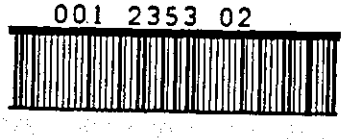

SOME STUDIES OF ELECTROPHILIC SPECIES

by

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A Doctoral Thesis
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requirements for the award of

Doctor of Philosophy
of the Loughborough University of Technology

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To Mum and Dad

This is to certify that I am responsible for the work submitted in this thesis, that the original work is my own except as specified in acknowledgements, and that neither the thesis nor the original work contained therein has been submitted to this or any other institution for a higher degree.

.....

Mark S. Cooper

ACKNOWLEDGEMENTS

I would first like to thank my supervisor, Dr. H. Heaney, for his friendly encouragement and guidance throughout the course of this work.

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CONTENTS

SUMMARY

The use of crystalline hydrogen peroxide adducts was investigated, as a convenient source of stable anhydrous hydrogen peroxide for performing various electrophilic oxidations. In the presence of Lewis acid catalysts, hydroxylation of aromatic hydrocarbons was achieved to generally give a mixture of the expected phenolic products. The yields and isomer distributions of the products varied with the different reagents and provided information regarding the nature of the electrophilic species involved. The adducts allowed convenient preparation of trifluoroperoxyacetic acid and were also effective as a replacement for high strength hydrogen peroxide solutions previously used for performing Baeyer-Villiger oxidations.

Triphenylsilylhydroperoxide is a stable, crystalline solid which, in the presence of Lewis acid catalysts was found to be a particularly potent electrophilic hydroxylating reagent.

Regiospecific hydroxylation was attempted by electrophilic displacement of a silicon, tin or mercury residue from the aromatic ring. Peroxides such as t-butylhydroperoxide and hydrogen peroxide, catalysed by aluminium chloride appear to be too reactive. Hydroxylation occurred at the unsubstituted aromatic carbons as well as by displacement of the metal group and a mixture of isomeric phenolic products was obtained in low yield. More selective (less electrophilic)

peroxide reagents such as mCPBA and t-butylperbenzoate/ aluminium chloride were more successful, reacting regio-specifically with aryl-stannanes to provide moderate yields of the expected phenolic product.

Regiospecific aromatic aminomethylation was similarly achieved by reaction of preformed Mannich reagents, such as N,N-dimethyl(methylene)iminium chloride with aryl-stannanes.

CHAPTER 1

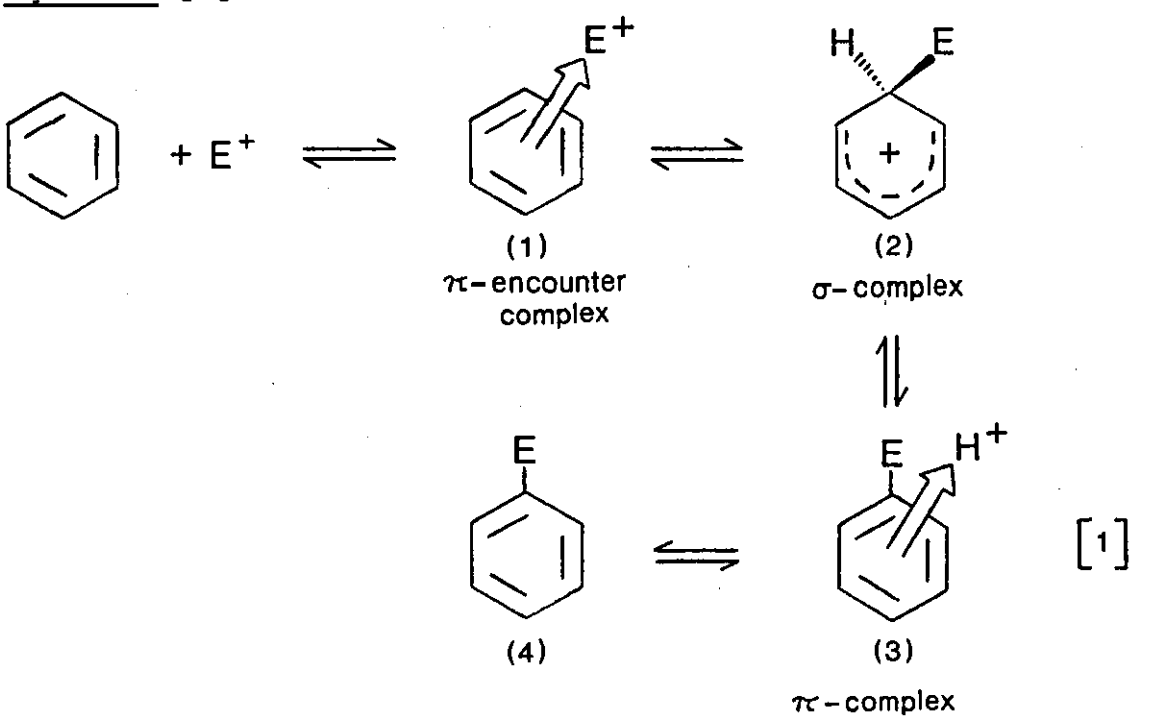
GENERAL INTRODUCTION

1. GENERAL INTRODUCTION

Electrophilic aromatic substitutions are amongst the most studied of organic chemical reactions and although it may have been assumed 20 years ago that most of the mechanistic features of the reaction had been clearly rationalised, this is now known not to be the case and progress towards solving these problems continues.

This general introduction provides a summary of the present knowledge of the electrophilic aromatic substitution reaction. The kinetic aspects relating to the selectivity of the substitution will be outlined and also the involvement of ipso- attack and the complications that result from this process will be discussed.

The mechanism involved in the reaction of electrophiles at an aromatic nucleus has been extensively investigated [1,2] and is considered to follow the general pathway outlined in Equation [1].

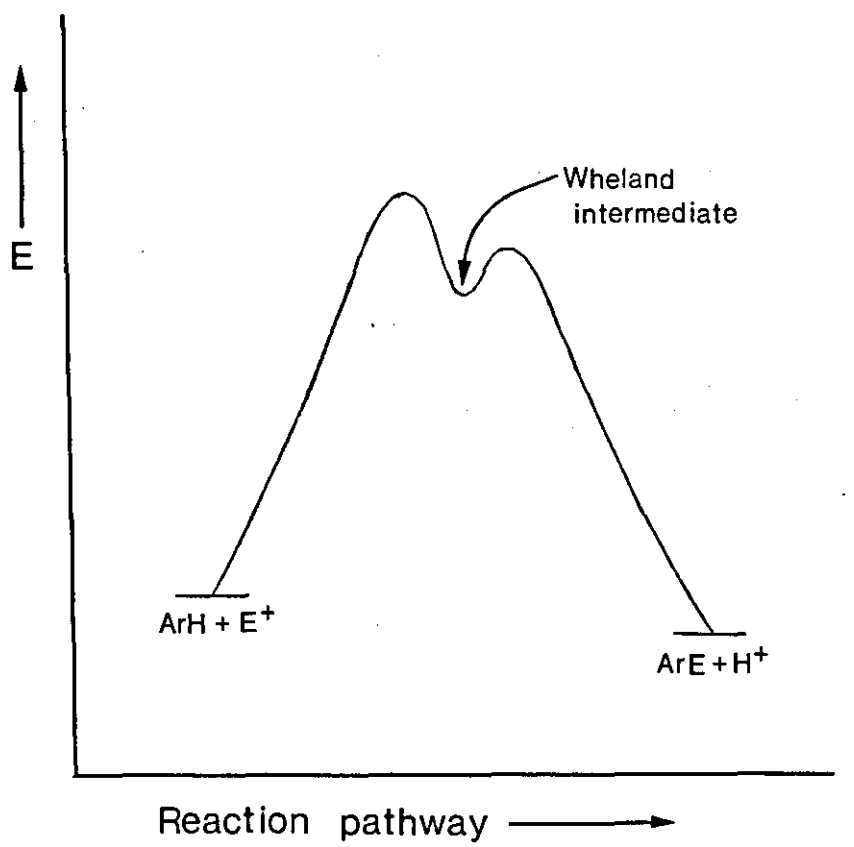


[1]

Attack of an electrophile (E^+) on an aromatic nucleus forms an initial π-encounter complex (1). This then converts to a σ-bonded complex (2) which proceeds to regain its aromaticity either by loss of a proton to obtain the product, or by reformation of the encounter complex and hence back to the starting reagents.

The rate-determining step in the majority of electrophilic substitutions is the formation of the σ-complex from the starting reactants. A typical energy profile is illustrated in Diagram 1.

Diagram 1 Potential energy profile for a typical aromatic substitution in which σ-complex formation is rate-limiting



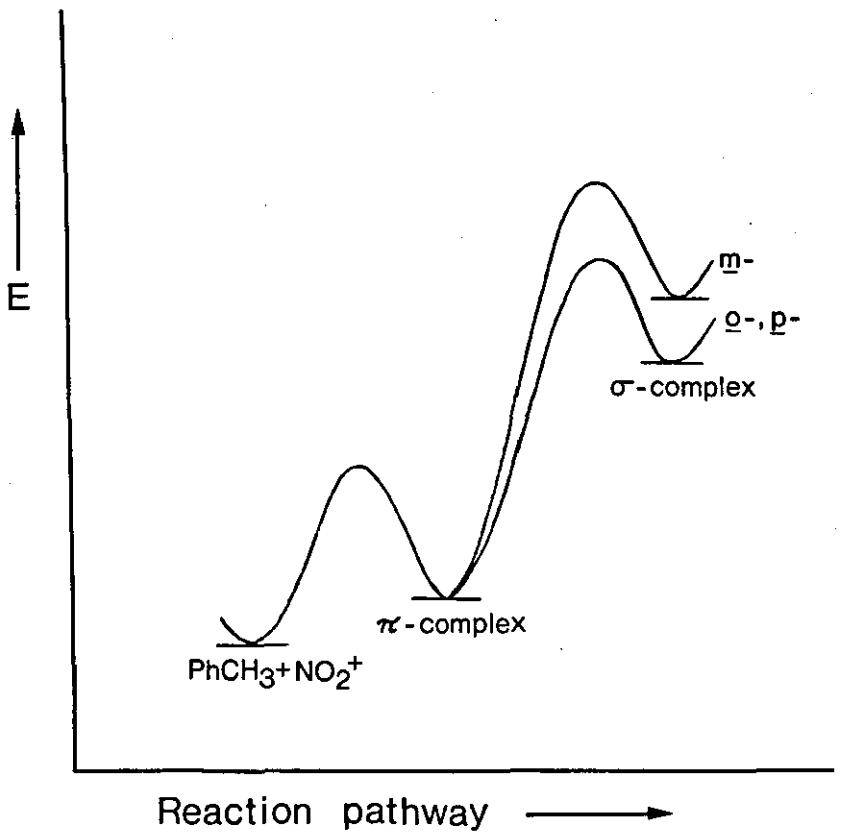
Electrophilic reagents differ in their selectivities, both in terms of the isomer distribution of the products (positional selectivity) and also the substrate selectivity (as may be represented by the $k_{toluene}/k_{benzene}$ rate ratio). Factors which must be taken into account when considering the selectivity of reaction between a substituted arene and an electrophile are: (i) Directive effects of substituents on the aromatic ring. (ii) Nucleophilicity of the arene. (iii) Reactivity of the electrophile. (iv) Steric factors.

Olah[3] suggested that the transition state for formation of the σ-complex from the reactants is not rigidly fixed, but may vary in its position along the reaction pathway to resemble either the reactants or the Wheland intermediate. Thus reactions are said to have 'early' or 'late' transition states dependent on the nature of the aromatic compound and the electrophile.

Kinetic studies of aromatic substitution[2] (in particular nitration reactions[4]) have led to various theories being proposed to account for the selectivity of the reaction. Nitration of toluene using a mixture of nitric and acetic acids gave results[5] which indicated a relative reactivity compared to benzene (i.e. $k_{toluene}/k_{benzene}$) of 24. The stabilizing effect of the methyl group is evidently important and suggests that the transition state leading to the σ-complex is rate-limiting in this case and that π-complex formation is a lower energy process. The reaction is therefore believed to be limited by σ-complex formation,

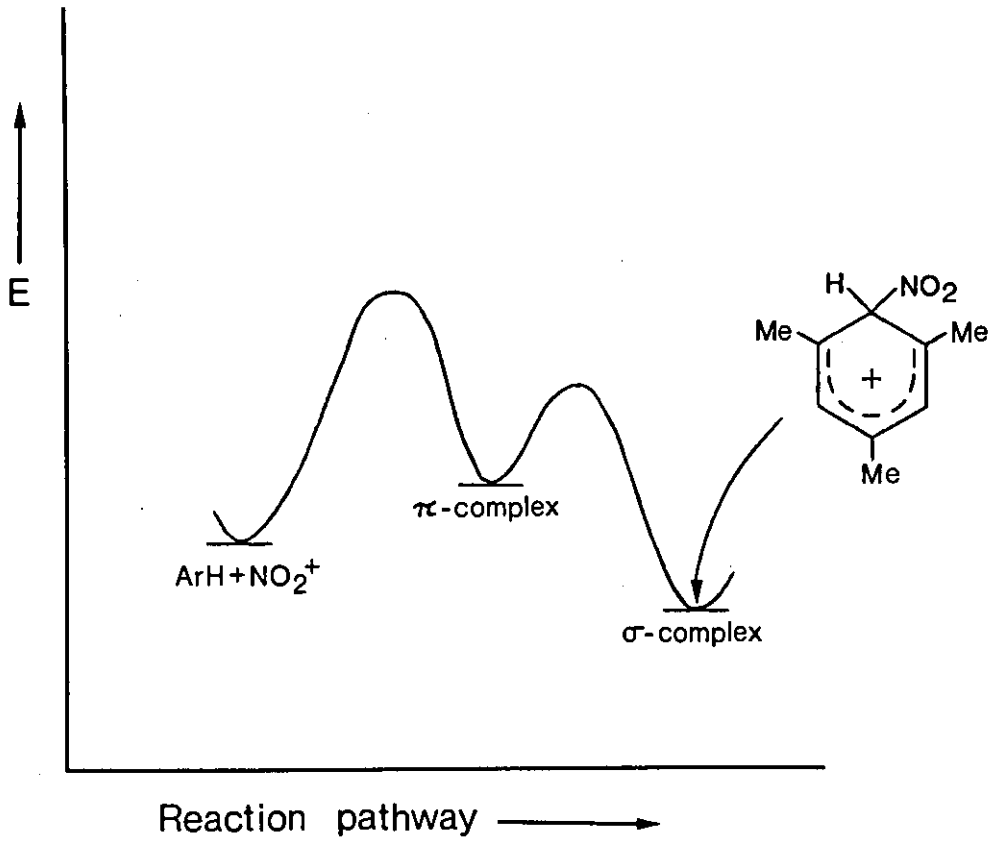
i.e. involves a 'late' transition state, and the energy profile is thought to be of the general form shown in Diagram 2.[6]

Diagram 2 Energy profile for nitration of toluene



Nitrations of aromatic hydrocarbons more reactive than toluene do not show the expected relative reactivities predicted from their σ- basicities. p-Xylene, m-xylene and mesitylene, nitrated using a HNO_3/H_2SO_4 mixture, might be expected to show increasing reactivity in this order, but in fact a limiting rate is reached of about 40 (relative to benzene).[5] In these reactions, nitration is believed to involve an 'early' transition state, i.e. π- complex formation is rate limiting as illustrated in Diagram 3.

Diagram 3 Energy profile for nitration of mesitylene using HNO_3/H_2SO_4



The theory of early and late transition states can thus account for the variation in substrate selectivity shown by different systems.

As a general rule early transition states tend to be shown by reactions of the more nucleophilic aromatics and by highly reactive electrophiles, while late transition states are shown by reactions of the weaker electrophiles. The results shown in Table 1 for the bromination of toluene, illustrate this effect.

Table 1 Electrophilic Bromination of Toluene[7]

Reagent	Solvent	k_t/k_b	Isomer ratio (%)		
			ortho-	meta-	para-
$Br_2/FeCl_3$	CH_3NO_2	7.1	71.8	1.6	27.3
$Br_2/SnCl_2$*	CH_3CO_2H	148.0			
Br_2	CH_3CO_2H	605.0	32.9	0.3	66.8
Br_2	CF_3CO_2H	258.0	17.6	0.2	82.4

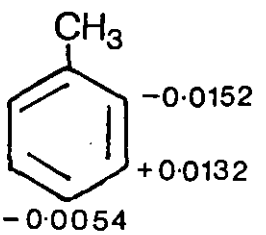
k_t/k_b = relative rate toluene/benzene

* Isomer ratio was not stated for this reagent

The brominating agents are presented in order of decreasing electrophilicity and show a corresponding increase in selectivity in terms of the toluene/benzene rate ratio. The $Br_2/FeCl_3$ reagent is considered to react with toluene by a process involving an early transition state, i.e. π-complex control, and the substrate selectivity is relatively low reflecting the similar π- basicities of toluene and benzene. These data suggest a change from π-complex control with the most reactive reagent ($Br_2/FeCl_3$) to σ-complex control with the other, less electrophilic reagents.

The positional selectivity is not so easily rationalised in terms of the reactivity of the reactants since steric factors must be taken into account.

Molecular orbital theory predicts[8] that reaction of toluene with soft electrophiles will occur predominantly at the para- position since the frontier electron population is highest at this position. With harder electrophiles involving π- complex control, the transition state is more characteristic of the starting reagents and, in this case, it is the total charge distribution around the aromatic ring which determines the position of reaction. The charge distribution in toluene[7] is:



Negative charge is highest at the ortho- positions and hence attack at these positions tends to predominate over attack at the para- position, providing that steric effects are not significant. This theory is consistent with the selectivity data for bromination of toluene (Table 1).

The correlation between the selectivity and reactivity of electrophiles is also illustrated by the arylsulphonation of toluene (Table 2). These results illustrate the trend of decreasing ortho-/para- substitution with decreasing reactivity of the electrophilic species. Steric effects are likely to be important in this case, reducing the

Table 2 $AlCl_3$ catalysed arylsulphonylation of toluene[7]

Reagent	k_t/k_b	Isomer ratio (%)		
		ortho-	meta-	para-
p-$NO_2C_6H_4SO_2Cl$-$AlCl_3$	2.8	54.5	7.9	37.4
$C_6H_5SO_2Cl$-$AlCl_3$	9.0	28.4	8.7	62.9
p-$CH_3C_6H_4SO_2Cl$-$AlCl_3$	17.0	14.5	1	85.5
p-$CH_3OC_6H_4SO_2Cl$-$AlCl_3$	83.0	5.6	1	94.4

k_t/k_b = relative rate toluene/benzene

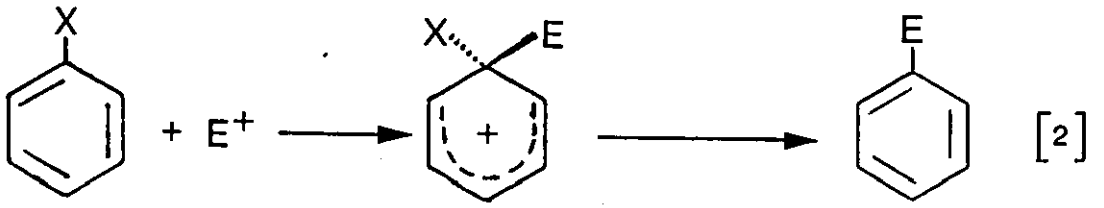
amount of ortho- substitution. The substrate selectivity (k_t/k_b) also shows the expected trend, although it should be noted that these values are not very meaningful because the rates for the more reactive electrophiles are likely to be controlled by the mixing of the reagents.[9]

This theory could also help to rationalise the selectivities shown by polymethylbenzenes towards electrophiles, but does not take into account the possibility of the electrophile attacking at an ipso- position.

ipso- Reaction

ipso- Substitution whereby a substituent, X, is displaced from the aromatic ring by an electrophilic species has long been known to occur where X is, for example, alkyl, acyl, halogen, $-SiR_3$, $-SO_3H$ and N_2Ar.[10]

Reaction proceeds through an ipso-arenium cation (5) (Equation [2])



[2]

(5)

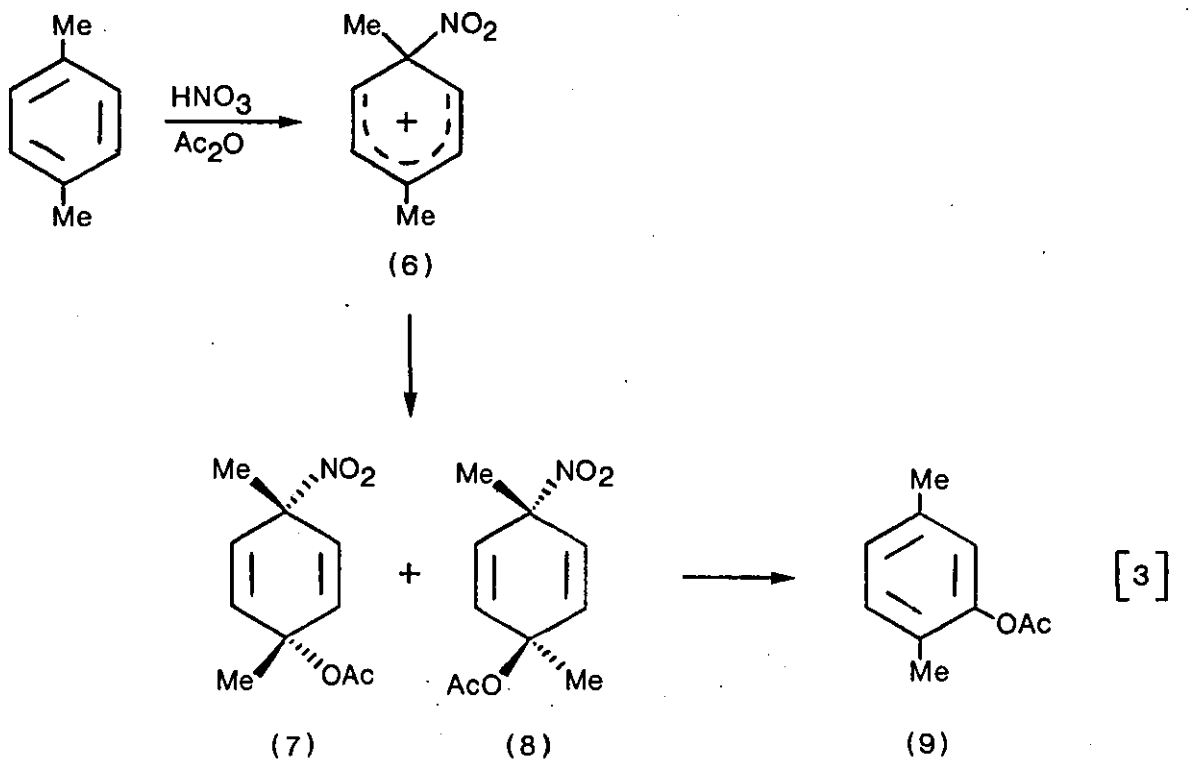
ipso-Electrophilic attack is therefore not a recently recognised concept. Alternative fates of the ipso-arenium ion are possible however, depending on the nature of X and E and the reaction conditions.[11] It is these processes which have led to mechanistic complications of electrophilic aromatic substitution, providing much interest in recent years.

Possible fates of the ipso-arenium cation are:

i) Capture by a nucleophile
ii) Rearrangement involving migration of E (the added electrophile group)
iii) Similar migration of substituent X
iv) Loss of X i.e. ipso- substitution
v) Loss of a proton or related group from a substituent remote from the ipso- position
vi) Return to the encounter complex or starting materials

(i) Capture by a nucleophile

The involvement of electrophilic ipso- attack with aromatic hydrocarbons has been demonstrated (Equation [3]) in the reaction of p-xylene with nitric acid in acetic anhydride.[12]

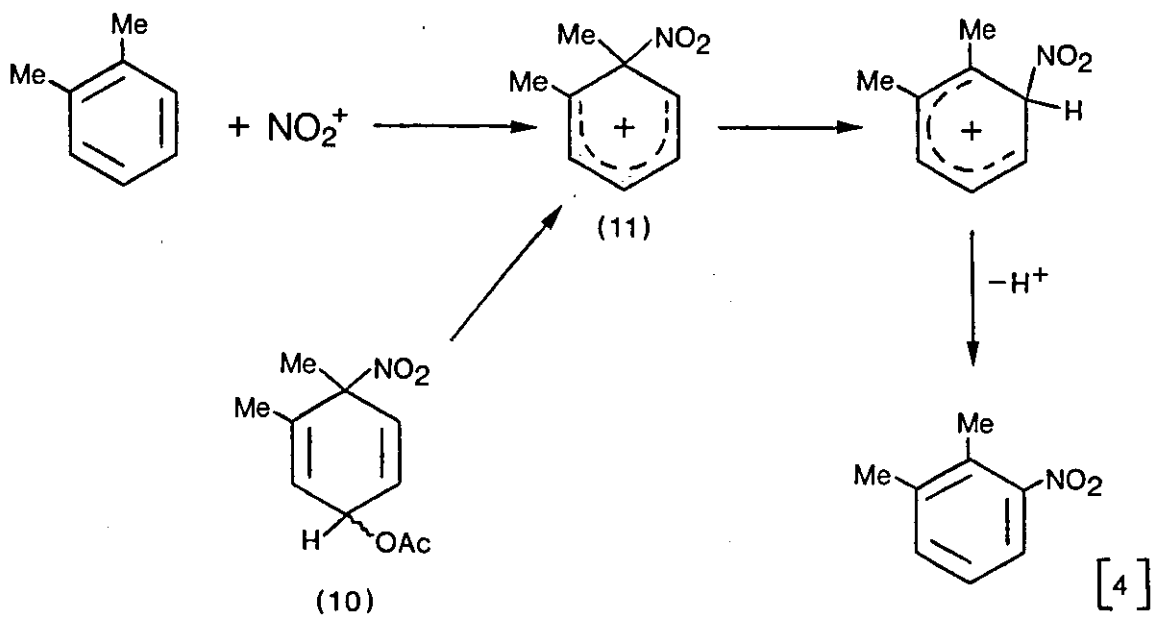


[3]

Isolation of adducts (7) and (8) supports a mechanism in which the initial step involves formation of an ipso-arenium cation (6) which is captured by acetate ion. Decomposition of the adducts apparently proceeds by an intramolecular mechanism to give the acetate (9).

