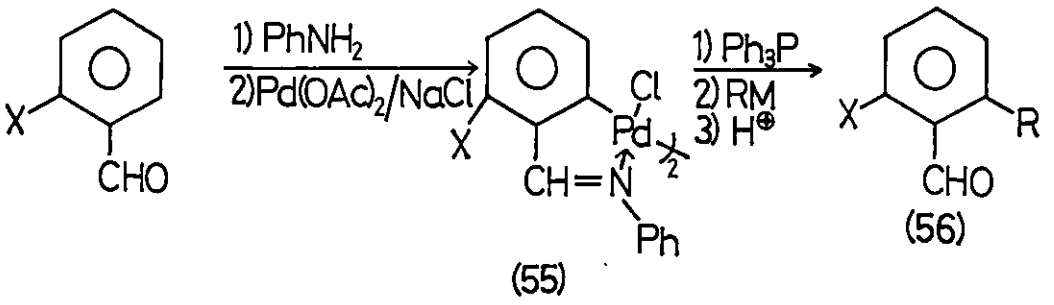


SCHEME 28

A selective method for ortho-alkylating or arylating benzaldehydes has been developed involving cyclometallated palladium complexes (55) (Table 14).[100] The added phosphine caused the splitting of dimer (55) into two phosphine coordinated monomer complexes. Subsequent metathetical exchange of the chloro group by alkyl or aryl groups, followed by

reductive elimination and cleavage of the imine with acid, resulted in the formation of the ortho-substituted benzladehydes (56).

TABLE 14 [100] Reaction of Benzaldehydes with Nucleophiles via Cyclometallated Palladium Complexes.



X	RM	Yield (56) (%) [a]
H	MeLi	95
CH_3	MeLi	86
CH_3	MeMgX	70
CH_3	n-PrLi	90
CH_3	i-PrLi	6
CH_3	n-BuLi	75
CH_3	s-BuLi	10
OMe	MeLi	85
Cℓ	MeLi	60

[a] Based on (55)

Secondary alkyllithiums also underwent the cross-coupling reaction but they were accompanied by isomerisation of the alkyl group in the alkyl palladium complex. No secondary product was formed from n-propyl

lithium and so it was proposed that the isomerisation process occurs to release the strain between the branched alkyl chain and the phenyl rings of the triphenylphosphine ligand.

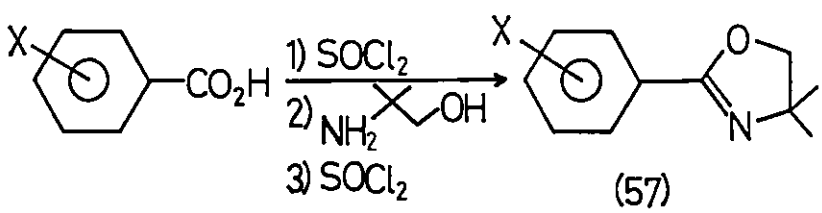
Unsubstituted benzaldehydes were obtained as by-products of these coupling reactions by reductive elimination from the palladium hydride complex produced by β-elimination of alkene from the intermediate alkyl palladium complex. The addition of phosphines retards the β-elimination process because of the increased stability of the alkyl palladium complex.

Azobenzenes and tertiary benzylic amines can also be ortho-alkylated via their cyclometallated palladium complexes.[100]

2) ARYLOXAZOLINES

Preparation

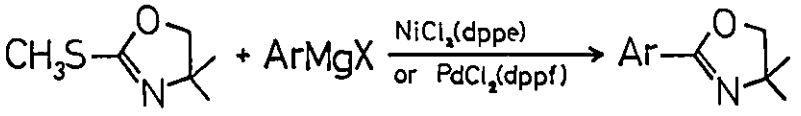
Aryloxazolines (57) are easily prepared from the corresponding benzoic acids (Scheme 29).[101]



(57)

SCHEME 29

An alternative method of preparation has recently been reported involving a palladium or nickel catalysed cross-coupling of aryl Grignard reagents with 2-(methylthio)-4,4-dimethyl-2-oxazoline (58) (Scheme 30).[102] This procedure may prove useful when the benzoic acid or benzonitrile precursors are not available.



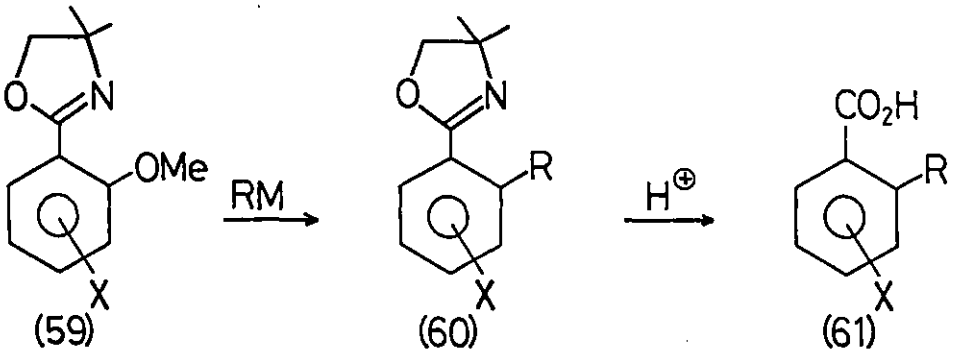
(58)

SCHEME 30

Nucleophilic Substitution Reactions

Meyers, et al.,[103] have found that the o-methoxy substituent of 2-methoxy-aryloxazolines (59) can be nucleophilically displaced by various Grignard and organolithium reagents (Table 15). The Grignard reagents were shown to be more effective than the analogous organolithium reagents.

TABLE 15 [103] Reaction of 2-methoxy-aryloxazolines with Grignard and Organolithium Reagents.

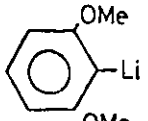
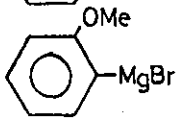
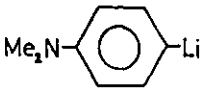
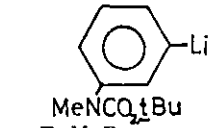


(59) (60) (61)

X	RM	Yield (60) (%)	Yield (61) (%)
H	n-BuLi	22	74
H	n-BuMgBr	85	
H	PhLi	45	75
H	PhMgBr	95	
3-OMe	n-BuLi	98	93
3-OMe	t-BuLi	95	45[a]
3-OMe	$PhCH_2MgBr$	6	
3-OMe	$Ph(CH_2)_2MgBr$	88	91
3-OMe	(E)- PhCH=CHMgBr	61	87

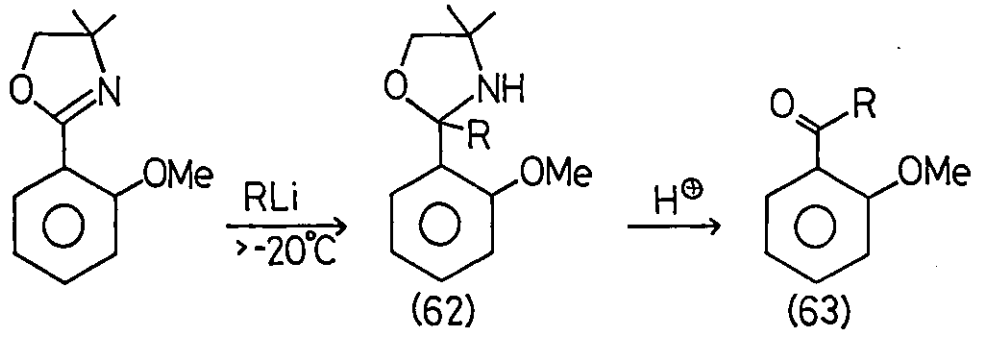
/... continued

TABLE 15 (continued)

X	RM	Yield (60) (%)	Yield (61) (%)
3-OMe	PhC≡CMgBr	31	67
3-OMe		13	
3-OMe		95	78
3-OMe		66	69
3-OMe		51	65[a]
4-OMe	EtMgBr	50	
4-OMe	n-BuLi	47	
6-OMe	n-BuLi	49	
6-OMe	$Ph(CH_2)_3MgBr$	18	
6-OMe	PhMgBr	50	

[a] hydrolysis performed on methiodide salt.

The reactions with organolithium reagents had to be performed at -30°C to -45°C because at higher temperatures (> -20°C) slow addition to the C=N link of the oxazoline occurred with formation of (62) (Scheme 31). Hydrolysis of (62) gave the ketone (63).

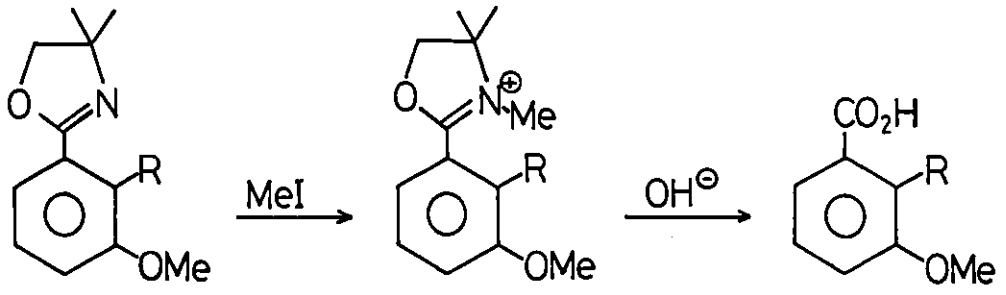


(62) (63)

SCHEME 31

A general side reaction that was observed, particularly with the Grignard reagents, was the formation of phenol (61, R=OH) in 5-50% yield.

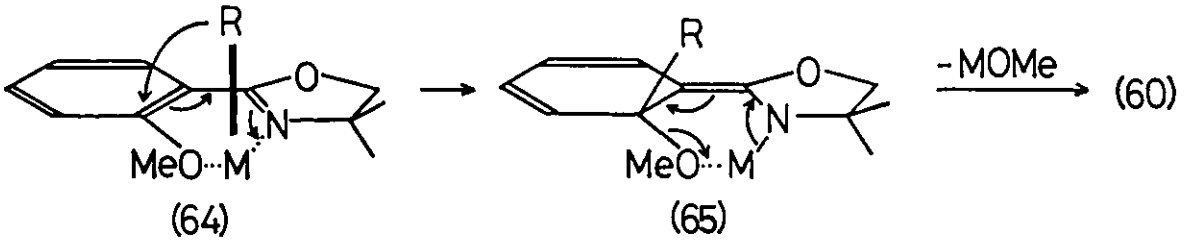
The oxazoline activating group was usually removed by acid hydrolysis. An alternative method was employed when acid sensitive substituents were present. This involved the formation of a methiodide salt followed by alkaline hydrolysis (Scheme 32).



SCHEME 32

Hydrolytic removal of the oxazoline group in 2,6-disubstituted-aryloxazolines has so far proved unsatisfactory, presumably because of the large steric effects which are operating.

The mechanism proposed for the reaction of the 2-methoxy-aryl-oxazolines (59) with organometallic reagents involves initial complexation of the metal to both the methoxyl group and the nitrogen atom of the oxazoline moiety (64) (Scheme 33). The R group of the organometallic then enters from the side, almost perpendicular to the aromatic ring, which would account for the lack of steric inhibition observed. The enamine like intermediate (65), in which the aromatic and oxazoline rings are coplanar, subsequently rearomatises to (60) by loss of MOMe.



SCHEME 33

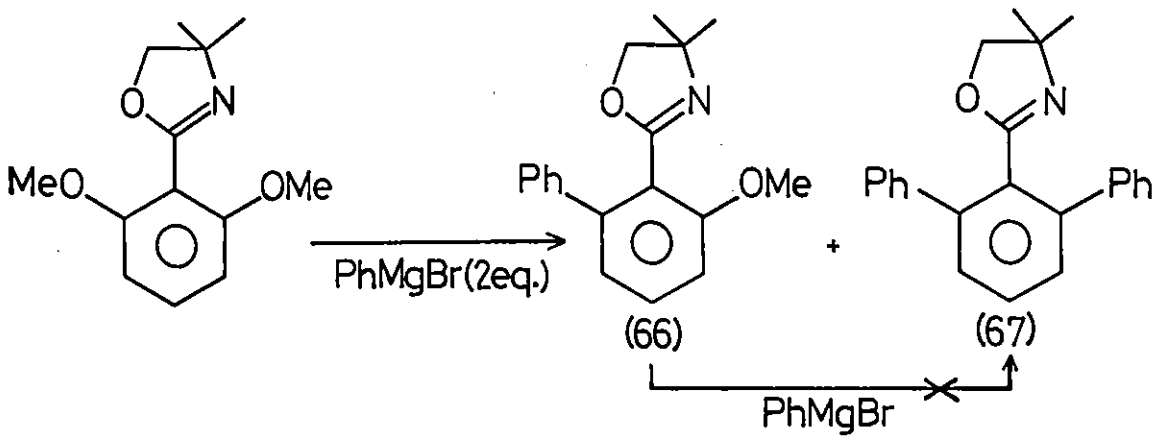
An addition-elimination mechanism has previously been invoked to explain the nucleophilic substitution of o-methoxy groups in 2,3-dimethoxy-benzonitrile and 2-methoxy-6-methyl-azobenzene by organometallic reagents.[104,105]

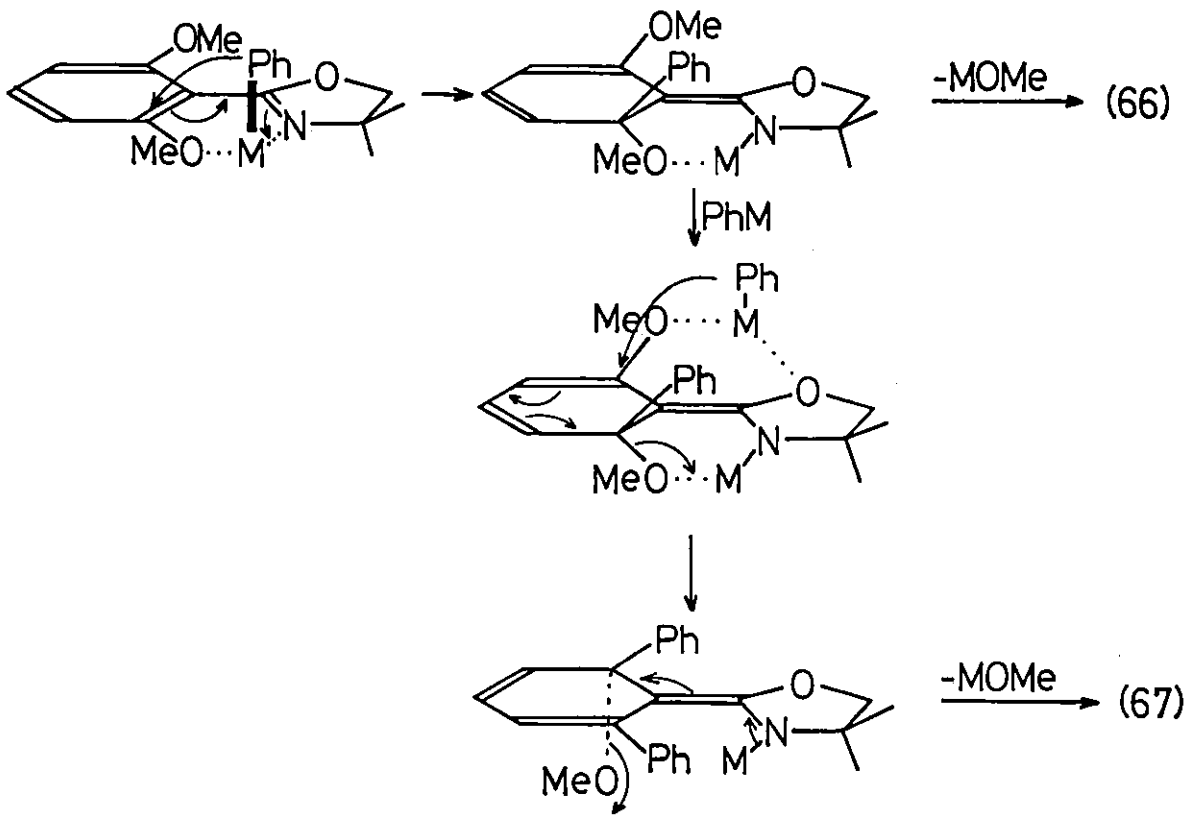
Organometallic complexation is fundamental to the 2-methoxy-aryloxazoline displacement reaction. The failure of anions to add to the aromatic ring can be due to either the anion in complex (64) being sufficiently stabilised to prohibit its addition or to the intramolecular complexation already present in the organometallic precluding any complexation with the aryloxazoline.

2,6-Dimethoxy-phenyloxazoline (59, X = 6-OMe) was found to be less reactive to organolithium reagents than the other 2-methoxy-aryloxazolines. This may be attributed to the fact that the two o-methoxy substituents inhibit the oxazoline from achieving coplanarity with the aromatic nucleus.

Aryloxazoline (59, X = 6-OMe), which has potentially two displaceable o-methoxy groups, reacted with two equivalents of phenyl magnesium bromide to yield a 1:1 mixture (93%) of the mono- and di-arylated products (66) and (67). (66) on treatment with phenyl magnesium bromide failed to produce any (67) thus disproving its intermediacy in the formation of the terphenyl derivative. A reaction pathway has been proposed to account for these observations (Scheme 34).

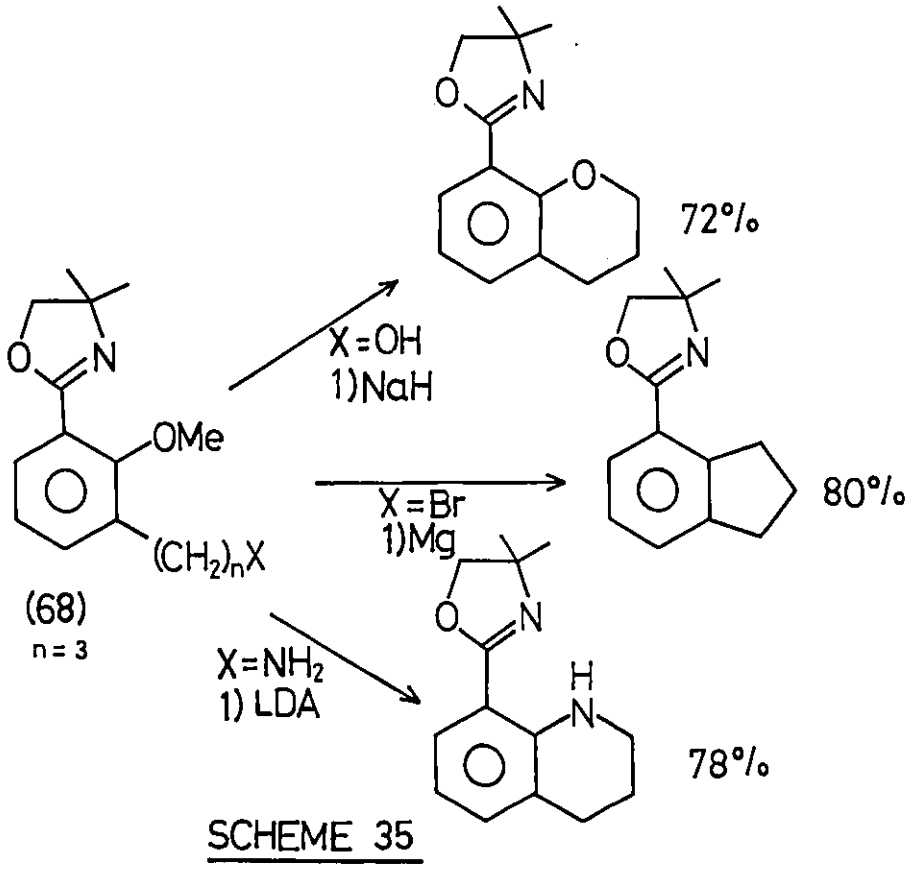
The displacement of the o-methoxy substituent in aryloxazolines has been investigated with other nucleophilic reagents. Lithioamines[106] and lithiotrimethylsilanes[103] have proved successful. An intramolecular


MeO
OMe
PhMgBr(2eq.)
Ph
OMe
(66)
Ph
Ph
(67)
PhMgBr


OMe
Ph
MeO···M
-MOMe
(66)
PhM
Ph
MeO····M
MeO···M
Ph
MeO
-MOMe
(67)

SCHEME 34

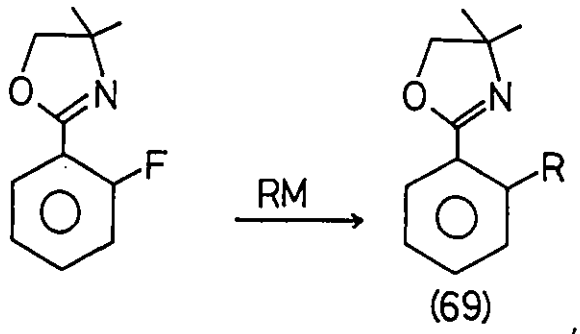
nucleophilic displacement has been used in the synthesis of a variety of benzo-fused ring systems (Scheme 35).[107] Similar reactions were also obtained with the aryloxazoline analogues (68, n = 2,4).



SCHEME 35

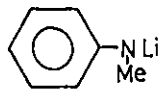
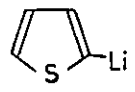
It has been found that the o-fluoro group of 2-fluoro-phenyloxazoline can be displaced by various lithium or magnesium (but not sodium or potassium) nucleophiles (Table 16),[108] the proposed mechanism being similar to that already described for methoxy displacement.

TABLE 16[108] Reaction of 2-fluoro-phenyloxazoline with Grignard and Organolithium Reagents.

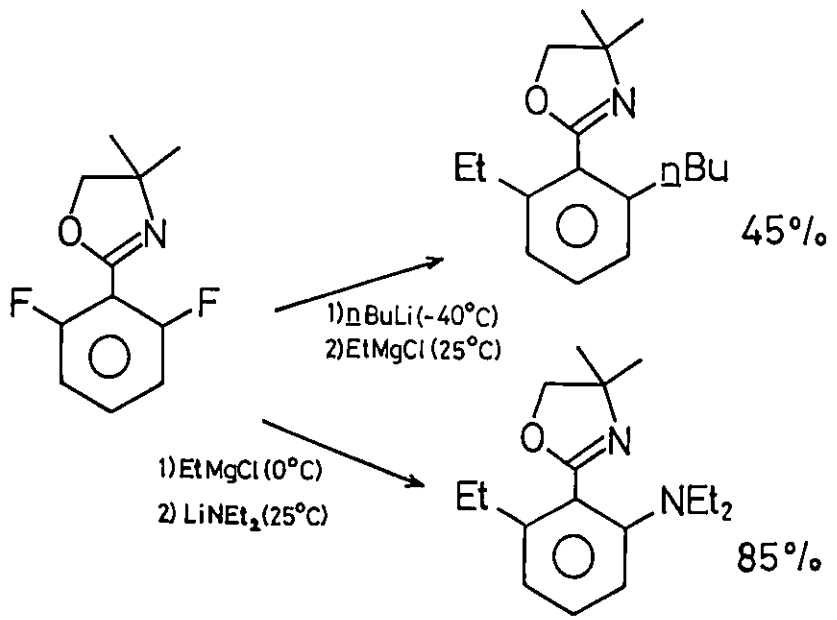


/... continued.

TABLE 16 (continued)

RM	Yield (69) (%)
n-BuLi	92
EtMgCℓ	95
LiN(i-Pr)$_2$	70
LiNEt$_2$	95
	98
	30

2,6-Difluoro-phenyloxazoline can be efficiently disubstituted, higher temperatures being required to introduce the second substituent due to steric crowding of the two ortho-groups. By controlling the conditions, two different substituents can be attached to the ring (Scheme 36). The order of addition of the two organometallics may be a critical factor in the formation of sterically crowded molecules.