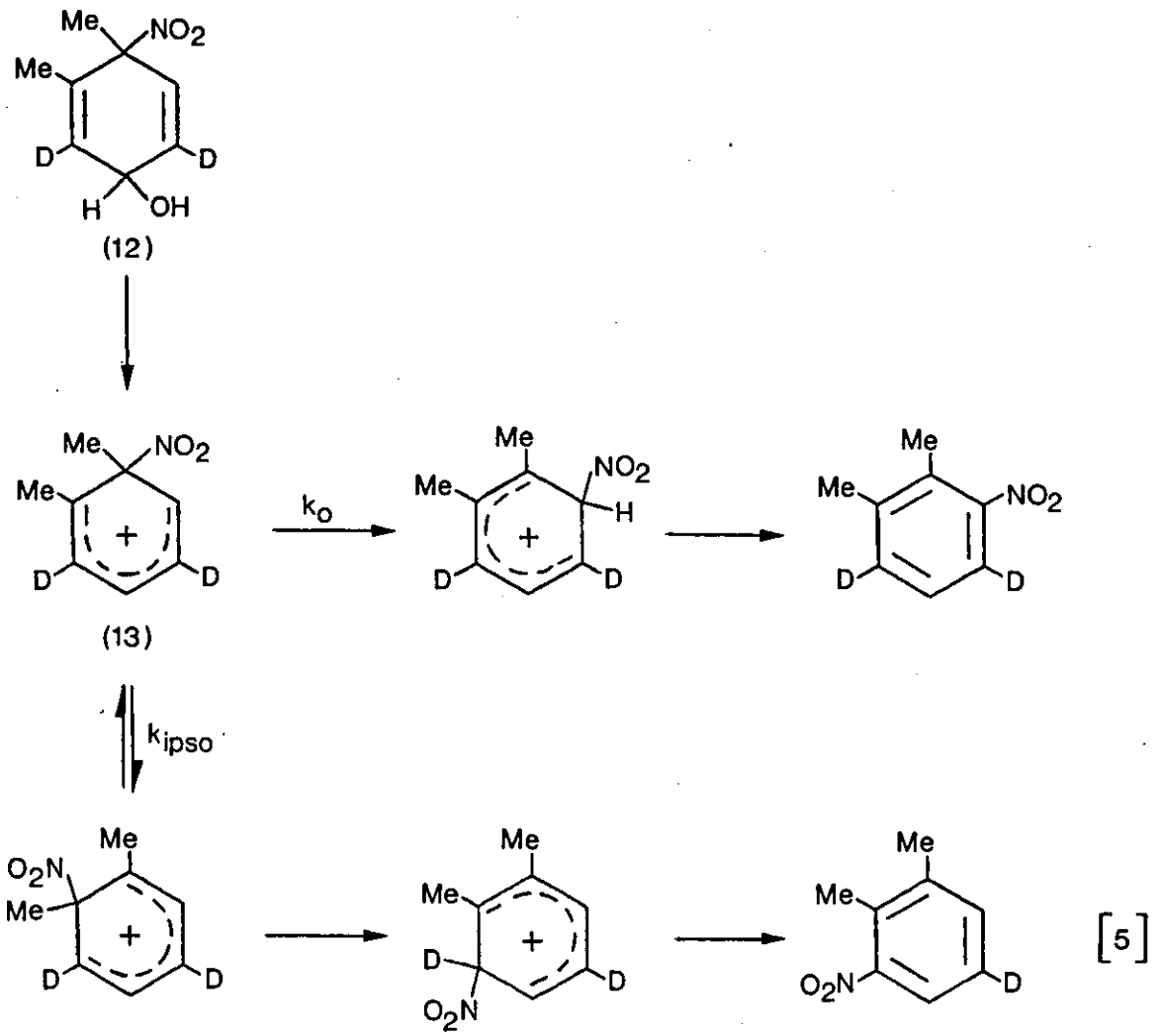
(ii) Migration of electrophile group, E

Nitration of o-xylene using a mixture of nitric and sulphuric acids leads to a mixture of 3- and 4- nitro o-xylene in yields dependent on the acidity.[13,14,15] Nitration proceeds largely by attack at the unsubstituted positions but some reaction has been shown to occur by ipso- attack, followed by rearrangement of the ipso-arenium cation (11), as shown in Equation [4]. The involvement of ipso- attack



[4]

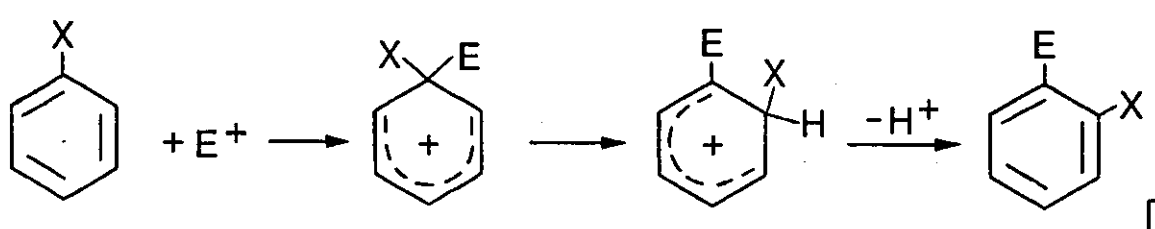
in the formation of 3-nitro o-xylene was supported by the observation that acidolysis of the ester (10) produces 3-nitro o-xylene via the ipso-arenium cation.[13] Two possible rearrangement processes may be envisaged. Studies of the labelled ipso- ion (13) obtained from the alcohol (12) have established (Equation [5]) the relative importance of these processes.[16] Rearrangement involving two successive



[5]

nitro shifts was found to be the major pathway occurring at about 50 times the rate (k_o) of the alternative nitro migration to the open position, i.e. $k_{ipso}/k_o \sim 50$.

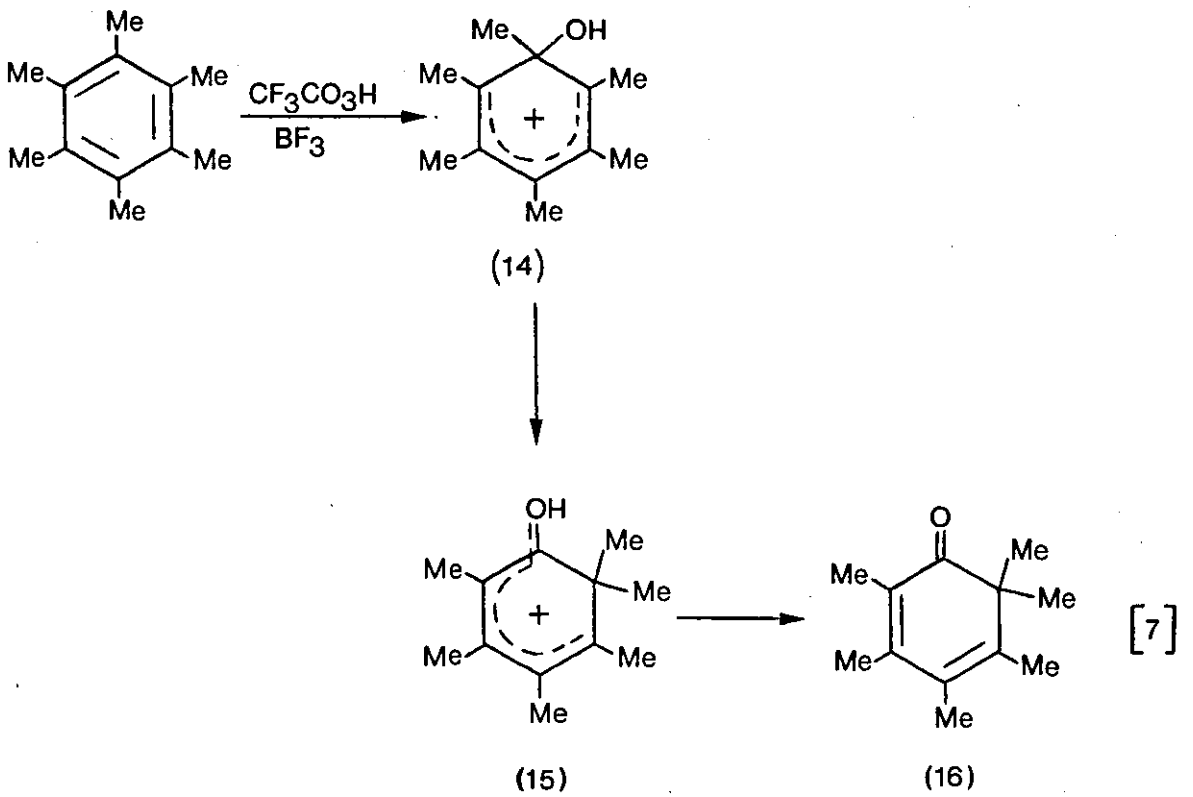
(iii) Migration of group X



[6]

This type of rearrangement (Equation [6]) is common in electrophilic hydroxylations where X is an alkyl group.

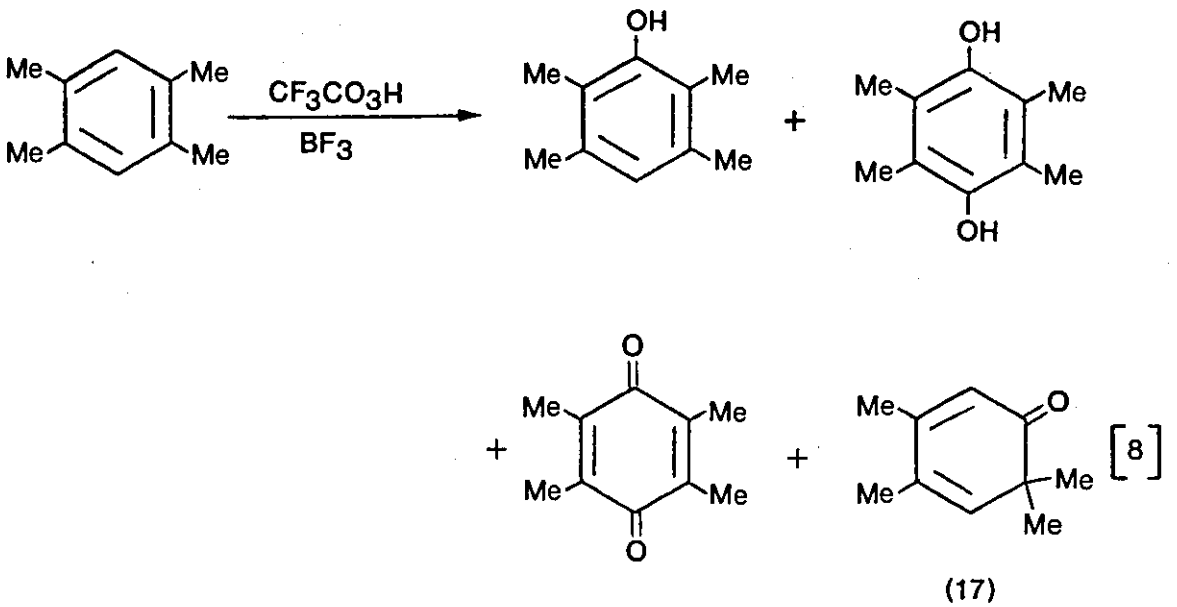
Hexamethylbenzene for example reacts with trifluoroperoxyacetic acid and boron trifluoride to afford hexamethylcyclohexa-2,4-dienone (16) as shown in Equation [7].[17]



[7]

Methyl migration in the ipso-arenium ion (14) is facilitated by the relatively low energy of the transition state leading to the new arenium ion (15) which is stabilised by involvement of electrons from the oxygen atom.

1,2,4,5-tetramethylbenzene, (Durene), also gives a rearranged product (17) as shown in Equation [8].[18]



(17)

The cyclohexadienone (17) results from a 1,2-methyl shift. Methyl migration occurs preferentially to the adjacent substituted position.

Although rearrangement of an ipso-arenium ion involving two successive alkyl shifts may be anticipated in the hydroxylation of certain substituted arenes, this has not as yet been verified. The formation of 2,3-xylenol from the hydroxylation of o-xylene, for example, may well result from such a process.

The involvement of ipso- attack in aromatic hydroxylation reactions will be discussed further in Chapter 2.

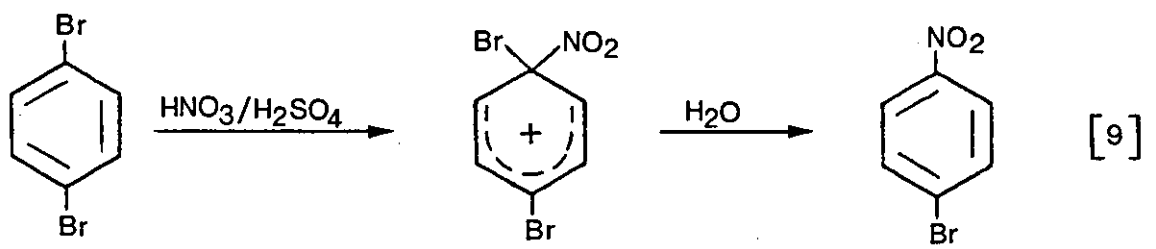
(iv) Loss of X (ipso- substitution)

Loss of the ipso- substituent X from the ipso-arenium cation occurs in certain cases where X^+ is a good leaving

group and where rearrangement is not a favourable process.

Displacement of an alkyl group in this way does not commonly occur, although secondary and tertiary alkyl groups are occasionally displaced. Nitration of p-cymene, for example, affords some p-nitrotoluene.[19]

There are also examples of electrophilic dehalogenation, decarboxylation and desulphonation, involving ipso- intermediates. For example, nitration of p-dibromobenzene[20] produces some p-nitrobromobenzene by the process shown in Equation [9].



[9]

The most useful application of ipso- substitution has been found in the reaction of aryl-metal derivatives with electrophiles. The increased nucleophilicity of the carbon-metal ring position, resulting from the polarity of this bond, and the good leaving ability of the metal substituents has been widely exploited for regiospecific introduction of an electrophile into the aromatic nucleus.

Silicon and tin derivatives have been most extensively used. The electrophilic cleavage of an aryl-silicon bond was first achieved by Ladenburg in 1907, obtaining bromobenzene

by the bromination of phenyltrimethylsilane.[21] Other metal derivatives which have been employed in this way include aryl-mercury[22] and aryl-thallium[23] compounds.

Although the main asset of the metal displacement reactions is the regiospecific nature of the substitution, the method additionally allows introduction of the less reactive electrophiles which would not normally react with the aromatic nucleus. An example is the nitroso-destannylation of p-tolyltrimethylstannane,[24] (nitrosation is normally only possible with phenols and tert-aminobenzenes). Various other electrophiles might be expected to benefit from this procedure. For example, reaction of aryl-metal compounds with weak electrophiles such as nitrilium salts, Vilsmeier reagents and Mannich reagents to achieve acylation, formylation,and aminomethylation might be anticipated, although no previous studies of such reactions have been reported.

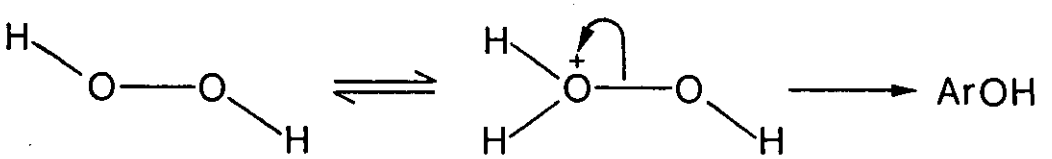
CHAPTER 2

ELECTROPHILIC AROMATIC HYDROXYLATION

2.1 INTRODUCTION

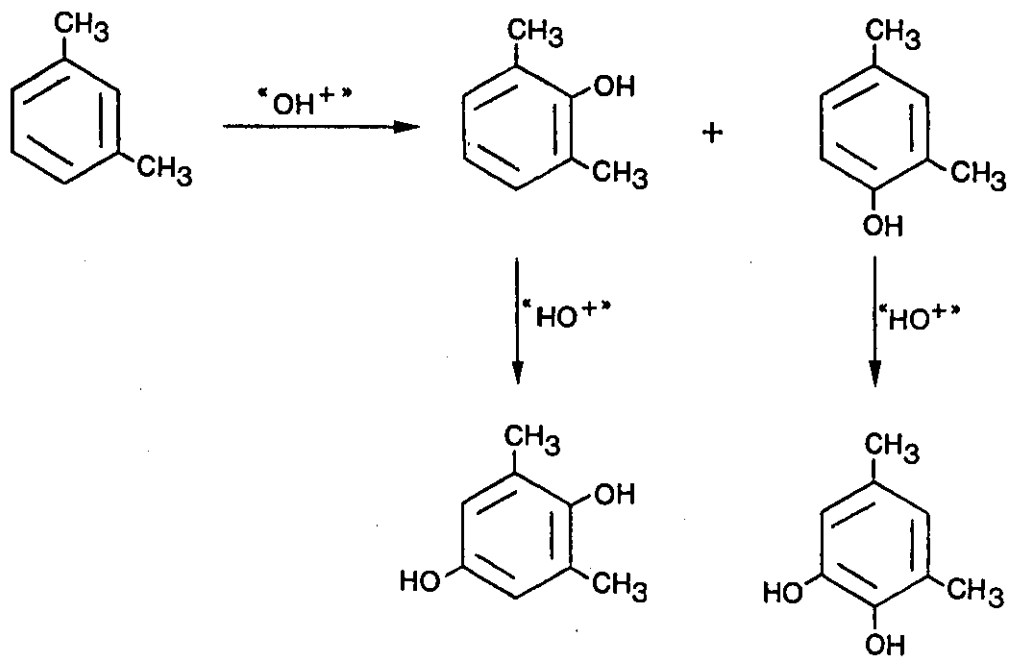
Electrophilic aromatic hydroxylation has been established only during the last 30 years and although most of the mechanistic details of the reaction appear to have been rationalised, the synthetic utility of this process as a method for direct preparation of phenols merits further development to optimise its efficiency under practical, non-hazardous conditions.

Electrophilic hydroxylation was first reported when Derbyshire and Waters obtained a good yield of mesitol from mesitylene using hydrogen peroxide in a mixture of acetic acid and sulphuric acid.[25] It was suggested that protonation of the hydrogen peroxide under these conditions occurred to a small extent, facilitating cleavage of the O — O bond to supply the required hydroxyl cation:



Mesitylene was a fortunate choice of substrate for this initial attempt at aromatic hydroxylation because the positions ortho- and para- to the hydroxyl group in the product (mesitol) are substituted, thus preventing further hydroxylation.

In 1962, McClure and Williams considered the possibility of using a Lewis acid, boron trifluoride, to promote heterolysis of hydrogen peroxide.[26] A solution of 90% hydrogen peroxide in boron trifluoride etherate was found to give phenolic products from m-xylene and toluene but yields were low and there was considerable contamination from products of further oxidation (Equation [10]).



[10]

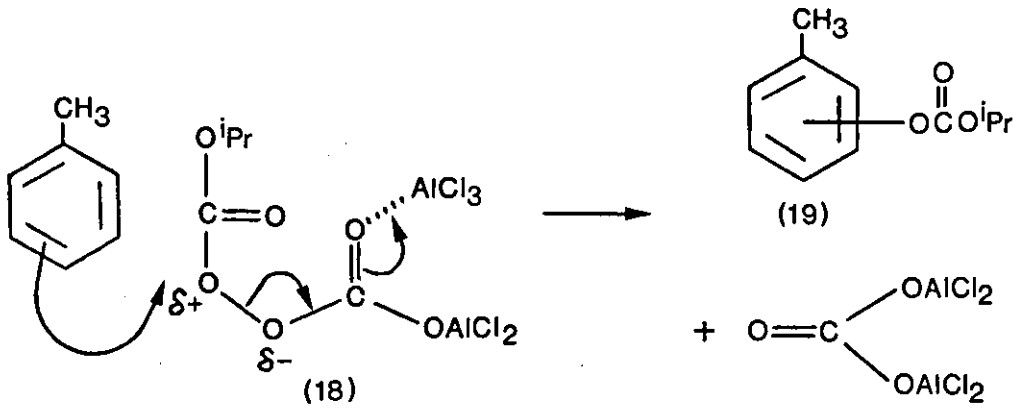
The initially formed mono-hydroxylated products are more reactive than the starting aromatic hydrocarbon towards the hydroxylating reagent and, as a result, further hydroxylation occurs. A mixture of mainly polyhydroxylated products was obtained and the yield of 2,4- and 2,6- xylenol was only 6%.

Organic peroxy-acids were likely precursors for the hydroxyl cation with an electron-withdrawing group, R, facilitating O — O bond cleavage:

A number of workers have employed trifluoroperoxyacetic acid alone,[27,28] or in the presence of boron trifluoride,[29,30] for hydroxylation of aromatic hydrocarbons. Mesitylene, for example, was hydroxylated by the boron trifluoride complex to give an 88% yield of mesitol and this reagent was generally found to be effective for hydroxylation of highly substituted arenes where further oxidation was inhibited.[18]

Although several efficient reagents had now been found for performing electrophilic hydroxylation, the potential of the reaction was limited until hydroxylation could be controlled to achieve clean monohydroxylation of simple aromatic hydrocarbons such as benzene, toluene and the xylenes.

Benzoyl peroxide[31] and diisopropyl peroxydicarbonate[32] catalysed by aluminium chloride were reasonably successful as reagents for performing controlled aromatic oxygenation in a Friedel-Crafts type reaction. The latter reagent, for example, gave a 50% yield of cresol from toluene upon hydrolysis of the initially formed aryl carbonate. A mechanism involving a polar peroxide-catalyst complex (18) was proposed as shown in Equation [11].



[11]

The product retains its carbonate structure (19) until hydrolysis and in this form is protected from further oxygenation.

A study of this peroxide with various Lewis acid catalysts indicated the following order of reactivity in aromatic oxygenation:[32]

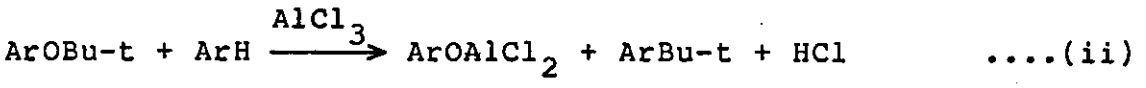
$$AlCl_3 < BF_3,\ AlBr_3 < SbCl_5 < FeCl_3,\ SnCl_4$$

Aromatic oxygenation has in recent years been reported using a wide range of peroxides catalysed by aluminium chloride, generally providing moderate yields of the mono-hydroxylated product. Peroxides which have been studied include t-butylperoxy isopropylcarbonate,[33] t-butylhydro-peroxide,[34] and bis(trimethylsilyl) peroxide.[35]

Oxygenation using t-butylperoxy isopropylcarbonate catal-ysed by aluminium chloride was considered to proceed by the

following series of reactions:

....(i)



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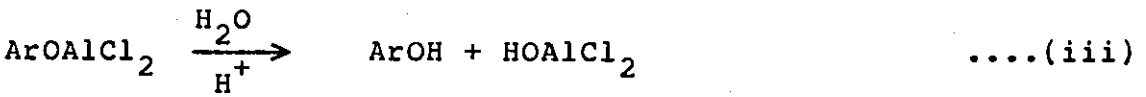


....(iii)

The aryl t-butylether initially formed, rapidly dealkylates under the reaction conditions affording species (22); the t-butyl cation released then reacting rapidly with the aromatic substrate in a competing side reaction.

Results obtained using 90% hydrogen peroxide in the presence of aluminium chloride[36] are given in Table 3.

Table 3 Aromatic Hydroxylation with $H_2O_2 - AlCl_3$[a]

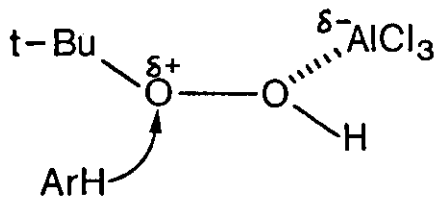
Aromatic	Yield[b] (%)	Isomer Distribution		
		o-	m-	p-
Anisole	70	44	<1	55
Toluene	40	60	8	32
Chlorobenzene	14	26	4	70
o-Xylene	35	2,3-:3,4- = 60 : 40		
Mesitylene	42			
Nitrobenzene	0			

[a] Aromatic/$AlCl_3$/90% H_2O_2 = 9-20 : 1.5 : 1; 0 - 5°, 2 hr.

[b] Based on limiting peroxide

A significant feature of the hydroxylations catalysed by aluminium chloride is the lack of products from further oxidation of the mono-hydroxylated derivative. This was presumed to be due to co-ordination of aluminium chloride to the oxygen of the phenolic product, thus deactivating the aromatic nucleus. The isomer distributions obtained with various alkylbenzenes are consistent with the concept of a mechanism involving electrophilic hydroxylation rather than free-radical species and this is also supported by the necessity of a Lewis acid catalyst and an absence of by-products that might be expected to arise from a free-radical process.

Hydroxylation using t-butylhydroperoxide and aluminium chloride has been shown[37] to involve a highly polarized complex (23) rather than the intermediacy of the t-butoxy cation which, if formed, rearranges rapidly.[38]

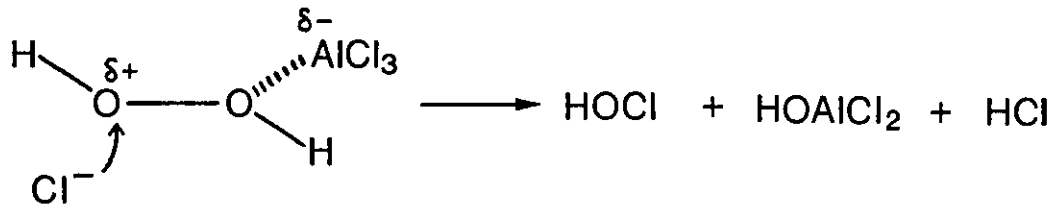


(23)

Hydroxylations using hydrogen peroxide are likely to involve a similar polar complex rather than free hydroxyl cation.

The hydroxylations using aluminium chloride catalysis unfortunately were found to suffer from a side reaction producing contaminating chlorinated phenols. Formation of hypochlorous acid from attack of chloride ion on the per-

oxide - $AlCl_3$ complex (24) could be anticipated, in a process competing with hydroxylation. For example, with hydrogen peroxide:



(24)

The hypochlorous acid, as a precursor for the chloronium ion, is thought to be responsible for the chlorination observed. With the H_2O_2 - $AlCl_3$ reagent, chlorinated phenols generally amounted to about 2 - 5% of the phenolic material.[36]

Hydrogen fluoride catalysed hydroxylation using 30% hydrogen peroxide has been studied[39] with a wide range of aromatic substrates and probably involves protonated hydrogen peroxide as the electrophilic species. Although successful for hydroxylation of polyalkylbenzenes such as mesitylene (74% yield of mesitol), reaction with toluene and the xylenes suffered from the problem of over-oxidation giving largely high boiling, polyhydroxylated products.

In recent years Olah has investigated the use of super acid type catalysts such as FSO_3H-SbF_5, HF-SbF_5[40] and HF-BF_3[41,42] systems, with 30% hydrogen peroxide. Simple aromatic hydrocarbons such as toluene, the xylenes and naphthalene[43] were hydroxylated in good yields with no appreciable contamination from polyhydroxylated products - protonation of the phenolic products by the super acid catalysts presumably

suppresses their reactivity. Results obtained using the $HF-BF_3$ catalyst[41] with a range of substrates are detailed in Table 4.

Table 4 Aromatic hydroxylation using 30% hydrogen peroxide in HF/BF_3 at -78°C

Aromatic Substrate	% Yield[a]	Isomer Distribution of Alkylphenols[b] (%)		
Benzene	37			
Toluene	52	70(2)	9(3)	21(4)
Ethylbenzene	58	65(2)	11(3)	24(4)
Cumene	43	48(2)	12(3)	40(4)
t-Butylbenzene	36	30(2)	14(3)	56(4)
p-Xylene	50	65(2,5)	35(2,4)	
o-Xylene	53	7(2,6)	66(2,3)	27(3,4)
Mesitylene	41	100(2,4,6)		

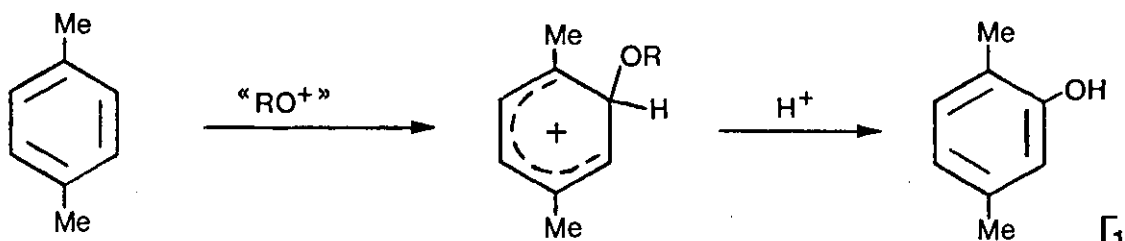
[a] Isolated yields based on aromatics.

[b] Parentheses show position of the substituents

Hypofluorous acid has also been reported effective as a hydroxylating agent[44] but, as with the hydrogen fluoride and super acid catalysed systems, practical applications are limited due to the special conditions and apparatus required to perform the reaction and the inconvenience and hazards involved in handling these catalysts.

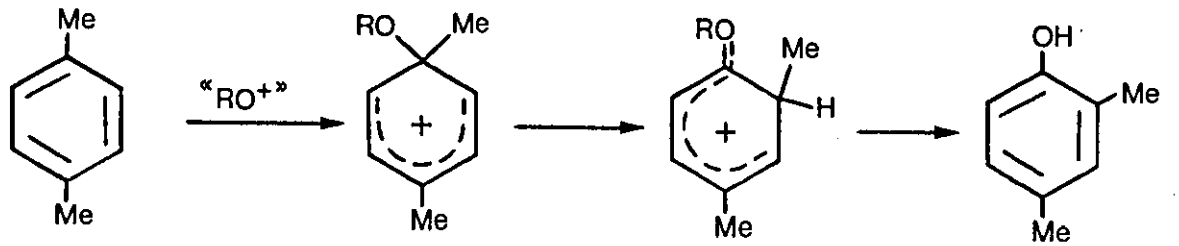
The various methods which have been discussed for performing aromatic hydroxylation are all believed to proceed by a heterolytic mechanism. The isomer distribution of the phenolic products is generally consistent with a heterolytic substitution process and this is supported by the observation that hydroxylation of certain polyalkylated benzenes proceeds by way of ipso- attack followed by a 1,2-alkyl shift.

A general reaction mechanism can be formulated involving an electrophilic oxygen-containing species, which will be designated for simplicity as 'RO^+', although a polarized peroxide species is more likely to be involved. Attack of this species on the aromatic substrate, for example p-xylene, may occur at an unsubstituted position as in normal aromatic substitution, with formation of a Wheland intermediate (25) which then re-aromatises by loss of a proton as shown in Equation [12].



(25) [12]

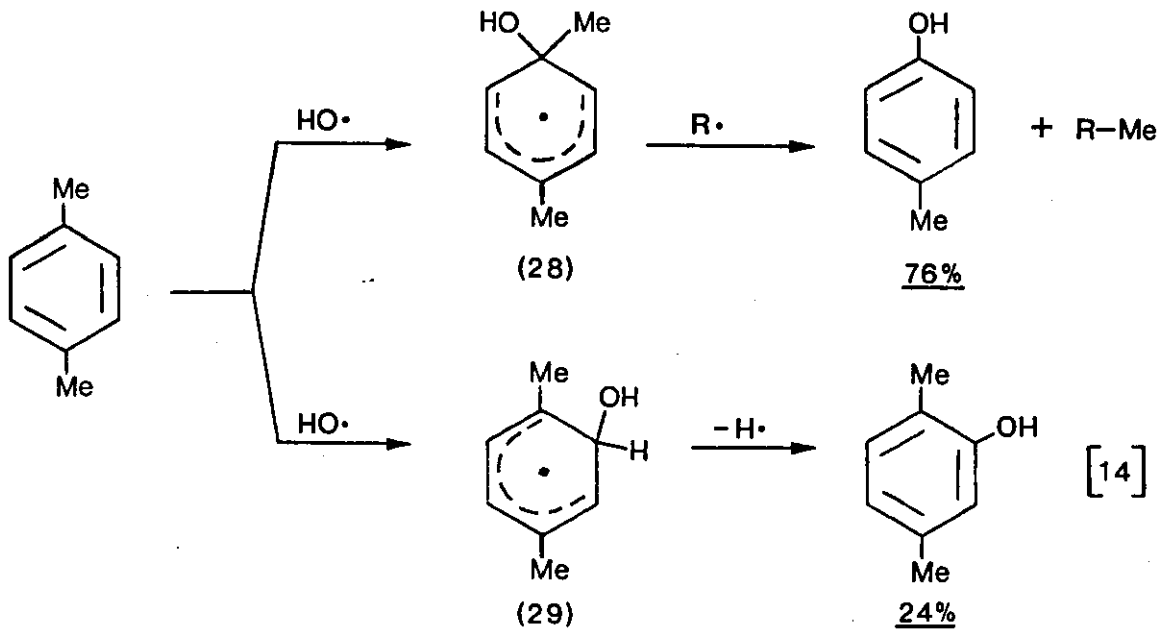
p-Xylene also yields some 2,4-xylenol, arising from attack of the hydroxylating species at an ipso- position followed by a 1,2-methyl shift in the ipso-arenium cation (26) producing a second, more stable arenium ion (27) which then re-aromatises by loss of a proton (Equation [13]).



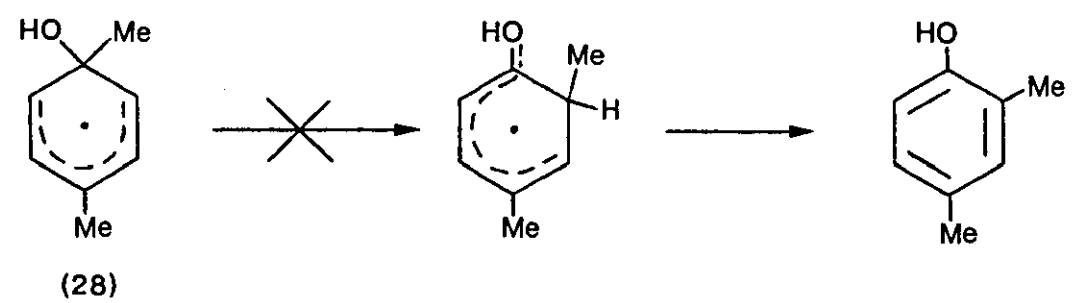
(26) (27) [13]

Methyl migration in the ipso-arenium ion is facilitated by the relatively low energy of the transition state leading to the new arenium ion. Although this offers a plausible explanation for the formation of 2,4-xylenol from p-xylene, the involvement of arene oxides, as suggested by Jerina and co-workers,[45] should not be disregarded as an alternative mechanism.

Free-radical hydroxylation, by comparison, has been found to proceed with alkyl benzenes largely by ipso- attack of the hydroxylating species, followed by loss of methyl radical from the cyclohexadienyl radical intermediate. Fentons reagent (Fe^{2+}/H_2O_2), for example, reacts with p-xylene yielding p-cresol as the major product[35] as shown in Equation [14]. Yields of phenolic products obtained were not specified but conversion was generally low using free-

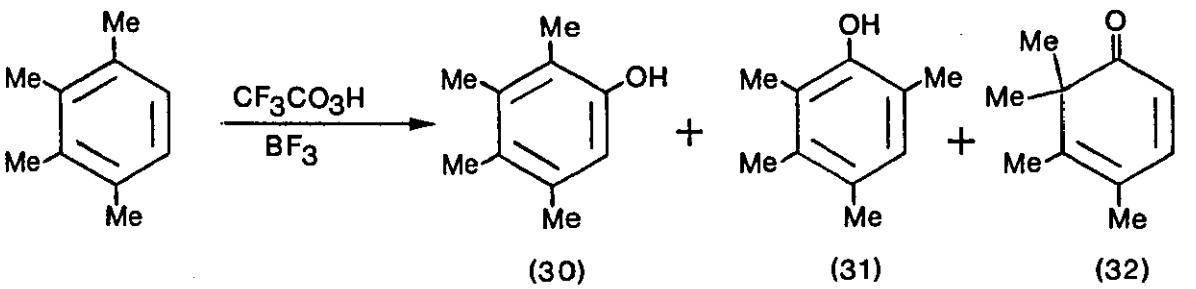


radical reagents. The ipso- dealkylation observed in aromatic hydroxylation using Fentons reagent is presumably a reflection of the high energy of the transition states that would be involved if rearrangement occurred as compared with that involved in dealkylation of the hydroxycyclohexadienyl radical intermediate (28):



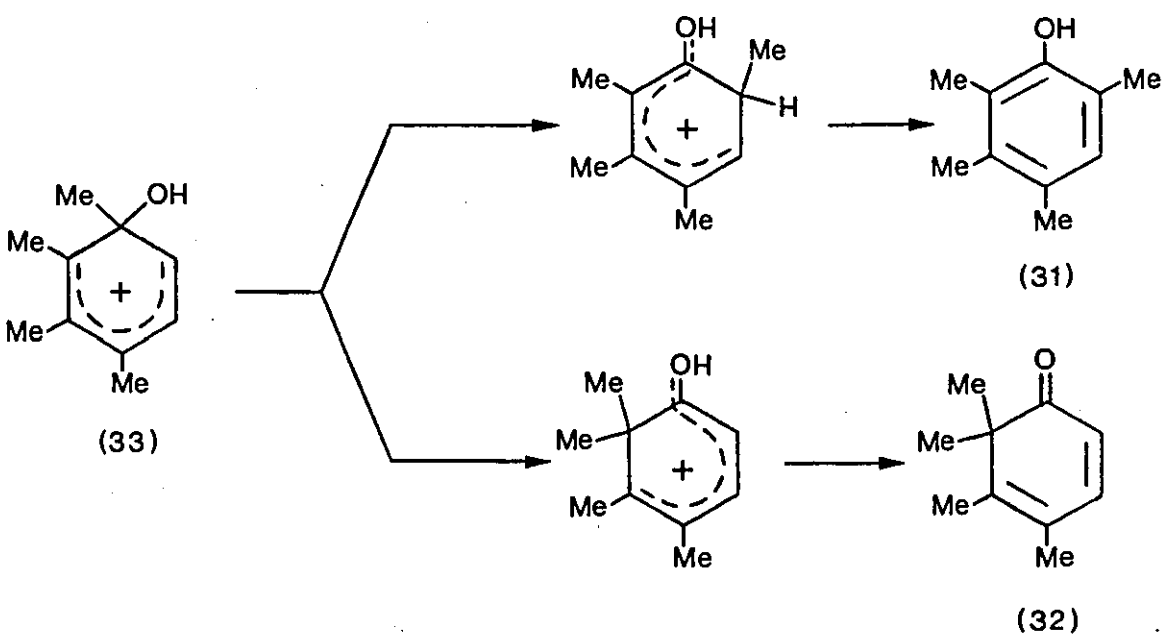
It is therefore possible to distinguish between hydroxylation reactions involving radical and cationic species from the phenolic products obtained. Peroxide reagents

catalysed by Lewis acid or super acid catalysts have thus been demonstrated to involve a heterolytic mechanism on the basis of phenolic products obtained as a result of methyl migration. Trifluoroperoxyacetic acid catalysed by boron trifluoride,for example,has been shown to react with a number of polyalkylated benzenes giving rise to products which obviously arise from methyl migration. For example[18] (Equation [15]):

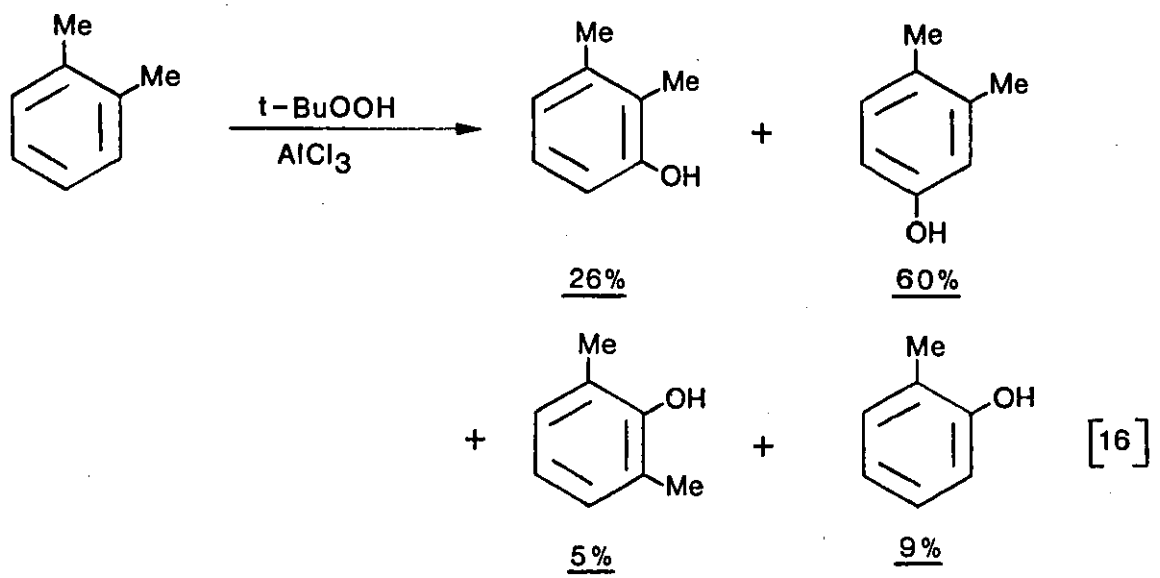


[15]

1,2,3,4-Tetramethylbenzene gives two products (31) and (32) resulting from a 1,2-methyl shift in the ipso-arenium ion (33):



The formation of 2,6-xylenol from electrophilic hydroxylation of o-xylene can be similarly accounted for by a 1,2-methyl shift. Thus hydroxylation of o-xylene by electrophilic reagents is normally characterised by formation of three isomeric xylenols, although with some reagents there is evidence of some demethylation producing o-cresol. For example, hydroxylation of o-xylene with t-butylhydroperoxide/aluminium chloride[35] has been found to give some o-cresol in addition to the expected xylenols as shown in Equation [16].

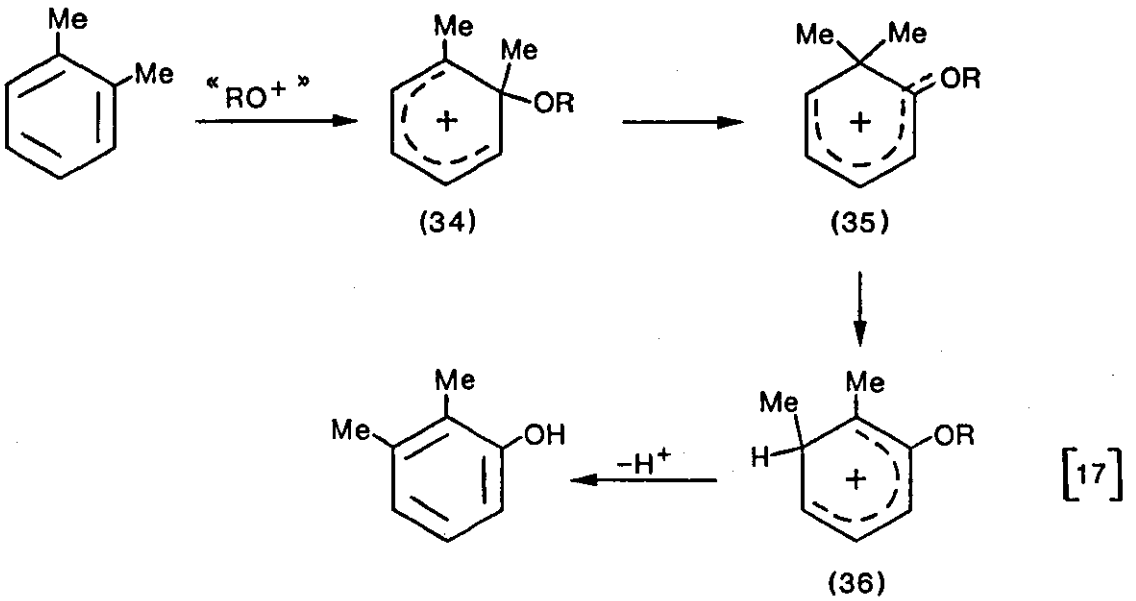


[16]

Yield of phenolic material was 50%. It is not clear as to how the o-cresol arises. It possibly results from a competing radical process, or may arise from electrophilic attack at an ipso- position with loss of the methyl group from the ipso-arenium cation rather than methyl migration.

Apatu[37] has suggested that 2,3-xylenol obtained from hydroxylation of o-xylene may result from a process involving ipso- attack of the reagent followed by two successive

methyl shifts, as illustrated in Equation [17]. Methyl



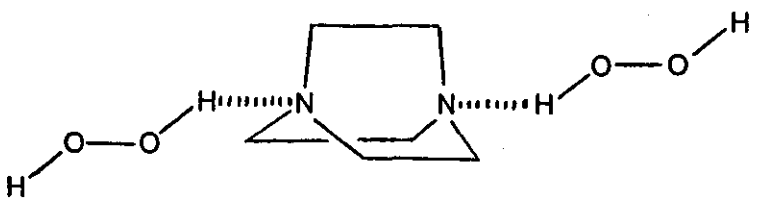
[17]

migration in the initially formed ipso-arenium ion (34) might be anticipated to the adjacent substituted carbon to produce a second arenium cation (35). A second methyl shift would then occur giving arenium ion (36) in order to allow re-aromatisation by loss of a proton, thus affording 2,3-xylenol. Formation of 2,3-xylenol from o-xylene is also expected from normal hydroxylation involving attack at an unsubstituted position, so it cannot be ascertained from the isomer distribution of the products as to whether this process involving two consecutive methyl migrations accounts for any formation of 2,3-xylenol. Hydroxylations of certain highly substituted arenes however support the feasibility of this process. For example, the cyclohexa-2,4-dienone product (32) from hydroxylation of 1,2,3,4-tetramethylbenzene (Equation [15]) has clearly involved methyl migration within an ipso-arenium ion to an already substituted adjacent carbon, in its formation.

Peroxide Adducts

Hydrogen peroxide and t-butylhydroperoxide have long been known to form crystalline, hydrogen-bonded adducts with amines such as 1,4-diaza[2.2.2] bicyclooctane (DABCO) and with certain other compounds. The adducts can generally be readily prepared from dilute (30%) hydrogen peroxide or 70% t-butylhydroperoxide solutions and are obtained as crystalline solids which generally show high stability, allowing safe handling and storage. The adducts therefore offer a convenient, safe source of anhydrous peroxide and it is surprising that these benefits have not been more fully exploited.

DABCO forms an adduct with hydrogen peroxide of 1:2 stoichiometry which has been assigned the following structure (37) on the basis of infra-red studies:[46]



(37)

Several uses of this adduct have been reported including preparation of bis(trimethylsilyl)peroxide,[47] the adduct replacing the high strength hydrogen peroxide used in the original method.

On heating the DABCO-hydrogen peroxide adduct to 60°C de-

composition occurs to afford the dioxide which can also form a hydrogen peroxide adduct (38).[46]

$$HOOH\cdots\cdots ON(CH_2CH_2)_3NO\cdots\cdots HOOH \qquad (38)$$

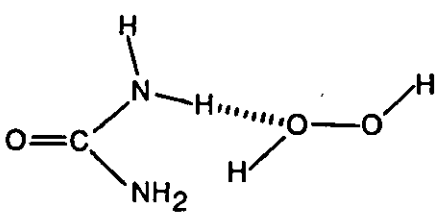
t-Butylhydroperoxide similarly forms a hydrogen-bonded complex with DABCO[48] (39) as a stable, crystalline solid which has been used in the synthesis of t-butylsilylperoxides.[49]

$$t\text{-}BuOOH\cdots\cdots N(CH_2CH_2)_3N\cdots\cdots HOOBu\text{-}t \qquad (39)$$

Hexamethylenetetramine forms adducts of 1:1 stoichiometry with both hydrogen peroxide and t-butylhydroperoxide,[50] hydrogen bonding occurring only to one of the hexamine nitrogens.

A crystalline hydrogen peroxide adduct has also been obtained when urea is crystallised from aqueous hydrogen peroxide.[51] The adduct has 1:1 stoichiometry and infrared studies[52] indicate that hydrogen bonding occurs between a peroxide oxygen and one of the urea hydrogens.

i.e.

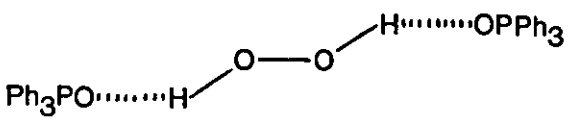


(40)

Alkali metal carbonates are also known to crystallise from aqueous hydrogen peroxide as stable solids containing a stoichiometric amount of active oxygen.[53] Sodium carbon-

ate, for example, forms a 'perhydrate' of composition $Na_2CO_3.1\frac{1}{2}H_2O_2$.

The hydrogen peroxide adducts generally suffer from a problem of insolubility in most organic solvents presenting experimental difficulties in their use as reagents. An adduct formed by triphenylphosphine oxide[54,55] however is soluble in a range of organic solvents. This adduct is again a stable, crystalline solid of composition $(Ph_3PO)_2 . H_2O_2$ and is believed[56] to have the structure (41):



(41)

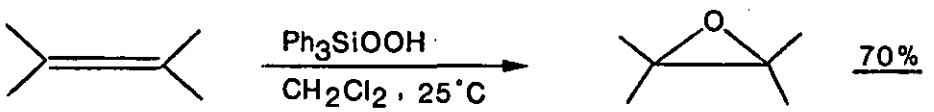
The adduct is reported to be capable of oxidising anthracene to anthraquinone[54] but there are no other reports of its use as an oxidant.

Other stable hydrogen peroxide adducts include those formed by dicyclohexylamine[57] - $[(C_6H_{12})_2NH]_2.H_2O_2$ - and guanidine.[58]

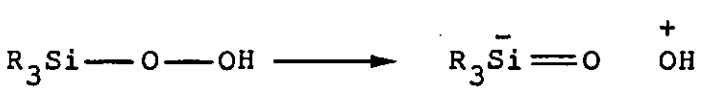
A Japanese patent[59] reports the use of urea-hydrogen peroxide adduct to perform aromatic hydroxylation with aluminium chloride catalysis, giving brief results but there is no other report of any of these adducts having been used to perform aromatic hydroxylation. Although there are several reports of the use of the adducts as a source of anhydrous hydrogen peroxide, for example in the preparation of certain organic peroxides[47,49,60] and for the <u>in situ</u> preparation of performic acid,[61] their use as direct oxidants has surprisingly not been exploited.

Triphenylsilylhydroperoxide Ph_3SiOOH

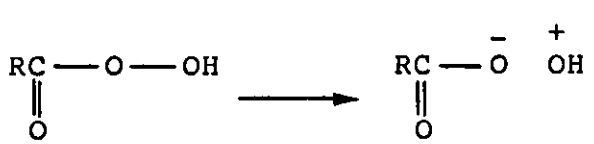
Silylhydroperoxides[62] have been found to show reactivity similar to per-acids in the epoxidation of olefins. Triphenylsilylhydroperoxide[63] is a stable, crystalline solid which is reported[64] to epoxidise olefins without the requirement of a catalyst, giving yields comparable to those obtained using mCPBA. For example:



Non-functionalised olefins, such as tetramethyl ethylene, are epoxidised as well as allylic alcohols. The epoxidation is considered to involve the hydroxyl cation (or its equivalent) as the reactive species and the enhanced reactivity of silylhydroperoxides relative to carbon hydroperoxides is considered to result from the stability of the silyl anion which would be formed on heterolysis of the oxygen - oxygen bond:



The silyl anion is stabilized by accommodation of the negative charge in the vacant d-orbitals of the silicon and is of similar stability to the carboxylate ion derived from reaction of per-acids, which in this case is stabilized by charge delocalisation with the carbonyl bond:



Trimethylsilylhydroperoxide, prepared *in situ*, has also found use as an electrophilic epoxidising agent.[65]

In view of the epoxidising ability of the silylhydroperoxides it was anticipated that they might be effective reagents for performing aromatic hydroxylation.

2.2 RESULTS AND DISCUSSION

Aromatic hydroxylation was studied using the hydrogen peroxide adducts in the presence of Lewis acid catalysts. Hydroxylations of the xylenes, toluene and mesitylene were performed using a large excess (approx. 10-fold) of the aromatic substrate and were normally carried out at 0°C in dichloromethane. The phenolic products were isolated by extraction into alkaline solution. A suitable internal standard was added and the yield and isomer distribution were determined by gas chromatography.

Aluminium chloride was the most effective catalyst, generally giving the monohydroxylated products with little contamination from higher boiling phenols that result from further oxidation. Triphenylsilylhydroperoxide in the presence of aluminium chloride was also studied and was found to be particularly effective as a hydroxylating agent.

Also reported in this chapter are results of Baeyer-Villiger oxidations performed using the hydrogen peroxide adducts in the presence of boron trifluoride.

2.2.1 Hydroxylation using peroxide adducts

2.2.1.1 Hydroxylation of o-xylene

The results obtained using the various peroxide adduct/Lewis acid reagents are shown in Table 5.

Table 5 Hydroxylation of o-xylene

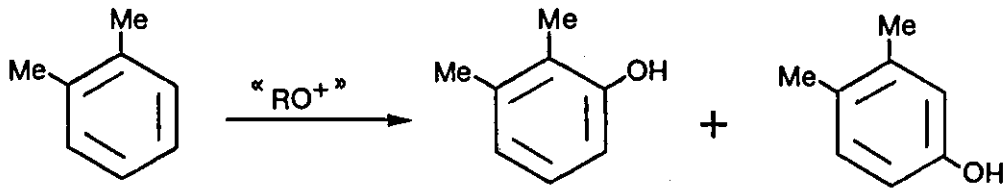
Reagent[a] (mole ratio)	Yield[b] (%)	Distribution of phenolic products (%)				Chlorinated[c] Xylenols (%)
		Xylenols			o-cresol	
		3,4-	2,3-	2,6-		
Urea-H_2O_2/$AlCl_3$(1:2)	44	45	40	15	0	4
Urea-H_2O_2/$TiCl_4$(1:2)	18	84	16	trace	0	10
Urea-H_2O_2/BF_3(1:2)	19	28	45	24	3	0
Urea-H_2O_2/$SnCl_4$(1:2)	17	24	45	31	0	5
$(Ph_3PO)_2.H_2O_2$/$AlCl_3$(1:2)	27	59	7	34	0	26
$(Ph_3PO)_2.H_2O_2$/$AlCl_3$(1:2)-40°C	25	56	32	12	0	3
$(Ph_3PO)_2.H_2O_2$/$AlCl_3$(1:4)	42	50	39	11	0	3
$(Ph_3PO)_2.H_2O_2$/$TiCl_4$(1:2)	25	98	2	trace	0	53
$(Ph_3PO)_2.H_2O_2$/BF_3(1:2)	5	39	45	15	1	0
DABCO$(H_2O_2)_2$/$AlCl_3$(1:4)	35	39	47	14	0	2
DABCO$(H_2O_2)_2$/$TiCl_4$(1:4)	9	82	17	1	0	19
DABCO$(O.H_2O_2)_2AlCl_3$(1:4)	46	38	47	14	1	2
DABCO(t-BuOOH)$_2$/$AlCl_3$(1:4)	5	54	34	9	3	2
$Na_2CO_3 1\frac{1}{2}H_2O_2$/$AlCl_3$(1:3)	35	41	43	16	0	3
$[(C_6H_{11})_2NH]_2.H_2O_2$/$AlCl_3$(1:4)	0					

[a] All reactions were performed at 0°C unless otherwise stated

[b] Yield of phenolic material based on the peroxide

[c] Yields of chlorinated phenols are expressed as a percentage of the total phenolic material

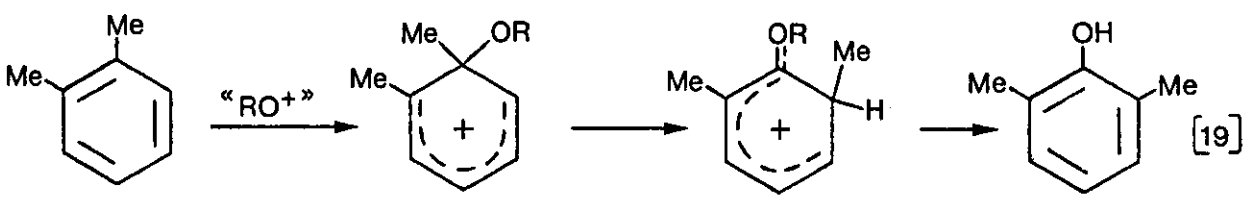
Attack of the electrophilic species (designated for simplicity as RO^+) at the unsubstituted positions leads to formation of 2,3- and 3,4-xylenol (Equation [18]).



[18]

Electron densities at these unsubstituted positions of o-xylene will be similar due to similar directing influences of the methyl groups. Therefore any large differences in reactivity at these positions can be attributed to steric factors inhibiting attack at the 3-position.

Formation of 2,6-xylenol results from ipso- attack of the reagent followed by a 1,2-methyl shift in the ipso-arenium cation as shown in Equation [19].

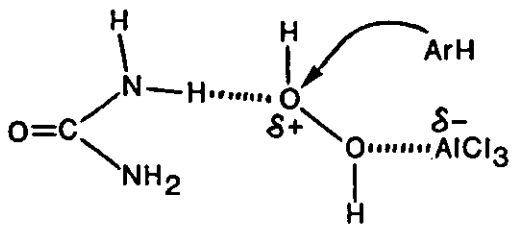


[19]

Alternatively rearrangement of this ipso- ion may occur involving two successive methyl shifts to produce 2,3-xylenol as discussed in the introduction.

The reaction is considered to involve a peroxide-Lewis acid complex undergoing nucleophilic attack by the aromatic sub-

strate. For hydroxylation using the urea-hydrogen peroxide adduct the following complex (42) could be formulated as the reactive species.