SCHEME 36

OTHER METHODS OF NUCLEOPHILIC AROMATIC SUBSTITUTION

1) $S_{RN}1$ REACTIONS

Aromatic $S_{RN}1$ reactions were reviewed by Bunnett[109] in 1978. A brief summary of the main features of this kind of substitution and a discussion of the more recent developments are included in this section.

Substitution occurs by a radical chain mechanism (Scheme 37). The chain process can be initiated by solvated electrons supplied by alkali metals in liquid ammonia,[110] electrons from an electrode set at a suitable potential[111] and photochemical stimulation.[112] The first two initiation methods involve the formation of the anion radical of the substrate, $ArX^{\cdot-}$, which then enters the propagation cycle. No significant evidence has been presented as to the exact nature of the photoinitiation process although it has been suggested that a photon induced electron transfer from the nucleophile to the substrate occurs *via* a charge transfer complex.[113]

$$ArX^{\cdot-} \longrightarrow Ar^{\cdot} + X^{-}$$

$$Ar^{\cdot} + Y^{-} \longrightarrow ArY^{\cdot-}$$

$$ArY^{\cdot-} + ArX \longrightarrow ArY + ArX^{\cdot-}$$

SCHEME 37

The commonly employed leaving groups for solvated electron initiated $S_{RN}1$ reactions are F, Cℓ, Br, I, NMe_3^+, OPh, $OPO(OEt)_2$, and SPh. Less electronegative groups were found to be unsuitable because cleavage of the radical anion intermediate led to the formation of phenyl anions instead of phenyl radicals.

The reactivity order of the leaving group in photolytically promoted substitutions is I ∿ Br > SPh >> Cℓ > F >> OPh.[112]

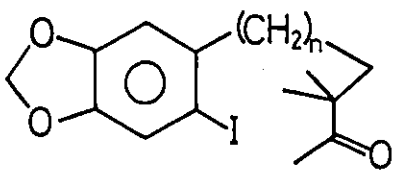
The nucleophiles which have been found to participate in aromatic $S_{RN}1$ reactions include ketone enolates,[114] ester enolates,[115] α-cyanoalkyl anions,[116] cyanide ion,[117] thiolates[118] and amide anion.[110] Phenoxide, acetylides and stabilised carbanions (e.g., diethyl malonate anion) have proved ineffective in these reactions.[115] It was suggested that β-dicarbonyl compounds are unreactive because they are insufficiently nucleophilic to combine fast enough with phenyl radicals to maintain the propagation cycle in competition with termination steps.

Electron transfer to the aryl radical competes with the initiation and propagation steps of the substitution pathway. A study of homogeneous $S_{RN}1$ aromatic substitution processes showed that the main termination steps involved electron transfer from $ArX^{\cdot-}$ and $ArNu^{\cdot-}$ to an aryl radical in solvents of low hydrogen donating ability.[117] The propagation cycle therefore produces the elements of its own destruction. The termination steps ultimately lead to the hydrogenolysis product and hence contribute to lowering substitution yields. However, the more rapid the rotation of the propagation cycle the less hydrogenolysis product will be formed.

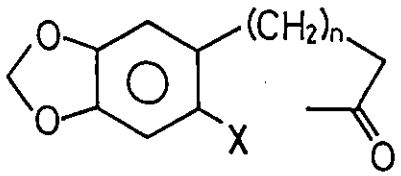
The nature of the halo group in the $S_{RN}1$ reactions of phenyl halides with enolates was found to influence the substitution process.[119] It was proposed that the better the leaving group the more rapidly ArX could be reduced by $ArNu^{\cdot-}$ and hence the lower the efficiency of the termination steps.[117] The yield of hydrogenolysis product increased on passing from I to Br, Cℓ and F. An additional termination step was also observed in these reactions involving the reduction of the $ArNu^{\cdot-}$ species to its corresponding alcohol.

It has been found that the yield of substitution product in low efficiency reactions can often be improved by increasing the ratio of nucleophile to substrate concentrations.[117]

The scope of carbon-carbon bond formation in photoinitiated intermolecular $S_{RN}1$ reactions has been investigated.[115] It was found that under comparable conditions a primary ketone enolate reacts more rapidly than either a tertiary enolate or the enolate from acetophenone. The slow reactions appear to be due to inefficient chain-carrying steps in the radical chain process; more intense . and longer irradiation gives complete conversion and reasonable yields. In those cases where there is a choice of coupling at a primary or tertiary carbon there is a higher selectivity for the less substituted site. Primary and secondary ester enolates react smoothly but tertiary ester enolates proceed very slowly.



(70)
n = 0, 2, 4



(71)

The factors effecting the intramolecular $S_{RN}1$ reactions of haloarenes were also examined.[115] Iodo ketone (70), where only the external enolate was formed, underwent cyclisation. The reaction with the higher analogue (70, n = 4) was less efficient and even under dilution conditions gave relatively low yields of cyclised material; the product from reduction of the iodide was also observed in this case.

The regio-selectivity of the reactions of ketone (71), which can give two enolate anions, were studied. Both the expected cyclised products were obtained from ketones (71; X = Br, n = 2,3), the larger ring product being preferred. No cyclised product was formed from (71; X = I, n = 1), reduction of the carbon-iodine bond occurring instead.

The low efficiency of the cyclisation with compounds (71; X = Br, n = 2,3) and the formation of an α,β-unsaturated ketone as a by-product from (71; X = Br, n = 3) suggested that a competing pathway operated when an internal enolate was available. Intramolecular hydrogen atom transfer from the β-position of the carbonyl unit to the proposed aryl radical was confirmed by deuterium labelling experiments. An analogous intermolecular pathway would also account for the rate retarding effect and reduced yields observed in the intermolecular $S_{RN}1$ reactions of enolates having an alkyl substituent in the 2-position.

An attempt to induce cyclisation of ester enolates onto aromatic rings proved unsuccessful.

The important advantages of an aromatic $S_{RN}1$ reaction pathway are that no activating substituents are required and that the nucleophile generally occupies the position vacated by the leaving group. The reaction mechanism is also tolerant of -R, -OR, -Ph, $-CO_2^-$ and -COR substituents, but $-O^-$ and $-NO_2$ groups have been found to interfere.[120]

An intramolecular $S_{RN}1$ reaction has been utilised by Semmelhack[121] to bring about the ring closure step (94%) in the synthesis of cephalotaxine (Scheme 28).

Indoles have been synthesised in good yields by a photostimulated reaction of ketone enolate ions with o-haloanilines.[122]

The replaceability of $-\overset{+}{N}Me_3$ and $-OPO(OEt)_2$ groups has special implications for synthesis as it enables aromatic amines and phenols, via their corresponding $-\overset{+}{N}Me_3$ and $-OPO(OEt)_2$ derivatives, to be considered as potential arylating agents for carbanions.

The side reaction in $S_{RN}1$ substitutions, involving electron capture of aryl radicals, has proved useful as a method of dehydroxylating phenols on a preparative scale, the phenols being converted to their phosphate esters before treatment with alkali metal in ammonia.[123]

2) OXIDATIVE SUBSTITUTIONS

A newly emerging class of reactions involves oxidative substitution. The aromatic molecule is first oxidised to a radical cation intermediate which is then trapped by a nucleophile to give a substituted product. The oxidants are generally metal ions but anodes have also been used to produce these substitutions.[124]

Toluene and anisole react with peroxydisulphate ion and copper(II) chloride (or bromide) to give mixtures of the corresponding o- and p-haloarenes.[125,126] The peroxy compound oxidises the substrate to produce a radical cation which is trapped by the copper(II) salt.

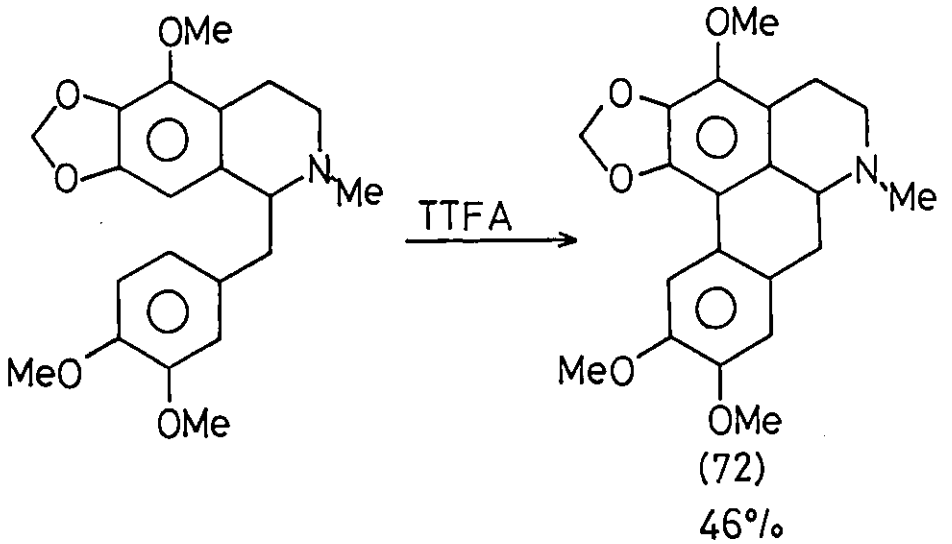
Cobalt(III) trifluoroacetate is a powerful oxidant and has enabled aromatics with ionisation potentials greater than that of benzene to undergo substitutions; chlorobenzene and benzonitrile have both been chlorinated by a lithium chloride/cobalt(III) trifluoroacetate mixture.[127]

The isomer distribution of the chlorotoluenes and dichlorobenzenes obtained from the reaction of a lithium chloride/cobalt(III) trifluoroacetate mixture with toluene and chlorobenzene, respectively, were different from those obtained when the aromatic substrates were reacted

with molecular chlorine. It was therefore suggested that the cobalt(III) chlorinations proceeded *via* a radical cation mechanism.

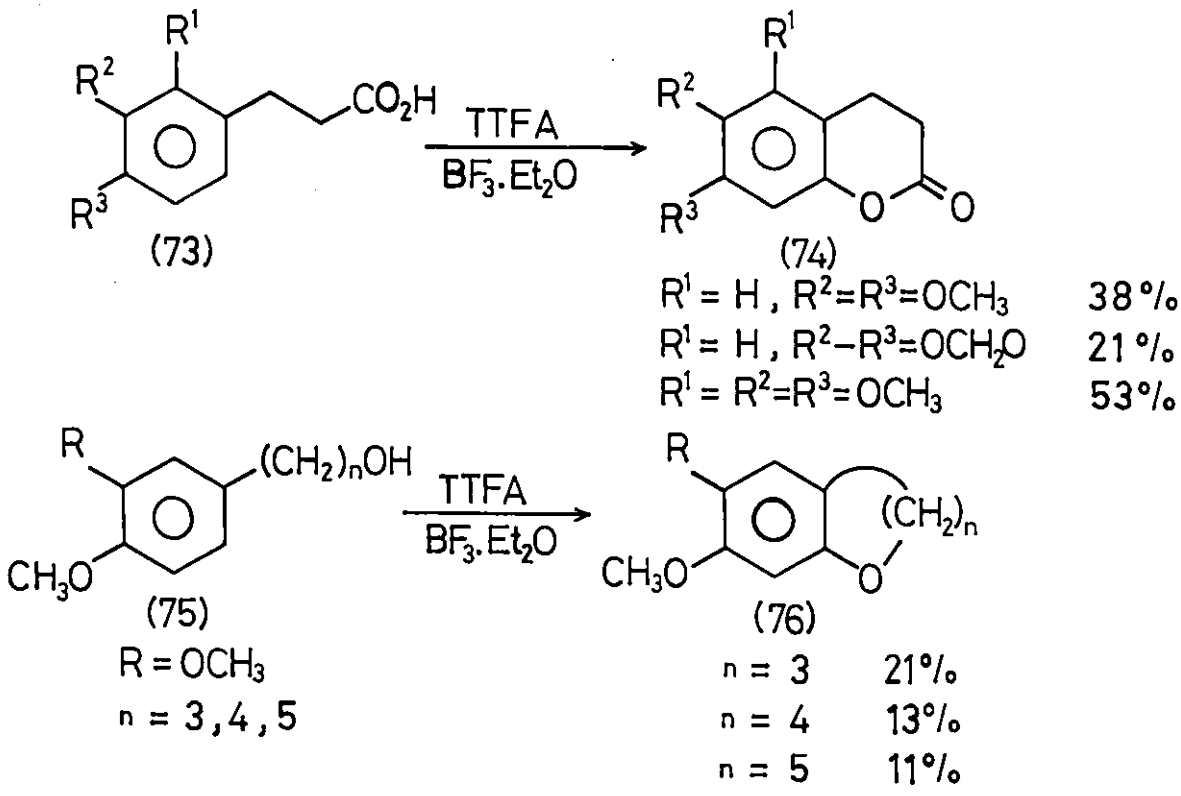
Symmetrical biaryls, including the sterically crowded 2,2'-6,6'-biaryls, have been prepared in good to excellent yields by the direct oxidative coupling of aromatic substrates using thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid.[128] This method is complementary to the Ullmann reaction[129] in that it is effective when the ring substituents are either electron donating or mildly electron withdrawing groups but failing when powerful electron withdrawing groups are present. One of the main advantages of this oxidative approach over other methods of biaryl synthesis is that the substrates no longer require a substituent group which must be lost in the coupling process.

Intramolecular coupling can also occur and has been utilised in the preparation of (±)ocoteine (72), an aporphine alkaloid (Scheme 38).[130]



SCHEME 38

Taylor, *et al.*[131] have found that radical cations can be trapped intramolecularly by suitably positioned carboxyl or alcohol groups (Scheme 39). A spirocyclohexadienone lactone was formed as a by-product in the arylalkanoic acid reactions.



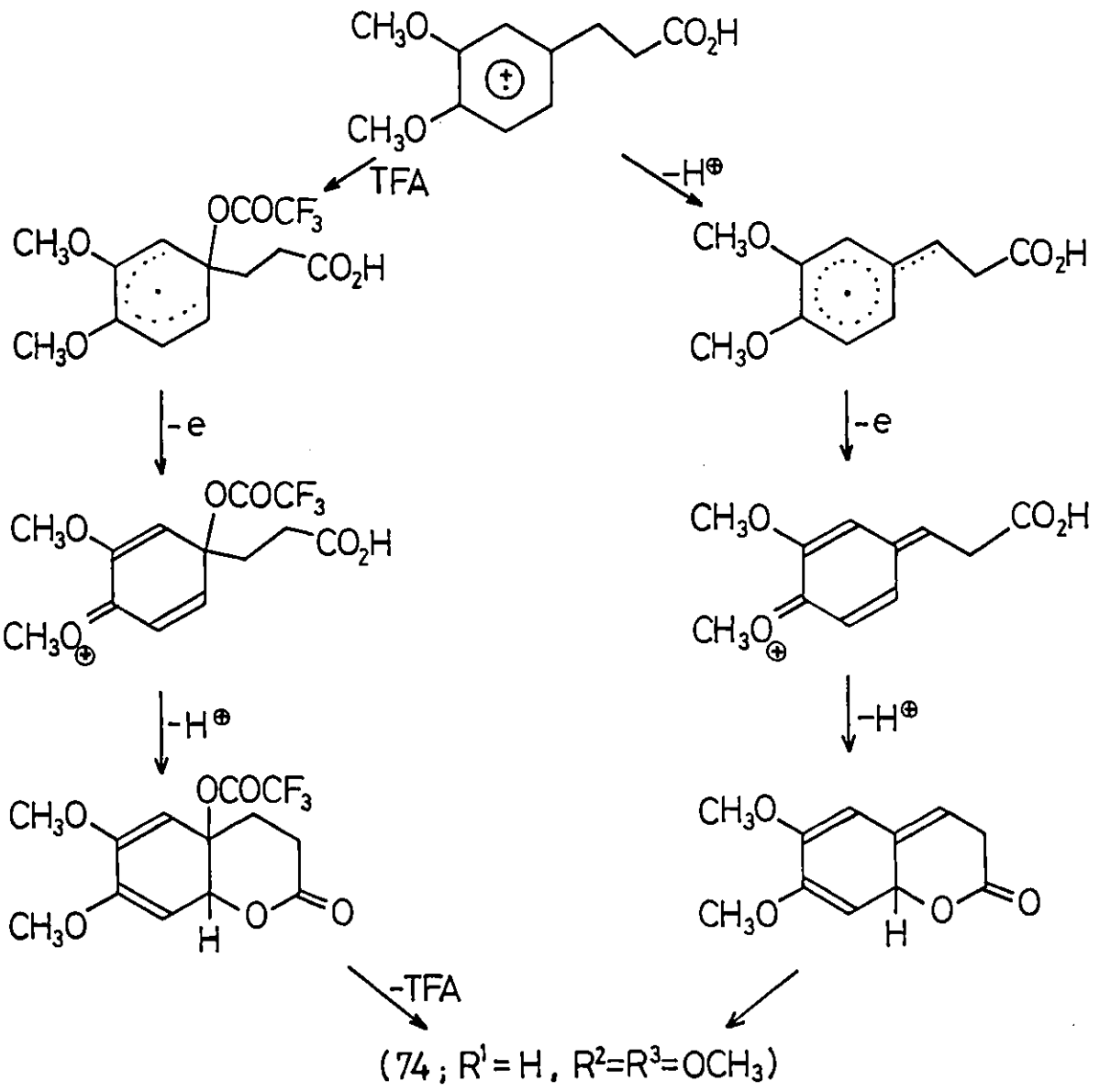
SCHEME 39

The position of the alkoxy substituent relative to the carboxyethyl group in (73) is thought to determine the fate of the radical cations. Substrates with a p-alkoxy group give dihydrocoumarins (74) whereas those without a p-alkoxy group undergo oxidative dimerisation to biaryls.

The additional methoxy group (R= OCH_3) in (75) was necessary for intramolecular cyclisation to the aromatic ring ; intramolecular cyclisation to the benzylic carbon atom occurred in (75; R = H, n = 4,5).

It is interesting to observe that electrochemical generation of the radical cation from (73; R^1= H, R^2 = R^3 = OCH_3) leads only to biaryl.[132] It has therefore been suggested that Tl^{III}, in addition to acting as an oxidant, may facilitate intramolecular reactions by complexing to both the aryl group and the carboxylic acid substituent.

Two pathways were proposed for the formation of dihydrocoumarin (74; R^1 = H, R^2 = R^3 = OCH_3) (Scheme 40). The first involved intermolecular capture of the radical cation by solvent (TFA), oxidation of the resulting radical, intramolecular Michael addition by the carboxylic acid group and aromatisation. The alternative mechanism involved deprotonation, oxidation and intramolecular Michael addition.



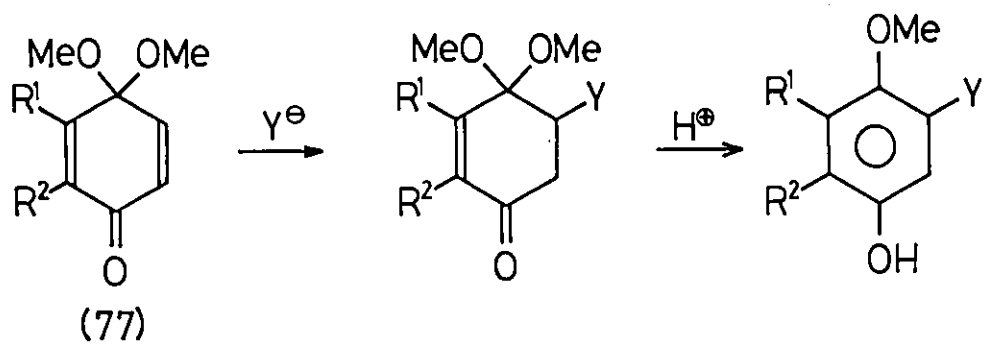
SCHEME 40

It is important to note that the oxidation potential of an aromatic substrate is the major factor which determines its reaction course when it is treated with thallium trifluoroacetate, i.e., electrophilic aromatic thallation or oxidative coupling.

Arylthallium (III) ditrifluoroacetates, which are obtained on aromatic thallation, react with a variety of anions to form compounds of the type $ArTlX_2$. These compounds have been found to be useful intermediates for the regio-specific synthesis of a wide range of functionalised aromatics including nitriles,[133] iodides[134] and fluorides.[135]

3) QUINONE MONOACETAL INTERMEDIATES

Substituted 4,4-dimethoxy-cyclohexa-2,5-dienones (77) are prepared from their corresponding 4-methoxy phenols by oxidation with thallium(III) nitrate.[136] These quinone monoacetals can be considered as aryl cation equivalents since they have been found to undergo 1,4-addition reactions with nucleophiles to produce substituted aryls on acidification (Scheme 41).[137]



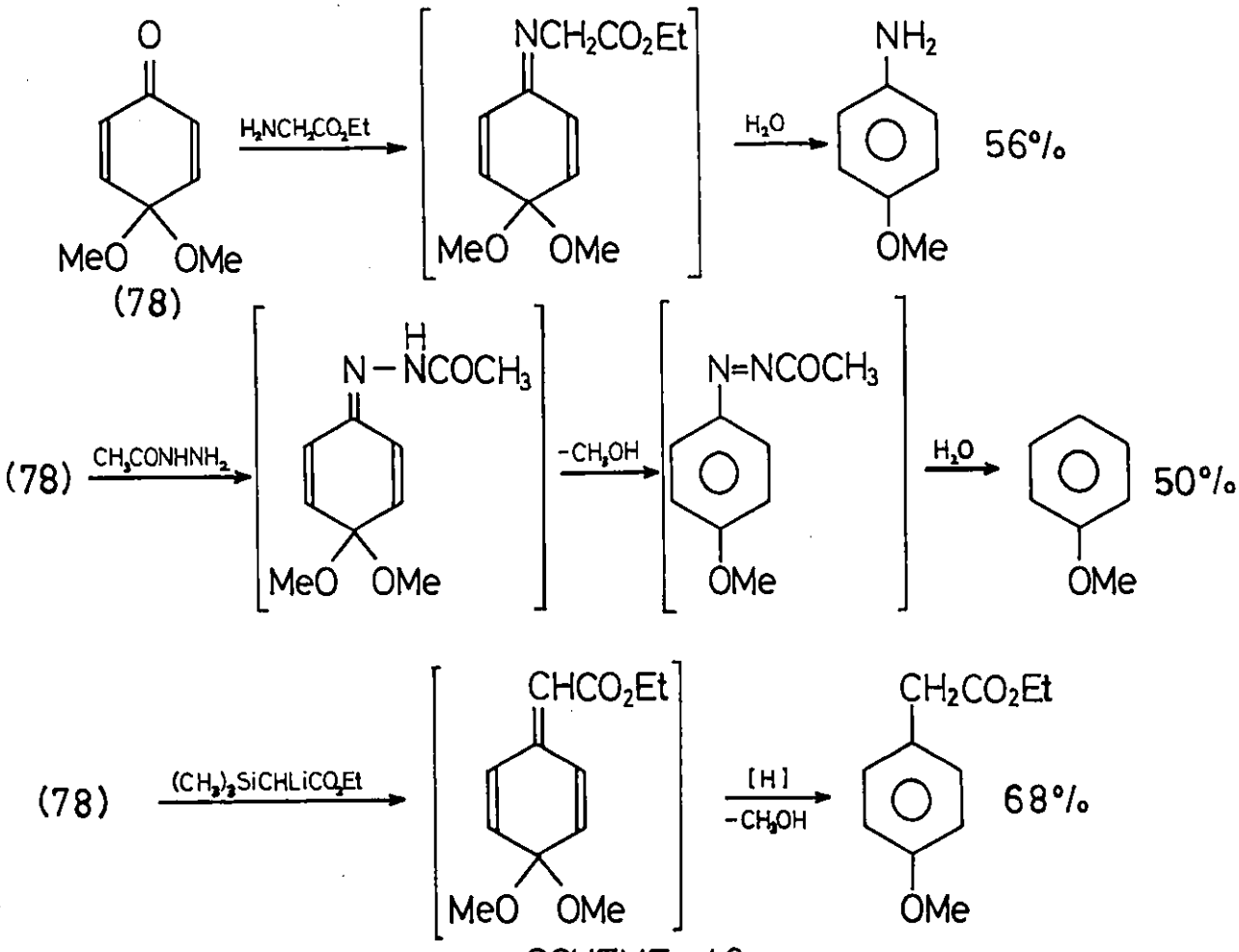
(77)

SCHEME 41

The addition of malonate anion to quinone monoacetals and the subsequent aromatisation by acid proceeded in good yield. However, the corresponding sequence with keto esters followed various alternative pathways depending on the conditions employed and the substituents present. The reactions with ethylacetoacetate involved an initial intermolecular Michael addition and the adduct produced then underwent either an intramolecular Michael reaction, with C- or O-alkylation, or an internal aldol condensation. Acidification resulted in aromatisation with the formation of benzofurans.

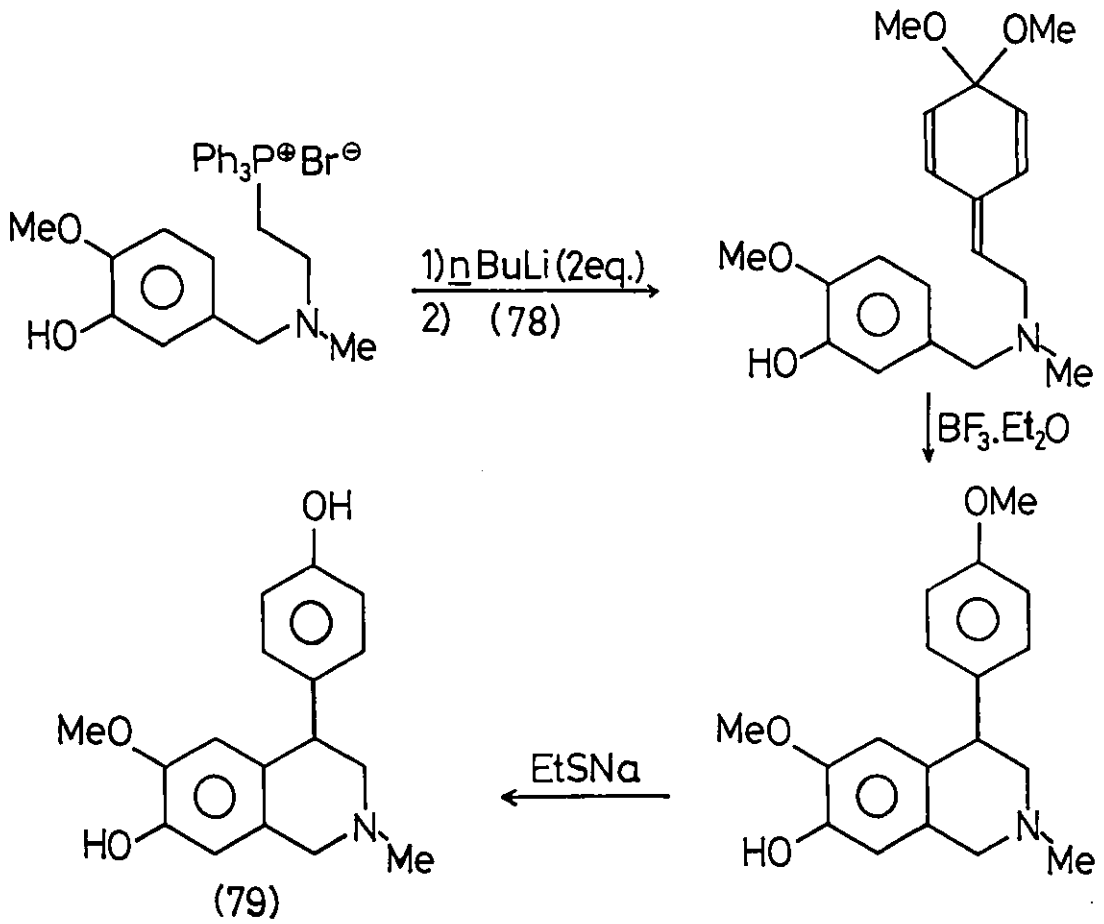
Alcohols, thiols and amines have also been reported to undergo 1,4-additions to quinone monoacetals.[138]

4,4-Dimethoxy-cyclohexa-2,5-dienone (78) has been used to effect the overall replacement of the hydroxyl group of the phenol precursor by amino, hydrogen and carbon substituents, among others (Scheme 42).[139]



SCHEME 42

The conversion of p-quinone monoacetals into p-quinone methide ketals and subsequent aromatisation represents a potential synthetic method for arylation of carbanions. Evans, et al.[140] have used such a sequence in the synthesis of the Amaryllidaceae alkaloid cherylline (79) (Scheme 43).



SCHEME 43

SUMMARY

Nucleophilic aromatic substitutions are facilitated by the introduction of various π-bonded electron withdrawing groups. Chromium tricarbonyl is considered to be a more useful activating group than manganese tricarbonyl and iron cyclopentadienyl because it can be introduced and removed in high yields and its η^6-(arene) complexes react efficiently with nucleophiles. These nucleophilic substitutions proceed with selective halo and regio-selective hydride replacement.

In addition to nucleophilic substitutions, tricarbonyl η^6-(arene) chromium(0) can be selectively metallated and these derivatives are capable of elaboration with a variety of electrophiles.[141] This diversity of reactivity that chromium tricarbonyl complexes exhibit make them potentially attractive synthetic intermediates but the high cost of chromium hexacarbonyl may prove prohibitive to its use in synthesis. However, methods of recovering the chromium tricarbonyl unit on decomplexation are being investigated.[20,142]

Tricarbonyl η^5-(cyclohexadienylium)iron(0) cations react with a variety of nucleophiles but the number of steps involved in bringing about an overall aromatic substitution greatly reduces the synthetic value of such a procedure.

Nickel(0) and palladium(0) complexes enable the halo group of aryl halides to be selectively replaced by nucleophiles. These oxidative addition-reductive elimination reactions are catalytic and proceed in good yields with a variety of anions.

Benzaldehydes, azobenzenes and tertiary benzylic amines can be ortho-alkylated or arylated via their cyclometallated palladium complexes.

The conversion of benzoic acids to their corresponding oxazolines enable o-methoxy and o-fluoro groups to be selectively replaced by certain nucleophilic reagents (RM). The metal complexes to both the oxazoline group and the ortho-substituent. The R group then enters from the side,almost perpendicular to the aromatic ring,which accounts for the lack of steric inhibition which is observed.

Chiral binaphthyls have recently been synthesised by a method involving the nucleophilic aromatic displacement of an o-methoxy group activated by chiral oxazoline.[143] Axially dissymmetric binaphthyl derivatives are of interest because of their extraordinary chiral recognition properties which enable the separation of racemic mixtures by selective complexation to one enantiomer.[144]

Aryloxazolines, like tricarbonyl η^6-(arene) complexes, undergo selective o-metallation reactions and subsequent elaboration with electrophiles.[101] This diversity of reaction has been utilised in the synthesis of several lignan lactones where electrophilic and nucleophilic processes were involved.[145]

No activating groups are necessary in radical chain substitutions ($S_{RN}1$) and the nucleophile occupies the position vacated by the leaving group. A number of leaving groups can be employed and the reactions are tolerant of various substituents. However, the failure of β-dicarbonyl anions to react suggests that good nucleophiles are required in $S_{RN}1$ reactions to maintain the propagation cycle in competition with the termination steps.

Symmetrical biaryls and dihydrocoumarins have been synthesised by aromatic oxidations with thallium(III) trifluoroacetate. These reactions involved radical cation intermediates.

Substituted 4,4-dimethoxy-cyclohexa-2,5-dienones can undergo simple transformations which result in an effective overall replacement of the hydroxy group of its phenol precursor by carbon substituents. These cyclohexadienones also react with nucleophilies via a 1,4-addition to give substituted aryls on acidification.

In conclusion, it is suggested that two of the methods of nucleophilic aromatic substitution which have been discussed are potentially of major synthetic importance. The first is the palladium or nickel catalysed replacement of halo substituents and the second involves the use of a chromium tricarbonyl activating group.

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NEW APPROACHES TO AROMATIC FLUORINATIONS

INTRODUCTION

a) Methods of Aromatic Fluorination

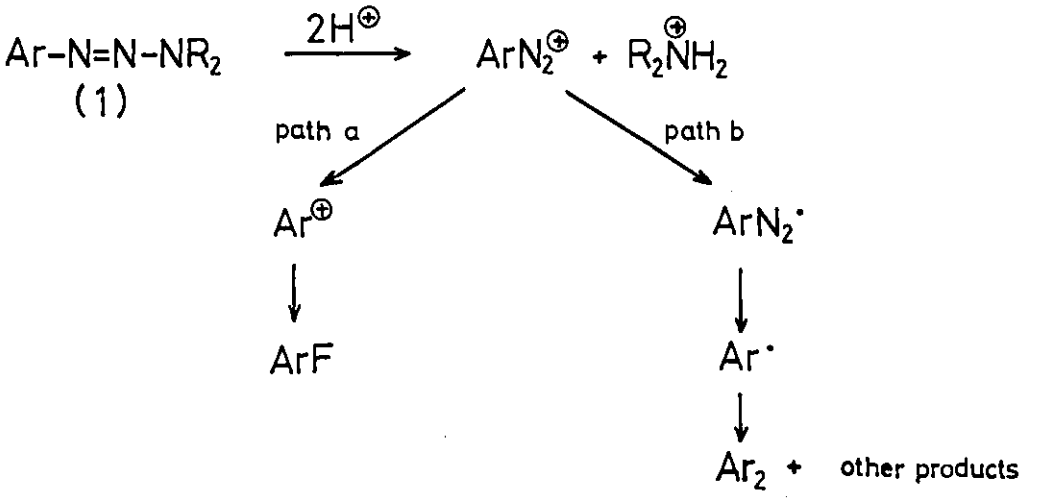
No general procedure is available for controlled monofluorinations of aromatic compounds, although the initial findings with xenon difluoride show great potential.[1] The two most widely used methods of introducing a fluoro group into an aromatic nucleus are nucleophilic fluoride displacements of activated halogen groups[2] and the Balz-Schiemann reaction.[3]

The applicability of the displacement method is limited because of the need to activate the ring to nucleophilic attack; the introduction and removal of the activating electron withdrawing substituents can often be problematical.

The Balz-Schiemann reaction involves the thermal decomposition of arenediazonium tetrafluoroborates or hexafluorophosphates[3] and results in the formation of isomerically pure fluoro products. The diazonium salts are readily produced by the diazotisation of aromatic amines under aqueous[4] or anhydrous conditions.[5]

The diazotisation of aminoarenes in hydrogen fluoride (aqueous,[6] pure[7] or 70% in pyridine[8]) yields aryl fluorides directly, obviating the need to isolate the diazonium salt intermediate. However, the pyridinium poly(hydrogen fluoride) diazotisation procedure sometimes gives rise to isomeric mixtures. A fast intramolecular 1,2-hydride shift in aryl cations, the ambident nature of aryldiazonium ions and the intermediacy of arynes have been suggested as possible explanations to account for the observed formation of isomers.

Fluorinations via diazotisation of aromatic amines in hydrogen fluoride often give poor yields. The major by-product of these reactions results from homolysis of the aryl-nitrogen bond in the diazonium ion. This is thought to be brought about by reduction with electron donors such as the lower nitrogen oxides [9] (Scheme 1, path b).



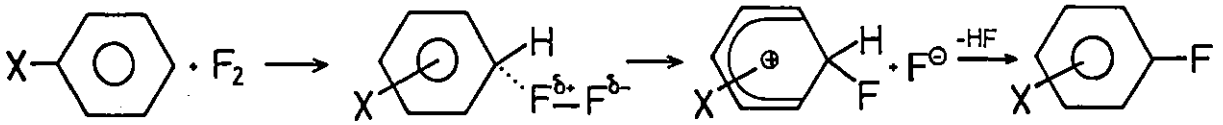
SCHEME 1

The treatment of aryl triazenes (1) with mild acids enable diazonium ions to be produced in the absence of nitrogen oxides. The generation of aryl cations can therefore be maximised if the reaction system is largely free of initiators of radical decomposition (Scheme 1, path a). Aryl fluorides have been obtained from their corresponding triazenes using pyridinium poly(hydrogen fluoride),[10] caesium fluoride/methanesulphonic acid[11] and 48% aqueous hydrofluoric acid.[12]

Aryl residues substituted with strongly electron withdrawing groups are not efficiently fluorinated by any of the dediazoniation methods that have been discussed.

Fluorine is a very powerful fluorinating agent and is useful in the preparation of perfluorocompounds. However, under controlled conditions it has been used to monofluorinate aromatic substrates in average yields.[13] These reactions were found to be unselective, although substitution was predominantly meta in nitrobenzene and ortho/para in toluene.

The experimental findings of fluorinations carried out in the dark at extremely low $[F_2]$:[substrate] ratios suggested that these reactions proceeded via electrophilic attack of a polarised fluorine molecule on the aromatic ring (Scheme 2).[14] It should be understood that extremely low substrate conversions (< 0.01%) were involved in these mechanistic studies and that under preparative conditions or considerably higher $[F_2]$:[substrate] ratios, polymerisation and addition processes can occur at the expense of ring substitution.



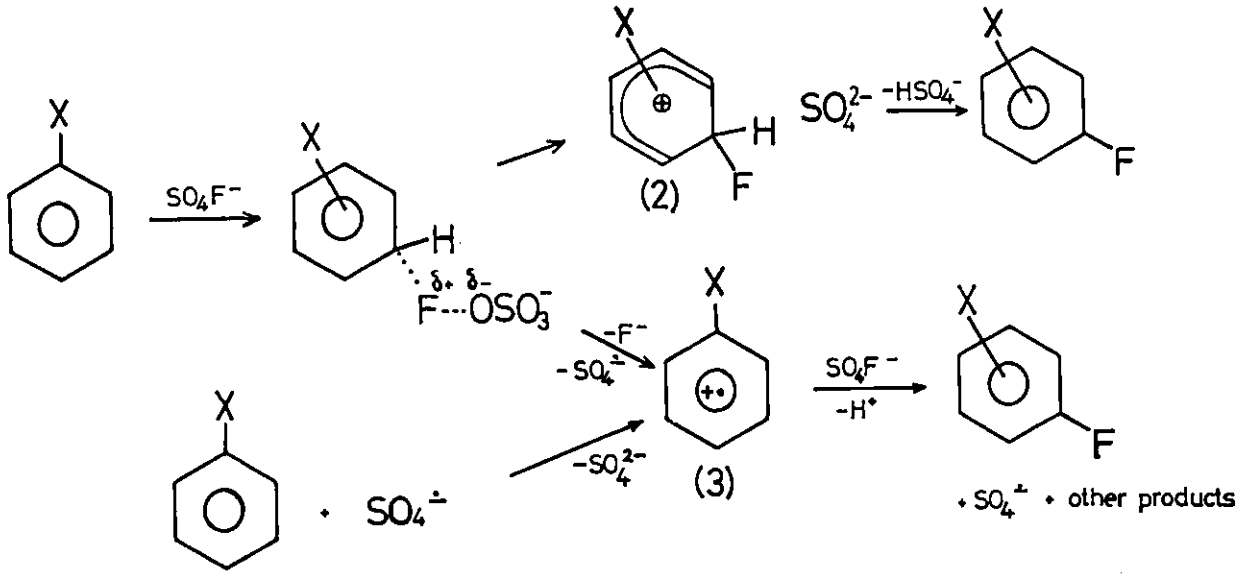
SCHEME 2

Fluoroxytrifluoromethane has been used to fluorinate aromatic compounds[15-17] and evidence suggests that these reactions are typical of perfluorofluoroxy reagents (e.g., SF_5OF, $CF_2(OF)_2$) in general.[18] The mechanism proposed for these fluorinations involves nucleophilic attack by the substrate on fluorine concerted with ejection of a suitable leaving group. The fluorine atom therefore never develops a deficiency of electrons. The ideal leaving groups must be highly electronegative to ensure disposition and have no unoccupied d-orbitals, the presence of which might facilitate nucleophilic attack upon that ligand or electron transfer.

The limitation in using fluoroxy reagents to bring about aromatic fluorinations is that an electron releasing substituent is required on the substrate to produce a predictable reaction. Unactivated benzenoid aromatics tend to give products of addition rather than substitution.

Fluoroxytrifluoromethane has also been used in photofluorination reactions; benzene, toluene and anisole when photolysed with fluoroxytrifluoromethane gave monofluoroaromatic products in yields of 65%, 34% and 42%, respectively.[19] These photofluorinations are considered to be radical chain reactions with either fluorine atoms or trifluoromethoxy radicals acting as chain carriers.

The fluoroxysulphate ion, SO_4F^-, has been shown to fluorinate aromatic compounds.[20,21] The product distributions and relative reactivities of the substrates were interpreted in terms of an initial electrophilic attack followed by the formation of either an arenium cation (2) or a radical cation (3) (Scheme 3). The arenium cation (2) subsequently produces fluorinated compounds, while the radical ion (3) brings about the additional formation of the various by-products. The free-radical process tends to predominate with deactivated substrates for which the arenium cation is relatively unstable.



SCHEME 3

The ortho isomer tends to predominate in the fluoroxysulphate reactions with the more reactive aromatics and the accompanying yields of the meta isomer are extremely small. Nitrobenzene and methyl benzoate gave mainly the meta product.

The extremely high ortho/para ratio observed in the products of the phenol reaction suggests that the fluoroxysulphate may hydrogen bond with the phenolic hydrogen and hence direct the fluorination.

Caesium and rubidium fluoroxysulphate salts have the advantage over many powerful fluorinating agents in that they are relatively stable compounds and can easily be prepared.[22] However, it should be emphasised that reasonable yields of monofluorinated products (> 30%) were only obtained when the fluoroxysulphate salts reacted with activated substrates.

Acetyl hypofluorite, prepared from elemental fluorine, possesses an electrophilic fluorine which is less polarisable and hence less reactive than the other known fluorinating compounds containing an OF moiety. This reagent enables relatively clean electrophilic fluorination reactions to occur with activated aromatics.[23]

A high ortho/para product ratio was observed in the acetyl hypofluorite reactions with substrates containing electron donating groups possessing an heteroatom. It was suggested that there was an interaction between the hypofluorite ion and the heteroatom which resulted in attack mainly at the ortho position.

Most reactive fluorinating agents yield addition products, the addition of fluorine to the aromatic ring being more exothermic by $\sim$ 15.5 Kcal/mole than is the substitution of fluorine for hydrogen. However, xenon difluoride has been found to yield monofluorinated

substitution products without any addition products being obtained.[1] This observation ruled out the possibility of fluorination occurring by generation of fluorine molecules or atoms.

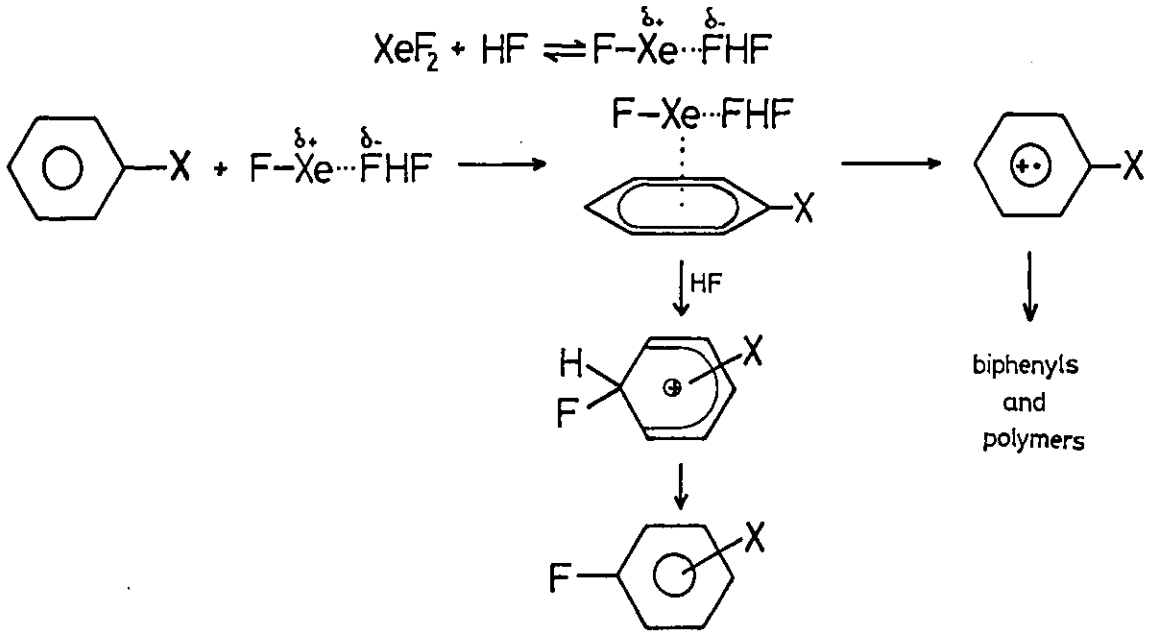
Small amounts of hydrogen fluoride are generally necessary for initiation of the xenon difluoride reaction. Once initiated, the reaction is auto-catalytic in hydrogen fluoride since about 1.2 moles of hydrogen fluoride is generated per mole of xenon difluoride added. It has been proposed that hydrogen fluoride facilitates the ionisation of xenon difluoride to XeF^+ and HF_2^-.

Aromatic compounds with oxidation potentials higher than that of benzene do not require hydrogen fluoride initiation, the aromatic substrate itself inducing the polarisation of xenon difluoride.[24]

Radical cations were initially thought to be intermediates in xenon difluoride fluorinations[25] but the effects of added chlorine and hydrogen chloride on these fluorinations indicated that radical cations were only involved in the formation of the biaryl by-products.[26]

A mechanism analogous to the nucleophilic assisted two electron transfer in anodic substitution was proposed.[26] The aromatic substrate combines with a polarised xenon difluoride-hydrogen fluoride molecule to form a π-complex which then reacts with hydrogen fluoride with the elimination of xenon (Scheme 4).

The addition of hydrogen chloride to the fluorination mixture resulted in the formation of both chloro and fluoro products. This, in conjunction with the findings that hydrogen chloride was not an effective catalyst for xenon difluoride reactions with aromatics and did not produce $XeFCl$ when reacted with xenon difluoride, lent support to the suggestion that the halo group was incorporated by an intermolecular reaction between hydrogen halide and the π-complex.