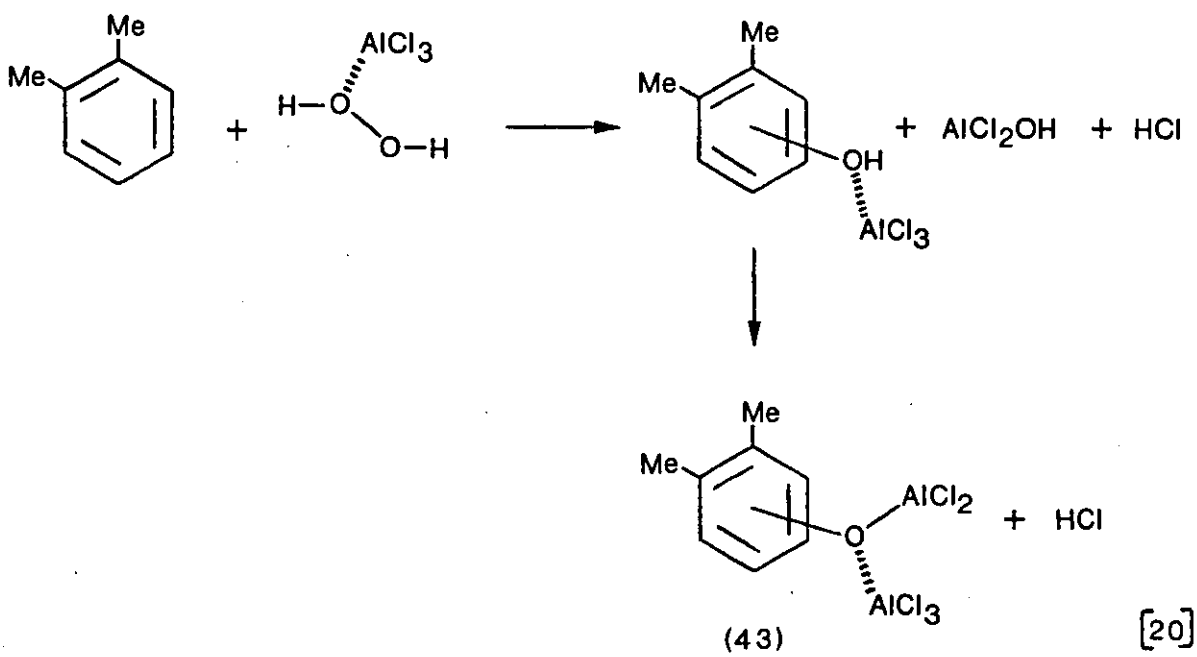
(42)

It is not known whether the hydrogen peroxide remains hydrogen-bonded to the urea as the transition state towards formation of the Wheland intermediate is approached, or whether it is free hydrogen peroxide that is involved. o-Xylene yielded 2,3- and 3,4-xylenol in similar amounts, (40:45 ratio) implying that the species involved is not particularly sterically demanding. This may be compared with a reported 60:40 ratio using 90% H_2O_2 /$AlCl_3$.[36] It therefore would appear from these results that the hydroxylation involves free hydrogen peroxide in the reactive species.

By comparison the BF_3 and $SnCl_4$ catalysed hydroxylations using the urea-hydrogen peroxide adduct gave a significantly larger 2,3 : 3,4-xylenol ratio and also a larger contribution from 2,6-xylenol. Reaction by ipso- attack is obviously a more important process in these reactions, indicated by the increased proportion of 2,6-xylenol, and may also account for the increased amount of 2,3-xylenol formed. Catalysis by titanium tetrachloride remarkably

gave no 2,6-xylenol and a low (16:84) ratio of 2,3-/3,4-xylenols using the urea-hydrogen peroxide adduct. This indicates a high steric demand of the attacking electrophilic species, a feature borne out by all the peroxide adducts studied with this catalyst. Similar results were obtained by Apatu[37] using t-butylhydroperoxide catalysed by $TiCl_4$ (12:88 ratio of 2,3-/3,4-xylenol; no 2,6-xylenol).

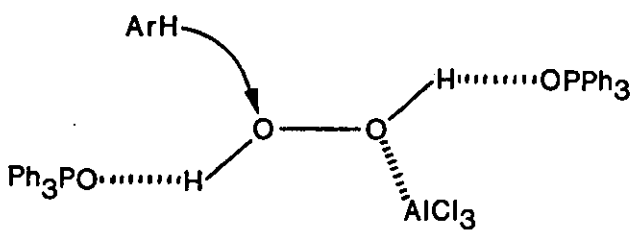
A 1:2 peroxide/Lewis acid ratio was generally used in the hydroxylations, an excess of the Lewis acid being required for co-ordination to the phenolic oxygen of the product.



(43) [20]

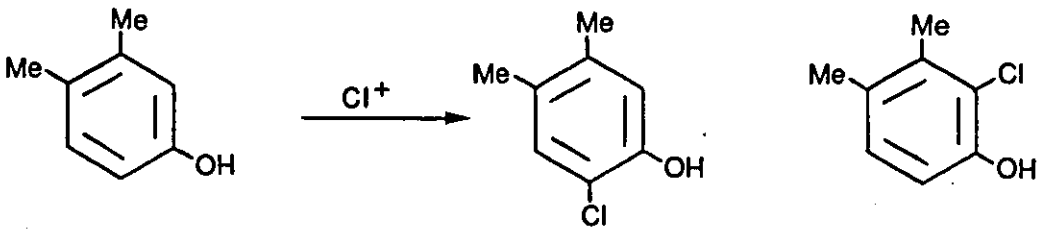
The phenolic product is believed to exist in the form of the aluminium oxide (43) with co-ordination of the phenolic oxygen to a second molecule of $AlCl_3$ protecting the phenol from further hydroxylation (Equation [20]).

Hydroxylations using the triphenylphosphine oxide adduct were initially performed using a 1:2 peroxide/Lewis acid ratio and provided some incongruous results in terms of the isomer distribution of the products. The large predominance of 3,4-xylenol over 2,3-xylenol suggests the involvement of a bulky, sterically demanding species as might be anticipated if the triphenylphosphine oxide was involved in the reactive species. On the basis of these results we suggest that reaction involves the electrophilic species (44).



(44)

Hence the preference for attack of o-xylene at the positions furthest from the methyl groups to yield 3,4-xylenol, although the relatively large proportion of 2,6-xylenol obtained, resulting from ipso- attack of the reagent, cannot be reasonably accommodated by this argument. Another anomalous feature of the hydroxylation using this reagent is the considerable contamination of the reaction products by chlorinated xylenols. The identity of these chlorinated products was confirmed by GLC/mass spectral analysis and they were found to be present as two isomeric derivatives. Experiments in which each of the xylenols was treated with the peroxide reagent under similar conditions established that these chlorinated xylenols derived from chlorination of 3,4-xylenol and are likely to be the isomers (45) and (46):



(45) (46)

Chlorination of the 2,3-xylenol and 2,6-xylenol also occurred in the o-xylene reaction but only as a minor process. The isomer ratios of the isolated xylenols are therefore not a true representation of the selectivity of the reaction since some of the 3,4-xylenol formed is consumed by chlorination.

When the hydroxylation was performed using a larger excess (4 equivalents) of $AlCl_3$ there was a remarkable reduction in the amount of chlorination and also an increase in the yield and a change in the isomer distribution.

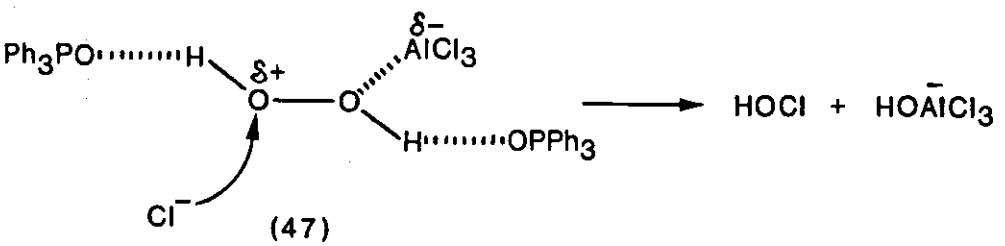
It is difficult to envisage how the proportion of $AlCl_3$ could have such an effect on the reaction. We suggest that co-ordination of triphenylphosphine oxide with the $AlCl_3$ may occur when a 4-fold excess of $AlCl_3$ is used, thus preventing hydrogen-bonding to the hydrogen peroxide, and that the reactive species is a complex of free hydrogen peroxide with $AlCl_3$ (Equation [21]).

$$(Ph_3PO)_2.H_2O_2 + 3AlCl_3 \longrightarrow 2Ph_3PO.AlCl_3 + H_2O_2.AlCl_3 \quad [21]$$

The less sterically demanding electrophilic species would account for the increased proportion of 2,3-xylenol obtained.

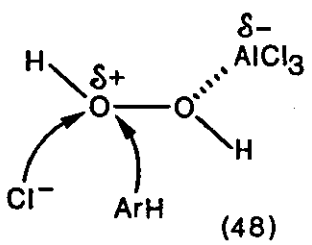
Chlorination results from the formation of hypochlorous acid produced by competing reaction of chloride ions with the peroxide-$AlCl_3$ complex.[36] A large bulky peroxide adduct-$AlCl_3$ complex (47) will hinder attack by o-xylene, favouring attack by the smaller chloride ion and hence producing larger amounts of hypochlorous acid.

i.e.



(47)

These results therefore provide further support for a bulky electrophilic species when a 1:2 $(Ph_3PO)_2.H_2O_2/AlCl_3$ ratio is employed. When the reaction is performed using four equivalents of $AlCl_3$, the reduced amount of chlorination can be attributed to the involvement of a smaller electrophilic species i.e. a complex of free hydrogen peroxide.

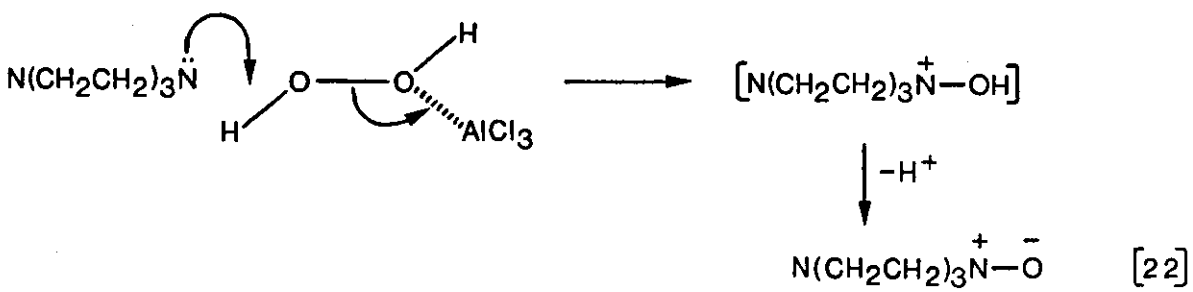


(48)

In this case attack by o-xylene is less restricted and predominates over attack by chloride ion due to the much

greater concentration of o-xylene molecules. Less hypochlorous acid is produced and so the amount of chlorination is reduced.

It is interesting to compare the DABCO and DABCO dioxide adducts of hydrogen peroxide in terms of their effectiveness as an oxidant with $AlCl_3$ catalysis, the dioxide giving a greater yield of xylenol under similar reaction conditions. Oxidation of DABCO under the reaction conditions may be anticipated[66] in a process competing with aromatic hydroxylation as formulated in Equation [22].



[22]

The occurrence of this oxidation when using the H_2O_2 adduct of DABCO may offer an explanation for the reduced effectiveness compared with the DABCO dioxide adduct. The t-butylhydroperoxide adduct of DABCO also gave a relatively low yield of xylenols which could be similarly explained. Attempted hydroxylation using the hydrogen peroxide adduct of dicyclohexylamine catalysed by $AlCl_3$ failed to yield any phenolic products.

2.2.1.2 Hydroxylation of p-xylene

Hydroxylation of p-xylene using the peroxide adduct/Lewis acid reagents gave the results shown in Table 6.

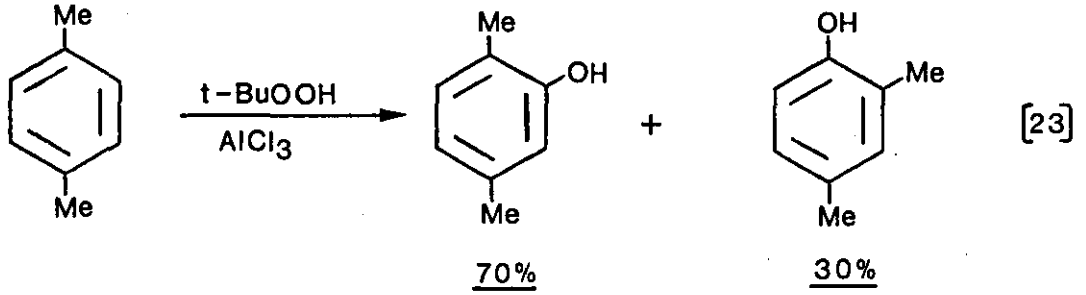
Table 6

Reagent (mole ratio)	Yield[a] (%)	Xylenol isomer distribution (%)		Chlorinated[b] xylenols (%)
		2,5-	2,4-	
Urea-H_2O_2/$AlCl_3$ (1:2)	43	67	33	0
Na_2CO_3.1½H_2O_2/$AlCl_3$ (1:3)	39	68	32	0
$(Ph_3PO)_2$.H_2O_2/$AlCl_3$ (1:2)	27	0	100	63
$(Ph_3PO)_2$.H_2O_2/$AlCl_3$ (1:4)	33	68	32	2
DABCO(O.H_2O_2)$_2$/$AlCl_3$ (1:4)	25	58	42	40
DABCO(O.H_2O_2)$_2$/$TiCl_4$ (1:4)	23	88	12	28

[a] Yield of phenolic products based on the hydrogen peroxide

[b] Expressed as a percentage of the total phenolic material

Hydroxylation of p-xylene using the urea, sodium carbonate and DABCO adducts catalysed by $AlCl_3$ gave mixtures of 2,5- and 2,4-xylenol. 2,5-Xylenol, resulting from hydroxylation at the unsubstituted positions was the major product, the isomer distributions being similar to those obtained by Apatu[37] using t-butylhydroperoxide/$AlCl_3$ (Equation [23]).



70% 30% [23]

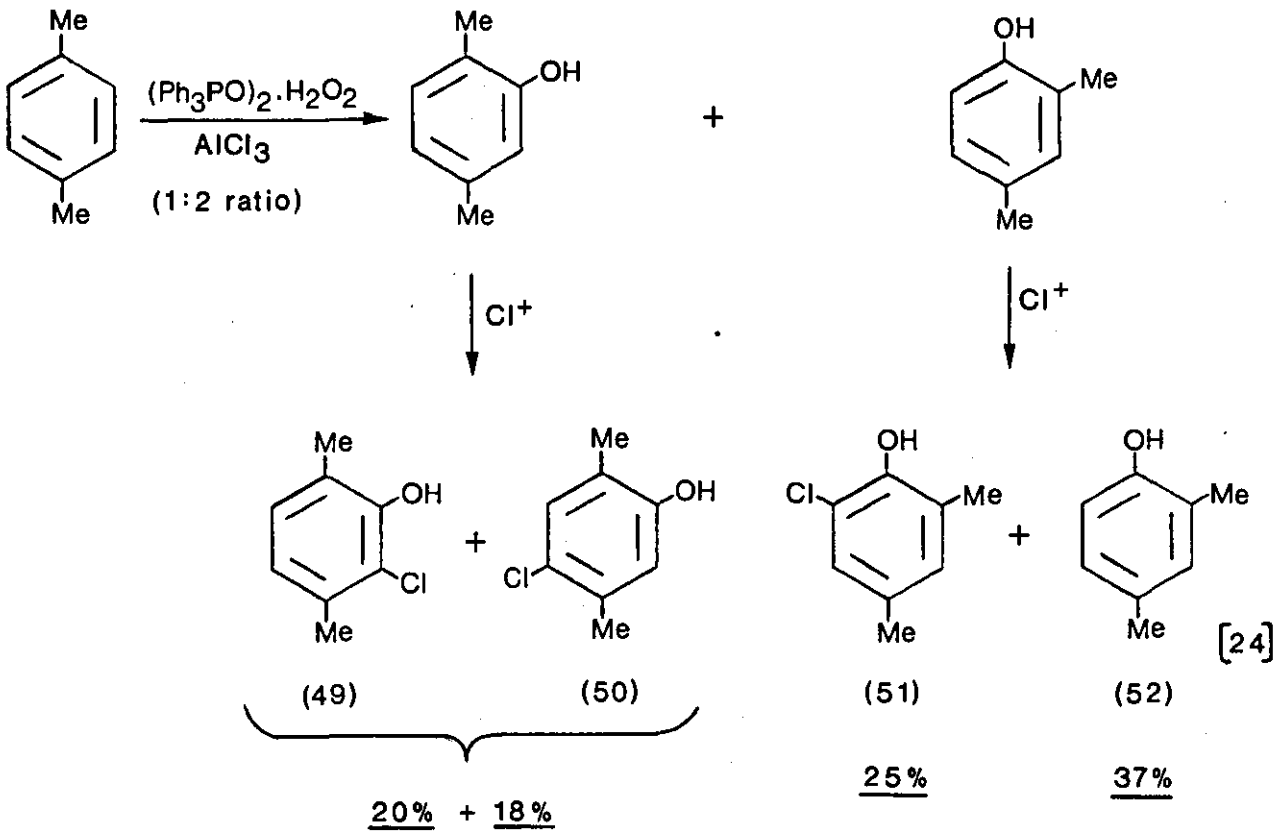
40% Yield of xylenols

The xylenol ratios obtained using the hydrogen peroxide adducts indicate similar reactivity of the hydroxylating species towards ipso- and unsubstituted positions, i.e. $k_H \simeq k_{ipso}$. These results are consistent with a relatively small electrophilic species showing little hindrance to attack at an ipso- position and therefore support the involvement of free hydrogen peroxide in the reactive species rather than the hydrogen-bonded adduct.

Hydroxylation using the $(Ph_3PO)_2.H_2O_2/AlCl_3$ reagent again provided some intriguing results. Initial studies using a 1:2 peroxide/$AlCl_3$ ratio yielded no 2,5-xylenol, the only phenolic products being 2,4-xylenol together with 63% (in terms of GLC integration) of chlorinated xylenols. GLC analysis showed these chlorinated xylenols to be present as three isomeric components. Analysis by GLC was performed firstly using the FFAP polar capillary column and identification was confirmed using the BP1 non-polar column, (GLC details are given in the experimental section). Several repetitions of the reaction produced similar results although on one occasion a small amount (~3%) of 2,5-xylenol was obtained.

Experiments in which 2,5-xylenol and 2,4-xylenol were treated with this hydroxylating agent, under similar conditions, established that two of these chlorinated products resulted from chlorination of 2,5-xylenol and the other chlorinated product derived from the 2,4-xylenol. It therefore appears that some 2,5-xylenol is formed, but it is all consumed by reaction with the chlorinating agent (hypochlorous acid) to produce the isomeric chlorinated xylenols.

Equation [24] illustrates the processes which are considered to be occurring to give rise to the four phenolic products. The distribution of these phenolic products



implies that 2,5- and 2,4-xylenol are initially formed in an approximately 2:3 ratio. The 2,5-xylenol is then apparently the more susceptible to chlorination, all of this

isomer being converted to the two isomeric chlorinated xylenols (49) and (50). The hydroxylation of p-xylene with this reagent therefore shows similar features to the hydroxylation of o-xylene, where attack at an ipso- position to yield 2,6-xylenol appears to occur more readily than attack at a position ortho- to a methyl group. As observed in the o-xylene hydroxylation the proportion of $AlCl_3$ used in the reaction is important. When the hydroxylation was performed using a larger proportion (4 equivalents) of $AlCl_3$ with the triphenylphosphine oxide adduct the reaction produced the expected xylenol ratio typical of normal electrophilic hydroxylation of p-xylene (predominantly 2,5-xylenol obtained) and was devoid of any chlorinated phenolic products.

These results are therefore consistent with the theory that, when the amount of $AlCl_3$ is limited to two equivalents, the electrophilic complex is a large, bulky species containing hydrogen-bonded triphenylphosphine oxide as discussed previously. This could explain the large amount of chlorination observed although the preference for reaction at an ipso- position rather than an unsubstituted position of p-xylene cannot be so readily accounted for.

When the proportion of $AlCl_3$ was increased to four equivalents (relative to the peroxide) the products obtained from p-xylene were consistent with the involvement of a relatively small electrophilic species.

Hydroxylation using the DABCO dioxide adduct catalysed by $AlCl_3$ gave an unusually high degree of chlorination producing the three isomeric chlorinated xylenols as 40% of the phenolic material.

2.2.1.3 Hydroxylation of m-xylene

The results obtained using the peroxide/Lewis acid reagents are shown in Table 7.

Table 7

Reagent (mole ratio)	Yield[a] of xylenols (%)	Distribution of xylenols (%)			Chlorin-[b] ated xylenols (%)
		2,4-	2,6-	3,5-	
Urea-$H_2O_2/AlCl_3$(1:2)	43	75	25	0	8
$Na_2CO_3.1\frac{1}{2}H_2O_2/AlCl_3$(1:3)	39	71	28	1	0
$(Ph_3PO)_2.H_2O_2/AlCl_3$(1:2)	35	68	32	<1	28
$(Ph_3PO)_2.H_2O_2/AlCl_3$(1:4)	45	69	30	1	8
DABCO$(H_2O_2)_2/AlCl_3$(1:4)	37	69	30	1	4
DABCO$(O.H_2O_2)_2/AlCl_3$(1:4)	48	71	28	1	2
DABCO(t-BuOOH)$_2/AlCl_3$(1:4)	30	85	13	2	1

[a] Yields are based on the hydrogen peroxide

[b] Chlorinated xylenols are expressed as a percentage of the total phenolic material

The expected xylenol isomers were obtained from m-xylene and in similar distributions with all the reagents studied. The isomer distribution obtained using the $(Ph_3PO)_2.H_2O_2$ / $AlCl_3$ reagent was not greatly affected by the proportion of $AlCl_3$ used, although chlorinated xylenols were formed in a significant amount (28%) when the $AlCl_3$ was limited to two equivalents.

2.2.1.4 o-Xylene/m-Xylene competition reaction

Hydroxylation of an equimolar o-xylene/m-xylene mixture was performed using the $(Ph_3PO)_2.H_2O_2/AlCl_3$ reagent (1:2 mole ratio). A large (40-fold) excess of xylene was used and the reaction was performed under the usual conditions.

Table 8 shows a comparison of the results with the hydroxylations of the individual xylenes.

Table 8

Aromatic	Yield (%)	Distribution of xylenols (%)					Chlorinated xylenols (%)
		2,4-	2,6-	3,4-	3,5-	2,3-	
o-xylene/ m-xylene (1:1 mixture)	24	62	18	10	0	0	19
o-xylene	27	0	34	59	0	7	26
m-xylene	35	68	32	0	1	0	28

The 2,4-/3,4-xylenol ratio obtained in the competition reaction indicates an approximate relative reactivity of m-xylene/o-xylene of 5:1.

The considerably greater reactivity shown by m-xylene suggests that π-complex formation is not the rate limiting process in this reaction. o-Xylene and m-xylene have similar π-basicities and hence would be expected to show similar reactivity if this was the case.

The relative σ- and π-complex stabilities for protonation of o- and m-xylene (relative to benzene = 1.0) are:

	Relative σ-complex stability($HF-BF_3$)[67]	Relative π-complex stability(HCl)[68]
o-xylene	7,900	1.8
m-xylene	1,000,000	2.0

It would appear then, that σ-complex control is operating, hydroxylation of m-xylene being favoured by the considerably greater stability of the σ-complex formed by reaction at the 4- and 6- positions.

2.2.1.5 Hydroxylation of toluene

The results obtained using the various peroxide adduct/Lewis acid reagents are shown in Table 9.

Table 9

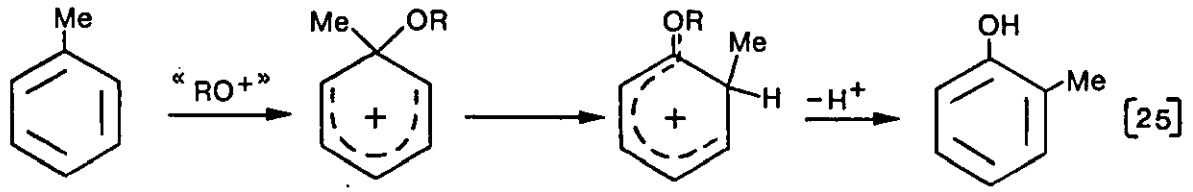
Reagent (mole ratio)	Yield[a] of cresol (%)	Isomer distribution of cresols (%)			Chlorinated[b] cresols(%)
		o-	m-	p-	
Urea-H_2O_2/$AlCl_3$(1:2)	47	58	5	37	5
Urea-H_2O_2/$TiCl_4$(1:2)	15	31	6	63	13
$(Ph_3PO)_2$.H_2O_2/$AlCl_3$(1:2)	20	18	3	79	38
$(Ph_3PO)_2$.H_2O_2/$AlCl_3$(1:4)	34	43	6	51	1
Na_2CO_3.$1\frac{1}{2}H_2O_2$/$AlCl_3$(1:3)	51	61	6	33	1
DABCO$(H_2O_2)_2$/$AlCl_3$(1:4)	34	61	8	31	17
DABCO$(H_2O_2)_2$/$TiCl_4$(1:4)	26	30	11	59	25
DABCO(O.$H_2O_2)_2$/$AlCl_3$(1:4)	45	61	6	33	2
Hexamine-H_2O_2/$AlCl_3$(1:2)	5	29	4	67	21

[a] Yields are based on the hydrogen peroxide

[b] Yields of chlorinated cresols are expressed as a percentage of the total phenolic material.

The isomer distributions of the cresols reflect the steric factors involved in the hydroxylation. The urea, sodium carbonate and DABCO adducts gave cresol distributions which indicate similar partial rate factors at the ortho- and para- positions and suggest that a relatively small electrophilic species is involved, in agreement with previous observations for the xylene hydroxylations. These results are comparable to the 40% yield of cresol (o-/m-/p-ratio = 60% : 8% : 32%) obtained by Kurz and Johnson[36] using 90% H_2O_2 catalysed by $AlCl_3$.

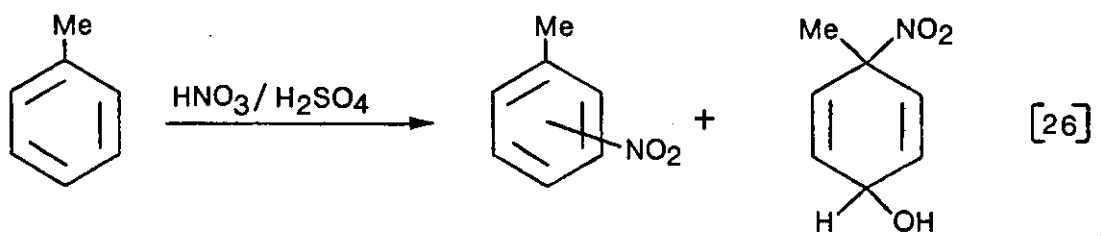
Some o-cresol may arise from ipso- attack followed by a methyl shift (Equation [25]).



[25]

(53)

This process is likely however to be of only minor importance, since the initial ipso-arenium cation (53) is relatively unstable compared with the arenium ions formed by attack at the ortho- and para- positions of toluene. Nitration of toluene using a mixture of nitric and sulphuric acids has been shown[14] to involve only about 4% of reaction by ipso- attack, indicated by formation of the ipso- adduct (54) (Equation [26]).



[26]

96%

(54)

4%

The isomer distributions obtained using the $(Ph_3PO)_2.H_2O_2$ / $AlCl_3$ reagent are consistent with the arguments proposed for the xylene hydroxylations. When a 1:2 peroxide/$AlCl_3$ ratio was used, p-cresol was the major product (18% ortho-, 79% para-cresol) and a considerable amount (38%) of chlorinated cresols was obtained as two components in the GLC

trace. Increasing the proportion of $AlCl_3$ to four equivalents again produced a significant change in the isomer ratio consistent with the involvement of a smaller electrophilic species, i.e. a complex of free hydrogen peroxide with $AlCl_3$.

2.2.1.6 Hydroxylation of mesitylene

Mesitol was obtained from all the reactions as a pale yellow solid which was shown by GLC analysis to be of high purity with no contamination from chlorinated products. The yields obtained are shown in Table 10. Mesitylene generally shows high reactivity towards electrophilic substitution due to the ortho-/para- directing influence of all three methyl substituents towards each unsubstituted carbon, although steric factors may be important with bulky electrophiles.