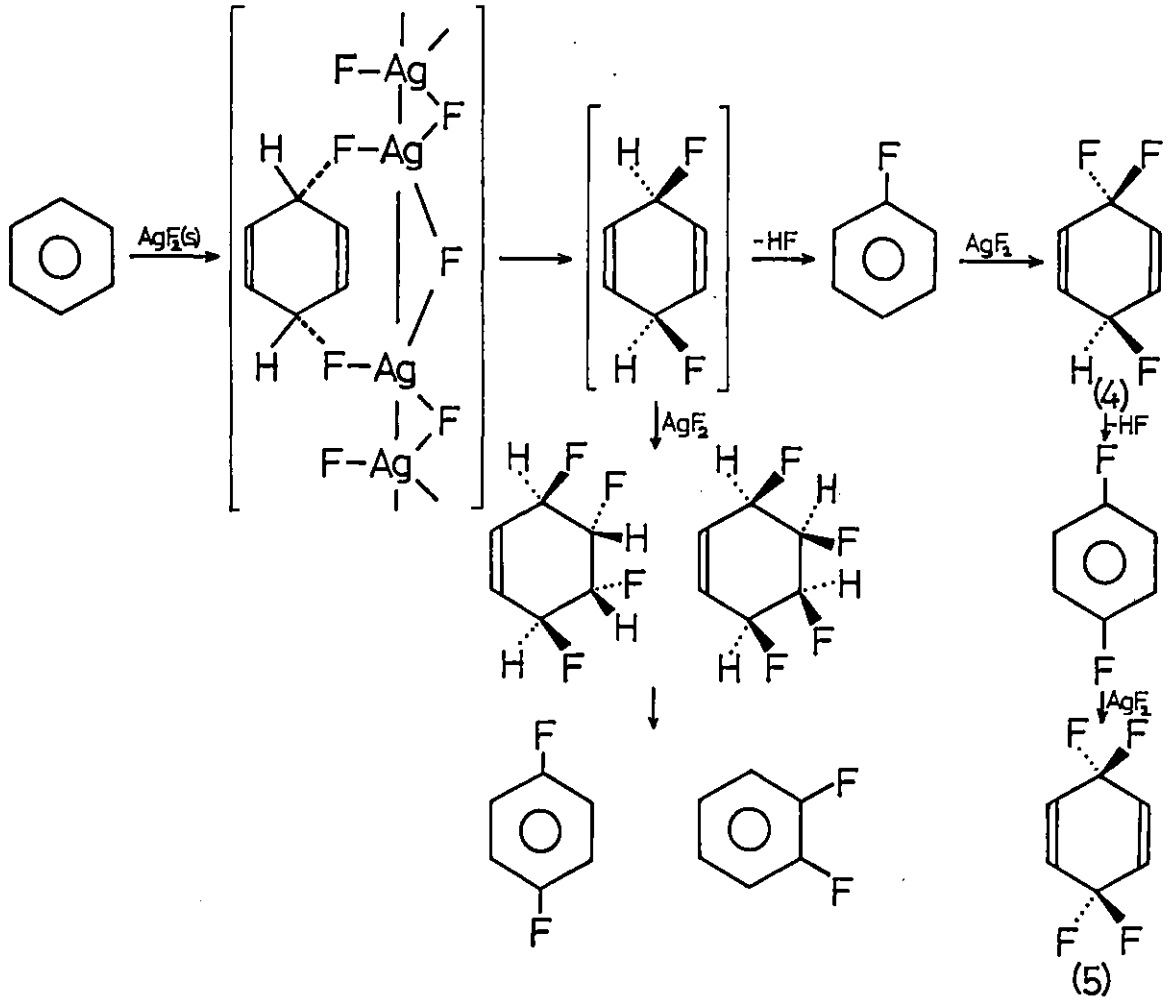


SCHEME 4

Aromatic fluorinations with xenon difluoride usually produce isomeric mixtures of the monofluorinated products in relatively high yields. The para isomer is favoured with activated aromatics except in the case of phenol which gives a high meta yield.[24] Meta substitution is preferred with nitrobenzene and benzotrifluoride.[26] The L-stereoisomer of 6-fluorodopa has been synthesised by direct fluorination with xenon difluoride.[27]

Oxidative aromatic fluorinations involving the use of high valency metal fluorides[28] or electrolytic methods [29] are of limited practical significance because of the large number of by-products that are produced and the strong preference for substrates with lower ionisation potentials. Radical cations are the reactive intermediates in these oxidation processes.

Silver difluoride has recently been found to selectively mono-fluorinate several aromatics.[30] The reactions are carried out in n-hexane and since neither silver difluoride nor silver fluoride is soluble in this solvent the reaction must occur on the solid surface. A careful analysis of the products of the benzene/silver difluoride reaction gave a useful insight into the mechanism (Scheme 5).



SCHEME 5

^{19}F-NMR studies on the reaction of fluorobenzene with silver difluoride provided independent evidence for the conversion sequence: fluorobenzene → (4) → p-difluorobenzene → (5). No o-difluorobezene was detected in this reaction which indicated that fluorobenzene was not an intermediate in its formation from benzene.

Free aromatic radical cations could not be intermediates in these fluorination reactions because both cis and trans isomers would have been anticipated in the addition products. It was proposed that the initial step involved an electrophilic oxidative cis-1,4-addition of two fluorine atoms from silver difluoride onto benzene. This process would probably

be facilitated by the close correspondence of the F-F distances in the complex structure of crystalline silver difluoride with the distance between the para positions in the benzene ring. Cis-1,2-additions may also occur but are less favoured geometrically.

p-Fluoroaromatics have been prepared by treating aryl hydroxylamines[31] or aryl azides[32] with anhydrous hydrogen fluoride. The azide method gives slightly higher yields and fewer by-products.

McKillop, et al.[33] have produced aryl fluorides by a simple three step process (Scheme 6). The yields obtained by this procedure are comparable to those produced by the Balz-Schiemann reaction. However, the aryl thallium(III) difluoride route is limited to aromatic substrates which contain neither powerful electron withdrawing groups nor oxygen or amino substituents. Aryl thallium(III)bis(tetrafluoroborate) is the most probable intermediate in the formation of aryl fluoride.

$$ArH \xrightarrow{TTFA} ArTl(OCOCF_3)_2 \xrightarrow{KF} ArTlF_2 \xrightarrow{BF_3} ArF$$

SCHEME 6

b) ^{18}F-Radiopharmaceuticals

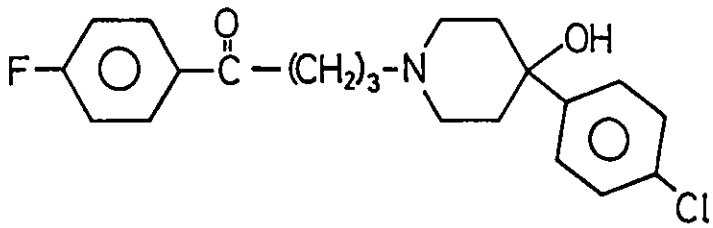
Monofluorinated aromatic ring systems often show enhanced or modified biological activity relative to the corresponding unfluorinated or phenolic compounds. This has led to an interest in the preparation of ^{18}F-radiopharmaceuticals for use in pharmacological tracer studies.[34]

^{18}F ($T_{\frac{1}{2}}$ 110 mins, β^+) is an artificially formed isotope of fluorine which can be produced with relative ease in both nuclear reactors and accelerators. It decays to ^{18}O mainly by positron emission. ^{18}F and

other β^+ emitters (e.g., ^{11}C, ^{13}N, ^{15}O) have become potentially important tools to the pharmacologist because in vivo detection using modern positron imaging devices gives more detailed positional information than is obtainable from a simple γ-emitter.

The synthesis of ^{18}F compounds have been comprehensively reviewed.[35,36] The relatively short half life of ^{18}F (110 mins) necessitates that the ^{18}F labelled compounds should be prepared by the most direct, rapid and high yielding route available. This, therefore, precludes the use of most of the conventional methods of fluorination because they require a large excess of fluorinating agent and long reaction times.

The commonest method of incorporating ^{18}F into an aromatic system is the Balz-Schiemann reaction.[35] ^{18}F is introduced by heterogeneous exchange between the diazonium tetrafluoroborate supported on an inert matrix and ^{18}F extracted from a recirculatory neon gas target.[37] [^{18}F]-Haloperidol(6)[38] is one of the many ^{18}F labelled compounds that have been prepared through a Schiemann type reaction. Unfortunately, the Balz-Schiemann reaction is very inefficient from a radiochemical point of view giving a maximum possible radiochemical yield of only 25%.



(6)

Labelled aryl fluorides have been prepared by the dediazoniation of aryldiazonium ions produced from triazenes with $H^{18}F$[12] or $Cs^{18}F$/methanesulphonic acid.[11] Theoretically all of the labelled fluoride ion could be utilised in the triazene method and so compounds of very high radio-

chemical yield could be produced. There is the added advantage that the starting triazenes are relatively stable and unlike the diazonium salts can be purified before fluorination, thus minimising contamination of the fluorine labelled products with impurities from the precursors of their decomposition products.

The recent synthesis of $[^{18}F]XeF_2$[39] may facilitate the direct radiofluorination of organic tracer molecules since it is known that xenon difluoride fluorinates a variety of organic compounds mildly and rapidly.[1]

Adam et al.[40] have synthesised $[^{18}F]$ fluorobenzene by cleaving the phenyl -tin bond of tributylphenyltin with $[^{18}F]F_2$. The tri-n-butyltin moiety can easily be attached to aromatic systems and so this approach may prove useful for the synthesis of $[^{18}F]$ fluoroaromatics if a good synthesis of dilute $[^{18}F]F_2$ in neon can be developed.

Aryl azides decompose in hydrogen fluoride to produce p-fluoranilines which can be reductively deaminated. This approach has been considered for the preparation of radiofluorinated compounds[12] but at present the long reaction times for the reductive deamination step prevent it from becoming a viable method for ^{18}F incorporation.

RESULTS AND DISCUSSION

The aim of the present research was to discover new methods of aromatic fluorination suitable for ^{18}F labelling.

At the outset of this project the Balz-Schiemann reaction was the general method of preparing radiofluorinated compounds[41] but the very nature of this process meant that the maximum possible radiochemical yield was only 25%. We therefore initially concentrated on approaches using fluoride ion. Such methods would have obvious ^{18}F synthetic possibilities because of the potentially higher radiochemical yields that could be obtained. Higher specific activities would also be possible as the radioactive reagent would have 'no carrier added'.

A recent quote by Wolf[34] concerning the synthesis of [^{18}F] fluoro-deoxyglucose expresses the ultimate goal of our own resarch, " The big breakthrough would be if somebody developed a high yield [40-50%] synthesis involving fluoride ion" .

The phenolic function is common in bioactive molecules and so our early investigations were directed at finding a method of replacing phenolic hydroxy groups by fluoride ion. We proposed to make the hydroxyl group into a sufficiently good leaving group to enable aromatic nucleophilic substitutions to occur in suitably activated substrates.

Phenols have previously been converted to their aryl fluorides by reaction with sulphur oxytetrafluoride[42] and by an indirect route involving the thermal decomposition of their corresponding fluoroformates.[43] However, these methods gave fairly low yields and were not generally applicable.

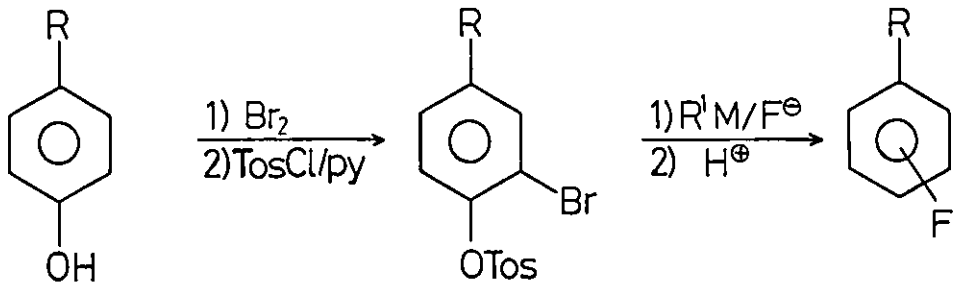
a) Arynes

The dehydroaromatic# bond in arynes is easily polarised by charged particles or dipoles and readily undergoes nucleophilic attack by a variety of anionic species.

Wittig and Hoffmann[44] found that aryl halides were formed in 20-45% yield when benzyne was generated from 1,2,3-benzothiadiazole-1,1-dioxide in the presence of halide ions. This is interesting because it constitutes the reverse of the reaction generally used for the formation of arynes in which aryl halides react with strong base. No mention was made of a benzyne/fluoride ion reaction.

Benzyne has been produced from 2-bromo-phenyl tosylate in 80% yield at -70°C by metal halogen interconversion, as evidenced by trapping with furan.[45] Phenol derivatives are therefore potential sources of aryne.

A route to aryl fluorides involving generation of aryne intermediates from phenol derivatives was proposed (Scheme 7). An isomeric mixture of m- and p-fluoroproducts would be anticipated from these reactions.

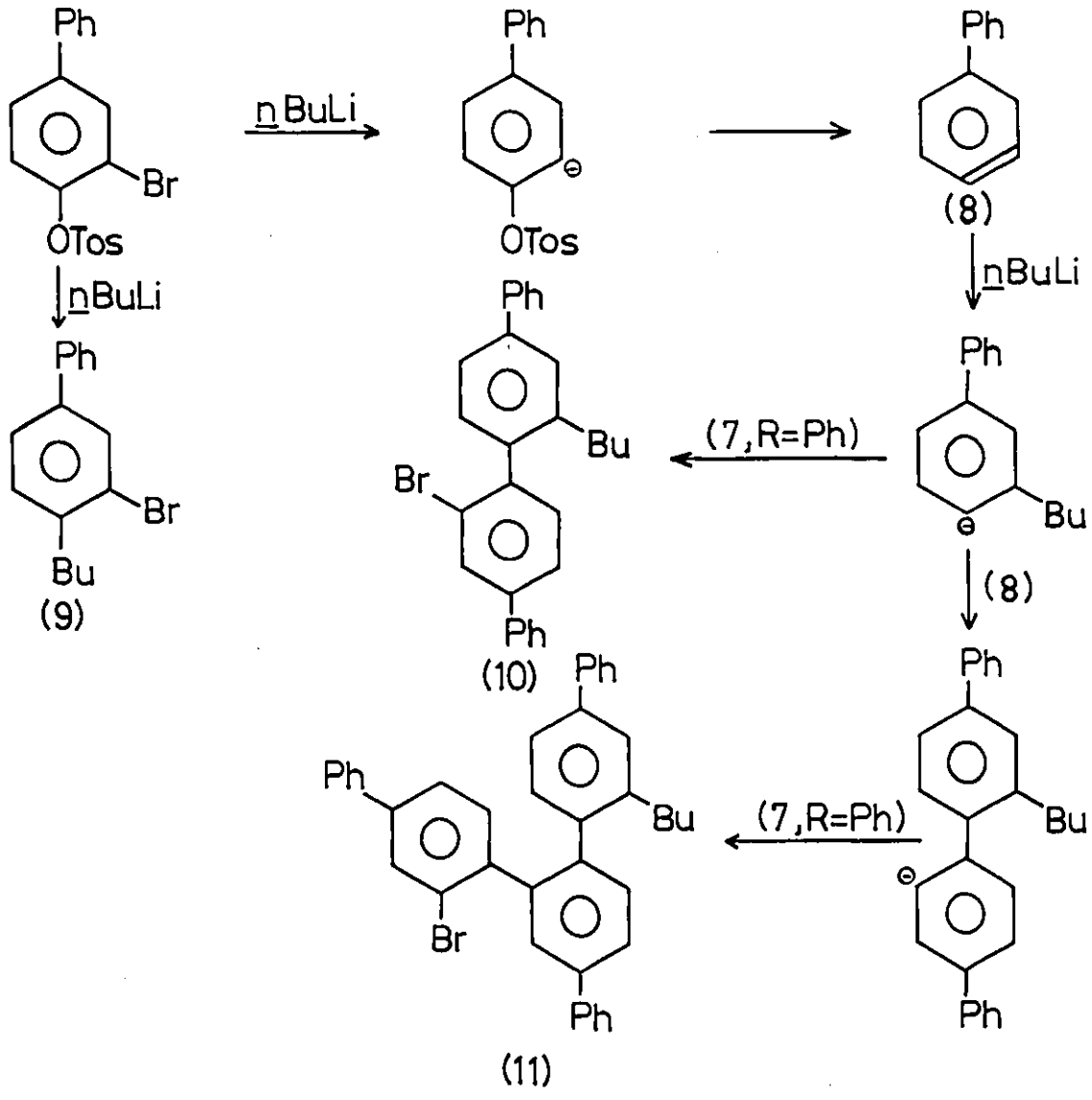


(7)

SCHEME 7

4-Phenylbenzyne was generated in 37% yield when the bromo tosylate (7, R = Ph) was treated with n-butyl lithium. Evidence for this was obtained by furan trapping which resulted in the formation of a mixture of 6- and 7-phenyl-1-naphthols.

An aryne/lithium fluoride reactionwas carried out using (7, R = Ph) as the aryne source. The main products were tentatively formulated as (9)-(11), formed *via* 4-phenylbenzyne (8) and/or direct aromatic nucleophilic substitutions (Scheme 8). A complex reaction mixture was obtained because the primary addition product of the nucleophilic base with 4-phenylbenzyne is also a potent nucleophile and can itself undergo addition or substitution reactions. It should be understood that isomeric mixtures are normally produced from aryne reactions and that it is only for convenience that one isomer is represented in Scheme 8.



SCHEME 8

The results from the 4-phenylbenzyne/lithium fluoride reaction indicated that n-butyl lithium was acting as a nucleophile. In an attempt to encourage fluoride ion attack on the aryne, bases of lower nucleophilic power were used for aryne generation.

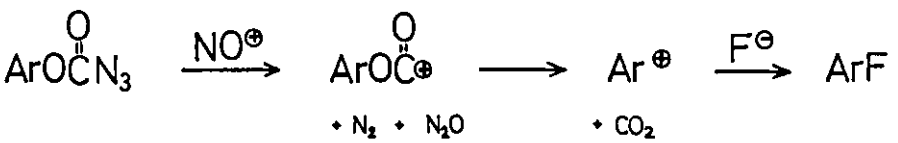
4-Phenylbenzyne was generated in 21% yield when 4-tosyloxy-biphenyl was reacted with lithium diisopropylamide, as shown by furan trapping. No fluoroaromatic product was observed from the corresponding aryne/lithium fluoride reaction. The main product obtained was 4-hydroxy-biphenyl. Similarly, 4-hydroxy-biphenyl was produced when the fluorination was attempted using sodium bistrimethylsilylamide as base. These results suggested that the nitrogen bases attacked the sulphur atom of the tosylate group.

It has recently been reported that fluorotoluene (11%) was produced when 4-methylbenzyne, generated by the action of aqueous potassium hydroxide on 4-iodotoluene in a sealed tube at 312°C, was reacted with a mixture of potassium chloride and sodium fluoride.[46] This observation by Bunnett during his competitive studies with various nucleophiles lends support to the feasibility of our aryne approach to aromatic fluorination.

The problem we encountered of nucleophilic competition between the base and fluoride ion for the dehydrobenzene could be circumvented if an alternative method of producing arynes, such as thermolysis of 1,2,3-benzothiadiazole-1,1-dioxide,[44] was adopted. However, many of these substrates would be inappropriate for the pharmaceuticals required and we would also be diverging from our original objective of finding a method of replacing a phenolic hydroxy group by a fluoro group. Consequently the method was abandoned in favour of other approaches.

b) Aryl Azidoformates

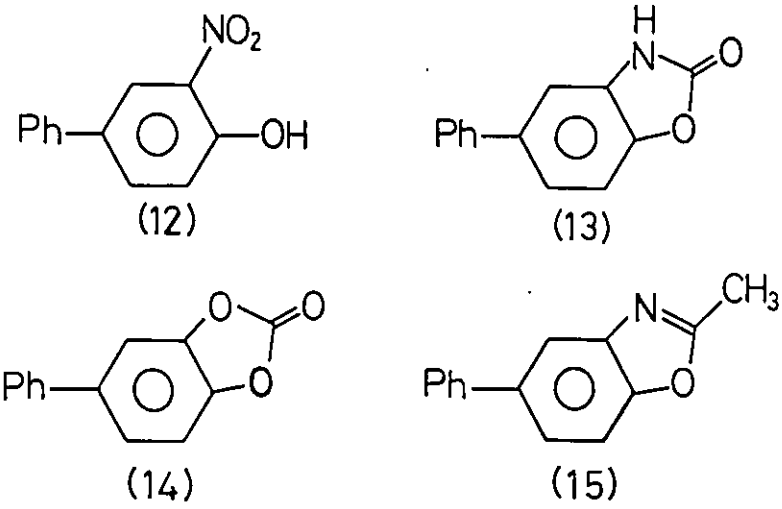
Alkyl azides react with nitrosonium compounds to give carbonium ions by loss of nitrogen and nitrous oxide.[47] This method enables cations to be produced without the concomitant formation of substances which may react with the cations, as occurs when water is formed during the deamination of primary amines by nitrous acid. By analogy, a possible route to aryl fluorides was proposed involving the generation of aryl cations from aryl azidoformates (Scheme 9).



SCHEME 9

4-Phenylphenyl azidoformate was prepared from 4-hydroxy-biphenyl *via* its chloroformate.[48] The azidoformate was treated with nitrosonium tetrafluoroborate in refluxing acetonitrile and the spectral data of the reaction products suggested that compounds (12)-(15) were formed. (12) was the major product being produced by nitrosation of the aromatic ring and (13) and (14) were probably formed *via* a nitrene intermediate.[49] However, it is unclear as to the mechanism involved in the formation of (15).

The azidoformate on treatment with nitrosonium tetrafluoroborate in the presence of anhydrous potassium fluoride produced (12) as the only isolatable compound.



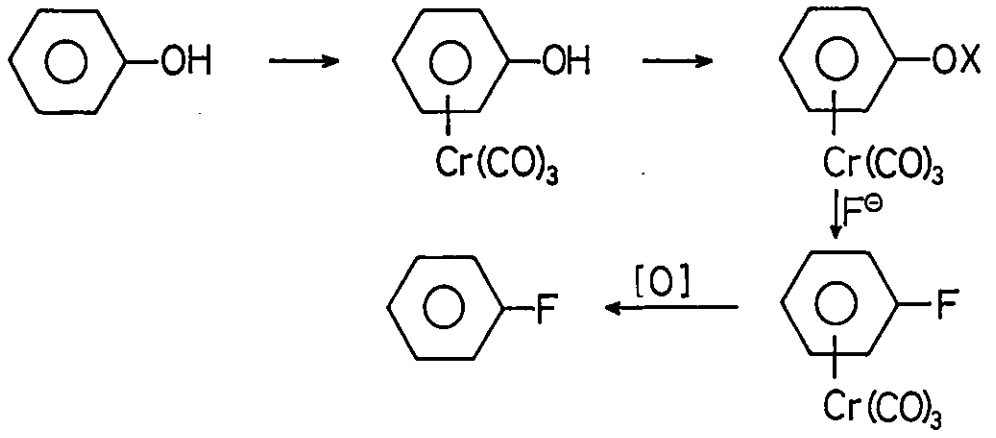
The absence of fluoroaromatic products or any evidence of aryl cation generation from the azidoformate reactions led us to consider alternative fluorination procedures.

c) Tricarbonyl η^6-(arene)chromium(0) Complexes

Nucleophilic aromatic substitutions are facilitated by the presence of electron withdrawing groups. An activating substituent that is currently of interest in organic research is the chromium tricarbonyl group.[50] This group, which π-bonds to the aromatic ring, can be introduced and removed efficiently and its η^6-(arene) complexes undergo halide and hydride displacements by a variety of nucleophiles.

A potentially simple route to aryl fluorides would involve nucleophilic attack by fluoride ion on an annular carbon atom, the site of attack being controlled by the use of a good leaving group. An aromatic fluorination pathway involving the use of tricarbonyl η^6-(arene)chromium(0) complexes was therefore proposed (Scheme 10).

Tricarbonyl η^6-(arene)chromium(0) complexes can be produced by treating the aromatic substrate with chromium hexacarbonyl in an ether solvent[51] or indirectly *via* an intermediate of the type $Cr(CO)_{6-n}L_n$ (L = CH_3CN,[52] py,[53] 2-picoline[54]).