The yields of mesitol obtained with the H_2O_2 adduct/$AlCl_3$ system are comparable with the 42% yield obtained by Kurz and Johnson[36] using 90% $H_2O_2/AlCl_3$.

Trifluoroperoxyacetic acid is known to be a potent electrophilic hydroxylating agent[27] which has been found to oxidise mesitylene in good yield. Use of the triphenylphosphine oxide-hydrogen peroxide adduct with trifluoroacetic anhydride allowed a safe and convenient preparation of trifluoroperoxyacetic acid under anhydrous conditions:

Table 10 Hydroxylation of mesitylene

Reagent (H_2O_2 adduct/Lewis acid mole ratio)		Yield[a] of mesitol (%)
Urea-H_2O_2/$AlCl_3$	(1:2)	40
Urea-H_2O_2/BF_3	(1:2)	16
$(Ph_3PO)_2$.H_2O_2/$AlCl_3$	(1:2)	12
$(Ph_3PO)_2$.H_2O_2/$AlCl_3$	(1:4)	42
$(Ph_3PO)_2$.H_2O_2/BF_3	(1:4)	28
DABCO$(H_2O_2)_2$/$AlCl_3$	(1:4)	37
DABCO$(O.H_2O_2)_2AlCl_3$	(1:4)	41
$(Ph_3PO)_2$.H_2O_2/$(CF_3CO)_2O$[b]		54
$(Ph_3PO)_2$.H_2O_2/$(CF_3CO)_2O$/BF_3[b]	(1:4)	71
85% H_2O_2/$(CF_3CO)_2O$/BF_3[b]	(1:2)	73
Urea-H_2O_2/$(CF_3CO)_2O$/BF_3[b]	(1:2)	9
Urea-H_2O_2/CF_3CO_2H[c]		39
Urea-H_2O_2/CF_3CO_2H[c]/BF_3	(1:6)	44
DABCO$(O.H_2O_2)_2$/$(CF_3CO)_2O$/BF_3[b]	(1:4)	8
$[(C_6H_{11})_2NH]_2$.H_2O_2/$(CF_3CO)_2O$/BF_3	(1:2)	2

[a] Yields are based on the peroxide adducts.

[b] Reactions used 1·2 equivalents of trifluoroacetic anhydride

[c] 4 equivalents of trifluoroacetic acid was used to allow dissolution of the urea-H_2O_2 adduct.

$$(Ph_3PO)_2.H_2O_2 + (CF_3CO)_2O \longrightarrow CF_3CO_3H + CF_3CO_2H + 2Ph_3PO$$

Mesitylene was hydroxylated by this reagent in dichloromethane giving a 54% yield of mesitol. The yield was improved to 71% when boron trifluoride was present - four equivalents of BF_3 etherate was found to be required for optimum yield.

The solubility of the triphenylphosphine oxide adduct is an important asset, allowing rapid formation of trifluoroperoxyacetic acid from the anhydride in a homogeneous system. The use of the urea and DABCO adducts for formation of the per-acid was attempted. A mixture of the H_2O_2 adduct, trifluoroacetic anhydride and BF_3 etherate was stirred in mesitylene/dichloromethane but the yields of mesitol were low, obviously due to the insolubility of the H_2O_2 adducts. The urea-H_2O_2 adduct is highly soluble in trifluoroacetic acid and a mixture of this adduct in four mole equivalents of trifluoroacetic acid was found to produce a homogeneous solution which was able to oxidise mesitylene to mesitol in 39% yield.

The dicyclohexylamine-H_2O_2 adduct, despite its solubility in dichloromethane was found to be ineffective for oxidation of mesitylene by the generation of trifluoroperoxyacetic acid in the presence of boron trifluoride. Oxidation of the amine to the N-oxide is perhaps the predominant reaction in this case.

2.2.1.7 Hydroxylation of Naphthalene

Hydroxylation of naphthalene using various peroxide adduct/Lewis acid reagents gave the results shown in Table 11.

Table 11

Reagent	Mole[a] ratio	Yield of naphthol (%)	Naphthol isomer distribution (%)		Chlorin-[b] ated naphthols (%)
			α-	β-	
Urea-H_2O_2/$AlCl_3$	1:1:2	16	34	66	6
Urea-H_2O_2/$AlCl_3$	5:1:2	24	54	46	3
$Na_2CO_3.1\frac{1}{2}H_2O_2$/ $AlCl_3$	5:1:3	28	74	26	8
$(Ph_3PO)_2.H_2O_2$/ $AlCl_3$	1:1:2	7	15	85	32
$(Ph_3PO)_2.H_2O_2$/ $AlCl_3$(-40°C)	1:1:2	4	53	47	40
$(Ph_3PO)_2.H_2O_2$/ $AlCl_3$	5:1:2	12	29	71	28
$(Ph_3PO)_2.H_2O_2$/ $AlCl_3$	5:1:4	26	42	58	10
t-BuOOH/$AlCl_3$	1:1:2	8	57	43	2

[a] Mole ratio of naphthalene/peroxide/$AlCl_3$.

[b] Expressed as a percentage of the total phenolic material.

All reactions were performed in dichloromethane at 0°C unless otherwise stated.

The phenolic products were analysed by gas chromatography using the carbowax column. 2,3-Xylenol was added as an internal standard.

Hydroxylation of naphthalene occurred to give a mixture of α- and β-naphthol. Initial studies were carried out using a 1:1 naphthalene/peroxide ratio, but yields under these conditions were poor.

(i) Hydroxylation using $Urea\text{-}H_2O_2/AlCl_3$ (1:1:2 ratio)

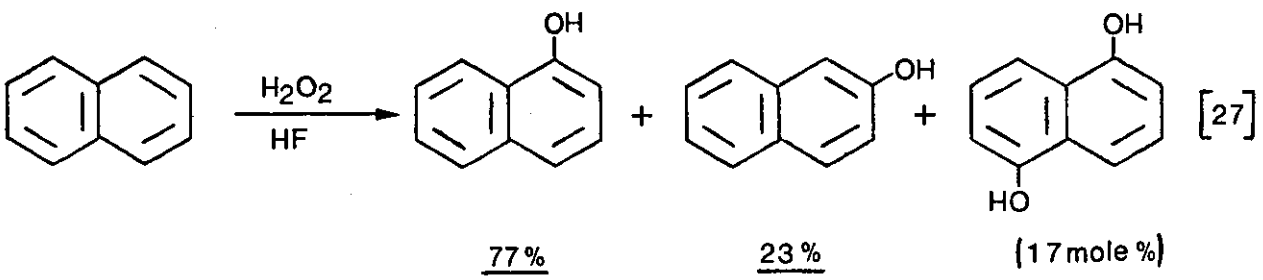
Naphthol was obtained in 16% yield along with a considerable amount of uncharacterised high boiling phenolic products from further oxidation of the naphthol.

(ii) Hydroxylation using $Urea\text{-}H_2O_2/AlCl_3$ (5:1:2 ratio)

Using a higher concentration of naphthalene (5 equivalents in the same volume of solvent) an improved yield of naphthol (24%) was obtained and a change in the isomer distribution (increased α-isomer) was observed. Also the reaction was cleaner, the mono-hydroxylated products accounting for ~95% of the isolated phenolic material. This compares with an 18% yield of naphthol (isomer ratio not indicated) reported by Kovacic and Kurz[33] using diisopropylperoxydicarbonate catalysed by aluminium chloride under similar conditions, (5:1:2 reagent ratio).

It should be noted that the isomer distribution observed for the equimolar urea-$H_2O_2/AlCl_3$ reaction is not a true reflection of the selectivity of the reagent since the products of further hydroxylation are more likely to derive from the α-naphthol, (hydroxylation of naphthalene using H_2O_2/HF[39] yielded 1,5-naphthalenediol from further hydroxylation of α-naphthol as the major component amongst the polyhydroxylated products). This would thus offer a possible explanation for the relative decrease in the proportion of α-naphthol obtained when a lower concentration of naphthalene was used - due to consumption of the α-naphthol by further hydroxylation.

Previous studies of hydroxylation of naphthalene have included the use of 30% hydrogen peroxide catalysed by hydrogen fluoride[39] which gave a 39% yield of naphthol along with 17 mole % of 1,5-naphthalenediol (Equation [27]).



[27]

35 wt % of high boiling, uncharacterised material was also obtained.

(iii) Hydroxylation using $(Ph_3PO)_2.H_2O_2/AlCl_3$

The hydroxylations were generally performed at 0°C in dichloromethane. The reaction proceeded rapidly, benefitting from the solubility of the adduct, and was found to have gone to completion (no peroxide remaining) after 12 hours. The amount of $AlCl_3$ used (2 or 4 equivalents) was found to affect the reaction in terms of the yield and isomer distribution of naphthol obtained. As discussed previously, the reactive species when a 1:2 peroxide/$AlCl_3$ ratio is used appears to be a bulky, sterically demanding species and is of decreased size and steric demand when the reaction is performed using a larger excess (4 equivalents) of $AlCl_3$.

Performing the hydroxylation at lower temperature (-40°C) produced a significant increase in the proportion of α-naphthol obtained. This change in the isomer distribution is as expected if the reaction involves a late transition state, due to the greater stability of the σ-complex obtained from attack at the α-position. The high β-/α-naphthol ratio obtained at room temperature is apparently a consequence of steric factors hindering α-attack.

2.2.2 Aromatic Hydroxylation using Triphenylsilylhydroperoxide (Ph_3SiOOH)

Preparation of Ph_3SiOOH

Triphenylsilylchloride was prepared from phenyllithium and silicon tetrachloride (Equation [28]) and was converted to the hydroperoxide by the method of Dannley and Jalics[63] (Equation [29]).

$$3PhBr \xrightarrow[\text{ether}]{6\ Li} 3PhLi + 3LiBr \xrightarrow{SiCl_4} Ph_3SiCl + 3LiCl \qquad [28]$$

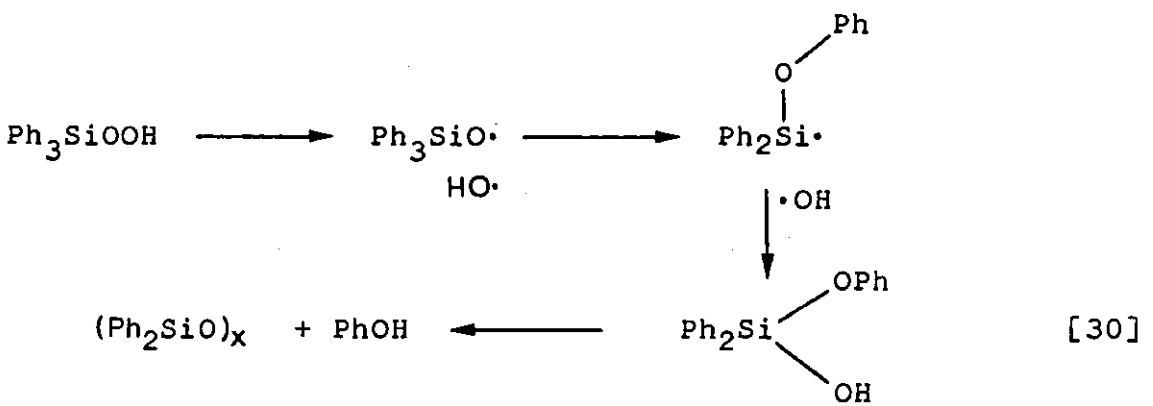
$$Ph_3SiCl \xrightarrow[\text{ether}]{NH_3} Ph_3SiNH_2 \xrightarrow[\text{ether}]{95\%H_2O_2} Ph_3SiOOH + NH_3 \qquad [29]$$

The hydroperoxide was prepared a number of times and was obtained as a colourless, crystalline solid, but its purity in terms of the active oxygen content was generally less than 90%, even after several recrystallisations.

Aromatic hydroxylation

The triphenylsilylhydroperoxide is soluble in a range of organic solvents, including dichloromethane, and in the presence of aluminium chloride was found to be effective for performing aromatic hydroxylation. Yields were comparable to published results using t-butylhydroperoxide/$AlCl_3$ and the reactions provided some interesting mechanistic details in terms of the selectivity of the reagent.

Hydroxylation was performed at room temperature in dichloromethane and was generally complete within a few hours. Phenolic products were isolated in the usual way, by alkaline extraction, and GLC analysis showed that the monohydroxylated products were obtained without any significant contamination from products of further oxidation or chlorinated derivatives. An unfortunate drawback however, was the formation of phenol resulting from decomposition of the silylhydroperoxide under the reaction conditions. Decomposition may involve homolytic cleavage of the peroxide bond[69] as illustrated in Equation [30].



[30]

2.2.2.1 Hydroxylation of mesitylene

Hydroxylation using triphenylsilylhydroperoxide produced a mixture of mesitol and phenol as shown in Table 12.

Table 12

Reagent	Yield of mesitol (%)	Yield of phenol[a] (%)
Ph_3SiOOH	19	25
$Ph_3SiOOH/AlCl_3$ (1:2)	33	6

[a] Yield of phenol from decomposition of the Ph_3SiOOH

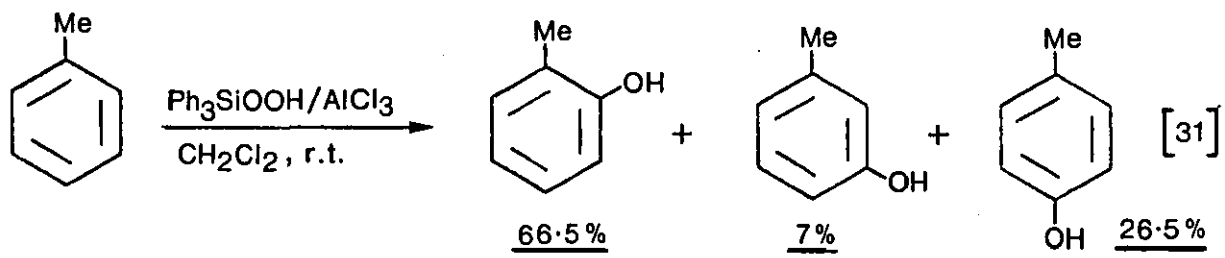
The reactions were performed at room temperature using a 20:1 mesitylene/Ph_3SiOOH ratio. Reaction time was 16 hours.

Phenolic products were analysed by GLC using the BP1 capillary column at 90°C.

The enhanced reactivity of triphenylsilylhydroperoxide relative to the more conventional hydroperoxides (e.g. t-butylhydroperoxide) was demonstrated by its ability to oxidise mesitylene in the absence of a catalyst.

2.2.2.2 Hydroxylation of toluene

Hydroxylation using the silylhydroperoxide catalysed by $AlCl_3$ gave a mixture of the isomeric cresols in 72% yield along with a 7% yield of phenol (from decomposition of the Ph_3SiOOH). GLC analysis (BP1 column) indicated the following isomer distribution (Equation [31]):

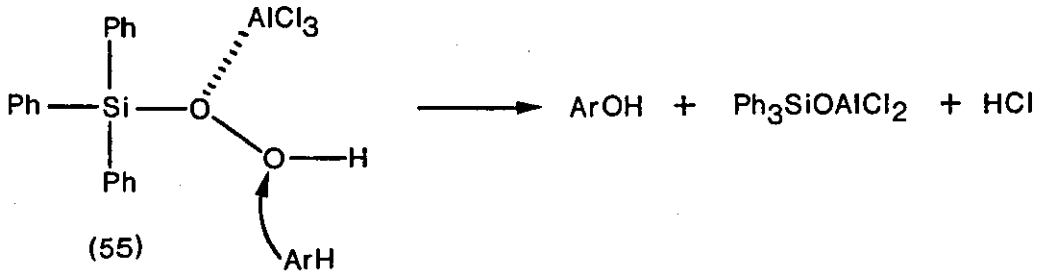


[31]

This compares with a 76% yield of cresol reported for hydroxylation using t-BuOOH/$AlCl_3$[34] (ratio o-/m-/p- = 56:8:36).

The orientation of the cresols suggests a highly reactive electrophilic species which is not very selective; i.e. re-

action is considered to involve an 'early' transition state. The results indicate a remarkable lack of steric control of the selectivity, which is not consistent with the bulky, sterically demanding species (55) which may be formulated involving the silylhydroperoxide complexed with $AlCl_3$.

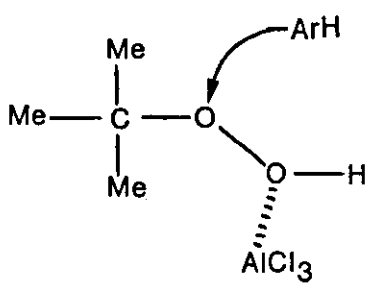


(55)

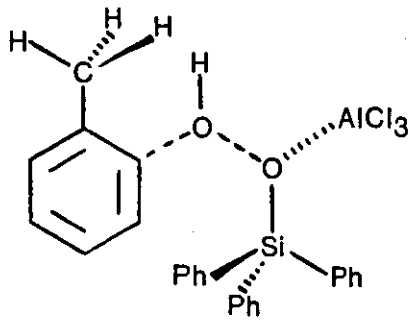
The $AlCl_3$ may co-ordinate to either of the peroxide oxygens but steric factors will favour attack by the arene at the oxygen furthest from the silicon, as shown, with the $AlCl_3$ co-ordinated to the other oxygen. Heterolysis of the peroxide bond in this direction is also favoured by the stability of the siloxy anion which results.

t-Butylhydroperoxide, by comparison, has been shown[34] to react by attack of the arene at the oxygen next to the t-butyl group.

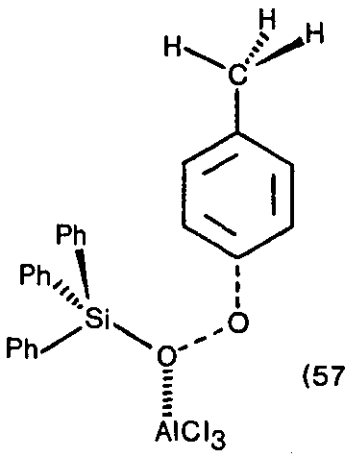
i.e.



A comparison of the steric interactions in the transition state species may help to explain the observed selectivity. The transition states for attack of the Ph_3SiOOH-$AlCl_3$ complex at the ortho- (56) and para- (57) positions of toluene may be considered to take the forms:



(56)

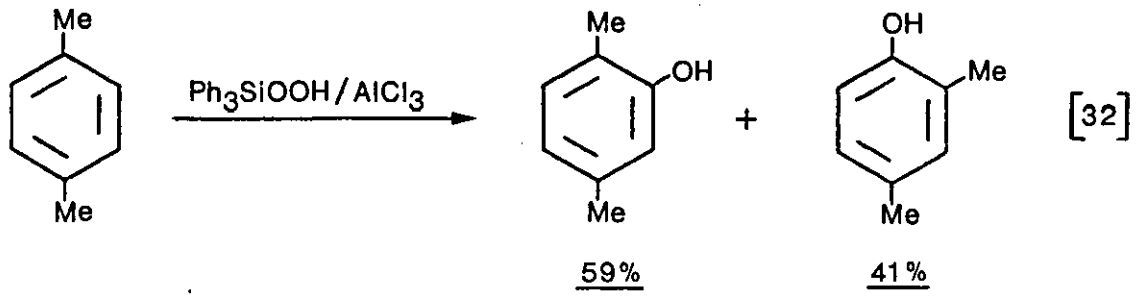


(57)

The triphenylsilyl group in the ortho- transition state species (56) is, in fact, quite well distanced from the methyl group of the toluene and steric interactions between these two groups may be considered to be of similar magnitude in the ortho- and para- species. Thus the selectivity of the reagent might not be greatly influenced by the methyl group and in view of these facts the high ortho-/ para- selectivity is not so surprising.

2.2.2.3 Hydroxylation of p-xylene

A 58% yield of xylenols was obtained (Equation [32]).



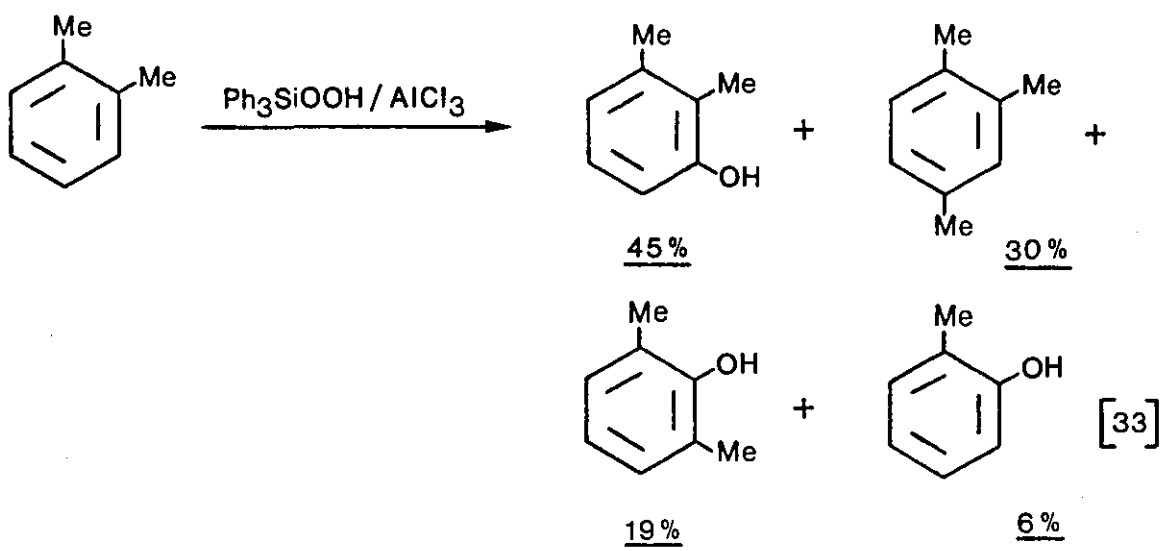
[32]

A 50:1:2 mole ratio of p-xylene /$Ph_3SiOOH/AlCl_3$ was used. No chlorinated xylenols were formed.
Phenol (10% yield) from decomposition of the Ph_3SiOOH was also obtained.

This result compares with a 40% yield of xylenol (70:30 2,5-/2,4- ratio) obtained by Apatu[37] using t-butylhydroperoxide/$AlCl_3$.

2.2.2.4 Hydroxylation of o-xylene

A 46% yield of phenolic products was obtained (Equation [33]).

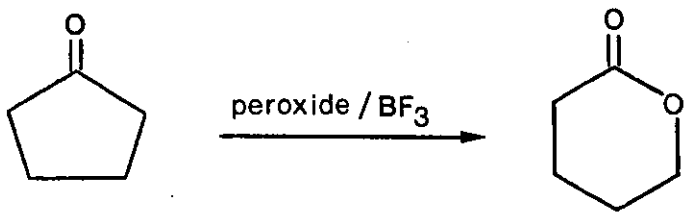


[33]

A 50:1:2 mole ratio of o-xylene/$Ph_3SiOOH/AlCl_3$ was used. A 4% yield of chlorinated xylenols and an additional 13% yield of phenol (from Ph_3SiOOH) were also obtained. This compares with a 50% yield of xylenols obtained by Apatu[37] using t-BuOOH/$AlCl_3$. (26:60:5:9 ratio of 2,3-/3,4-/2,6-xylenol/o-cresol).

2.2.3 Baeyer-Villiger oxidation

Baeyer-Villiger oxidation has previously been achieved[26] using 90% hydrogen peroxide in the presence of boron trifluoride etherate. Use of the hydrogen peroxide adducts would offer a safer and more convenient method. Results obtained for the oxidation of cyclopentanone to δ-valerolactone (58) are shown in Table 13.



(58)

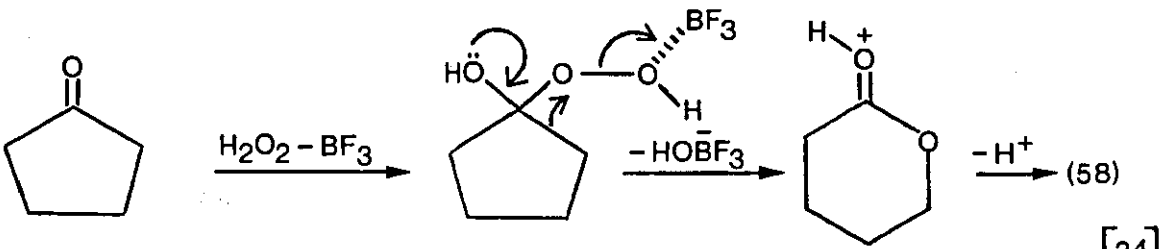
Table 13

Peroxide	Yield[a] of lactone (%)
86% H_2O_2	59
Urea-H_2O_2	38
$Na_2CO_3.1\frac{1}{2}H_2O_2$	46
$DABCO(O.H_2O_2)_2$	31
$(Ph_3PO)_2.H_2O_2$	42
$[(C_6H_{11})_2NH]_2.H_2O_2$	49

[a] Yields are based on the limiting reagent.

The reactions were performed using a 1:1:2 ketone/peroxide/BF_3 ratio.

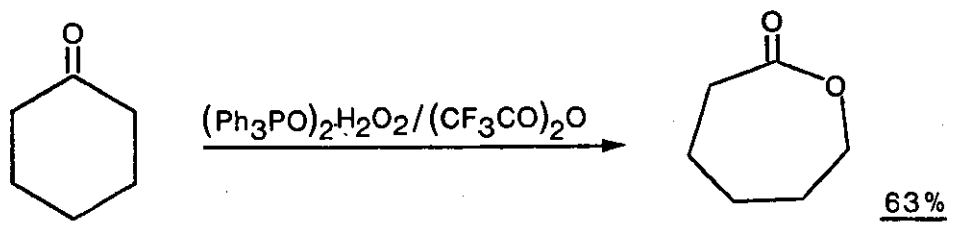
The yields were not particularly good and in all cases were lower than was obtained using 86% hydrogen peroxide catalysed by BF_3. The oxidation is thought[26] to proceed by way of a peroxide-ketone adduct (59), co-ordination of the boron trifluoride facilitating heterolysis of the peroxide bond as shown in Equation [34].



(59)

[34]

Trifluoroperoxyacetic acid prepared from the triphenylphosphine oxide adduct and trifluoroacetic anhydride was also an effective oxidant. Cyclohexanone was oxidised to ε-caprolactone (60) in 63% yield (Equation [35]).



(60)

[35]

This compares with a reported 76% yield obtained using trifluoroperoxyacetic acid prepared with 90% hydrogen peroxide.[70] The triphenylphosphine oxide appears to have an inhibiting effect on the reaction, perhaps due to co-ordination to the hydrogen peroxide causing steric hindrance.

CHAPTER 3

REACTION OF ELECTROPHILES WITH ARYL-METAL COMPOUNDS

3.1 INTRODUCTION

3.1.1 General Introduction

Reactions involving electrophilic displacement of a metal residue from an aryl-metal compound have been widely studied, providing a useful method for introduction of a substituent at a specific site on an aromatic ring.

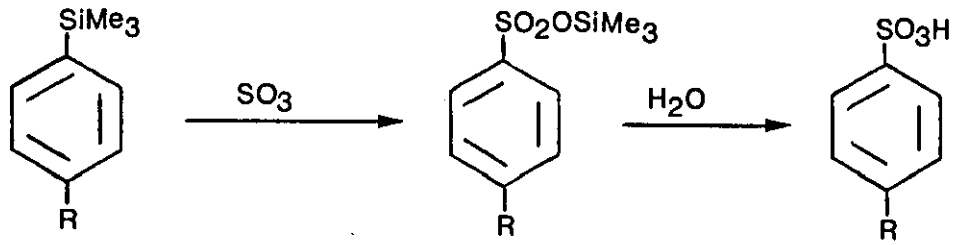
The high reactivity of alkali-metal compounds with electrophiles is well recognised but in many cases their use is not compatable with the reaction conditions and other functionalities present. This has led to the development of electrophilic substitution reactions using less reactive aryl-metal compounds such as silicon, tin, mercury, and thallium derivatives. These are generally stable compounds which can be conveniently handled, do not normally require anhydrous or inert conditions and are inert to the presence of most organic functional groups.