OX = good leaving group

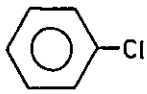
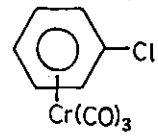
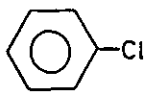
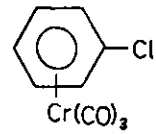
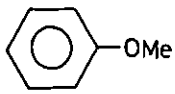
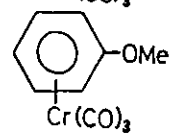
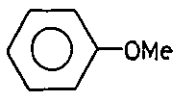
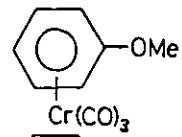
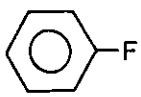
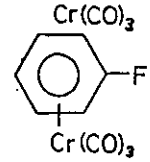
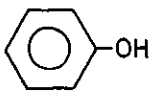
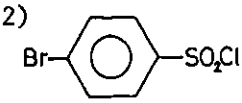
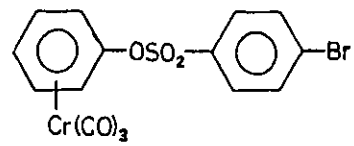
SCHEME 10

Our initial attempts with the direct method proved unsuccessful and recent studies have shown that the choice of solvent is important to the rate of complexation.[55] However, tricarbonyl η^6-(arene)chromium(0) complexes were prepared using several $Cr(CO)_{6-n}L_n$ intermediates (Table 1).

(Tricarbonyl)tris(pyridine)chromium(0) was the intermediate preferred for the formation of the η^6-(arene) complexes; its ease of preparation, relative stability and shorter reaction times made it a convenient source of chromium tricarbonyl. However, the necessity of using a Lewis acid (BF_3.etherate) to bring about its complexation reactions may cause problems when sensitive substituents are present in the substrates being complexed. Pentacarbonyl(pyridine)chromium(0) was obtained as a stable by-product of the (tricarbonyl)tris(pyridine)-chromium(0) reactions by a disproportionation process.[53]

The other intermediates used in preparing tricarbonyl η^6-(arene)-chromium(0) compounds also have their disadvantages. (Tricarbonyl)tris-(acetonitrile)chromium(0) was reacted <u>in situ</u> because of the pyrophoric nature of the solid and the higher temperatures used in the 2-picoline method caused some decomposition of the η^6-(arene) products.

TABLE 1 Preparation of tricarbonyl η^6-(arene)chromium(0) complexes.

Substrate	Reagent	Product	Yield (%)
	$(py)_3Cr(CO)_3$		89
	$(py)_3Cr(CO)_3$		42
	$(CH_3CN)_3Cr(CO)_3$		55
	$(py)_3Cr(CO)_3$		81
	(2-picoline)$Cr(CO)_5$		84
	$(py)_3Cr(CO)_3$[a]		28
	1) $(py)_3Cr(CO)_3$ 2)  /pyridine		54

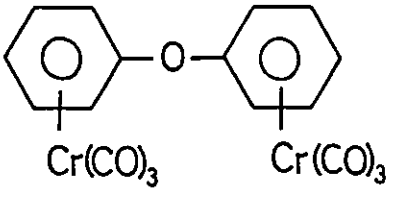
[a] fluorobenzene was used as solvent in the complexation reaction

Tricarbonyl η^6-(brosyloxybenzene)chromium(0) was prepared by reacting tricarbonyl η^6-(phenol)chromium(0) with brosyl chloride in pyridine at R.T. The η^6-(phenol) complex was difficult to purify by the standard chromatographic procedure because of its ready air oxidation[51] and so it was reacted in its impure form.

Fluoride ion unencumbered by strong solvation forces is a potent nucleophile. 18-Crown-6 solubilises potassium fluoride by complexation with the metal atom and the 'naked' fluoride ion produced has been used to displace other halo groups in suitably activated substrates.[56]

Tricarbonyl η^6-(brosyloxybenzene)chromium(0) was reacted with KF/18-crown-6. A t.l.c. of the reaction showed that two chromium tricarbonyl compounds were produced but attempts at isolating the products proved unsuccessful presumably because of their ease of oxidation. An n.m.r. of the crude reaction mixture confirmed that a tricarbonyl η^6-(arene)-chromium(0) complex had been formed but the spectral pattern obtained did not resemble that of the desired η^6-(fluorobenzene) complex.

A mass spectrum was taken of the crude tricarbonyl η^6-(brosyloxybenzene)chromium(0)/KF reaction mixture. The peaks at 432 and 230 were tentatively assigned to the molecular ions of the chromium(0) complex (16) and tricarbonyl η^6-(phenol)chromium(0), respectively. The isotopic pattern around 432 was in general agreement with that expected for $C_{18}H_{10}Cr_2O_7$.



(16)

The mechanism proposed to account for the formation of (16) involves an initial attack by the 'hard' fluoride ion on the 'hard' sulphonyl centre of tricarbonyl η^6-(brosyloxybenzene)chromium(0). The aryloxy anion so liberated can then attack the 'soft' aryl centre of a second molecule of substrate. An analogous reaction was observed by a co-worker during concurrent investigations into the displacement of oxyanions by fluoride ion in a series of nitroaryl sulphonates.[57] KF/18-crown-6 reacted with 4-brosyloxy-nitrobenezene to produce a mixture of di(4-nitrophenyl)ether and 4-nitrophenol.

The aim at the outset of this research had been to find a method of replacing a phenolic hydroxy group by a fluoro group. It was now decided to adopt a broader approach to aromatic fluorination.

The possibility of fluoride ion displacement of chloride in tricarbonyl η^6-(chlorobenzene)chromium(0) was investigated. The basis for considering this approach was that the chromium tricarbonyl group was known to have an electron withdrawing power comparable to a p-nitro substituent[51] and that fluoride ion displaces chloride from 4-chloronitrobenzene in 72% yield.[58]

The literature reaction involving the replacement of the chloro group in tricarbonyl η^6-(chlorobenzene)chromium(0) by methoxyl was repeated. The η^6-(anisole) complex was isolated in 73% yield (lit.[51] 90%).

Tricarbonyl η^6-(chlorobenzene)chromium(0) was reacted with caesium fluoride in HMPA at 120°C for two days. The reaction mixture gave a positive silver nitrate test indicating that chloride ion was released. The chromium tricarbonyl group was cleaved from its η^6-(arene) complexes upon treatment with iodine in ether.[59] G.l.c. analysis of the ether phase

after work up revealed the presence of benzene and chlorobenzene but no fluorobenzene was detected. Benzene has previously been observed as a by-product of displacement reactions on the η^6-(chlorobenzene) complex but the nature of the reducing species is not clear.[60]

An equilibrium between the η^6-(chlorobenzene) and η^6-(fluorobenzene) chromium(0) compounds would be anticipated if fluorination were to occur. The tricarbonyl η^6-(chlorobenzene)chromium(0)/CsF reaction was repeated in the presence of silver fluoride in an attempt to push the equilibrium towards the η^6-(fluorobenzene) complex by removing chloride ion in the form of its silver salt. Once again benzene and chlorobenzene were produced. No fluorobenzene was obtained.

The failure to observe fluorobenzene in the chloro displacement reactions suggests that the 'hard' nature of the fluoride ion is unfavourable to reaction on the 'soft' aromatic ring.

d) Aryl palladium(II) Complexes

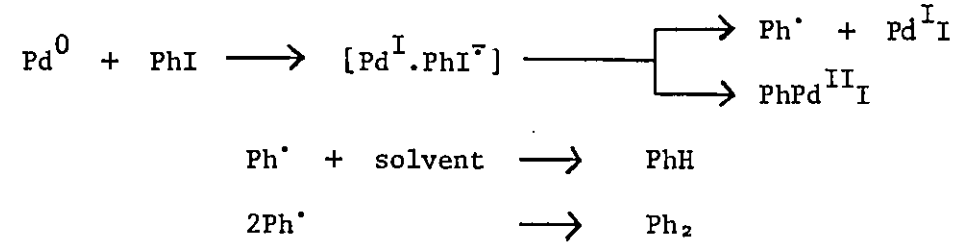
d^8-Metal complexes enable the halo group of unactivated aryl halides to be selectively replaced by various nucleophiles.[61,62] These reactions are catalytic and are thought to involve a three step process: oxidative addition, metathetical exchange and reductive elimination.

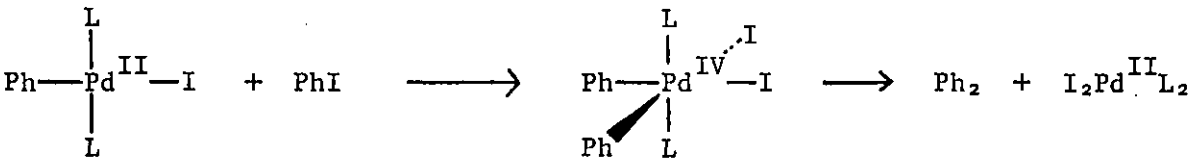
It was proposed to investigate the feasibility of a Pd^{II} catalysed aromatic fluorination procedure.

A literature cyanation reaction was repeated.[63] G.l.c. analysis indicated that iodobenzene was converted almost quantitatively to benzonitrile using a palladium(II) acetate/potassium cyanide mixture. The Pd^{II} salt was probably reduced to a Pd^0 species which then entered the oxidative addition - metathetical exchange - reductive elimination cycle.

A fluorination was attempted by a similar procedure to the cyanation reaction except that potassium fluoride was used instead of potassium cyanide. Benzene and biphenyl were produced. Small amounts of these products have previously been observed in Pd^{II} catalysed cyanation reactions.[63]

Several mechanisms are suggested to account for the formation of benzene and biphenyl in the attempted fluorination reaction (Scheme 11).





SCHEME 11

Aryl radicals have been generated by an analogous mechanism during the oxidative addition of aryl halides to Ni^0 complexes.[64] However, it is possible that the phenyl radicals may also be produced by simple homolysis of the phenyl-palladium bond in $PhPd^{II}I$.

Stille[65] has shown that the addition of methyl iodide to [1,2-bis-(diphenylphosphino)ethane] dimethyl palladium(II) caused a rapid elimination of ethane. It was suggested that the 1,1-reductive elimination involved a concerted process from a Pd^{IV} intermediate. It is therefore reasonable to propose that biphenyl is produced by a similar pathway.

It is interesting to note that diaryl Ni^{III} has been postulated as the intermediate in nickel catalysed biaryl synthesis.[66] The experimental results showed that no Ni^{IV} species was involved. These findings suggest that there are profound differences between nickel and palladium in these reactions and so too strong an analogy with the more studied nickel reactions should not be made.

A series of fluorinations were attempted using an iodobenzene/palladium(II)acetate/potassium fluoride mixture in the presence of different additives. The first of these reactions was carried out with added triphenylphosphine.

The powerful σ-donating ability of the phosphine ligand was expected to give the intermediate Pd^{II} oxidative addition product greater stability. Two independent facts suggested that the added phosphine might also assist the reductive elimination step. Firstly, dianion bis(phosphine)-palladium(II) complexes have been found to undergo cis-trans isomerisation with excess phosphine, the reaction proceeding via a five-coordinate transition state.[67] Secondly, investigations into nickel catalysed cross-coupling reactions showed that an increased rate of reductive elimination was obtained when the two organo groups to be coupled were in a cis configuration in the intermediate Ni^{II} complex.[68]

The products of the attempted fluorination reaction with added triphenylphosphine were benzene and biphenyl. Some of the biphenyl may be formed by a process involving reversible oxidative addition of triphenylphosphine to Pd^{0}, followed by a redistribution step to give a diphenyl Pd^{II} species, which then reductively eliminates the coupled product.[69]

It has subsequently been shown that the σ-donating ability of the phosphines inhibits the reductive elimination of ethane from cis dimethyl bis(phosphine)palladium(II) complexes since the elimination proceeds via a dissociative mechanism.[65] This suggests that the reductive elimination step itself is more important than cis-trans isomerisation in the overall elimination process and so added phosphine would not be advantageous in our palladium catalysed reactions.

The fluorination was attempted with added 18-crown-6. Fluoride ion unencumbered by strong solvation forces is known to be a more potent nucleophile[56] and therefore should encourage metathetical exchange with the iodo group in the intermediate iodo(phenyl)Pd^{II} complex. Benzene and biphenyl were the only products observed.

The fluorination was carried out with added thallium(I) fluoride. It was hoped that the thallium salt would complex with the iodo group in the phenyl Pd^{II} intermediate and thus assist halo exchange. No fluorobenzene was detected.

It has previously been shown that Pd^{II} catalysed cyanations were unsuccessful if $[Pd^{II}] < [CN^-]$[70]; the Pd^{II} was rapidly trapped by cyanide ion and no Pd^{II} was available to act as a source of Pd^0. The fluorination was therefore attempted using $[Pd^{II}] > [F^-]$ but once again benzene and biphenyl were obtained.

The fluorination reactions with iodobenzene/palladium(II)acetate/potassium fluoride, with or without additives, proved unsuccessful. It had been proposed that the fluorinations would proceed via an iodo(phenyl)Pd^{II} complex which would then undergo metathetical exchange and the fluoro(phenyl)Pd^{II} species generated would reductively eliminate fluorobenzene. Substitution would therefore occur by a three stage process.

In an attempt to identify the blocked stage, several halo(aryl)bis-(triphenylphosphine)palladium(II) complexes were prepared by oxidative addition of aryl halide to tetrakis(triphenylphosphine)palladium(0).[71,72] Fluorination reactions were then carried out on these Pd^{II} complexes (Table 2) but again benzene and biphenyl were the only products observed.

TABLE 2 Attempted fluorinations of halo(phenyl)Pd^{II} complexes.

Palladium Complex	Reagents	Reaction Conditions
$PhPd^{II}I(PPh_3)_2$	KF	120°C, 1 day[a]
$PhPd^{II}I(PPh_3)_2$	KF, TℓF	80°C, 1 day[a]
$PhPd^{II}I(PPh_3)_2$	KF, TℓF	80°C, 1 day[b]
$PhPd^{II}I(PPh_3)_2$	KF, $K_2Cr_2O_7$	120°C, 1 day[a]
$PhPd^{II}Br(PPh_3)_2$	KF	120°C, 1 day[a]
$PhPd^{II}Br(PPh_3)_2$	KF, TℓF	80°C, 1 day[b]
$PhPd^{II}Br(PPh_3)_2$	KF, AgF	80°C, 1 day[b]

[a] HMPA [b] HMPA/glyme (1:4)

Henry[73] has found that oxidants play an important role in Pd^{II} catalysed aromatic substitutions. It has subsequently been suggested that these substitutions occur *via* Pd^{IV} intermediates generated by oxidation of aryl Pd^{II} complexes.[74]

The reaction of $PhPd^{II}I(PPh_3)_2$ with KF in the presence of potassium dichromate failed to give any fluorobenzene. Benzene and biphenyl were produced.

A fluorination reaction was attempted using silver fluoride, it being hoped that the silver salt would complex with the bromo group in $PhPd^{II}Br(PPh_3)_3$ and thus encourage the metathesis step. No fluorobenzene was observed in the reaction.

Kochi, et al.[75] have studied nickel catalysed halogen exchanges with aryl halides. They found that these reactions could attain equilibrium; the same mixture of phenyl halides was obtained from equimolar mixtures of either iodobenzene and tetra n-butyl ammonium bromide or bromobenzene and tetra n-butyl ammonium iodide. The mechanism proposed to account for the halide exchange involved a Ni^{I} species (Scheme 12).

$$NiXL_3 + X'^{\ominus} \rightleftharpoons NiXX'L_2^{\ominus} + L \rightleftharpoons NiX'L_3 + X^{\ominus}$$

$$NiX'L_3 + ArX \rightleftharpoons (ArX)NiX'L_2 + L$$

$$(ArX)NiX'L_2 \rightleftharpoons \left[\begin{array}{c} X' \\ Ar \quad NiL_2 \\ X \end{array}\right] \rightleftharpoons (ArX')NiXL_2$$

$$(ArX')NiXL_2 + L \rightleftharpoons NiXL_3 + ArX'$$

SCHEME 12

The nickel catalysed halogen exchange reactions with fluoride ion proved unsuccessful. However, it should be pointed out that under the same experimental procedure only 2% cyanation was observed which is in marked contrast to the almost quantitative yields that have been obtained under different reaction conditions.[76]

In our fluorination reactions involving Pd^{II} species we attempted to assist the halogen exchange by complexing the group to be replaced with silver or thallous ion. Therefore if a mechanism analogous to the nickel catalysed halogen exchange were operating then it would be anticipated that complexation would push the equilibrium in the desired direction with production of aryl fluorides.

The failure of the palladium catalysed fluorination reactions suggests that the formation of the palladium-fluorine bond is not favoured, presumably because the fluoride ion is too 'hard' a nucleophile to react with the 'soft' palladium.

It has been reported that the acetylacetonate ligand (acac) of allyl (acac) palladium(II) can be cleaved off with hydrogen chloride, halogen, N-bromo-succinimide or metal halides ($A\ell C\ell_3$, $FeC\ell_3$, $HgC\ell_2$) to give a halo (allyl) palladium(II) complex.[77] We therefore investigated the possibility of producing a fluoro(phenyl)palladium(II) complex *via* an analogous pathway by reacting phenyl (acac) triphenylphosphine palladium(II) with hydrogen fluoride. Subsequent reductive elimination in the fluoro (phenyl) Pd^{II} species would result in the formation of fluorobenzene.

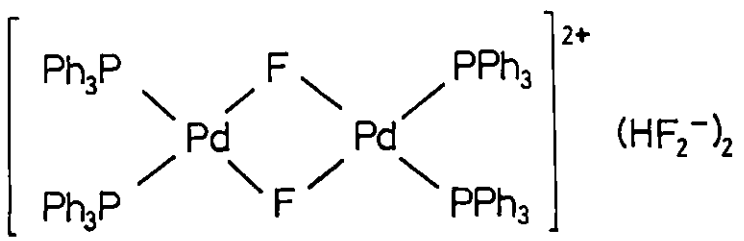
Phenyl(acac)triphenylphosphine palladium(II) was prepared by reaction of thallium acetylacetonate with bromo(phenyl)bis(triphenylphosphine) palladium(II). This palladium complex has not been reported in the literature although the corresponding nickel complex is known.[78]

The phenyl(acac)Pd^{II} complex was reacted with hydrogen bromide in the presence of triphenylphosphine and elemental analysis of the product indicated the formation of dibromo bis(triphenylphosphine)palladium(II).

70% Hydrogen fluoride in pyridine was reacted with a solution of the phenyl(acac)palladium(II) complex and triphenylphosphine in toluene at 80°C for 2 hrs. Benzene was detected in the reaction mixture. Cleavage of the aryl group has previously been observed in the reaction of a phenyl(acac) Ni^{II} complex with hydrogen chloride.[78]

The $(HF)_n$.pyridine reaction was repeated in an attempt to determine the fate of the palladium material. The infrared spectrum of the isolated product showed no Ph-Pd or carbonyl stretches. Elemental analysis indicated that fluorine was incorporated but the data did not correspond to the expected difluoro bis(triphenylphosphine)palladium(II) compound. However, $(PPh_3)_2PdF_3H$ gave fairly good agreement.

$(PPh_3)_3PtF_3H$ has been reported in the literature and is obtained by reaction of hydrogen fluoride with tetrakis(triphenylphosphine) platinum(0).[79] By analogy with this we tentatively assign the structure of the palladium complex as (17).

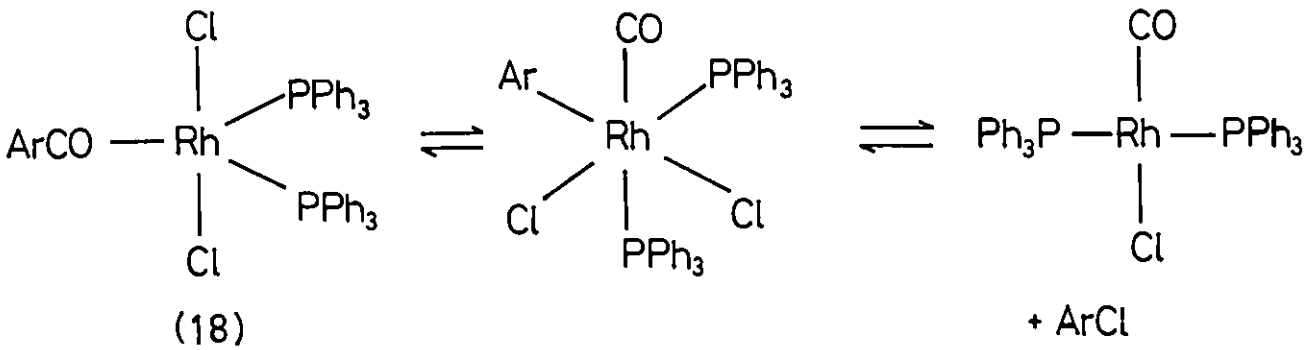


(17)

e) Nickel catalysed decarbonylation

Aryl fluorides have been obtained by decarbonylation of aroyl fluorides using tris(triphenylphosphine)rhodium(I) chloride.[80] It was found that these reactions, unlike those with aroyl chlorides and bromides, were not catalytic. It was proposed that halogen exchange occurred between the aroyl fluoride and the rhodium complex to produce tris(triphenylphosphine)rhodium(I) fluoride which is inactive in decarbonylation reactions.

Tsuji[81] subsequently showed that (carbonyl)bis(triphenylphosphine)-rhodium(I) chloride was a more efficient catalyst than tris(triphenylphosphine)rhodium(I) chloride in aroyl decarbonylations. He suggested that oxidative addition of the aroyl halide to either rhodium complex produced the same five coordinate intermediate (18). Complex (18) then rearranged and reductively eliminated aryl halide with regeneration of (carbonyl)bis(triphenylphosphine)rhodium(I) chloride (Scheme 13).



SCHEME 13

It has been reported that aroyl nickel compounds are unstable and show a marked tendency for the Ni-C(O)Ar to eliminate carbon monoxide.[82] It was proposed that the elimination process involved a three centre transition state with the ability of the Ni^{II} ion to form a higher

coordination number being the driving force. Some support for this mechanism was provided by the isolation of a σ-benzoyl nickel complex with tris(bornyl)phosphite ligands, the bulky phosphite ligands apparently preventing expansion of coordination of Ni^{II}.

Chloro(phenyl)bis(triphenylphosphine)nickel(II) has been produced by reacting benzoyl chloride with tetrakis(triphenylphosphine)nickel(0).[82] This in conjunction with the findings of a co-worker who showed that aryl halide could be released from halo(aryl)Ni^{II} complexes [83] suggested a possible route to aryl fluorides involving a nickel catalysed decarbonylation of aroyl fluorides (Scheme 14).

$$ArCOF + Ni^{0} \xrightarrow{-CO} ArNi^{II}F \longrightarrow ArF + Ni^{0}$$

SCHEME 14

Tetrakis(triphenylphosphine)nickel(0) was prepared by reducing dichloro bis(triphenylphosphine)nickel(II) with sodium borohydride. The Ni^{0} complex was then reacted with benzoyl fluoride. No colour change was observed when the benzoyl fluoride was added. We would have expected a colour change from red to yellow/orange if Ni^{0} was oxidised to Ni^{II}. This observation and the failure to detect any benzene or fluorobenzene led us to conclude that no reaction had occurred.

f) Aryl-mercury compounds

At this point we decided to broaden our approach to aromatic fluorination by considering alternative fluorinating agents.

McKillop *et al.*[33] had recently reported the synthesis of aryl fluorides by the reaction of aryl thallium(III) difluorides with boron

trifluoride. This approach gave good yields of aryl fluorides with alkyl substituted aryls but poor yields were obtained when either powerful electron withdrawing groups, oxygen or amino substituents were present.

The findings of the thallium work led us to investigate the reaction of aryl mercurials with the higher antimony fluorides, species particularly effective in fluorination by displacement of other halides.[84]

There are various methods of synthesising aryl mercurials.[85] The most versatile of these, despite its problems of isomer formation and polymercuration, involves the reaction of mercury(II) salts with aromatic substrates and results in the direct replacement of a C-H group by a C-Hg group. This is an electrophilic substitution process and obeys the usual rules of aromatic electrophilic substitution provided that the reactions are carried out under mild conditions. The rates of these mercurations depend upon the mercurating system; $Hg(OAc)_2/HCl O_4$ mercurates faster than $Hg(OAc)_2/CH_3COOH$ because it produces $Hg(OAc)^+$ which is a more powerful electrophile than unionised $Hg(OAc)_2$.