Examples of this type of reaction with an aryl-metal compound date back to the first preparation of nitrosobenzene by the action of nitrosyl bromide on diphenylmercury:[71]

$$Ph_2Hg \xrightarrow{NOBr} PhNO + PhHgBr$$

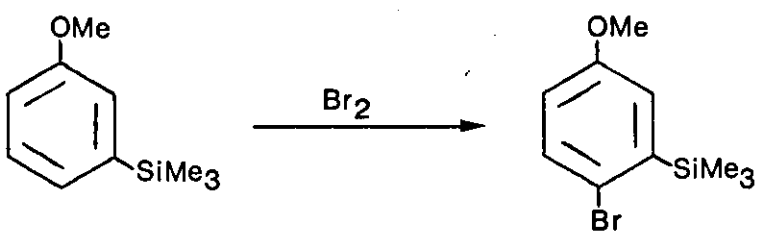
Eaborn has demonstrated regiospecific introduction of a variety of electrophiles by substitution at an aryl-silicon bond.[72,73] For example, sulphur trioxide reacts with aryl-

trimethylsilanes to obtain the sulphonic acid (Equation [36]).



[36]

The regiospecific nature of the reaction results from the polarity of the carbon-metal bond directing attack by the electrophilic species to this more nucleophilic carbon of the aromatic ring. However, in examples where the silyl group is positioned meta- to an ortho-/para- directing group, reaction at an unsubstituted carbon can compete. This is illustrated by the bromination of m-anisyltrimethylsilane[74] (Equation [37]).



[37]

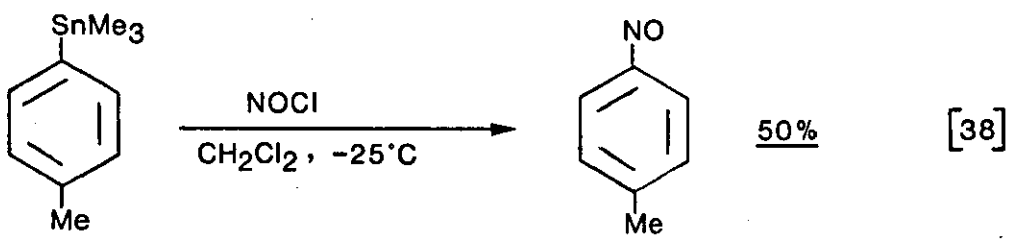
In this case the directing influence of the methoxy group takes precedence over the polarity of the carbon-silicon bond in determining the position at which the bromine attacks and no reaction occurs by displacement of the silyl group.

The use of a more electropositive metal enhances the reactivity of the aryl-metal compound and also can eliminate competing reaction at the unsubstituted positions on the

aromatic ring. The relative rates of protodemetallation of the Group IV $PhMEt_3$ compounds by aqueous methanolic perchloric acid illustrates this effect:[75]

M	Si	Ge	Sn	Pb
Relative rate	1	36	2.5×10^5	2×10^8

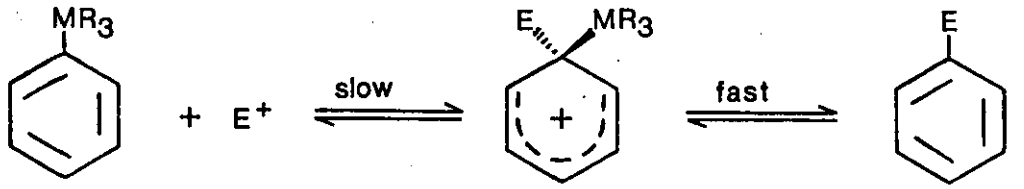
Aryl-tin compounds have found wide application in recent years, superseding the silanes in many situations, particularly in reactions with the less reactive electrophiles. Thus nitrosation of p-tolyltrimethylstannane can be achieved by use of nitrosyl chloride under mild conditions,[24] (Equation 38]),



50% [38]

whereas reaction of the trimethylsilane requires catalysis by aluminium chloride.

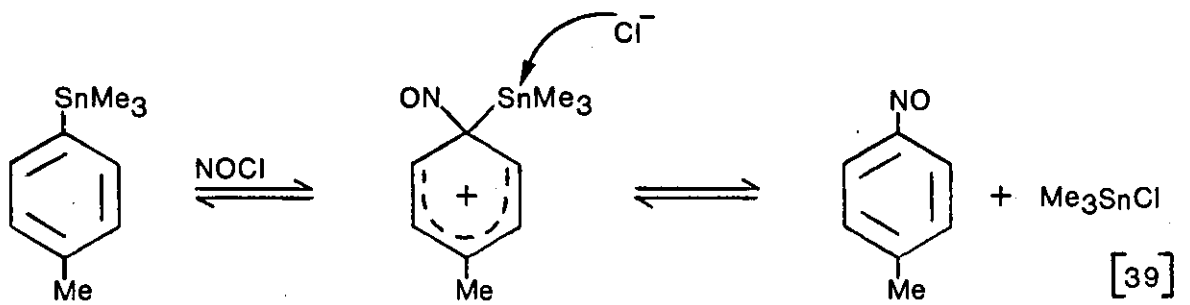
The reaction of aryl-metal compounds with electrophiles is believed to proceed by a general mechanism similar to that of normal aromatic substitution, involving an ipso-Wheland intermediate (61).



(61)

M = Sn or Si

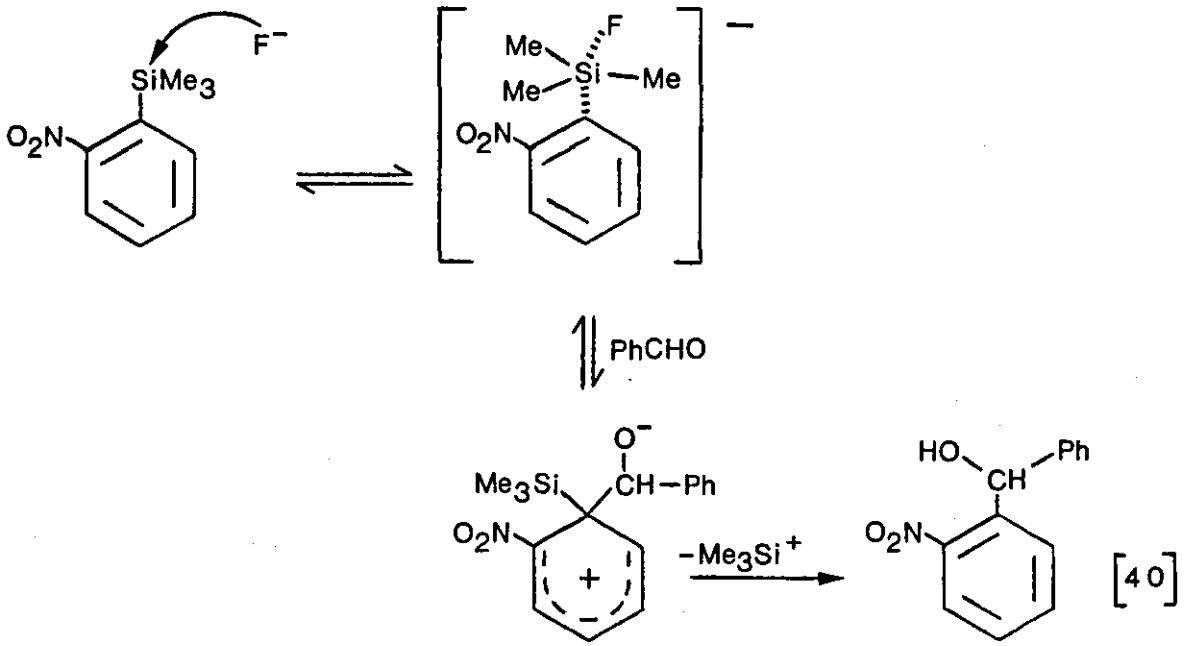
Kinetic studies have shown that it is the interaction of the electrophilic species with the aromatic ring to form the Wheland intermediate which is the rate-determining step. Thus in the reaction of p-tolyltrimethylstannane with nitrosyl chloride, attack of chloride ion probably assists C-Sn bond cleavage (Equation [39]),



[39]

but since this process is not rate-limiting, reactions of this type are generally not amenable to nucleophilic catalysis. Effenberger, however, has observed that aryl-silanes having electron-withdrawing groups on the aromatic ring undergo electrophilic substitution with aldehydes,[76] apparently by an alternative mechanism since the presence of a nucleophilic catalyst is essential. Thus o-nitrophenyltrimethylsilane reacts with benzaldehyde in the presence of a catalyst such as KF, Bu_4NF or $KOC(CH_3)_3$. It is considered that weakening of the aryl-silicon bond, induced by the fluoride ion, is involved with at least partial evolution of aryl anion, and that this is the rate-limiting pro-

cess of the reaction. Substituents which stabilise negative charge therefore enhance the reactivity. The proposed mechanism for this reaction is shown in Equation [40].



[40]

The necessity for a nucleophilic catalyst and the failure of any reaction to occur with o-methoxyphenyltrimethylsilane provide support for this mechanism.

The wide range of electrophilic substitutions that have been performed with aryl-tin compounds include bromination,[77] iodination,[78,79] fluorination,[80] nitration,[81] nitrosation,[24] alkylation,[82] sulphonylation,[83] and sulphenylation,[84] the reaction in all cases occurring regio-specifically. These studies have generally concentrated on use of the trimethyl-tin derivatives, despite the expense of trimethyltin chloride required for their preparation, apparently to ensure that steric hindrance is minimized. The use of the tributyltin derivatives is economically more

practical since tributyltin chloride is a much cheaper reagent, and has been demonstrated (the bromination, fluorination and sulphenylation examples), but reduced reactivity might be anticipated due to steric factors. Kinetic studies of the reaction of aryltrialkylstannanes with iodine[85] have confirmed the effect that the size of the stannyl group has on the reactivity:

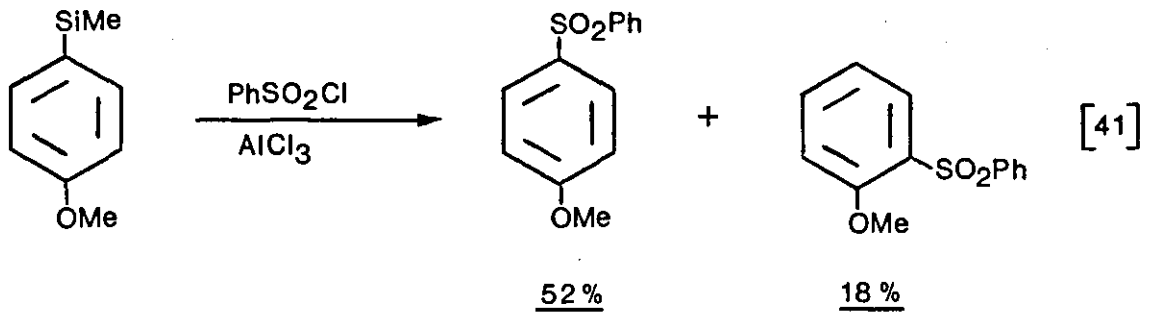
$$ArSnR_3 \xrightarrow{I_2} ArI + R_3SnI$$

Relative reactivities of aryltrialkylstannanes towards iodine

Ar	R = CH_3	$n\text{-}C_4H_9$	$i\text{-}C_3H_7$
Phenyl	1	0.25	0.037
1-Naphthyl	1	0.25	0.029
2-Naphthyl	1	0.36	0.059

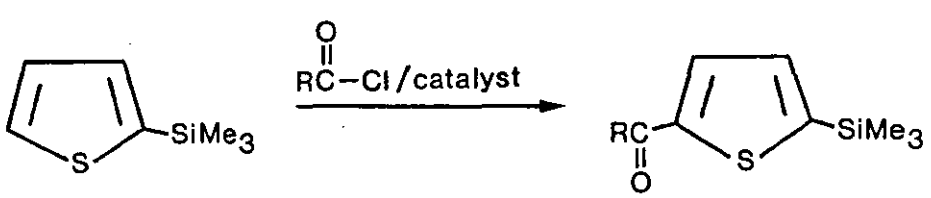
Increased bulk of the stannyl group results in lower reactivity towards iodine, indicating appreciable interactions between the incoming and leaving groups.

The greater reactivity of aryl-tin compounds relative to aryl-silanes has been illustrated by their sulphonylation using organosulphonyl chlorides in the presence of aluminium chloride.[83] Whereas aryltrimethylstannanes react regiospecifically by cleavage of the carbon-tin bond, the corresponding trimethylsilanes yielded a mixture of the isomeric sulphone products as exemplified in Equation [41].



It would appear then, that the sulphonylating reagent is not very selective and, despite the polarity of the carbon-silicon bond favouring attack at this position, some reaction does occur at the unsubstituted carbons. In the formation of the o-methoxyphenylsulphone the trimethylsilyl group had obviously been removed by protolytic cleavage, but the authors do not indicate whether this protolysis occurred during the sulphonylation reaction or during the work-up procedure.

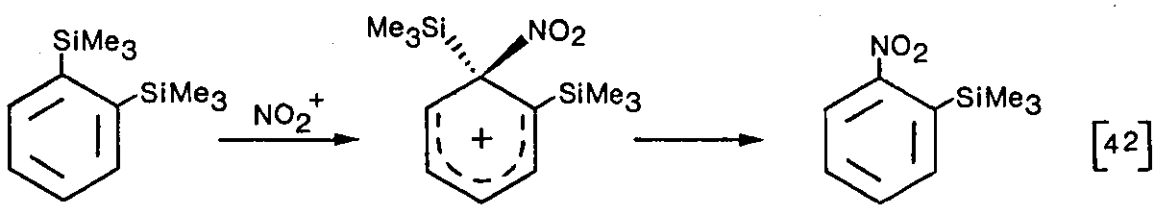
The effect of steric factors on these aromatic demetallation reactions, particularly with the less reactive silane derivatives, is illustrated by the acylation of 2-thienyltrimethylsilane with an acyl chloride in the presence of a Lewis acid:[86]



(62)

In this case reaction was found to occur only at the 5-position to obtain the 5-acyl-2-thienyltrimethylsilane (62), steric factors apparently inhibiting attack at the carbon-silicon bond.

Steric effects do not always hinder reaction but may in certain cases cause acceleration of the substitution. When a bulky substituent is being displaced, (e.g. R_3Sn- or R_3Si-), steric compression between it and an ortho- substituent is relieved as the transition state is reached, since the carbon atom undergoing substitution changes towards sp^3 hybridization. The nitration of o-bis(trimethylsilyl)benzene[87] provides an example (Equation [42]).

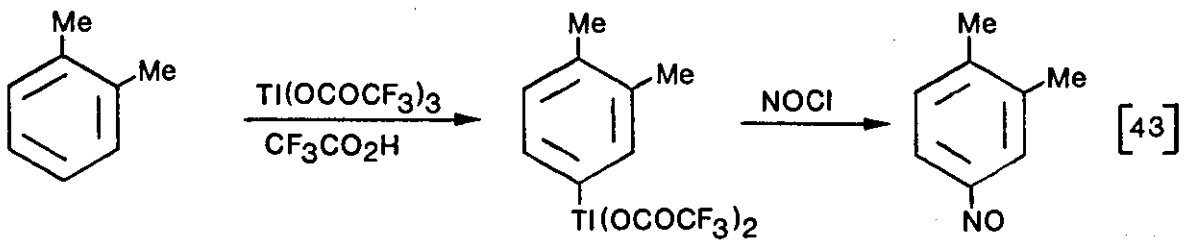


[42]

This reaction occurs at seven times the rate of nitration of the para-isomer. The transition state shows some character of the Wheland intermediate with partial deformation of the Me_3Si- group away from the plane of the ring and a consequent reduction of steric compression.

Aryl-thallium[23] and mercury compounds[22,88] have also been successfully employed for introduction of a substituent by an electrophilic displacement reaction. Since these compounds can often be prepared with high regioselectivity by direct metallation of the aromatic ring,[89] this method has

provided a useful route to regiospecific aromatic substitution. An example is the nitrosation of o-xylene via the thallium bis(trifluoroacetate) derivative (63),[90] reaction occurring exclusively at the 4-position, as illustrated in Equation [43].



[43]

(63)

3.1.2 Hydroxy-demetallation reactions

There is surprisingly no report of hydroxy-demetallation reactions having been attempted involving displacement of a trialkyl-silyl or stannyl group from an aromatic ring. Although regiospecific hydroxylation can be achieved by oxidation of aryl-Grignard or aryl-lithium reagents, the use of a silicon or tin derivative might prove more useful in many synthetic situations where the inertness of these metal groups towards other functionalities is of importance. Also the ability to isolate and handle the aryl-metal compounds without the need for anhydrous or inert conditions is an attractive feature.

(i) Oxidation of aryl-Grignard reagents

Aryl-Grignard reagents have long been known to react with hydrogen peroxide to yield phenols[91] and more recently the reaction has been studied with a variety of organic peroxides including t-butylhydroperoxide, t-butylperbenzoate benzoyl peroxide,[92] and dialkylperoxides.[93]

The use of t-butylhydroperoxide as the oxidant[92] involves initial reaction with the Grignard reagent to form a magnesium salt:

$$t\text{-BuOOH} + RMgX \longrightarrow t\text{-BuOOMgX} + RH$$

This magnesium salt of the hydroperoxide is then able to effect oxidation of the Grignard reagent to give the phenolic product. The active hydrogen of the hydroperoxide therefore effectively decomposes one equivalent of the Grignard reagent and the overall stoichiometry of the reaction is:

$$t\text{-BuOOH} + 2RMgX \longrightarrow t\text{-BuOMgX} + ROMgX + RH$$

An example of this reaction is the oxidation of p-tolylmagnesium bromide to give p-cresol in 90% yield (based on the amount of hydroperoxide consumed).

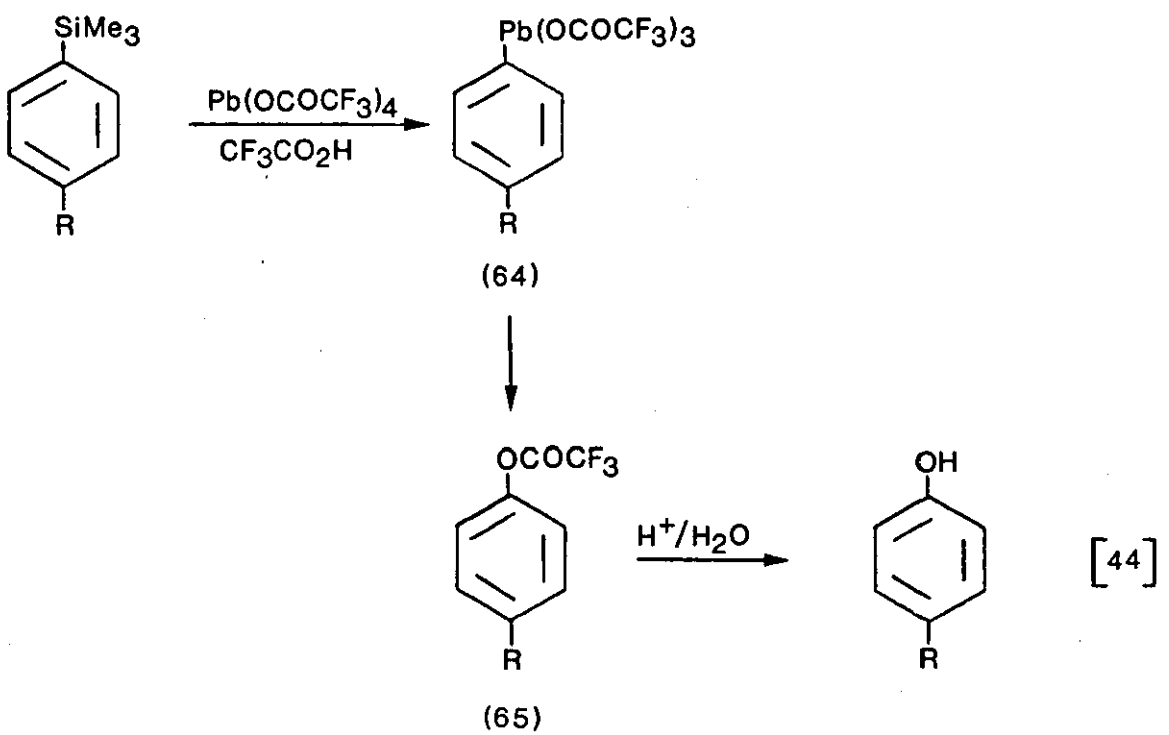
Aryl-lithium compounds are similarly oxidised by various peroxides[93,94] and generally show greater reactivity than the Grignard reagents.

(ii) Oxidation of aryl-thallium compounds

Oxidation of aryl-thallium compounds has been reported using trifluoroperoxyacetic acid,[95] but the initially formed phenolic product was susceptible to further oxidation by the per-acid producing good yields of the 1,4-quinone.

(iii) Aryl-lead derivatives as a route to phenols

Pinhey and co-workers have developed a novel method for preparation of phenols[96] involving reaction of aryltrimethylsilanes with lead tetrakistrifluoroacetate. The reaction proceeds via the aryl-lead derivative (64) which rapidly decomposes to give the aryltrifluoroacetate (65), as shown in Equation [44].



(iv) Oxidation of aryl pentafluorosilicates

Organopentafluorosilicates have been found to show remarkable reactivity towards some electrophilic reagents, including oxidation by mCPBA.[97] Thus a variety of alkylpentafluorosilicates have been oxidised to the corresponding alcohol.

$$K_2[RSiF_5] \xrightarrow[DMF]{mCPBA} ROH$$

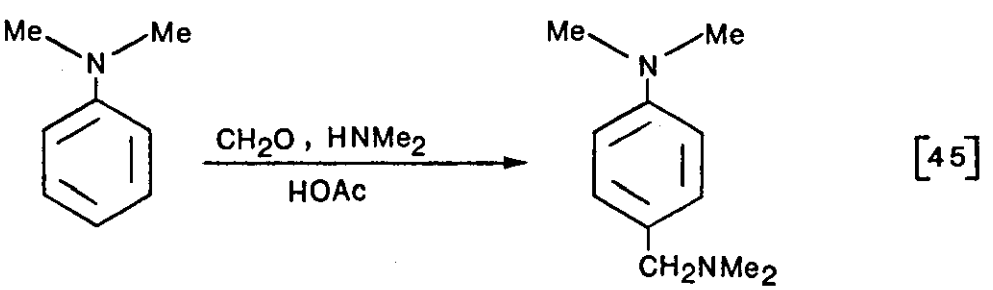
R = n-C_8H_{17}- , n-$C_{12}H_{25}$- , $MeO_2C(CH_2)_{10}$- or Ph-

The pentafluorosilicates may be readily prepared by treatment of the trichlorosilyl derivative with potassium fluoride; the dipotassium salt being obtained as a stable crystalline solid. This was considered by these authors to provide the first method for direct introduction of an oxygen functionality into an organic group by cleavage of a silicon-carbon bond. These studies were mainly concerned with oxidation of alkylsilicates although it was reported that phenylpentafluorosilicate was oxidised to give a 64% yield of phenol. The oxidation was not carried out using any other aryl silicates but is likely to be generally applicable, the oxidation presumably occurring regiospecifically, although this has not been confirmed.

3.1.3 Aromatic Aminomethylation (Mannich reaction)

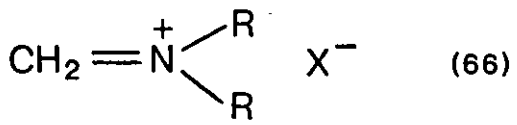
The introduction of an aminomethyl group into an aromatic nucleus by reaction with methyleneiminium salts is an example of the Mannich reaction.[98] The electrophilic species involved is not very reactive and reaction only occurs with particularly nucleophilic arenes. Thus heterocyclic compounds such as indoles[99] and pyrroles[100] have been widely studied as also have benzenoid compounds whose nucleophilicity is enhanced by hydroxy,[101] alkoxy[102] or amino[103] groups. Benzenoid compounds less nucleophilic than m-dimethoxybenzene[102] have not been reported to undergo Mannich reactions.

The classical method for performing the Mannich reaction involves the in situ generation of the electrophilic species by use of aqueous solutions of the aldehyde and amine in a protic solvent. N,N-dimethylaniline, for example, reacts at the para- position[103] as shown in Equation [45].



[45]

Recently, preformed Mannich salts of the type (66)[104] have found increased use, generally showing increased reactivity [105] and allowing the reactions to be performed under aprotic conditions.



(66)

$X^- = I^-, Cl^-$ or CF_3COO^-

The methyleneiminium salts (known as Eschenmoser salts) can be prepared by various methods[106-110] and may be isolated as crystalline, hygroscopic solids.

The reaction of N,N-dialkyliminium salts with aryl-lithium [111] and aryl-Grignard[109,112,113] reagents has been widely exploited to allow regiospecific introduction of an -amino-alkyl residue into an aromatic nucleus with which reaction would not normally occur. The reaction of aryl-stannanes or silanes with Mannich reagents has not previously been studied but would be of value in situations where the use of the more reactive lithium or magnesium derivatives is not appropriate. In addition, the tin and silicon derivatives would allow mechanistic features of the reaction, including steric effects, to be studied.

3.2 RESULTS AND DISCUSSION

3.2.1 Hydroxy-demetallation reactions using peroxide/Lewis acid reagents

Hydroxy-demetallation reactions were attempted using various Lewis acid catalysed peroxide reagents and gave the results shown in Table 14.

Hydroxylation using t-butylhydroperoxide or the hydrogen peroxide adducts catalysed by $AlCl_3$ was not very successful. The yields of phenolic products were low and in most cases there was some contamination from the undesired isomers.

Two possible reasons for the failed regioselectivity of the reaction may be proposed:

1. The reaction conditions are causing removal of the metal residue by protolytic cleavage, and hydroxylation of the aromatic hydrocarbon (i.e. toluene) is occurring.

2. Steric factors inhibit attack of the hydroxylating reagent at the carbon-metal bond; attack at the less hindered unsubstituted carbon thus occurs in competition with the hydroxy-demetallation process.

(i) t-Butylhydroperoxide/$AlCl_3$

Hydroxylation of the tolyltributylstannanes using this reagent gave largely the expected isomer from hydroxy-demet-

Table 14 $RC_6H_4M \xrightarrow{'HO^+'} RC_6H_4OH + M^+$

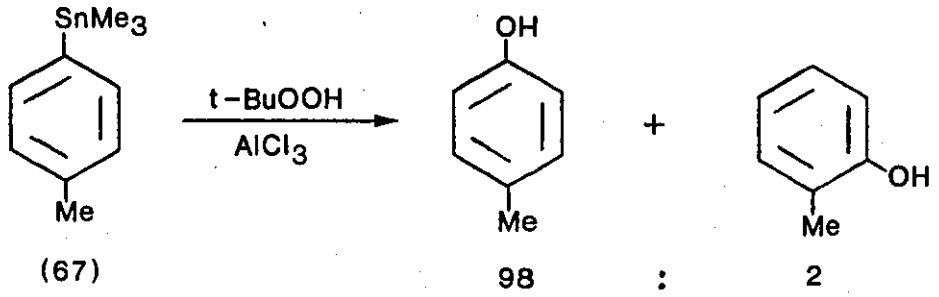
Substituent, R	Metal group, M	Reagent	Mole ratio[a]	Yield[b] (%)	Isomer distribution of phenols (%)			Chlorinated[c] phenols (%)
					o-	m-	p-	
4-methyl	$SnBu_3$	Urea-H_2O_2/$AlCl_3$	1:1:2	15	29	3	68	20
4-methyl	$SnBu_3$	t-BuOOH/$AlCl_3$	2:1:2	5	4	0	96	12
4-methyl	$SnBu_3$	t-BuOOH/BF_3	2:1:2	16	2	0	98	0
4-methyl	$SnMe_3$	t-BuOOH/$AlCl_3$	2:1:2	11	2	0	98	9
2-methyl	$SnBu_3$	Urea-H_2O_2/$AlCl_3$	1:1:2	14	40	4	56	13
2-methyl	$SnBu_3$	t-BuOOH/$AlCl_3$	2:1:2	4	95	0	5	10
2-methyl	$SnBu_3$	90%H_2O_2/$AlCl_3$	1:1:2	11	53	4	43	16
2-methyl	$SnBu_3$	90%H_2O_2/$(CF_3CO)_2O$/BF_3	1:1:5	2	100	0	0	0
4-methyl	$SiMe_3$	t-BuOOH/$AlCl_3$	2:1:2	5	35	3	62	15
4-methoxy	$SnMe_3$	Urea-H_2O_2/$AlCl_3$	1:1:2	15	52	2	46	23
4-methoxy	$SiMe_3$	Urea-H_2O_2/$AlCl_3$	1:1:2	24	61	3	36	9
4-methoxy	$SiMe_3$	Na_2CO_3.1½H_2O_2/$AlCl_3$	1:1:3	23	59	2	39	15

[a] Mole ratio of aromatic substrate/ peroxide/$AlCl_3$.