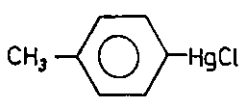
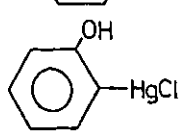
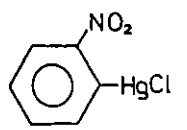
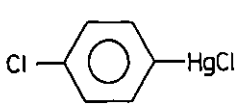
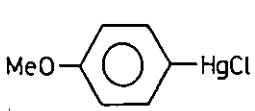
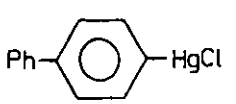
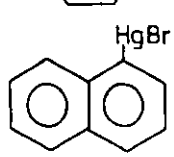
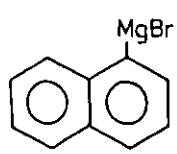
Grignard and organolithium reagents are very useful in organomercury synthesis because of their availability, reactivity and ease of handling. The organometallic reagents are generally reacted with the mercury(II) halide corresponding to the organic halide from which the metallic reagent was prepared since this avoids the complication of anion exchange and hence problems in purification. Excess magnesium must be removed from Grignard reagents to prevent reductive processes occurring.

A valuable alternative to mercuration and transmetallation procedures for the preparation of arylmercury salts is the diazo method. It involves the initial formation of the double salt of aryldiazonium halide and mercury(II) halide followed by its copper induced decomposition.

A developing area of organomercurial synthesis is the use of organoboranes because of their ready accessibility through hydroboration. Other useful approaches, although less general, involve the loss of CO_2, SO_2 or SO_3 from an appropriate Hg^{II} salt.

A selection of aryl mercurials were prepared (Table 3). Many of these compounds were synthesised by direct mercuration with mercury(II) acetate.

TABLE 3 Preparation of Aryl Mercurials

Aryl Mercurial	Reaction	Yield (%)
PhHgCℓ	1) $PhNH_2/NaNO_2$ 2) $HgCℓ_2$	64
PhHgOAc	PhH, $Hg(OAc)_2$, CH_3CO_2H	61
PhHgBr	PhHgOAc, KBr	92
PhHgF	1) PhHgOAc, NaOH 2) aq. HF	37
	p-$CH_3C_6H_4SO_2Na/HgCℓ_2$	53
	1) $PhOH/Hg(OAc)_2$ 2) NaCℓ	26
	1) $PhNO_2/Hg(OAc)_2$ 2) NaCℓ	30
	1) $PhCℓ/Hg(OAc)_2$ 2) NaCℓ	18
	1) $PhOMe/Hg(OAc)_2$ 2) NaCℓ	44
	1) $Ph_2/Hg(OAc)_2/HCℓO_4/CH_3CO_2H$ 2) NaCℓ	9
	 /$HgBr_1$	47

One of the classical methods of fluorinating aliphatic halo compounds involves the replacement of the halo group by fluorine using the 'Swarts reagent'.[84] This reagent consists of a mixture of antimony trifluoride with a varying amount of chlorine, bromine or antimony pentachloride. The power of this fluorinating agent increases with the increasing amount of the pentavalent antimony up to the composition of SbF_3X_2. We therefore decided to try reacting antimony trifluoride dichloride with phenyl mercuric chloride.

Freshly sublimed antimony trifluoride was heated with an equivalent of antimony pentachloride. Phenyl mercuric chloride was then added and the mixture heated. G.l.c. analysis of the distillate from the reaction indicated that chlorobenzene was the major product but of far more significance to us was the formation of trace amounts of fluorobenzene. Benzene was also produced.

Hudlicky[86] has reported that antimony trifluoride dichloride can be produced by heating antimony trifluoride with an equivalent of antimony pentachloride. No specific reaction conditions were given in this report and so it is possible that under our conditions incomplete conversion to antimony trifluoride dichloride occurred. Unreacted antimony pentachloride may therefore be responsible for the bulk of the chlorobenzene produced. However, competition between the fluorination and chlorination processes would have been expected even if antimony trifluoride dichloride had been formed satisfactorily because it is known that this reagent is a more powerful chorinating agent than antimony pentachloride.[87]

Antimony pentafluoride was chosen as an alternative fluorinating source in order to remove the problem of competing chlorination. This reagent is also known to be a more powerful fluorinating agent than antimony trifluoride dichloride[88] and should therefore favour the fluorination process with aryl mercurials.

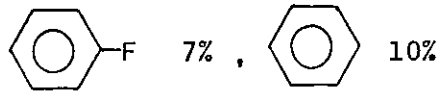
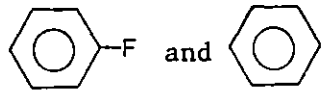
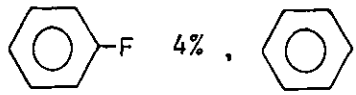
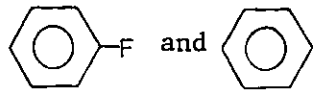
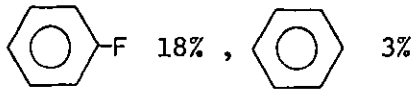
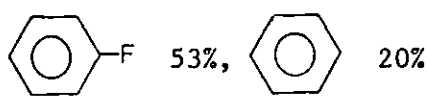
Phenyl mercuric chloride was added to a solution of antimony pentafluoride in freon 112 at room temperature. The reaction was continued for 1 hr and then the temperature was raised to 120°C. G.l.c. analysis of the distillate indicated that fluorobenzene and benzene were present in yields of 7% and 10%, respectively. G.l.c. coupled mass spectrometry confirmed that the products were fluorobenzene and benzene.

Phenyl mercuric chloride/antimony pentafluoride reactions were carried out under various conditions (Table 4). It was found that the best yield of fluorobenzene (53%) was obtained by adding a solution of antimony pentafluoride in freon 112 to a stirred suspension of the mercurial in the same solvent at -30°C. The reaction was allowed to warm up to room temperature overnight. The solvent was then removed by distillation and the residue was pyrolysed at 300°C with the volatiles being trapped in a liquid nitrogen cooled cold finger.

The significance of the $HgCl$ group to the fluorination process was investigated by reacting benzene with antimony pentafluoride under the conditions which had given the best yield of fluorobenzene from the $PhHgCl/SbF_5$ reactions. G.l.c. analysis of the distillate indicated a possible trace of fluorobenzene (< 1%) along with recovered benzene (78%). From these findings it is apparent that the $HgCl$ group is important to the success of the fluorination.

Phenyl mercuric bromide and phenyl mercuric fluoride were reacted with antimony pentafluoride using the standard procedure. The yields of fluorobenzene obtained were 52% and 38%, respectively. These yields are of a similar order to that obtained with phenyl mercuric chloride and suggest that the nature of the halo group attached to the aryl

Table 4 Reactions of phenyl mercuric chloride with antimony pentafluoride

Reaction Conditions	Comments
PhHgCℓ added to a solution of SbF_5 in freon 112 at room temperature. Reaction continued for 1 hour and then heated to 120°C.	 7% , 10%
As above, using 3 eq. SbF_5.	 and observed but in much lower yields than above
PhHgCℓ added to SbF_5 at room temperature. The reaction then heated to 130°C.	 4% ,
PhHgCℓ added to a solution of SbF_5 at -30°C. Reaction left overnight at room temperature.	
a) heated to 80°C	 and obtained in low yields
b) residue heated to 300°C	 18% , 3%
A solution of SbF_5 added to a suspension of PhHgCℓ in freon 112 at -30°C and reaction left overnight at room temperature. Reaction heated to 80°C to remove volatiles and then residue pyrolysed at 300°C.	 53%, 20%

mercurial is not critical in the fluorination. This probably rules out the possibility that the fluorination involves an initial fluorine-halo atom exchange, especially as it has been reported that pyrolysis of phenyl mercuric fluoride produces Ph_2Hg.[89]

G.l.c. analysis of the distillates obtained from the $PhHgX/SbF_5$ reactions before pyrolysis indicated only trace amounts of fluorobenzene. The bulk of the fluoroaromatic product was therefore generated during pyrolysis. However, fluorobenzene had originally been produced in 7% yield when phenyl mercuric chloride was added to an antimony pentafluoride solution at room temperature. It was observed that this reaction was extremely exothermic and it is thought that localised decomposition probably occurred.

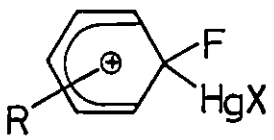
Antimony pentafluoride was reacted with p-tolyl mercuric chloride under the conditions which had proved most successful in the corresponding phenyl mercuric chloride reactions. G.l.c. coupled mass spectrometry showed that fluorotoluene and toluene were produced. Additional products were also observed, the main ones being chlorotoluene and a chlorofluoro toluene. The g.l.c. spectrum of the reaction mixture showed that the peak which had been confirmed by mass spectrometry as being fluorotoluene consisted of two overlapping peaks. G.l.c. enhancement suggested that p-fluorotoluene was the major of these two peaks and since the mass spectrum had not indicated any contaminants the minor peak is tentatively assigned as a fluorotoluene isomer. p-Fluorotoluene and toluene were formed in 5.5% and 39% yields, respectively. The amount of chlorotoluene produced was not quantified but its peak area indicates that its yield would be of a similar order to that of p-fluorotoluene.

There are several possible mechanisms to account for the formation of the fluoro and chloro products. One of these involves an initial complexation between the p-tolyl mercuric chloride and antimony pentafluoride followed by thermal decomposition of the complex (Scheme 15). The reactive species generated during the pyrolysis may be either an aryl cation or an aryl radical. Aryl cations are currently proposed as intermediates in the analogous decomposition of aryl diazonium salts.[90]

$$ArHgCl + SbF_5 \longrightarrow ArHg^{+}SbF_5Cl^{-} \xrightarrow{\Delta} ArF + ArCl$$

Scheme 15

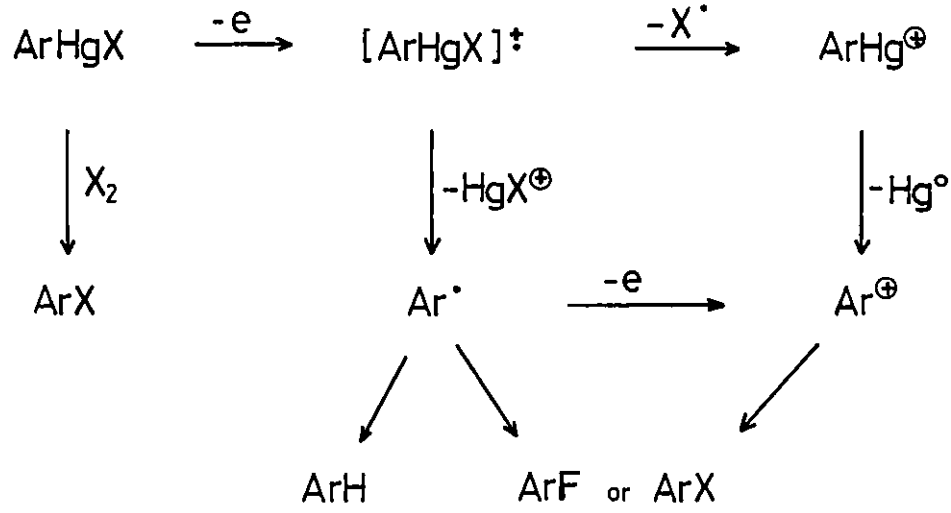
The metal-carbon bond in organomercury compounds is rather unreactive in comparison with that in the organic compounds of other group II metals. Many of the principal reactions that arylmercurials undergo involve electrophilic substitution at carbon, one of the best examples being their reaction with halogens.[91] It is therefore reasonable to propose that the aryl mercurials may be fluorinated by electrophilic substitution, the reaction proceeding via the arenium ion (18).



(18)

Antimony pentafluoride is an oxidant and has been shown to be capable of producing aryl radical cations.[87] We therefore suggest that the radical cation $[ArHgX]^{+\cdot}$ may be generated during the p-tolyl mercuric

chloride/antimony pentafluoride reaction and that this can decompose in various ways to give the fluoro and chloro products (Scheme 16).



Ar = p-tolyl , X = Cl

SCHEME 16

A similar pathway has been proposed to account for the formation of bromobenzene when phenyl mercuric bromide was reacted with nitrosonium salts.[92] The radical cation $[PhHgBr]^{+\cdot}$ was generated in the reaction and it decomposed to give phenyl or bromo radicals. Bromobenzene was then formed either by bromodemercuration of phenyl mercuric bromide or by further oxidation of the phenyl radical to the aryl cation which was subseuqently brominated.

Chloroproducts may also be formed by the production of antimony fluoro chloro species during the p-tolyl mercuric chloride/antimony pentafluoride reaction which are capable of acting as chlorinating agents.

The freon 112 solvent used in the p-tolyl mercuric chloride/antimony pentafluoride reaction may be a source of chlorine atoms since it is

known that carbon tetrachloride acts as a chlorinating agent in the presence of antimony pentafluoride.[87]

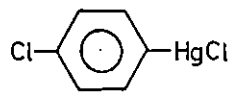
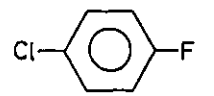
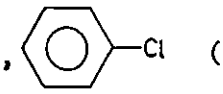
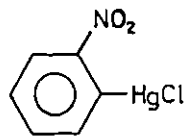
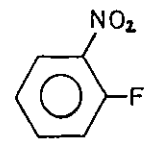
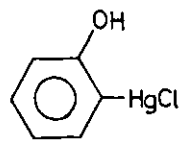
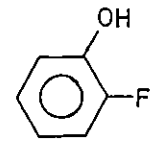
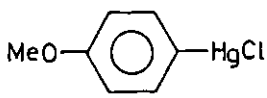
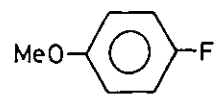
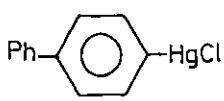
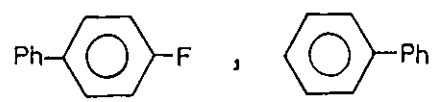
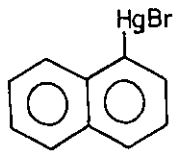
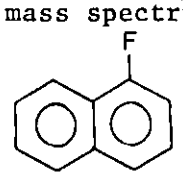
A p-tolyl mercuric chloride/antimony pentafluoride reaction was carried out in liquid sulphur dioxide. The mercurial was added to the antimony pentafluoride solution at $-78^{o}C$ and the reaction continued at $-30^{o}C$ for 4 hrs. Pyrolysis of the reaction mixture in the usual way gave p-fluorotoluene and toluene in yields of 0.1% and 5.5%, respectively. The yield of fluorotoluene obtained was markedly lower than from the corresponding freon reaction and so all subsequent fluorination reactions were carried out in freon 112.

Attempts were made to improve the yield of fluorotoluene by modifying the reaction conditions of the p-tolyl mercuric chloride/ antimony pentafluoride reactions. Refluxing the reaction mixture before pyrolysis made little difference to the product yields. However, the use of a five-fold excess of antimony pentafluoride greatly reduced the amount of fluorotoluene and toluene produced. The excess antimony pentafluoride may react further with the products released during pyrolysis.[87]

Other aryl mercurials were reacted with antimony pentafluoride by the standard procedure (Table 5).

The preliminary results from the aryl mercury/antimony pentafluoride reactions indicate that aryl fluorides are obtained from various substrates Further investigations are necessary to optimise conditions but the initial findings suggest that the scope of this fluorination procedure is comparable with that of the Tl^{III} method.

TABLE 5 Reaction of aryl mercurials with antimony pentafluoride.

Aryl Mercurial	Comment
	 (1.5%),  (27%)
	g.l.c. indicated 
	g.l.c. indicated 
	no  detected
	mass spectrum showed  + chloroaromatic products
	mass spectrum showed 

The mercury-carbon bond in aryl mercurials is known to be susceptible to electrophilic substitution at carbon. We therefore tentatively suggest that an arenium ion (18) is the more probable intermediate in the aryl mercury fluorination process. However, the intermediacy of aryl cations or aryl radicals can not be completely discounted. Aryl radicals are likely to be involved in the formation of aromatic hydrocarbons.[93]

The aryl mercury/antimony pentafluoride fluorination procedure is unlikely to be of value in ^{18}F synthesis because of the unfavourable ratio of labelled to unlabelled fluorine in $[^{18}F]SbF_5$. We had originally hoped that it might be possible to use a higher antimony fluoro chloro compound, such as $[^{18}F]SbFCl_4$, but the competition between chlorination and fluorination processes observed with SbF_3Cl_2 showed that this was not feasible.

$[^{18}F]$ Fluorobenzene has recently been prepared by treating a phenyltin derivative with $[^{18}F]F_2$.[40] It is therefore possible that aryl mercurials would undergo an analogous reaction since they are susceptible to electrophilic substitution.

CONCLUSION

At the start of this research we had been interested in finding a general method of aromatic monofluorination suitable for application to ^{18}F-radiopharmaceutical work. The Balz-Schiemann reaction was the standard procedure for preparing ^{18}F labelled aromatic compounds but the very nature of this process meant that low radiochemical yields were obtained. It was this problem of poor incorporation that led us to consider approaches utilising fluoride ion. Such procedures would have obvious ^{18}F synthetic possibilities because of the potentially higher radiochemical yields and specific activities that could be obtained. However, the various methods investigated using fluoride ion proved unsuccessful. It is thought that the 'hard' nature of the fluoride anion proved prohibitive to the required modes of reaction.

In the last few years several alternative methods of ^{18}F labelling have been developed.[11,39,40] The initial findings sugggest that the best of these involves the use of $[^{18}F]XeF_2$ and this reagent has the added advantage that it can be used to monofluorinate a wide range of substrates. However, a good method of aromatic fluorination using fluoride ion is still being sought by ^{18}F radiopharmaceutical researchers.[34]

In the later stages of our research a broader approach to aromatic fluorination was adopted. It was found that aryl fluorides could be prepared by treating aryl mercuric halides with antimony pentafluoride. The initial findings suggest that the scope of this procedure is comparable to McKillop's thallium method. Further work is necessary to obtain a better understanding of the mechanism of this fluorination process and to optimise reaction conditions.

EXPERIMENTAL

Reaction Conditions

Anhydrous conditions were used unless otherwise stated. Solvents were dried prior to use according to standard techniques.[94]

All fluorination reactions were performed under nitrogen. Reactions involving chromium tricarbonyl compounds and palladium or nickel complexes were carried out under nitrogen using degassed solvents.

Potassium and caesium fluoride were dried in a nickel crucible by heating to just below fusion point with constant stirring and then allowed to cool in a vacuum dessicator. Lithium, silver and thallium fluorides were dried *in vacuo* at 110°C for 24 hrs.

Product Characterisation

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Infra red spectra were recorded on a Perkin Elmer 257 grating spectrophotometer. ^{1}H Nuclear magnetic resonance spectra were recored on a Varian T60 spectrophotometer, in deuterochloroform using tetramethylsilane as internal standard. Mass spectra were measured on an A.E.I. MS9 instrument operating at 70 eV.

Microanalysis were carried out by the microanalytical laboratory, Imperial College.

Gas-Liquid chromatographs were recorded on either a Perkin-Elmer F11 or F33 gas chromatograph. 15% Carbowax on chromosorb W 80-100 mesh and silicon grease were the columns used.

Organic extracts were dried over sodium sulphate.

Merck Kieselgel GF_{254} was used for analytical and preparative thin layer chromatography. BDH active aluminium oxide (neutral, grade I) was used for column chromatography.

3-Bromo-4-hydroxybiphenyl

Bromine (16.1 g, 101 mmoles) was added dropwise to a solution of 4-hydroxybiphenyl (16.3 g, 96 mmoles) in carbon tetrachloride (50 mls) at room temperature. After two hours, the solvent was removed under reduced pressure. Recrystallisation from petroleum ether (bp. 40-60°C) gave 3-bromo-4-hydroxybiphenyl (21.1 g, 88%), m.p. 93-94°C (lit.,[95] m.p. 93.5-94.5°C), ν_{max} (nujol) 3250 cm^{-1}, δ 5.40 (1 H, s), 7.03 (1 H, d, J_{ortho} = 8 Hz), 7.0-7.7 (6 H, m), 7.67 (1 H, d, J_{meta} = 2 Hz).

3-Bromo-4-tosyloxybiphenyl

Tosyl chloride (8.4 g, 44 mmoles) was added to a solution of 3-bromo-4-hydroxybiphenyl (10.0 g, 40 mmoles) in pyridine (100 mls) at 0°C. The reaction was continued for 16 hrs. at 4°C and long needles of pyridine hydrochloride separated out during this period. The entire reaction mixture was poured with stirring into ice/water (300 mls). An oily liquid was obtained. The resulting mixture was ether extracted (2 x 100 mls) and the extract washed first with 2 M hydrochloric acid (100 mls) and then with water (100 mls). The ether phase was dried over sodium sulphate and the solvent evaporated under reduced pressure. The traces of pyridine remaining were removed by azeotroping with toluene (30 mls). The solid which resulted was recrystallised from ether to give 3-bromo-4-tosyloxybiphenyl (11.8 g, 73%), m.p. 84.5-85°C, ν_{max} (nujol) 1360, 1175 cm^{-1}, δ 2.45 (3 H, s), 7.1-8.0 (12 H, m). (Found: C, 56.71; H, 3.70; Br, 19.54. $C_{19}H_{15}BrO_3S$ requires C, 56.58; H, 3.75; Br, 19.81%).

Furan trapping of 4-phenylbenzyne produced from 3-bromo-4-tosyloxybiphenyl/n-butyl lithium

n-Butyl lithium (0.46 mls of 2.68 M solution in hexane ≡ 1.23 mmoles) was added to a solution of 3-bromo-4-tosyloxybiphenyl (0.50 g, 1.24 mmoles) in a mixture of glyme (10 mls) and furan (2.5 mls), under nitrogen, at -78°C. The reaction was continued for 30 mins. at -78°C and then allowed to warm up to room temperature. After two hours, the reaction mixture was acidified with aqueous acetic acid (10 mls, 5% v/v) and then extracted with ether (2 x 10 mls). The ether extract was dried over sodium sulphate and the solvent removed under reduced pressure. Isolation by preparative t.l.c. on silica using benzene as the eluting solvent gave a mixture of the 6- and 7-phenyl-1-naphthols (102 mg, 38%), ν_{max} (nujol) 3400 cm^{-1}, δ 4.9 (1 H, s), 6.6-8.4 (11 H, m), m/e 220 (M^+).

Attempted fluorination of 4-phenylbenzyne generated from 3-bromo-4-tosyloxybiphenyl/n-butyl lithium

3-Bromo-4-tosyloxybiphenyl (0.50 g, 1.24 mmoles) was reacted with n-butyl lithium (0.46 mls of 2.68 M solution in hexane ≡ 1.23 mmoles) in the presence of lithium fluoride (0.53 g, 20.4 mmoles) using similar reaction conditions and work up procedure to those described previously for the furan trapping experiment. Isolation by preparative t.l.c. on silica using 30% benzene/petroleum ether (b.p. 40-60°C) as the eluting solvent gave (9) (55 mg, 15%), ν_{max} ($CC\ell_4$) 3030, 2930, 2850, 1595, 1465, 1385, 695 cm^{-1}, δ ($CC\ell_4$) 1.00 (3 H, t), 1.2-1.9 (4 H, m), 2.77 (2 H, m), 7.1-7.8 (8 H, m), m/e 290 (M^+), 288, 247, 245; (10) (14 mg), ν_{max} ($CC\ell_4$) 3050, 3030,

2930, 2850, 1595, 1465, 1385, 695 cm^{-1}, δ ($CC\ell_4$) 0.80 (3 H, t), 1.0-1.9 (4 H, m), 2.50 (2 H, m), 7.1-7.8 (16 H, m), m/e 442 (M^+), 440, 318; (11) (41 mg), ν_{max} ($CC\ell_4$), 3030, 2930, 2850, 1600, 1465, 1375, 895, 695 cm^{-1}, δ ($CC\ell_4$) 0.83 (3 H, t), 1.0-1.7 (4 H, m), 2.57 (2 H, m), 6.9-7.9 (24 H, m), m/e 594 (M^+), 592, 470.

4-Tosyloxybiphenyl

Tosyl chloride (8.6 g, 45 mmoles) was added to a solution of 4-hydroxybiphenyl (7.0 g, 41 mmoles) in pyridine (100 mls) at 0°C. The reaction was continued for 16 hrs. at 4°C. The reaction mixture was poured with stirring into ice/water (300 mls). The solid obtained was filtered off, washed with water and dried in vacuo. Recrystallisation from glacial acetic acid gave 4-tosyloxybiphenyl (11.9, 89%), m.p. 177-178°C (lit.,[96] m.p. 177°C), ν_{max} (nujol) 1375 cm^{-1}, δ 2.43 (3 H, s), 6.9-8.0 (13 H, m).

Furan trapping of 4-phenylbenzyne produced from 4-tosyloxybiphenyl/lithium diisopropylamide

A furan trapping reaction was carried out by a similar procedure to that described previously. 4-Tosyloxybiphenyl (0.50 g, 1.54 mmoles) was used as substrate and lithium diisopropylamide (0.191 g of diisopropylamine and 0.97 mls of 1.9 M methyl lithium ≡ 1.84 mmoles) as base. Isolation by t.l.c using benzene as eluant gave a mixture of the 6- and 7-phenyl-1-naphthols (71 mg, 21%), ν_{max} (nujol) 3400 cm^{-1}, δ 5.4 (1 H, s), 6.6-8.5 (11 H, m).

Attempted fluorination of 4-phenylbenzyne generated from 4-tosyloxybiphenyl/lithium diisopropylamide

4-Tosyloxybiphenyl (0.50 g, 1.54 mmoles) was reacted with lithium diisopropylamide (0.189 g of diisopropylamine and 0.97 mls of 1.9 M methyl lithium ≡ 1.84 mmoles) in the presence of lithium fluoride (0.52 g, 20 mmoles) by the standard procedure. The major product was isolated by t.l.c. using benzene as the eluting solvent and was identified as 4-hydroxybiphenyl (46 mg, 17%), m.p., 163-164°C (lit., [97] m.p., 164-165°C), ν_{max} (nujol) 3360, δ 5.0 (1 H, s), 6.86 (2 H, d, J_{ortho} = 9 Hz) 7.1-7.7 (5 H, m), 7.46 (2 H, d, J_{ortho} = 9 Hz).

Attempted fluorination of 4-phenylbenzyne from 4-tosyloxybiphenyl/sodium bistrimethylsilylamide

4-Tosyloxybiphenyl (0.50 g, 1.54 mmoles) was reacted with sodium bistrimethylsilylamide (0.248 g hexamethyldisilazane and 0.037 g sodium hydride ≡ 1.54 mmoles) in the presence of lithium fluoride (0.43 g, 16.5 mmoles) using the general procedure. The product was isolated by t.l.c. and shown to be 4-hydroxybiphenyl (36 mg, 14%), m.p., 164°C.

4-Phenylphenyl chloroformate

Triethylamine (6.0 g, 59 mmoles) was added dropwise with stirring to a solution of 4-hydroxybiphenyl (10.0 g, 59 mmoles) and phosgene (≃ 20 g, 200 mmoles) in ether (200 mls) at 0°C. A flocculent white precipitate was produced. After 1 hr., the ether and excess phosgene were removed under reduced pressure. The residue was triturated with

ether and distillation of the ethereal solution under reduced pressure gave 4-phenylphenyl chloroformate (10.5 g, 77%), m.p., 39-40°C (lit.[98] m.p., 39-40°C), ν_{max} (nujol) 1785 cm^{-1}.

4-Phenylphenyl azidoformate

A solution of 4-phenylphenyl chloroformate (5.0 g, 21 mmoles) in ether (40 mls) was added to a gently stirred suspension of sodium azide (2.1 g, 32 mmoles) in ether (100 mls) at room temperature. After 2 d., the solution was filtered and the ether evaporated off. Recrystallisation from ether gave 4-phenylphenyl azidoformate (4.4 g, 86%), m.p., 97-98°C, ν_{max} (nujol) 2160, 1750 cm^{-1}. (Found: C, 65.22; H, 3.76; N, 17.57. $C_{13}H_9N_3O_2$ requires C, 65.27; H, 3.79; N, 17.56%).

Attempted fluorination of 4-phenylphenyl azidoformate with nitrosonium tetrafluoroborate

4-Phenylphenyl azidoformate (0.40 g, 1.7 mmoles) was added to a solution of nitrosonium tetrafluoroborate (0.91 g, 7.7 mmoles) in acetonitrile (10 mls) at room temperature. The reaction mixture was refluxed for 4 d. A dark brown solution was produced. The solvent was evaporated off and the residue extracted with benzene. The extract was filtered and concentrated under reduced pressure. Isolation by preparative t.l.c. using benzene as eluant gave 5-phenyl-1,3-benzodioxol-2-one (14) (3 mg), ν_{max} ($CC\ell_4$) 1775, 1585, 1490, 1375, 1215, 1170, 910, 700 cm^{-1}, m/e 212 (M^+); 2-methyl-5-phenyl-benzoxazole (15) (6 mg), ν_{max} (nujol) 3430, 3050, 2960, 1610, 1585, 1525, 1485, 1265, 1205, 835, 755, 690 cm^{-1}, (Found: M^+ 209.0844. $C_{14}H_{11}NO$ requires 209.0841); 3-nitro-4-hydroxybiphenyl

(12) (69 mg, 20%), m.p., 65-66°C (lit.[99] m.p. 66-67°C), ν_{max} (nujol) 3440, 3070, 2970, 1610, 1595, 1530, 1515, 1340, 1275, 1200, 1115, 860, 835, 755, 725 cm^{-1}, m/e 215 (M^+); 5-phenyl-benzoxazole (13) (6 mg), ν_{max} ($CC\ell_4$) 3300, 1770, 1630, 1485, 1385, 1250, 960, 705 cm^{-1}, (Found: M^+ 211.0633. $C_{13}H_9NO_2$ requires 211.0633).

Attempted fluorination of 4-phenylphenyl azidoformate with nitrosonium tetrafluoroborate/potassium fluoride

4-Phenylphenyl azidoformate (0.25 g, 1.0 mmoles) was added to a mixture of nitrosonium tetrafluoroborate (0.81 g, 6.9 mmoles) and potassium fluoride (0.5 g, 8.6 mmoles) in acetonitrile (10 mls) at room temperature. The reaction was refluxed for 16 hrs. and then worked up as described previously. Isolation by preparative t.l.c. using benzene/petroleum ether (b.p. 40-60°C) (1:1) gave 3-nitro-4-hydroxybiphenyl (93 mg, 41%), m.p., 64-65.5°C, ν_{max} 3440.

(Tricarbonyl)tris(pyridine)chromium(0) [53]

Chromium hexacarbonyl (4.0 g, 18 mmoles) and pyridine (30 mls) were refluxed (oil bath temp. 160°C) in aromatic free petroleum ether (b.p. 80-100°C) (30 mls) for 30 hrs. The reaction mixture was cooled to 0°C. The red needles of (tricarbonyl)tris(pyridine)chromium(0) which separated out were filtered off, washed thoroughly with petroleum ether, dried *in vacuo* and stored under nitrogen at 0°C (6.1 g, 90%), ν_{max} (nujol) 1890, 1750 cm^{-1} (lit.[100] ν_{max} 1895, 1760 cm^{-1}).

Preparation of tricarbonyl η^6-(arene)chromium(0) compounds

a) Use of (tricarbonyl)tris(pyridine)chromium(0) [53]

Freshly distilled boron trifluoride etherate (1.85 g, 13 mmoles) was added slowly to a stirred suspension of (tricarbonyl)tris(pyridine)-chromium(0) (1.5 g, 4.0 mmoles) in a mixture of aromatic substrate (2 mls) and ether (30 mls). The mixture was refluxed for 4 hrs. After cooling to room temperature, the reaction mixture was washed with water, dried and the solvent evaporated under reduced presssure. The residue was chromatographed on neutral alumina using ether/petroleum ether (b.p. 40-60°C) (1:9) as eluant. Pentacarbonyl(pyridine)chromium(0) eluted first (m.p., 94.5-95.5°C; lit.[53] m.p., 94-95°C) followed by the tricarbonyl η^6-(arene)chromium(0) compound.

b) Use of (tricarbonyl)tris(acetonitrile)chromium(0) [52]

Chromium hexacarbonyl (2.0 g, 9.1 mmoles), acetonitrile (20 mls) and the aromatic substrate (40 mls) were refluxed (oil bath temp. 165°C) for 2.5 d. in a Strohmeier 'closed cycle' apparatus. The dark reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was extracted with ether. The extract was filtered through kieselguhr and the ether evaporated under reduced pressure. The tricarbonyl η^6-(arene)chromium(0) compound was isolated by the chromatographic procedure described previously.

c) Use of a (2-picoline)chromium(0) intermediate [54]

Chromium hexacarbonyl (2.0 g, 9.1 mmoles), 2-picoline (30 mls) and the aromatic substrate (30 mls) were refluxed (oil bath temp. 150°C) for 4 d. in a Strohmeier apparatus. The dark red reaction mixture was

allowed to cool and the solvents were removed under reduced pressure. The yellow-green solid was extracted with ether. The extract was filtered through kieselguhr and concentrated under reduced pressure. The tricarbonyl η^6-(arene)chromium(0) compound was isolated by the standard chromatographic procedure.

The tricarbonyl η^6-(arene)chromium(0) compounds prepared by methods (a)-(c) are listed in TABLE 1.

Tricarbonyl η^6-(benzene)chromium(0), m.p., 161-162°C (lit.[101] m.p., 161.5-163°C), ν_{max} (nujol) 1960, 1855 cm^{-1}, δ ($CC\ell_4$) 5.30 (6 H, s); tricarbonyl η^6-(chlorobenzene)chromium(0), m.p., 102-103°C (lit.[51] m.p., 102-103°C), ν_{max} (nujol) 1950, 1875 cm^{-1}, δ 4.9-5.3 (1 H, m), 5.46 (4 H, d, J = 4 Hz), m/e 250 (M^+), 248; tricarbonyl η^6-(anisole)-chromium(0), m.p., 84-85°C (lit.[101] m.p., 83-84°C), ν_{max} (nujol) 1940, 1855 cm^{-1}, δ 3.87 (3 H, s), 4.83 (1 H, t, J_1 = 6 Hz), 5.07 (2 H, d, J_2 = 6 Hz), 5.53 (2 H, t, J_1 = 6 Hz, J_2 = 6 Hz), m/e 244 (M^+); tricarbonyl η^6-(fluorobenzene)chromium(0), m.p., 123-124°C (lit.[51] m.p., 122.5-124°C), ν_{max} (nujol) 1955, 1880, δ 4.6-5.1 (1 H, m), 5.1-5.8 (4 H, m), m/e 232 (M^+).

Tricarbonyl η^6-(brosyloxybenzene)chromium(0)

Phenol (0.38 g, 4.0 mmoles) was reacted with tricarbonyl tris-(pyridine)chromium(0) (Method a). The crude product obtained upon work up was dissolved in pyridine (5 mls) and 4-bromobenzene sulphonyl chloride (1.2 g, 4.7 mmoles) was added at room temperature in the

dark. After 16 hrs., water was added and the reaction mixture ether extracted. The extract was dried and the solvent removed under reduced pressure. Isolation by column chromatography gave tricarbonyl η^6-(brosyloxybenzene)chromium(0) (0.98 g, 54%), m.p. 143-143.5°C, ν_{max} (nujol) 1965, 1885, 1385 cm^{-1}, δ 4.7-5.6 (5 H, m), 7.8 (5 H, s). (Found: C, 39.91; H, 2.00; Br, 17.65. $C_{15}H_9BrCrO_6S$ requires C, 40.11; H, 2.02; Br, 17.79%).

18-Crown-6 [102]

A solution of bis(2-chloroethyl)ether (112 g, 0.78 mole) in THF (40 mls) was added to a warm, vigorously stirred mixture of 85% potassium hydroxide pellets (104 g, 1.58 moles), tetraethylene glycol (61 g, 0.31 mole) and THF (250 mls). The reaction mixture was refluxed for 18 hrs. The reaction was cooled and evaporation under reduced pressure yielded a brown slurry. Dichloromethane (250 mls) was added and the resulting mixture filtered. The filtrate was dried over magnesium sulphate, concentrated under reduced pressure and then distilled (35.6 g, b.p. 100-160°C at 0.02 mm). The slightly discoloured distillate was dissolved in acetonitrile (80 mls) and the solution cooled to -45°C. The resultant white precipitate of 18-crown-6 acetonitrile complex was filtered off and distilled to give pure 18-crown-6 (18.3 g, 22%), m.p., 37-38°C (lit.[102] m.p., 38-38.5°C), ν_{max} (nujol) 1350, 1250, 1125 cm^{-1}, δ 3.70 (s).

Attempted fluorination of tricarbonyl η^6-(brosyloxybenzene)chromium(0)

A mixture of tricarbonyl η^6-(brosyloxybenzene)chromium(0) (0.40 g, 0.89 mmole), potassium fluoride (0.26 g, 4.5 mmoles) and 18-crown-6 (0.12 g, 0.45 mmole) in glyme (10 mls) was refluxed for 3 d. The reaction was cooled and ether (10 mls) added. The reaction mixture was washed with water, dried and the solvents removed under reduced pressure. An n.m.r. of the solid obtained showed that a new chromium tricarbonyl compound was formed. A t.l.c. of the residue indicated that two chromium tricarbonyl complexes had been produced but attempts to isolate these materials by column chromatography proved unsuccessful. A mass spectrum was obtained of the crude reaction mixture, m/e 432 (M^+) ≡ $C_{18}H_{10}Cr_2O_7$ indicating the presence of di[tricarbonyl η^6-(phenyl)-chromium(0)]ether (16).

Reaction of methoxide ion with tricarbonyl η^6-(chlorobenzene)chromium(0) [51]

Tricarbonyl η^6-(chlorobenzene)chromium(0) (0.10 g, 0.40 mmole) and sodium methoxide (from 25 mg of sodium ≡ 1.1 mmoles) in methanol (10 mls) were heated under reflux for 6 hrs. The reaction was cooled and ether (10 mls) added. The resulting mixture was washed with water, dried and the solvents removed under reduced pressure. Isolation by column chromatography gave tricarbonyl η^6-(anisole)chromium(0) (71 mg, 73%), m.p., 83-84°C (lit.[101] m.p., 83-84°C), δ 3.82 (3 H, s), 4.7-5.8 (5 H, m).

Attempted fluorination of tricarbonyl η^6-(chlorobenzene)chromium(0)

1) With caesium fluoride

A mixture of tricarbonyl η^6-(chlorobenzene)chromium(0) (0.25 g, 1.0 mmole) and caesium fluoride (0.53 g, 3.5 mmoles) in HMPA (4 mls) was stirred at 120°C for 2d. The reaction mixture was cooled and was found to give a positive silver nitrate test. Iodine (0.8 g, 3.1 mmoles) in ether (3 mls) was added. After 3 hrs., the resulting mixture was washed first with 5% aqueous sodium bisulphite solution (5 mls) and then with water (5 mls). The ether phase was analysed by g.l.c. Benzene and chlorobenzene were observed but no fluorobenzene was detected.

2) With caesium fluoride/silver fluoride

Tricarbonyl η^6-(chlorobenzene)chromium(0) (0.25 g, 1.0 mmole) was added to a mixture of caesium fluoride (0.48 g, 3.2 mmole) and silver fluoride (0.26 g, 2.0 mmole) in HMPA (4 mls). The reaction conditions and work up procedure were the same as those described previously. G.l.c. analysis of the ether phase showed that benzene and chlorobenzene were obtained.

Palladium catalysed cyanation of iodobenzene [63]

Iodobenzene (0.21 g, 1.0 mmole) was added to potassium cyanide (0.12 g, 1.8 mmoles) in HMPA (2 mls). The mixture was stirred at 100°C for 0.5 hr. and a solution of palladium(II) acetate (15 mg, 0.067 mmole) in HMPA (0.5 mls) was added. The temperature of the reaction mixture was raised to 160°C and the reaction continued for 16 hrs. The reaction

mixture was cooled, diluted with ether, washed with brine, dried and concentrated under reduced pressure. G.l.c. analysis showed that benzonitrile was produced essentially quantitatively.

Attempted palladium catalysed fluorination of iodobenzene

1) With potassium fluoride/palladium(II) acetate

A solution of palladium(II) acetate (9 mg, 0.040 mmoles) in HMPA (0.5 mls) was added to a mixture of iodobenzene (0.20 g, 0.98 mmoles), potassium fluoride (0.15 g, 2.6 mmoles) and HMPA (2 mls) at 100°C. The reaction was continued for 16 hrs. at 160°C. The reaction mixture was cooled and g.l.c. analysis showed that benzene was produced. The reaction mixture was diluted with ether, washed with 5% orthophosphoric acid, then with brine, dried and concentrated under reduced pressure. Isolation by preparative t.l.c. using carbon tetrachloride as eluant gave biphenyl (18 mg, 24%), m.p., 69-70°C (lit.,[103] m.p., 71°C), identical with an authentic sample (i.r., n.m.r.).

2) With potassium fluoride/palladium(II)acetate/triphenylphosphine

The previous reaction was repeated with added triphenylphosphine (76 mg, 0.29 mmoles). G.l.c. analysis indicated the formation of benzene and t.l.c. the production of biphenyl.

3) With potassium fluoride/palladium(II)acetate/18-crown-6

The reaction described in (1) was repeated with added 18-crown-6 (120 mg, 0.45 mmoles). Benzene and biphenyl were detected.

4) With potassium fluoride/thallium(I)fluoride/palladium(II) acetate

A solution of palladium(II) acetate (13 mg, 0.058 mmoles) in HMPA (0.5 mls) was added to a stirred mixture of thallium(I)fluoride (0.32 g, 1.4 mmoles), potassium fluoride (0.13 g, 2.2 mmoles) and iodobenzene (0.20 g, 0.98 mmoles) in HMPA (2 mls) at 100°C. The reaction was continued at 140°C for 2d. G.l.c. analysis indicated the formation of benzene and t.l.c. the production of biphenyl.

5) With potassium fluoride/palladium(II) acetate

The reaction described in (1) was repeated using different amounts of potassium fluoride (23 mg, 0.40 mmoles) and palladium(II) acetate (106 mg, 0.47 mmoles). Benzene and biphenyl were obtained.

Tetrakis(triphenylphosphine)palladium(0) [104]

Palladium(II) chloride (3.0 g, 17 mmoles) and triphenylphosphine (22.2 g, 85 mmoles) in DMSO (200 mls) were heated (oil bath temp. 150°C) until complete solution occurred. The heat source was removed and the mixture stirred for approximately 15 mins. Hydrazine hydrate (3.5 g, 70 mmoles) was added over a period of 1 min. and the reaction cooled with a water bath. After 30 mins., the yellow crystals of tetrakis-(triphenylphosphine)palladium(0) were filtered off, washed with cold ethanol, then with cold ether, dried under reduced pressure and stored under nitrogen at 0°C (17.8 g, 91%), m.p., 112-115°C (dec.) [lit.,[104] m.p., 116°C (dec)].

Iodo(phenyl)bis(triphenylphosphine)palladium(II)

A mixture of iodobenzene (1.65 g, 8.1 mmoles) in benzene (10 mls) was added to a stirred suspension of tetrakis(triphenylphosphine)-palladium(0) (10.3 g, 8.9 mmoles) in benzene (250 mls) at room temperature. After 2 hrs, the reaction mixture was filtered and the solid washed with benzene (50 mls). The filtrate was concentrated under reduced pressure and the solid residue was triturated with ether to remove triphenylphosphine. Recrystallisation from benzene/cyclohexane gave iodo(phenyl)bis(triphenylphosphine)palladium(II) (5.16 g, 76%), m.p., 182-187°C (dec.) [lit.,[71] m.p., 171-186°C (dec.)].

Bromo(phenyl)bis(triphenylphosphine)palladium(II)

A mixture of bromobenzene (0.63 g, 4.0 mmoles) and tetrakis(triphenyl-phosphine)palladium(0) (5.0 g, 4.3 mmoles) in benzene (100 mls) were refluxed for 2 hrs. The reaction mixture was filtered and the solid washed with hot benzene (40 mls). The filtrate was concentrated under reduced pressure. The solid was washed with ether and recrystallisation from benzene/cyclohexane gave bromo(phenyl)bis(triphenylphosphine)-palladium(II) (2.69, 85%), m.p., 215-218°C (dec.) [lit.,[72] m.p., 216-220°C (dec.)].

Attempted fluorinations of halo(phenyl)bis(triphenylphosphine)palladium(II)

1) With potassium fluoride

A mixture of iodo(phenyl)bis(triphenylphosphine)palladium(II) (1.51 g, 1.81 mmoles) and potassium fluoride (0.50 g, 8.6 mmoles) in HMPA (5 mls) was stirred at 120°C for 1 d. G.l.c. analysis indicated the formation of benzene and t.l.c. the production of biphenyl.

A similar reaction was carried out with bromo(phenyl)bis(triphenylphosphine)palladium(II). Benzene and biphenyl were observed.

2) With potassium fluoride/thallium(I) fluoride

A mixture of iodo(phenyl)bis(triphenylphosphine)palladium(II) (1.52 g, 1.82 mmoles), potassium fluoride (0.51 g, 8.8 mmoles) and thallium(I) fluoride (0.61 g, 2.7 mmoles) in HMPA (5 mls) was stirred at 80°C for 1 d. Benzene and biphenyl were formed.

3) With potassium fluoride/thallium(I) fluoride

The previous reaction was repeated using a mixed solvent system consisting of HMPA (1 ml) and glyme (4 mls). Benzene and biphenyl were detected.

A similar reaction was performed on bromo(phenyl)bis(triphenylphosphine)-palladium(II). Benzene and biphenyl were obtained.

4) With potassium fluoride/potassium dichromate

Reaction (1) with iodo(phenyl)bis(triphenylphosphine)palladium(II) was repeated in the presence of potassium dichromate (0.54 g, 1.8 mmoles). Benzene and biphenyl were produced.

5) With potassium fluoride/silver(I) fluoride

A mixture of bromo(phenyl)bis(triphenylphosphine)palladium(II) (1.50 g, 1.91 mmoles), silver fluoride (0.52 g, 4.1 mmoles) and potassium fluoride (0.49 g, 8.4 mmoles) in a mixed solvent system consisting of HMPA (1 ml) and glyme (4 mls) was stirred at 80°C for 1 d. Benzene and biphenyl were observed.

Thallium(I)acetylacetonate

Thallium(I) formate (10.0 g, 40 mmoles) was dissolved in water (10 mls). A solution of sodium (1.6 g, 70 mmoles) in absolute ethanol (30 mls) was added and the mixture refluxed for 2 hrs. The reaction mixture was filtered and the oily layer of thallium(I) ethoxide separated off. The oil was dissolved in benzene (100 mls) and a mixture of acetylacetone (4.4 g, 44 mmoles) in benzene (25 mls) was added at room temperature. After 1 hr., the solvent was removed under reduced pressure. Recrystallisation from benzene/cyclohexane gave thallium(I) acetylacetonate (8.3 g, 68%), m.p., 157-158.5°C (lit.,[105] m.p., 158°C), ν_{max} 1610, 1585, 1505, 1455, 1390, 1230, 1195, 1010, 910, 770 cm^{-1}, δ 1.92 (6 H, s), 5.20 (1 H, s).