[b] Yield of phenolic products based on peroxide reagent.

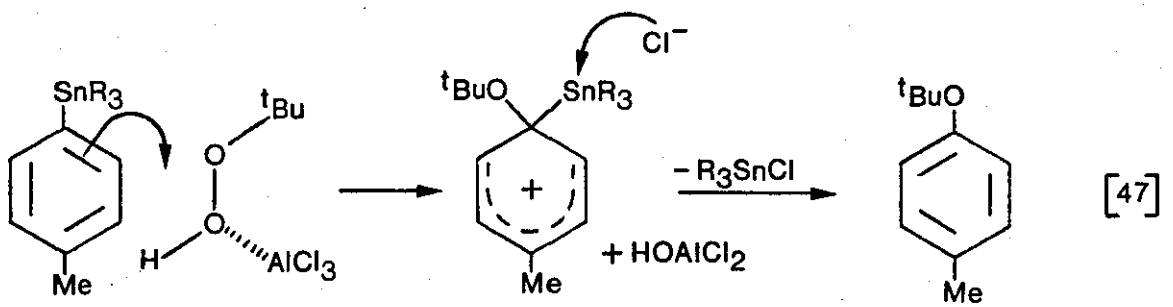
[c] Chlorinated products expressed as a percentage of the total phenolic material.

allation. For example p-tolyltrimethylstannane (67) gave an 11% yield of phenolic products (Equation [46]).



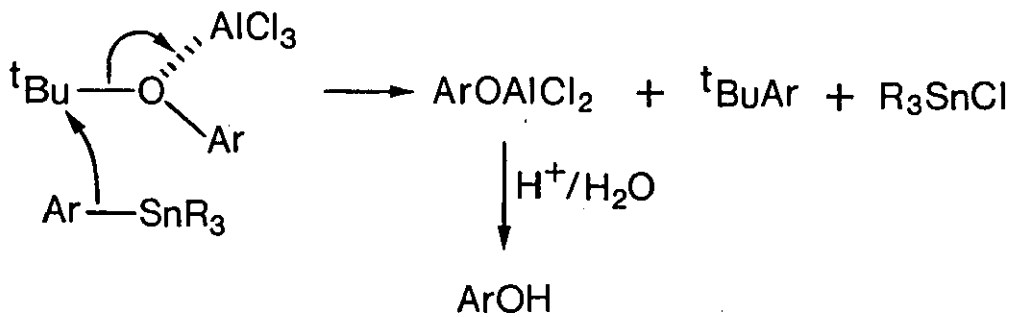
(67) 98 : 2 [46]

Attack of the reagent is evidently occurring predominantly at the carbon-tin bond although a small amount of the alternative cresol was also detected. The reactions were performed using a 1:1 aryl-stannane/peroxide ratio and the isolated phenolic products were composed mainly of the monohydroxylated derivatives (generally >95%), so there did not appear to be any significant amount of over-oxidation. The reaction is considered to involve attack by the t-BuOOH $-AlCl_3$ complex as shown (Equation [47]) to produce the ipso-Wheland intermediate (68) which then rearomatises by loss of the trialkylstannyl cation to afford the aryl t-butyl ether (69).



(68) (69) [47]

Hashimoto and Koike, in their studies[34] of the reaction of toluene with t-BuOOH/$AlCl_3$, have suggested that the initially formed t-butyl ether provides a source of t-butyl cation in the presence of $AlCl_3$, which can alkylate a second molecule of toluene. A similar process might be anticipated in the aryl-stannane reaction (Equation [48]).

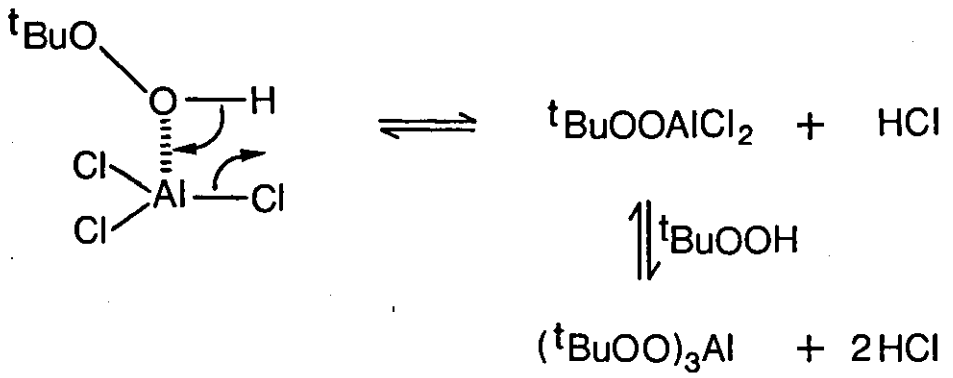


[48]

This competing alkylation process would consume some of the aryl-stannane and may be partly responsible for the low yields obtained. The yields of phenolic products from the aryl-stannane reactions are in fact comparable to the yield of cresol (12%) obtained when toluene was subjected to the same hydroxylating conditions using a 1:1 toluene/peroxide ratio (cresol ratio = 63% ortho-, 7% meta-, 30% para-).

The hydroxylation of a silicon derivative (p-tolyltrimethylsilane) not only produced a low yield of phenolic products but also showed poor selectivity, giving a large proportion (38%) of the undesired cresol isomers. We initially suspected that the failed regioselectivity was due to protolytic cleavage of the aryl-silicon bond by hydrogen chloride produced from the hydroperoxide/$AlCl_3$ reagent.

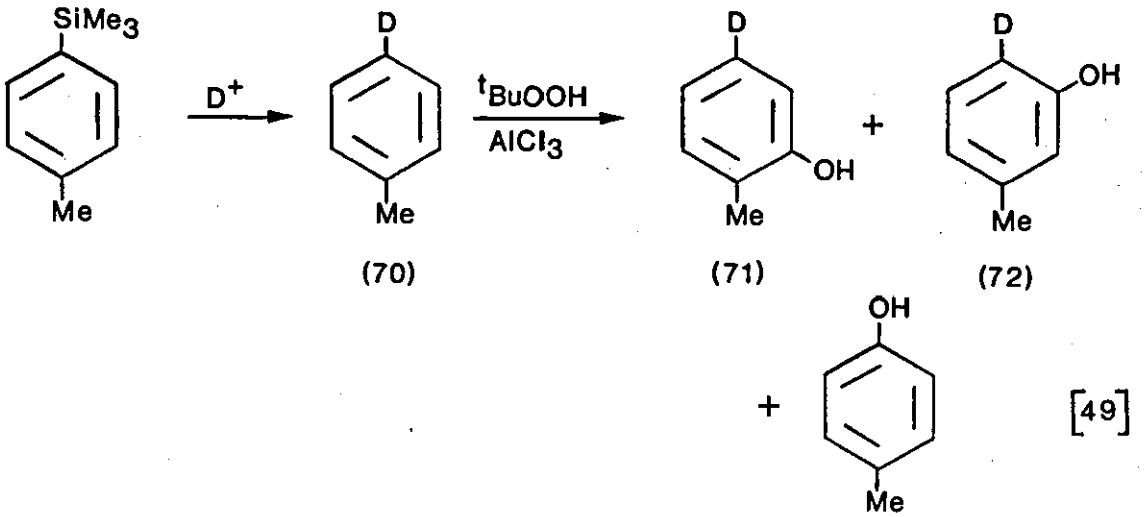
Decomposition of the t-BuOOH-$AlCl_3$ complex might occur to a small extent by the following mechanism:



Such a process is known to occur in the presence of aluminium trialkoxides.[114]

i.e. 3 t-BuOOH + $Al(OR)_3$ ⟶ $(t\text{-BuOO})_3Al$ + 3ROH

In order to ascertain whether any hydrogen chloride so produced was causing cleavage of the aryl-metal bond, we performed the aryl-silane hydroxylation using deuterated t-butylhydroperoxide (t-BuOOD), under stringently anhydrous conditions. Protolytic cleavage of the aryl-silane would produce p-deuterio-toluene (70), which upon hydroxylation would give the cresols (71) and (72) containing deuterium incorporated in the aromatic ring as illustrated in Equation [49].

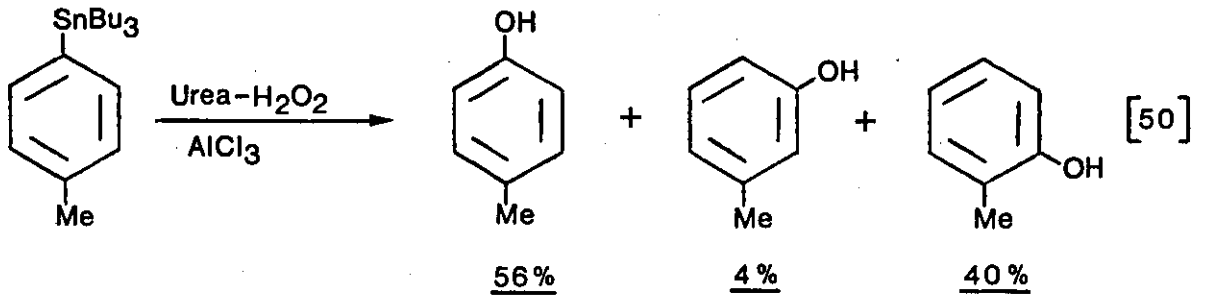


[49]

GLC/Mass spectral analysis of the phenolic products however indicated that no deuterated cresol was produced. We therefore conclude that the aryl-silicon bond is insufficiently polar to control the selectivity of attack by the highly reactive hydroxylating species. Although some reaction occurs by ipso- attack at the aryl-silicon bond, reaction also occurs at the other positions involving displacement of a proton.

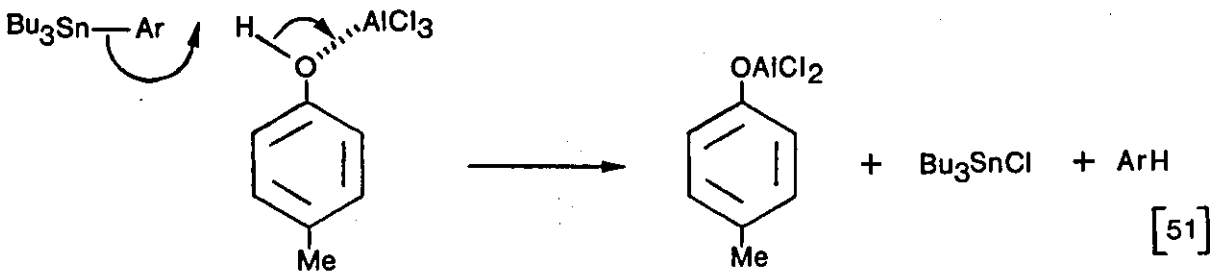
(ii) Urea-H_2O_2/$AlCl_3$

Hydroxylation of the aryl-stannanes did not show the desired regio-selectivity and the yields of phenolic products were again low. p-Tolyltributylstannane, for example, gave a 14% yield of phenolic products (Equation [50]).



[50]

The phenolic products, under the reaction conditions, may act as a proton source causing protolytic cleavage of the aryl-stannane in a competing reaction (Equation [51]).



[51]

Toluene produced in this way may then be hydroxylated, although preferential reaction of the hydroxylating reagent with the aryl-stannane would be expected.

Performing the hydroxylation using 90% hydrogen peroxide in the presence of $AlCl_3$ gave similar results in terms of the yield and isomer distribution.

(iii) t-Butylhydroperoxide/$^{BF}3$ etherate

Reaction with p-tolyltributylstannane occurred regioselectively, giving a 16% yield of p-cresol. A considerable amount of polyhydroxylated material was, however, also obtained.

Trifluoroperoxyacetic acid (prepared from 90% H_2O_2 and trifluoroacetic anhydride) in the presence of boron trifluoride, was also found to produce mainly polyhydroxylated products - only a 2% yield of cresol was obtained from o-tolyltributylstannane.

3.2.2 Hydroxydemetallation using t-Butylperbenzoate/$AlCl_3$

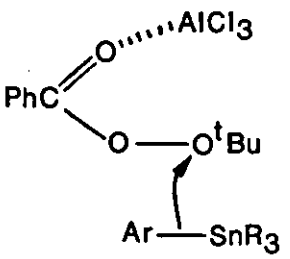
Hydroxylation of aryl-tin and silicon derivatives using t-butylperbenzoate catalysed by $AlCl_3$ was found to achieve the desired regiospecific reaction as illustrated in Table 15.

Table 15 $RC_6H_4M \xrightarrow{HO^+} RC_6H_4OH$

Substituent, R	Metal residue M	Yield of cresol,(%)	Isomer distribution of cresols, (%)		
			o-	m-	p-
4-methyl	$SnBu_3$	40	0	0	100
3-methyl	$SnBu_3$	27	0	100	0
2-methyl	$SnMe_3$	35	100	0	0
4-methyl	$SiMe_3$	2	0	0	100

Although the aryl-stannanes gave moderate yields of cresol (27 - 40%), the less reactive silicon derivative yielded only a trace of cresol.

The success of this reagent could be attributed to its relatively low reactivity - no reaction was observed with toluene. The reactive species, as a result, is highly selective and reacts only at the most nucleophilic position on the aromatic ring, i.e. at the carbon-tin bond. The electrophilic species is likely to be a complex of $AlCl_3$ with the carbonyl oxygen of the t-butylperbenzoate and reaction is considered to proceed as illustrated in Equation [52] to initially yield the aryl t-butyl ether.



$$\longrightarrow \quad ArO^tBu + PhCO_2AlCl_2 + R_3SnCl \qquad [52]$$

This complex is similar to the reactive species believed to be involved in hydroxylations using t-butylperoxy isopropyl-carbonate[33] but is of markedly lower reactivity due to the effect of the phenyl group counteracting the electron-withdrawing effect of the co-ordinated $AlCl_3$. The initially formed aryl t-butyl ether is likely to decompose under the reaction conditions with the released t-butyl cation causing cleavage of the aryl-stannane:

$$t\text{-}BuOAr + ArSnR_3 \xrightarrow{AlCl_3} ArOAlCl_2 + t\text{-}BuAr + Bu_3SnCl$$

GLC analysis of the neutral organic material recovered from the reactions confirmed that t-butyltoluene was formed in amounts comparable with the yield of cresol.

3.2.3 Hydroxydemetallation using m-chloroperbenzoic acid

m-Chloroperbenzoic acid, which is unreactive towards unactivated aromatic compounds,[115] was found to effect hydroxydestannylation of aryl-stannanes to give a clean yield of the expected cresol isomer. The yields however were not particularly good even after prolonged reaction times. The results are shown in Table 16.

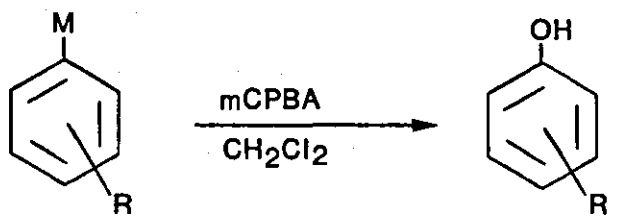


Table 16

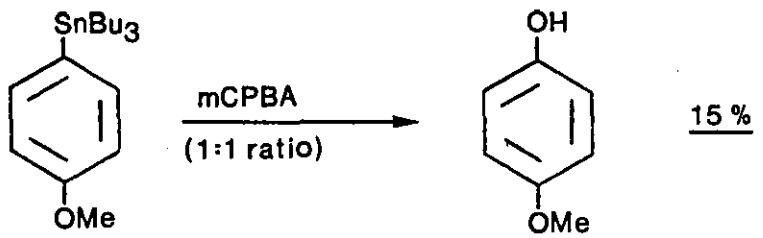
Substituent R	Metal group, M	Aromatic/ mCPBA ratio	Yield of cresol (%)	Cresol distribution (%)		
				o-	m-	p-
4-methyl	$SnBu_3$	2:1	38	0	0	100
4-methyl	$SnBu_3$	1:1	22	0	0	100
4-methyl	$SnBu_3$	1:2	28	0	0	100
4-methyl	$SnMe_3$	1:1	26	0	0	100
2-methyl	$SnBu_3$	1:2	34	100	0	0
2-methyl	$SnMe_3$	1:2	30	100	0	0
4-methyl	$SiMe_3$	2:1	0			

All reactions were performed in dichloromethane at room temperature. Reaction time was 24 hours.

Yields are based on the limiting reagent.

Phenolic products were analysed using the BP1 capillary column.

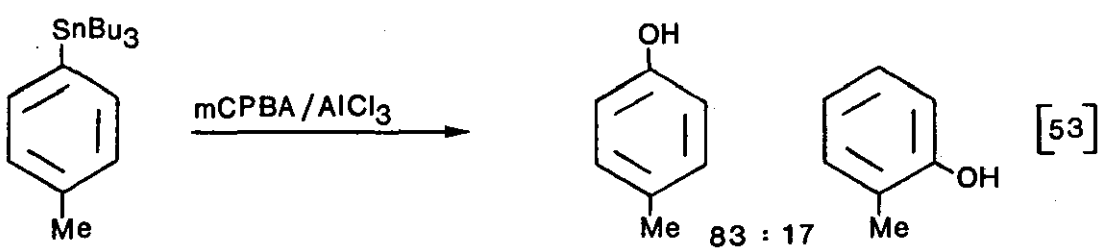
p-Methoxyphenyltributylstannane (73) gave only a low yield of p-methoxyphenol:



(73)

The use of two equivalents of mCPBA did not improve the yield (13%) and there was evidence of products from further hydroxylation of the p-methoxyphenol. Anisole under similar conditions (1:1 anisole/mCPBA ratio) gave only a trace (3%) of p-methoxyphenol, most of the anisole being recovered. It would appear that steric factors hindering attack by the per-acid are responsible for the low yields.

Attempted catalysis of the reaction with $AlCl_3$ did not improve the yield and gave a mixture of the cresol isomers (Equation [53]).



1:1:2 ratio of $ArSnBu_3/mCPBA/AlCl_3$. 18% yield

The addition of tetrabutylammonium fluoride did not have any catalytic effect. This indicates that loss of the tributylstannyl cation from the Wheland intermediate is not the rate-limiting process; a feature which appears to be general for all the hydroxy-demetallation reactions studied.

3.2.4 Hydroxydemetallation using triphenylsilylhydroperoxide

Hydroxylation of aryl-tin and silicon derivatives was attempted using triphenylsilylhydroperoxide, either alone or in the presence of a Lewis acid. The results are shown in Table 17.

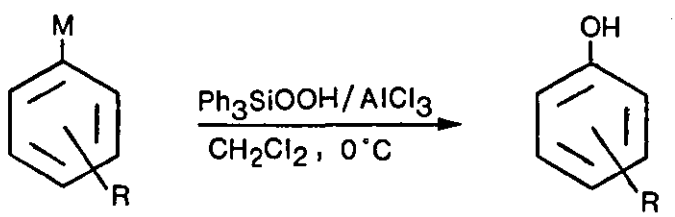


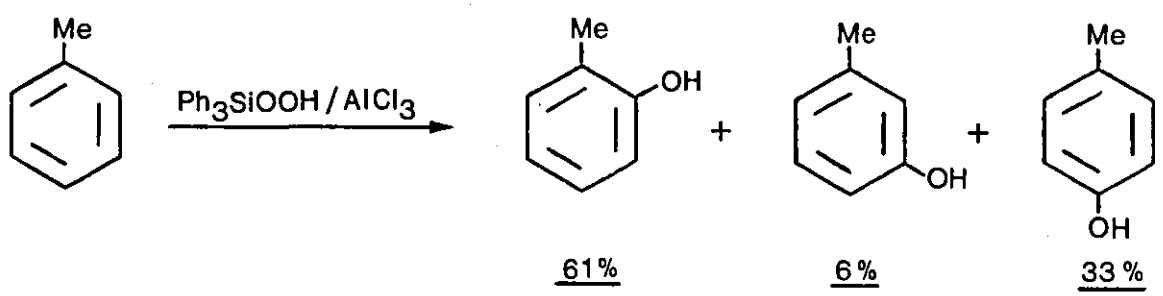
Table 17

Substituent, R	Metal residue M	Lewis acid	Reagent ratio	Yield[a] of cresol (%)	Cresol distribution, (%)		
					o-	m-	p-
4-methyl	$SnMe_3$	$AlCl_3$	2:1:2	27	39	4	57
2-methyl	$SnBu_3$	$AlCl_3$	2:1:2	23	65	3	32
4-methyl	$SiMe_3$	$AlCl_3$	2:1:2	6	38	3	59
2-methyl	$SnBu_3$	BF_3	2:1:2	6	82	1	17
2-methyl	$SnBu_3$	-	2:1:0	1	100	0	0
2-methyl	$SnMe_3$	-	2:1:0	4	100	0	0
4-methyl	$SnMe_3$	-	2:1:0	9	0	0	100

[a] Yields are based on the Ph_3SiOOH

The Lewis acid catalysed hydroxylations gave results consistent with previous reactions using the hydrogen peroxide $-AlCl_3$ reagents. Mixtures of the isomeric cresols were obtained. The high reactivity, and hence low selectivity, of the $Ph_3SiOOH/AlCl_3$ reagent again appears to be the problem, reaction occurring at the unsubstituted aromatic positions as well as by displacement of the metal residue.

These results compare with a 16% yield of cresol obtained from toluene under similar conditions. (2:1 toluene/Ph_3SiOOH ratio):



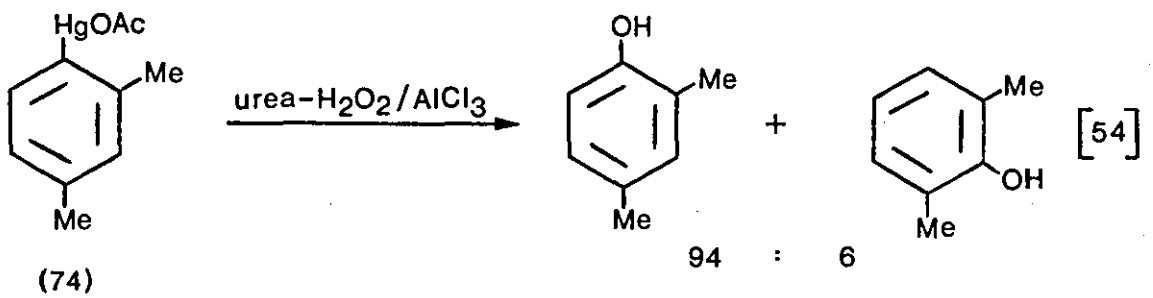
In the absence of a Lewis acid the triphenylsilylhydroperoxide was found to hydroxylate the aryl-stannanes regiospecifically, but the yield of cresol was low, even after prolonged reaction times.

Chlorinated phenolic products were not obtained from any of the reactions, but phenol from decomposition of the Ph_3SiOOH was produced in all the reactions in varying amounts.

3.2.5 Hydroxy-demercuration

Hydroxylation of several aryl-mercury compounds was attempted.

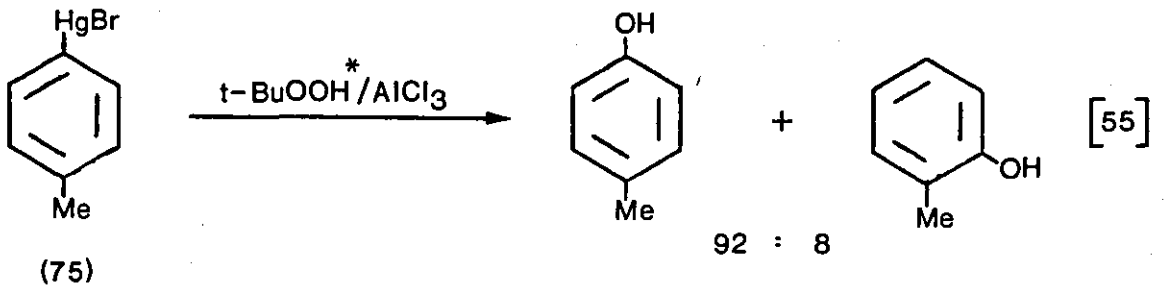
(i) 2,4-Dimethylphenylmercuric acetate (74), prepared from direct mercuration of m-xylene[116] was hydroxylated using the urea-$H_2O_2/AlCl_3$ reagent to give a 10% yield of xylenols as shown in Equation [54].



(74)

2,6-Xylenol is apparently formed from attack of the reagent at the 3-position of the aryl-mercury compound, with subsequent loss of the mercury residue during acid work-up. Some of the 2,4-xylenol probably also results from attack at an unsubstituted position (5-position) rather than by displacement of the mercury group.

(ii) Hydroxylation of p-tolylmercuric bromide (75) using t-BuOOH/$AlCl_3$ gave a 23% yield of phenolic products as shown in Equation [55].



(75)

* anhydrous solution in CH_2Cl_2.

3.2.6 Oxidation of aryl-Grignard reagents

Aryl-Grignard reagents were oxidised to the corresponding phenolic products using the hydrogen peroxide adducts of urea and DABCO dioxide. These results are illustrated in Table 18.

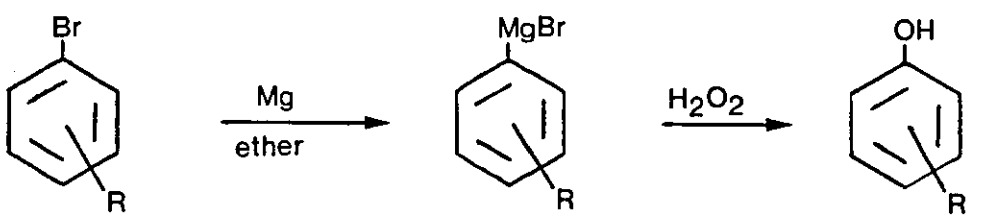


Table 18

Substituent, R	Peroxide	Aryl bromide /peroxide ratio	Yield[a] of phenolic products (%)
4-methyl	urea-H_2O_2	2.2:1	49
3-methyl	urea-H_2O_2	2.2:1	28
3-methyl	urea-H_2O_2	1.1:1	0
4-methoxy	urea-H_2O_2	2.2:1	32
4-methyl	DABCO$(O.H_2O_2)_2$	2.2:1	31
3-methyl	DABCO$(O.H_2O_2)_2$	2.2:1	43
3-methyl	$(Ph_3PO)_2.H_2O_2$[b]	2.2:1	0
3-methyl	DABCO(t-BuOOH)$_2$[b]	2.2:1	31
3-methyl	t-BuOOH[c]	2.2:1	77
4-methyl	t-BuOOH[c]	2.2:1	80

[a] Yield is based on peroxide. (The DABCO adduct is considered to provide 2 mole equivalents of peroxide)

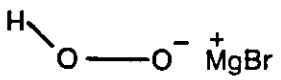
[b] Added as a solution in dichloromethane

[c] Anhydrous solution in dichloromethane

The peroxide adducts potentially provide a stable, anhydrous reagent for oxidation of aryl-Grignard reagents but the yields showed no improvement when compared with the use of anhydrous t-butylhydroperoxide.

The oxidations were performed by addition of the peroxide adducts to the Grignard reagent in ether and the relatively poor yields are possibly a reflection of the insolubility

of the adducts. A 2:1 Grignard/peroxide ratio was found to be necessary for efficient reaction. By analogy with the proposed mechanism for oxidation using t-butylhydroperoxide, oxidation using the hydrogen peroxide adducts is thought to proceed by initial reaction with the Grignard reagent to form a magnesium hydroperoxide salt:



This magnesium salt is apparently then able to effect oxidation of the Grignard reagent although the mechanism for this process is not clear.