Phenyl(acetylacetonate)triphenylphosphine palladium(II)

A solution of bromo(phenyl)bis(triphenylphosphine)palladium(II) (6.0 g, 7.6 mmoles) in benzene (100 mls) was added to a vigorously stirred solution of thallium(I)acetylacetonate (2.4 g, 7.9 mmoles) in benzene (100 mls) at room temperature. After 16 hrs., the reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was washed with cold ether (5 mls) and recrystallisation from benzene gave white crystals of phenyl(acetylacetonate)-triphenylphosphine palladium(II) (2.94 g, 71%), m.p., 178-179°C (dec.), ν_{max} 3060, 1590, 1570, 1515, 1485, 1440, 1395, 1265, 1200, 1105, 1095, 1070, 1025, 1000, 925, 770, 750, 740, 695 cm^{-1}, δ 1.65 (3 H, s), 1.93 (3 H, s), 5.33 (1 H, s), 1.9-3.5 (20 H, m). (Found: C, 64.20; H, 4.96; P, 5.86. $C_{29}H_{27}PPdO_2$ requires C, 63.92; H, 4.99; P, 5.68%).

Reaction of phenyl(acetylacetonate)triphenylphosphine palladium(II) with hydrogen bromide

Hydrogen bromide was bubbled through a refluxing solution of phenyl (acetylacetonate)triphenylphosphine palladium(II) (100 mg, 0.18 mmole) and triphenylphosphine (53 mg, 0.20 mmole) in THF (50 mls). After 4 hrs., the solvent was removed under reduced pressure. The solid residue was washed with cold ether. Recrystallisation from benzene/ cyclohexane gave orange crysals of dibomo-bis(triphenylphosphine)-palladium(II) (117 mg, 81%) m.p., 256-258°C (dec.) [lit.,[106] m.p., 253°C (dec.)] . (Found: C, 54.65; H, 3.80; Br, 20.26; P, 7.51. $C_{36}H_{30}Br_2P_2Pd$ requires C, 54.68; H, 3.82; Br, 20.21; P, 7.83%).

Attempted fluorinations of phenyl(acetylacetonate)triphenylphosphine palladium(II) with pyridinium poly(hydrogen fluoride)

1. Pyridinium poly(hydrogen fluoride) (1.62 g $\sim$ 57 mmoles HF) was added to a solution of phenyl(acetylacetonate)triphenylphosphine palladium(II) (197 mg, 0.36 mmole) and triphenylphosphine (104 mg, 0.40 mmole) in toluene (50 mls). The reaction mixture was stirred at 80°C for 2 hrs. G.l.c. analysis indicated the formation of benzene.

2. Pyridinium poly(hydrogen fluoride (1.9 g $\sim$ 66 mmoles HF) was added to a solution of phenyl(acetylacetonate)triphenylphosphine palladium(II) (208 mg, 0.38 mmole) and triphenylphosphine (102 mg, 0.39 mmole) in THF (50 mls) at room temperature. The reaction mixture was refluxed for 4 hrs. The solvent was removed under reduced pressure and the solid residue was washed with cold ether. Recrystallisation from benzene/

cyclohexane gave (17) (264 mg, crude weight) m.p., 117-120°C (dec.), ν_{max} (nujol) 1585, 1480, 1435, 1335, 1310, 1185, 1115, 1025, 995, 925, 905, 885, 750, 735, 690 cm^{-1} (Found: C, 62.62; H, 4.43; P, 8.33; F, 7.90. $C_{36}H_{31}F_3PdP_2$ requires C, 62.76; H, 4.54; P, 8.99; F, 8.27%).

Bis(triphenylphosphine)dichloronickel(II) [107]

A solution of nickel chloride hexahydrate (23.8 g, 0.10 mole) in water (25 mls) was diluted with glacial acetic acid (400 mls). Triphenylphosphine (52.5 g, 0.20 mole) in glacial acetic acid (200 mls) was added. The mixture was stirred at room temperature for 1 hr. and then left for 16 hrs. The blue-green crystals of bis(triphenylphosphine)-dichloronickel(II) were filtered off, washed with glacial acetic acid and dried over potassium hydroxide *in vacuo* (38.1 g, 58%), m.p., 247-249°C (dec.) [lit.,[107] m.p., 247-250°C (dec.)].

Tetrakis(triphenylphosphine)nickel(0)

A solution of sodium borohydride (0.30g, 7.9 mmoles) in ethanol (10 mls) was added dropwise to a mixture of bis(triphenylphosphine) dichloronickel(II) (2.4 g, 3.7 mmoles) and triphenylphosphine (2.0 g, 7.6 mmoles) in ethanol at room temperature. After 4 hrs., the reaction mixture was decanted. The reddish-brown crystals of tetrakis(triphenyl-phosphine)nickel(0) obtained were washed several times with ethanol and dried *in vacuo* (3.8 g, 93%), m.p., 122-126°C (dec.) [lit.,[108] m.p., 123-128°C (dec)].

Benzoyl fluoride

A mixture of potassium fluoride (8.3 g, 140 mmoles) and 18-crown-6 (16 mg, 0.061 mmole) in benzoyl chloride (6.2 g, 44 mmoles) was refluxed for 16 hrs. The reaction mixture was filtered and distilled through a Vigreux column. Redistillation of the first fraction gave benzoyl fluroide (0.51 g, 9%), b.p., 150°C (lit.,[109] b.p., 154-5°C), ν_{max} (neat) 1810 cm^{-1}.

Attempted decarbonylation of benzoyl fluoride with tetrakis(triphenylphosphine)nickel(0)

Benzoyl fluoride (317 mg, 2.56 mmoles) was added to a solution of tetrakis(triphenylphosphine)nickel(0) (2.84 g, 2.57 mmoles) in toluene at 0°C. The reaction was stirred at room temperature for 6 hrs. No colour change was observed and g.l.c. analysis failed to detect any fluorobenzene or benzene.

Phenyl mercuric chloride [110]

A solution of sodium nitrite (7.50 g, 0.109 mole) in water (40 mls) was added slowly with stirring to a mixture of aniline (10.0 g, 0.107 mole), hydrochloric acid (25 mls,D1.17) and ice (80 g) at -5°C, care being taken to ensure that the reaction temperature remained below 5°C. The phenyl diazonium chloride solution produced was then added to a mixture of mercuric chloride (29.1 g, 0.107 mole), cuprous chloride (21.4 g, 0.107 mole), hydrochloric acid (25 mls, D 1.17) and ice (50 g), the temperature again being kept below 5°C during the addition. The reaction

was continued for 4 hrs. at 0°C. The precipitate was filtered, washed with water and dried *in vacuo*. Recrystallisation from benzene gave phenyl mercuric chloride (21.4 g, 64%), m.p., 246-248°C (lit.,[110] m.p., 251°C), ν_{max} (nujol) 3080, 3055, 1575, 1485, 1435, 1335, 1065, 1020, 1000, 725, 695, 665 cm^{-1}, m/e 314 (M^+), 279, 237, 202.

Phenyl mercuric acetate[111]

Mercuric acetate (33.8 g, 0.106 mole) was added over a period of 1 hr. to a gently refluxing mixture of benzene (30.7 g, 0.393 mole) and acetic acid (124.3 g, 2.07 moles). The reaction mixture was refluxed for 1.5 d. The solvents were removed under reduced pressure and the solid obtained extracted with boiling toluene. The hot solution was filtered and allowed to cool. The phenyl mercuric acetate which crystallised out was filtered off and dried *in vacuo* (21.8 g, 61%), m.p., 144-147°C (lit.,[112] m.p., 149°C), ν_{max} (nujol) 3075, 3055, 3020, 1590, 1480, 1430, 1370, 1310, 1045, 1020, 1000, 925, 905, 730, 690, 665 cm^{-1}.

Phenyl mercuric bromide.

Phenyl mercuric acetate (2.5 g, 7.4 mmole) was dissolved in hot benzene (150 mls). A solution of potassium bromide (0.95 g, 8.0 mmole) in water (20 mls) was added slowly with stirring. The reaction mixture was sitrred for 3 hrs. at room temperature. The precipitate was filtered, washed with water and dried *in vacuo*. Recrystallisation from acetone gave phenyl mercuric bromide (2.43 g, 92%) m.p., 264-268°C (lit.,[113] m.p., 275°C), ν_{max} (nujol) 3080, 3050, 1580, 1480, 1433, 1330, 1300, 1160, 1060, 1015, 995, 725, 690, 665 cm^{-1}.

Phenyl mercuric hydroxide [114]

A solution of sodium hydroxide (8.0 g, 0.20 mole) in water (100 mls) was added to phenyl mercuric acetate (33.6 g, 0.105 mole) in benzene (200 mls) at room temperature. The reaction was vigorously stirred for 2 hrs. Phenyl mercuric hydroxide was filtered off, washed with benzene and dried in vacuo (18.7 g, 60%), ν_{max} (nujol) 3280, 3065, 3045, 1575, 1480, 1435, 1160, 1065, 1025, 995, 915, 905, 725, 695 cm^{-1}.

Phenyl mercuric fluoride [114]

Aqueous hydrofluoric acid (4.2 g of 40% aq. HF ≡ 0.084 mole of HF) was added to phenyl mercuric hydroxide (12 g, 0.041 mole) in ethanol (40 mls) at room temperature. The addition of the acid caused most of the solid to dissolve. The reaction was continued with stirring for 5 hrs. during which time a white slurry was produced. The reaction mixture was stored overnight at 5°C and then filtered. The solid obtained was air dried and extracted with acid free chloroform (300 mls) for 1.5 d. using a Soxhlet extraction technique. The chloroform extract was concentrated under reduced pressure to yield phenyl mercuric fluoride (6.95 g, 58%), m.p., > 270°C (lit., [114] m.p., > 300°C), ν_{max} (nujol) 3040, 1575, 1480, 1435, 1330, 1305, 1260, 1145, 1065, 1020, 995, 725, 695 cm^{-1} (Found: C, 24.48; H, 1.73; F, 4.81. C_6H_5FHg requires C, 24.29; H, 1.70; F, 6.40%).

p-Tolyl mercuric chloride [115]

A solution of sodium p-tolyl sulphinate (35.0 g, 0.196 mole) in boiling water (100 mls) was added cautiously to a solution of powdered mercuric chloride (44.0 g, 0.162 mole) in water (150 mls) at 70°C. Rapid

gas evolution occurred and a heavy curdy precipitate was formed. Water (100 mls) was added after the initial frothing had ceased and the mixture was boiled for 3 hrs. The hot reaction mixture was filtered. The solid obtained was washed with water until the washings gave no precipitate with sodium hydroxide and then dried in vacuo at 110°C. Recrystallisation from o-xylene gave p-tolyl mercuric chloride (28.1 g, 53%), m.p., 224-227°C (lit.,[115] m.p., 230°C), ν_{max} (nujol) 3070, 3050, 3020, 1620, 1600, 1495, 1390, 1305, 1210, 1195, 1110, 1075, 1040, 1025, 955, 940, 790 cm^{-1}.

o-Hydroxyphenyl mercuric chloride [116]

Mercuric acetate (20 g, 0.063 mole) was added slowly with stirring to phenol (10 g, 0.11 mole) at 170°C. When all the mercuric acetate had dissolved the reaction mixture was poured carefully into boiling water (400 mls). The mixture was boiled for 10 mins. and then filtered. A solution of sodium chloride (4.5 g, 0.077 mole) in boiling water (25 mls) was added immediately to the filtrate. The hot reaction mixture was filtered to remove the p-hydroxyphenyl mercuric chloride which precipitated and the filtrate was allowed to cool overnight. The material which crystallised out was filtered off and recrystallisation from water gave o-hydroxyphenyl mercuric chloride (5.3 g, 26%), m.p., 148-150°C (lit.,[116] m.p., 152°C), ν_{max} (nujol) 3410, 1590, 1570, 1470, 1450, 1440, 1360, 1345, 1280, 1215, 1150, 1110, 1050, 1030, 950, 865, 820, 755 cm^{-1}.

o-Nitrophenyl mercuric chloride [117]

Mercuric acetate (20 g, 0.063 mole) was added slowly with stirring to nitrobenzene (104 g, 0.85 mole) at 150°C. After 6 hrs. the reaction mixture was allowed to cool. The mixture was filtered and a solution of sodium chloride (4.0 g, 0.068 mole) in water (25 mls) was added. The resulting reaction mixture was steam distilled to remove the excess nitrobenzene. The solid residue of the steam distillation was filtered off, washed with water, dried in vacuo and then finely crushed. The powder was extracted with petroleum ether (250 mls, bpt. 80-120°C) for 1.5 d. using a Soxhlet extractor. The extract was concentrated under reduced pressure and the solid obtained was recrystallised from glacial acetic acid to give o-nitrophenyl mercuric chloride (6.8 g, 30%), m.p., 179-181°C (lit.,[117] m.p., 181-182°C), ν_{max} (nujol) 3100, 1590, 1560, 1510, 1330, 1300, 1255, 1100, 1040, 1035, 965, 855, 795, 730, 705 cm^{-1}, m/e 359 (M^+), 313.

p-Chlorophenyl mercuric chloride [118]

Mercuric acetate (20 g, 0.063 mole) was added with stirring to chlorobenzene (73.2 g, 0.65 mole) at 120°C. The reaction mixture was refluxed for 3 hrs. and then the excess chlorobenzene was removed by steam distillation. The solid residue of the steam distillation was filtered off and extracted with aliquots of hot benzene (3 x 100 mls). The hot benzene extracts were combined and allowed to cool. The material which crystallised out first was filtered off and recrystallisation from ethanol gave p-chlorophenyl mercuric acetate (4.9 g, 21%) m.p., 186-190°C (lit.,[118] m.p., 193°C), ν_{max} (nujol) 1590, 1315 cm^{-1}.

A warm solution of sodium chloride (1.0 g, 0.017 mole) in water (20 mls) was added slowly with stirring to a hot solution of p-chlorophenyl mercuric acetate (4.0 g, 0.011 mole) in ethanol (200 mls). The reaction mixture was stirred for 30 mins. at room temperature. The white crystalline solid was filtered off and recrystallisation from ethanol gave p-chlorophenyl mercuric chloride (3.3 g, 88%), m.p., 218-222°C (lit.,[118] m.p., 225°C), ν_{max} (nujol) 3050, 1565, 1480, 1450, 1425, 1380, 1260, 1100, 1025, 1015, 950, 880, 810, 780, 745 cm^{-1}.

p-Methoxyphenyl mercuric chloride [119]

Mercuric acetate (10.0 g, 0.031 mole) was added with stirring to anisole (26.4 g, 0.24 mole) at 130°C. After 2 d. at 130°C the reaction mixture was filtered and a solution of sodium chloride (2.0 g, 0.034 mole) in hot water (30 mls) was added with stirring to the warm filtrate. The mixture was steam distilled to remove the excess anisole. The residue of the distillation was filtered off, washed with water, dried and then continuously extracted with ethyl acetate (200 mls) for 2 d. using a Soxhlet extractor. The extract was concentrated under reduced pressure and recrystallisation of the solid obtained from ethyl acetate gave p-methoxyphenyl mercuric chloride (4.7 g, 44%), m.p., 240-246°C (lit.,[119] m.p., 252.5°C), ν_{max} (nujol) 3090, 3010, 1595, 1575, 1500, 1460, 1445, 1395, 1310, 1285, 1250, 1185, 1100, 1080, 1030, 1010, 825, 820, 810, 790 cm^{-1}.

p-Biphenyl mercuric chloride [120]

Mercuric acetate (15 g, 0.047 mole) was added with stirring to a mixture of biphenyl (15 g, 0.097 mole), acetic acid (70 mls) and 70% perchloric acid (0.5 mls) at room temperature. The reaction mixture was stirred for 18 hrs. at room temperature. The thick slush was then poured into water (200 mls). The solid obtained was filtered off and dissolved in hot acetone (200 mls). The hot acetone solution was filtered and a warm solution of sodium chloride (3.5 g, 0.060 mole) in water (30 mls) was added. p-Biphenyl mercuric chloride precipitated and was filtered off, washed first with acetone, then with warm benzene and dried in vacuo (1.6 g, 9%), m.p., > 270°C (lit.,[120] m.p., > 360°C), ν_{max} (nujol) 1550, 1485, 1450, 1380, 1080, 1010, 920, 825, 765, 760, 700 cm^{-1}.

1-Naphthyl mercuric bromide [113]

A solution of 1-bromonaphthalene (1.5 g, 7.2 mmole) in dry ether (20 mls) was added slowly to a mixture of magnesium turnings (0.19 g, 7.8 mmole) and iodine (1 mg) in dry ether (30 mls). The reaction was continued with warming until most of the magnsium had reacted. The solution was filtered and mercuric bromide (3.20 g, 8.9 mmol) was added in small portions with vigorous stirring. The reaction mixture was refluxed for 4 hrs. and then the ether was removed under reduced pressure. The residue was washed with ether (5 mls) and triturated twice with dilute hydrochloric acid (1%; 2 x 20 mls). The solid remaining was filtered off and washed with hot water, alcohol and ether.

Recrystallisation from pyridine gave 1-naphthyl mercuric bromide (1.4 g, 47%), m.p., 199-200°C (lit.,[113] m.p., 202°C), ν_{max} (nujol) 3070, 3050, 3020, 1590, 1560, 1505, 1255, 1210, 1135, 1020, 960, 950, 855, 815, 785, 765, 730 cm^{-1}.

Fluorination of phenyl mercuric chloride with antimony trifluoride dichloride

Freshly sublimed antimony trifluoride (1.18 g, 6.6 mmoles) was heated with antimony pentachloride (1.81 g, 6.0 mmoles) at 120°C for 16 hrs. The reaction mixture was cooled to 0°C and phenyl mercuric chloride (1.71 g, 5.46 mmoles) was added with stirring. The reaction was heated at 120°C for 3 hrs. and then the volatiles were distilled into a cold finger. G.l.c. analysis of the distillate showed that chlorobenzene was the major product. Fluorobenzene and benzene were observed in trace amounts.

Fluorination of phenyl mercuric chloride with antimony pentafluoride

1) Phenyl mercuric chloride (0.80 g, 2.6 mmoles) was added to a stirred solution of antimony pentafluoride (0.63 g, 2.9 mmoles) in freon 112 (3 mls) at room temperature. After 1 hr, the reaction was heated to 120°C. G.l.c. analysis of the distillate indicated the formation of fluorobenzene (7%) and benzene (10%). G.l.c. coupled mass spectrometry confirmed that the products were fluorobenzene and benzene.

2) Reaction (1) was repeated using 3 eq. of antimony pentafluoride. A much lower yield of fluorobenzene was observed.

3) Phenyl mercuric chloride (1.38 g, 4.4 mmoles) was added to antimony pentafluoride (1.12 g, 5.2 mmoles) at room temperature. Green fumes were given off and the colour of the reaction mixture changed from white to purple to green. The reaction was heated to 130°C. G.l.c. analysis of the distillate showed that fluorobenzene (4%) and benzene were produced.

4) Phenyl mercuric chloride (1.01 g, 3.2 mmoles) was added to a stirred solution of antimony pentafluoride (0.93 g, 4.3 mmoles) in freon 112 (5 mls) at -30°C. The reaction was left overnight at room temperature. The reaction mixture was then heated to 80°C to remove the volatiles. G.l.c. analysis of the distillate indicated trace amounts of fluorobenzene and benzene. The residue of the reaction was pyrolysed at 300°C. A g.l.c. of the material in the cold trap showed that fluorobenzene (18%) and benzene (3%) were produced.

5) A solution of antimony pentafluoride (0.97 g, 4.5 mmoles) in freon 112 (3 mls) was added to a stirred suspension of phenyl mercuric chloride (0.78 g, 2.49 mmoles) in freon (5 mls) at -30°C. Similar reaction conditions were used to those described in reaction (4). Fluorobenzene (53%) and benzene (20%) were detected.

Reaction of benzene with antimony pentafluoride

A solution of antimony pentafluoride (1.12g, 5.2 mmoles) in freon (3 mls) was added to a mixture of benzene (0.45g, 5.8 mmoles) in freon (5 mls) at -30°C. There was an immediate brown colouration. The reaction mixture was left overnight, heated to 80°C and the

residue pyrolysed. G.l.c. analysis showed a possible trace of fluorobenzene (< 1%) and recovered benzene (78%).

Fluorination of phenyl mercuric halides with antimony pentafluoride

Phenyl mercuric bromide (0.75 g, 2.1 mmoles) was reacted with antimony pentafluoride (0.87g, 4.0 mmoles)using similar reaction conditions to those described previously in reaction (5) of the corresponding phenyl mercuric chloride reactions. Fluorobenzene and benzene were detected in yields of 52% and 5%, respectively.

Phenyl mercuric fluoride (0.86g, 2.9 mmoles) was reacted with antimony pentafluoride (1.14g, 5.3 mmoles) by a similar procedure. Fluorobenzene and benzene were observed in yields of 38% and 2%, respectively.

Fluorination of p-tolyl mercuric chloride with antimony pentafluoride

1) A solution of antimony pentafluoride (1.04g, 4.8 mmoles) in freon (2 mls) was added to a stirred suspension of p-tolyl mercuric chloride (1.04 g, 3.2 mmoles) in freon (4 mls) at -30°C. The reaction was left overnight at room temperature, heated to 80°C to remove the volatiles and the residue pyrolysed at 270°C. G.l.c. analysis of the distillate showed that p-fluorotoluene and toluene were formed in 5.5% and 39% yields, respectively. G.l.c. coupled mass spectrometry confirmed that fluorotoluene and toluene were produced. Chlorotoluene and several chloro fluorotoluenes were also observed.

2) A reaction similar to (1) was carried out except that the reaction mixture was refluxed overnight after the addition of antimony pentafluoride. p- Fluorotoluene (3.6%) and toluene (24%) were detected.

3) A solution of antimony pentafluoride (1.13g, 5.2 mmoles) in freon (2 mls) was added to a refluxing mixture of p-tolyl mercuric chloride (1.0g, 3.1 mmoles) in freon (4 mls). The reaction was continued overnight, the volatiles removed by distillation and the residue pyrolysed at 270°C. p-Fluorotoluene (1.6%) and toluene (4.5%) were obtained.

4) Reaction (1) was repeated using 5 eq. of antimony pentafluoride. A much lower yield of p-fluorotoluene was observed.

5) p-Tolyl mercuric chloride (1.94g, 5.9 mmoles) was added to a solution of antimony pentafluoride (1.85g, 8.5 mmoles) in sulphur dioxide (10 mls) at -78°C. The reaction was continued at -30°C for 4 hrs and then allowed to warm to room temperature. The residue was pyrolysed at 270°C. G.l.c. analysis of the material in the cold trap showed that p-fluorotoluene (0.1%) and toluene (5.5%) were produced.

Reaction of other aryl mercurials with antimony pentafluoride

A freon solution of antimony pentafluoride was added to a stirred suspension of the aryl mercurial in freon at -30°C. The reaction was left overnight at room temperature. The reaction mixture was then heated to 80°C to remove the solvent and the residue was pyrolysed at 270°C. The residue of the pyrolysis was triturated with ether and the ether extract added to the material in the cold trap. The combined mixture was concentrated by distillation and was analysed by either g.l.c. or mass spectroscopy. The results of these reactions are shown in TABLE 5.

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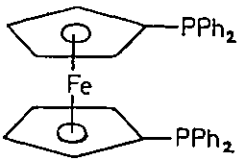
ABBREVIATIONS

HMPA	hexamethylphosphoramide
LiTMP	lithio-2,2,6,6-tetramethylpiperidide
LDA	lithium diisopropylamide
NBS	N-bromosuccinimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dppe	$Ph_2PCH_2-CH_2-PPh_2$
dppf	
TTFA	thallium trifluoroacetate
TFA	trifluoroacetic acid
py	pyridine
DMSO	dimethyl sulphoxide