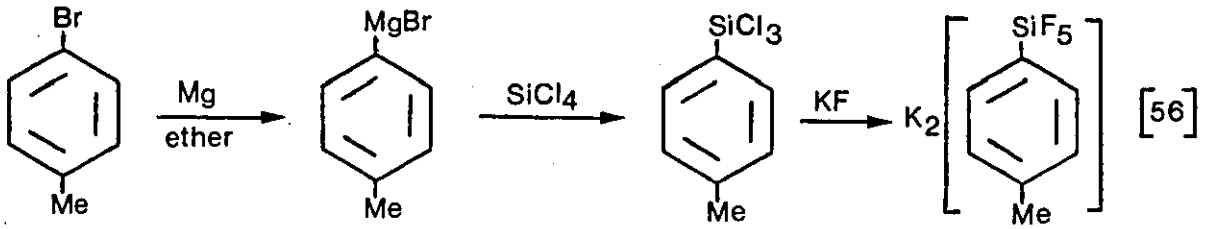
The t-butylhydroperoxide adduct of DABCO (added as a solution in dichloromethane) gave a greatly reduced yield of cresol compared with the use of an anhydrous solution of t-butylhydroperoxide in dichloromethane.

The hydrogen peroxide adduct of triphenylphosphine oxide, for some reason failed to produce any phenolic material - no reaction of the Grignard reagent occurred. The hydrogen bonding perhaps prevents reaction of the hydrogen peroxide with the Grignard reagent in this case.

3.2.7 Oxidation of p-Tolylpentafluorosilicate

p-Tolylpentafluorosilicate was prepared by the method of Tamao[117] by treatment of the trichlorosilyl derivative with

potassium fluoride; the dipotassium salt being obtained as a stable crystalline solid. The overall procedure is shown in Equation [56].



Oxidation was attempted using various reagents and in all cases gave p-cresol as the only phenolic product. The yields obtained are shown in Table 19.

$$K_2[p\text{-}CH_3C_6H_4SiF_5] \xrightarrow{\text{'}\overset{+}{O}H\text{'}} p\text{-}CH_3C_6H_4OH$$

Table 19

Reagent[a]	Solvent	Yield of p-cresol[b] (%)
mCPBA	DMF	70
MMPP[c]	DMF	65
$(Ph_3PO)_2.H_2O_2/(CF_3CO)_2O$	CH_2Cl_2/DMF	22
$(Ph_3PO)_2.H_2O_2/(CF_3CO)_2O/BF_3$	CH_2Cl_2	38
87% $H_2O_2/(CF_3CO)_2O$	CH_2Cl_2/DMF	58
Urea-$H_2O_2/AlCl_3$	CH_2Cl_2	4
t-BuOOH[d]/$AlCl_3$	Ch_2Cl_2	2
Ph_3SiOOH	DMF	0

[a] A 1.2:1 peroxide/p-tolylpentafluorosilicate ratio was used in all reactions. All reactions were performed at room temperature.

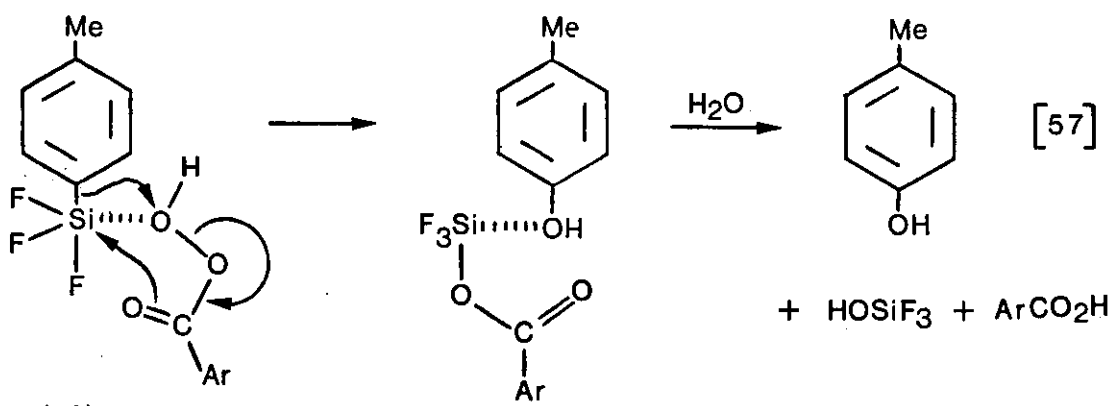
[b] Yields are based on the pentafluorosilicate.

[c] MMPP = magnesium monoperphthalate

[d] Anhydrous solution of t-BuOOH in dichloromethane.

Tamao and co-workers,[97] in their studies, showed that phenylpentafluorosilicate was oxidised to phenol (64% yield) using mCPBA and our results confirm that the reaction occurs regiospecifically and in good yield. Magnesium monoperphthalate, a stable, commercially available reagent, was also found to effect oxidation giving a similar yield of p-cresol.

The mechanism of the oxidative cleavage is not clear but it has been suggested that co-ordination of mCPBA to the silicon to form species (76) may be involved with the reaction proceeding as shown in Equation [57].



[57]

(76)

(Ar = m-ClC_6H_4-)

The carbon-silicon bond in species (76) would be highly polarized and susceptible to rearrangement as shown, involving intramolecular migration of the aryl group to the oxygen of the mCPBA. The reactions were carried out by addition of the per-acid to a solution of the pentafluorosilicate in dimethylformamide (DMF) and the donor properties of the solvent appear to be important suggesting that co-ordination of the solvent with the silicon also plays a part in the mechanism.

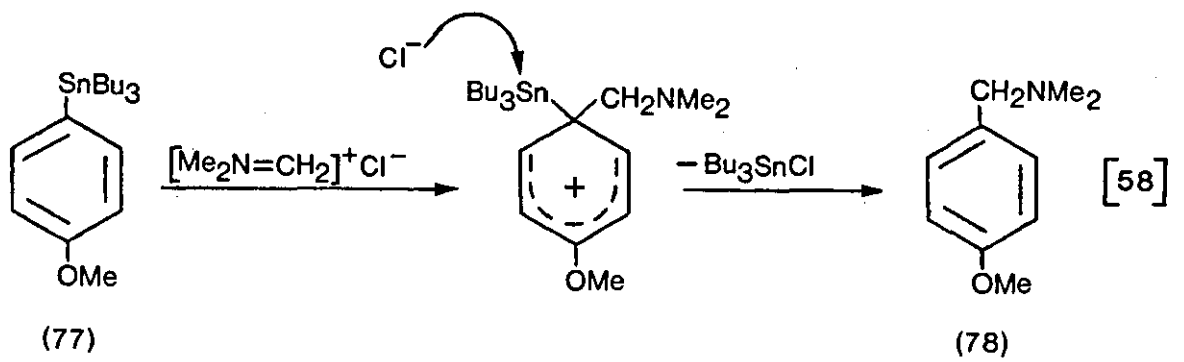
Triphenylsilylhydroperoxide, which has been shown to be similar in many respects to mCPBA in its reactivity as an electrophilic oxidising agent, failed to oxidise p-tolylpentafluorosilicate. This observation provides evidence in favour of the proposed mechanism for oxidation using mCPBA; the carbonyl group of the per-acid apparently being necessary for oxidation to occur.

Trifluoroperoxyacetic acid, prepared from 87% hydrogen peroxide and trifluoroacetic anhydride also effected oxidation (58% yield of p-cresol) but the reagent prepared from the $(Ph_3PO)_2.H_2O_2$ adduct was less effective.

The peroxide - $AlCl_3$ reagents produced mainly polyhydroxylated products, and only low yields of cresol (mainly p-cresol) were obtained.

3.2.8 Mannich Reaction of Aryl-stannanes

Reaction of the Eschenmoser salt, N,N-dimethyl(methylene)-iminium chloride with a variety of aryl-stannanes yielded the expected aminomethyl derivative by displacement of the stannyl group. Thus 4-methoxyphenyltributylstannane (77) gave a 75% yield of N,N-dimethyl-4-methoxybenzylamine (78). Reaction is considered to proceed as shown in Equation [58].



(77) (78) [58]

The reactions were normally performed by addition of the aryl-stannane to a stirred suspension of the preformed methyleneiminium salt in dichloromethane. Heating the reaction mixture under reflux helped reduce the reaction times, but the reactions tended to be cleaner and gave better yields when performed at room temperature.

No reaction was observed when 4-methoxyphenyltrimethylsilane was stirred with an excess of N,N-dimethyl(methylene)-iminium chloride over a prolonged period of time, while 2-methoxyphenyltrimethylsilane gave only a trace of the aminomethylated derivative.

The results obtained using various aryl-stannanes are reported in Table 20.

$$ArSnR_3 + [Me_2N{=}CH_2]^+ Cl^- \longrightarrow ArCH_2NMe_2 + R_3SnCl^a$$

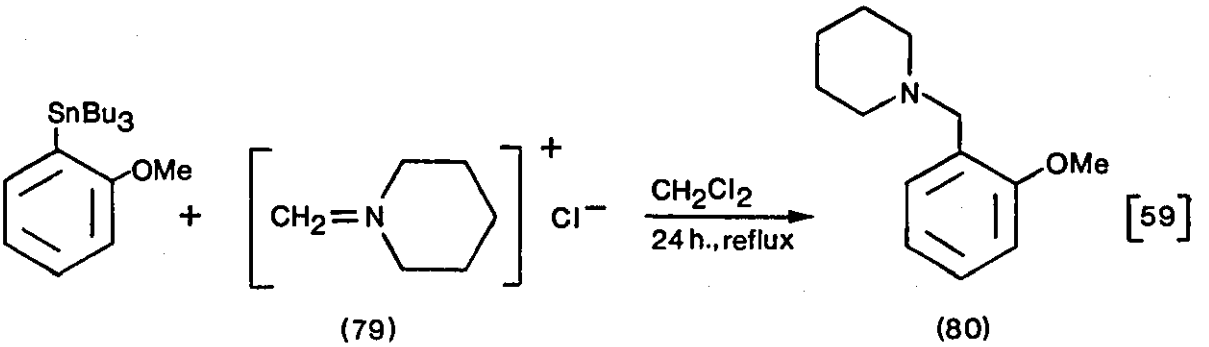
Table 20 Reaction of Aryl-stannanes with Eschenmoser's Salt

Aromatic residue	Alkyltin residue	Solvent	Conditions	Yield (%)
phenyl	$SnMe_3$	CH_2Cl_2	24h reflux	65
o-tolyl	$SnBu_3$	CH_2Cl_2	48h reflux	51
m-tolyl	$SnBu_3$	CH_2Cl_2	48h reflux	60
m-tolyl	$SnBu_3$	CH_3CN	4h reflux	39
p-tolyl	$SnBu_3$	CH_2Cl_2	24h reflux	67
o-anisyl	$SnBu_3$	CH_2Cl_2	15h reflux	70
p-anisyl	$SnBu_3$	CH_2Cl_2	3 days RT	75
p-anisyl	$SnBu_3$	CH_2Cl_2	15h reflux	70
p-anisyl	$SnMe_3$	CH_2Cl_2	21h RT[b]	71
1-naphthyl	$SnBu_3$	CH_2Cl_2	24h reflux	66
3-thienyl	$SnMe_3$	CH_2Cl_2	60h RT	66

[a] Reactions carried out using $R_2NCH_2NR_2$: $ArSnR_3$ = 3:2

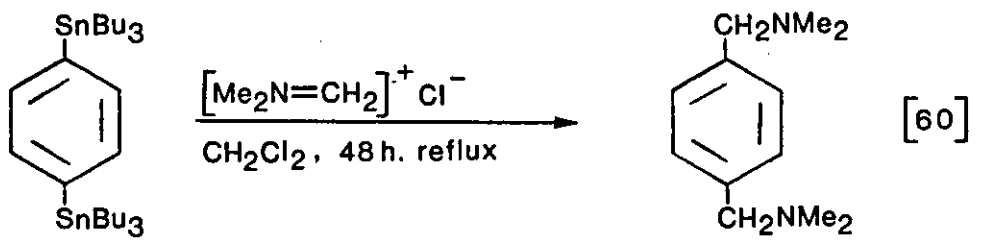
[b] Reaction preceded by 3h at -20°C.

Methylenepiperidinium chloride (79) reacted with 2-methoxyphenyltributylstannane to give 2-piperidinomethylanisole (80) in 57% yield (Equation [59]).



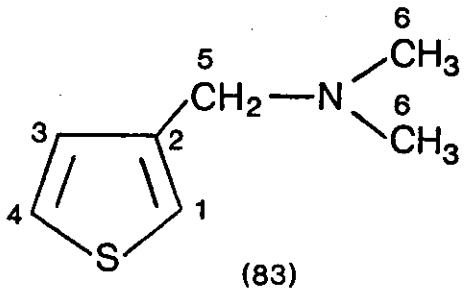
(79) (80)

p-Bis(tributylstannyl)benzene (81) reacted with N,N-dimethyl(methylene)iminium chloride to give p-bis(N,N-dimethylaminomethyl)benzene (82) in 58% yield (Equation [60]).



(81) (82)

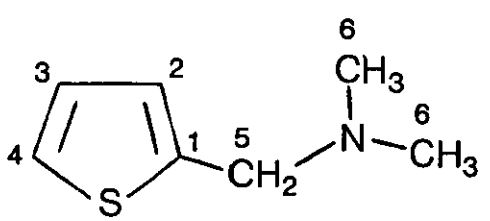
The aminomethylation of 3-thienyltrimethylstannane illustrates the potential of the method for achieving unusual regiospecificity. Reaction occurred exclusively at the 3-position by displacement of the trimethylstannyl group, to afford the aminomethyl derivative (83) in 66% yield. The identity of the product was confirmed by its ^{13}C NMR spectrum. The ^{13}C NMR shifts (ppm) were assigned as shown:



(83)

1.	122.8 (d)	4.	125.5 (d)
2.	139.7 (s)	5.	59.0 (t)
3.	128.5 (d)	6.	45.2 (q)

2-(N,N-dimethylamino)methyl thiophene (84), prepared for comparison by direct aminomethylation of thiophene,[118] gave the following ^{13}C NMR data:



(84)

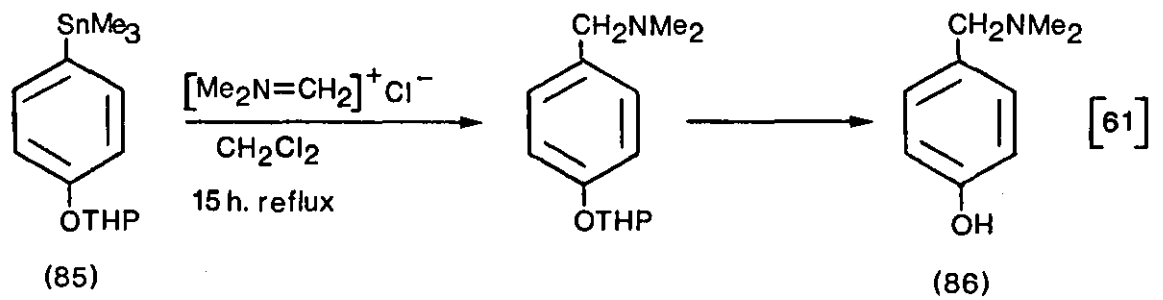
1.	142.4 (s)	4.	125.9 (d)
2.	125.0 (d)	5.	58.3 (t)
3.	126.4 (d)	6.	45.0 (q)

The 3-(N,N-dimethylamino)methyl thiophene obtained from the destannylation reaction was shown by the NMR spectrum to be of high purity with no contamination from the 2-isomer.

There have been no previously reported reactions of 3-stannylthiophenes with electrophiles. However it is interesting

to note that 3-trimethylsilylthiophene reacts with the more electrophilic acyl chloride/$AlCl_3$ reagents at the 5-position rather than by displacement of the trimethylsilyl group.[86]

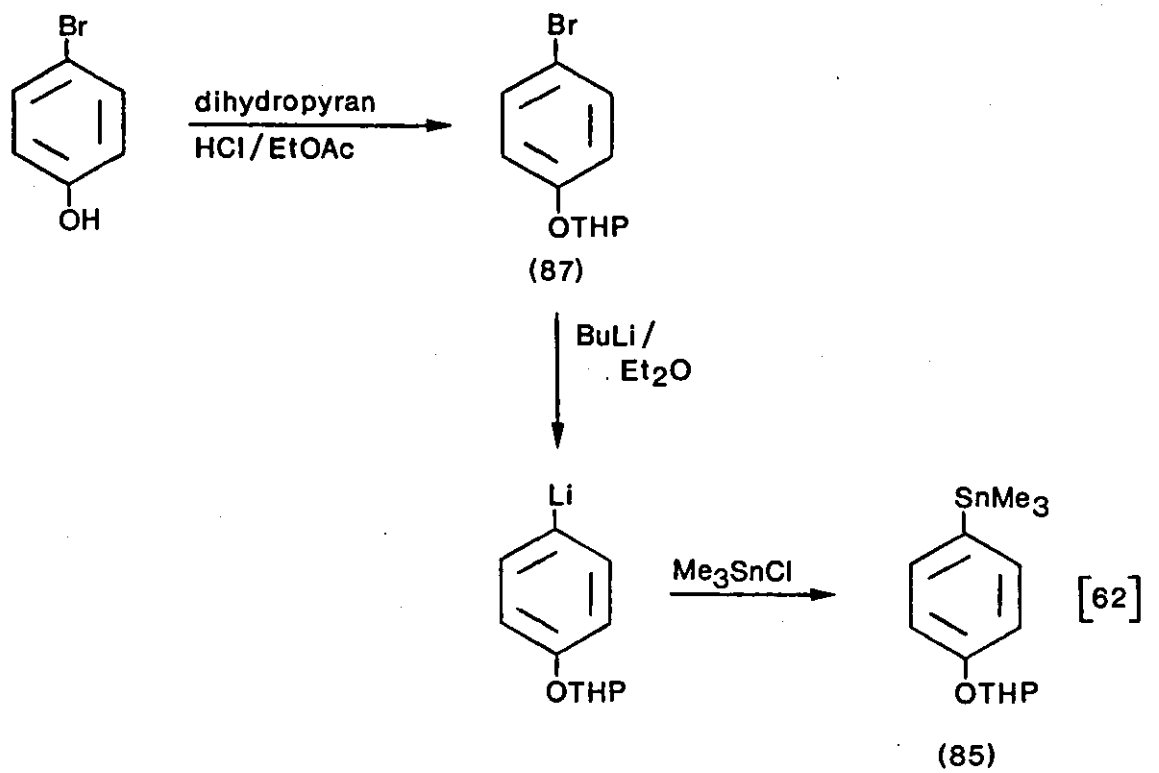
Phenol reacts with Eschenmoser's salt under phase transfer conditions, regiospecifically, to yield the 2-aminomethyl derivative.[119] We were able to prepare 4-(N,N-dimethylaminomethyl)phenol (86) from the protected stannylphenol derivative (85) as shown in Equation [61].



(85) (86) [61]

THP = tetrahydropyranyl

The protected trimethylstannylphenol derivative (85) was prepared from p-bromophenol as illustrated in Equation [62].

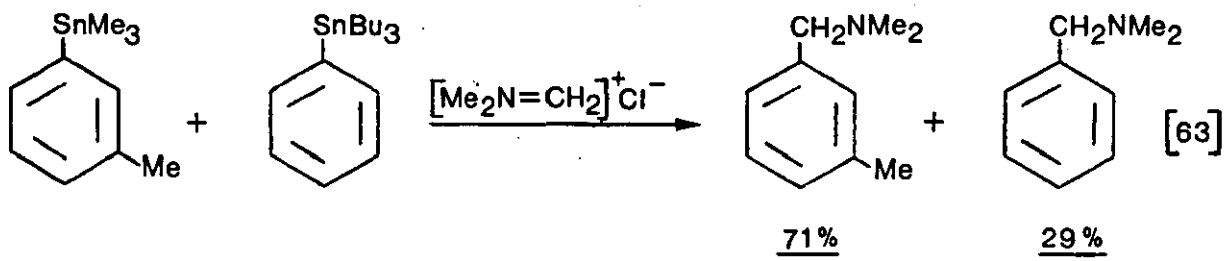


The reaction of Eschenmoser's salt with aryl-stannanes was not catalysed by fluoride ion - addition of tetrabutylammonium fluoride did not have any effect. This indicates that the rate-determining step of the reaction is formation of the Wheland intermediate as is generally observed in electrophilic demetallation reactions.

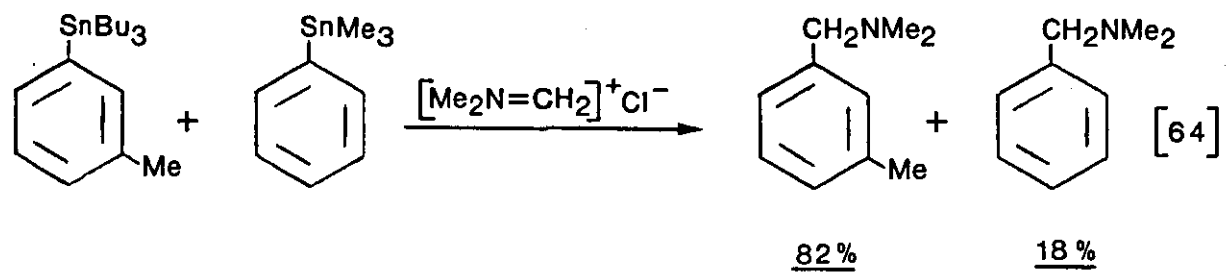
A series of competition reactions was carried out in order to obtain more information about the steric requirements of the destannylation reactions.

(i) A competition reaction was performed in which N,N-dimethyl(methylene)iminium chloride was allowed to compete for a large excess of equimolar amounts of phenyltrimethylstannane and m-tolyltributylstannane. Analysis of the iso-

lated aminomethylated derivatives by gas chromatography indicated the ratio of products as shown in Equation [63].

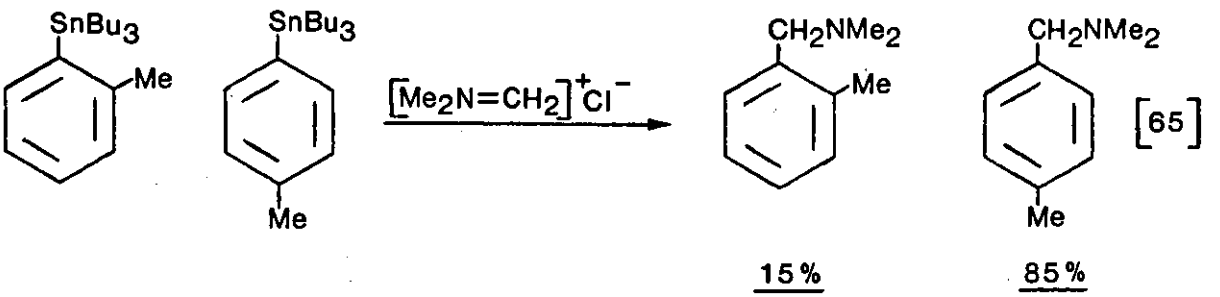


However, performing the competition reaction using the opposite aryl-stannane derivatives (i.e. phenyltrimethyl-stannane and m-tolyltributylstannane) remarkably gave a similar product ratio as shown in Equation [64].



It would appear from these results that there is no great advantage in using the less bulky trimethylstannyl derivatives; the greater reactivity of the m-tolyl derivatives presumably being a result of the slight activating effect of the methyl group. The results imply that perhaps the transition state leading to the Wheland intermediate occurs at a later stage than in some electrophilic destannylation reactions and that there is a greater relief of steric strain when the tributylstannanes are used.

(ii) Steric acceleration might be anticipated in the reaction of an aryl-stannane containing an ortho- substituent. A competition reaction between o- and p-tolyltributylstannane however, indicated that such an effect was not operating and, in fact, a high para-/ortho- ratio was obtained as shown in Equation [65].

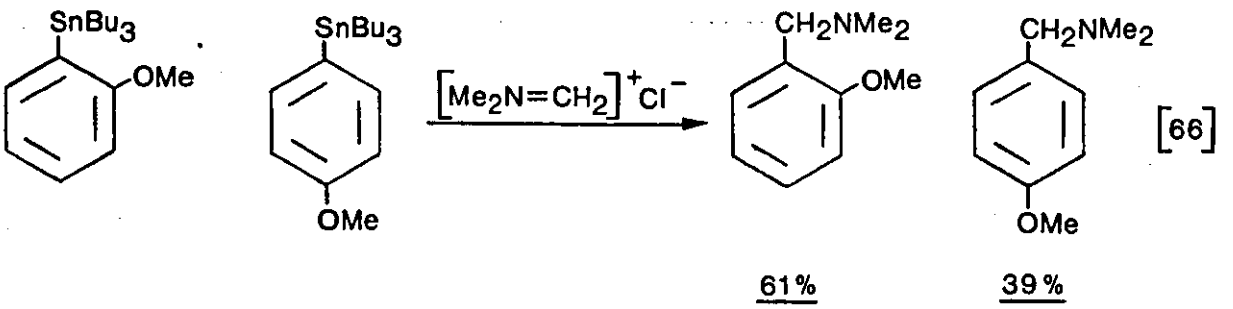


[65]

15% 85%

It appears that the effect of steric hindrance by the methyl group in the reaction of o-tolyltributylstannane is in this case of greater importance than the effect of steric acceleration, with the result that the highly selective electrophile reacts preferentially with the para-isomer.

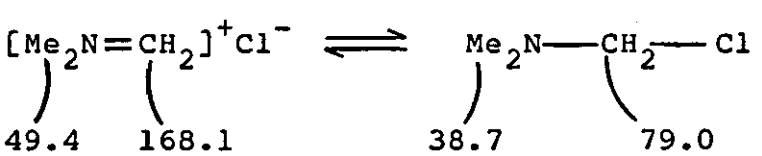
(iii) The presence of an ortho- oxygen function was found to have a significant effect. A competition reaction between o-methoxyphenyl- and p-methoxyphenyl- tributylstannane gave the isomer ratio shown in Equation [66].



[66]

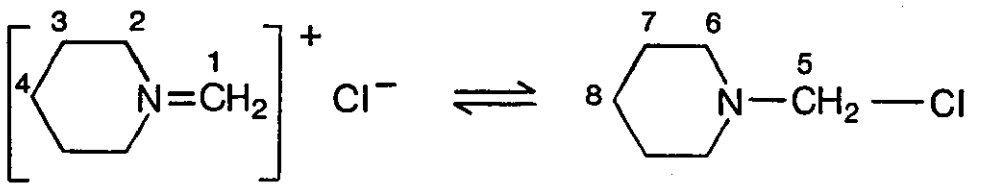
This result suggests that some co-ordination of the electrophile with the methoxy group may occur prior to attack at the nucleophilic centre.

The ionic structure of the Eschenmoser salts when in the solid state has never been in doubt - the crystalline nature of the salts and their insolubility in virtually all organic solvents substantiate this. However, the ^{13}C NMR spectra of the salts in solution (SO_2/CD_2Cl_2 solvent) indicate that an equilibrium exists between the ionic and covalent forms. The ^{13}C NMR spectrum of N,N-dimethyl(methylene)iminium chloride indicates the presence of four different carbons and the chemical shifts (δc/ppm) were assigned as shown:



The peaks at 49.4 and 168.1 ppm appeared as triplets in the proton decoupled spectrum, due to coupling to the quaternary nitrogen.

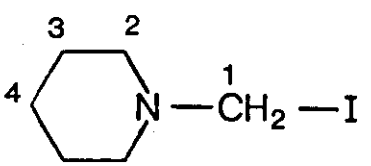
The ^{13}C NMR spectrum of methylenepiperidinium chloride showed similar features, also suggesting an equilibrium situation when in solution. The chemical shifts (in SO_2/CD_2Cl_2 solvent) for this salt were assigned as shown:



1. 164.0 ppm
2. 60.5
3. 26.5
4. not assigned
5. 78.9
6. 49.3
7. not assigned
8. not assigned

The peaks at 60.5 and 164.0 ppm appeared as triplets in the proton decoupled spectrum.

Methylenepiperidinium iodide, prepared by the method of Bryson,[109] gave a ^{13}C NMR spectrum which indicates that in solution (d_6-DMSO) the salt exists entirely in the covalent form. Only four peaks appeared in the proton decoupled spectrum, and the chemical shifts (δc/ppm) were assigned as follows:



1. 78.0 ppm
2. 48.3
3. } 22.0 and 21.3
4. }

3.2.9 Mannich reaction of Benzyl-stannanes

Benzyltributylstannane was found to react with N,N-dimethyl-(methylene)iminium chloride to afford N,N-dimethyl-2-phenyl-ethylamine (88) in 46% yield (Equation [67]).

$$PhCH_2SnBu_3 \xrightarrow[CH_2Cl_2,\ reflux]{Me_2N^+=CH_2Cl^-} PhCH_2CH_2NMe_2 \quad [67]$$

46% (88)

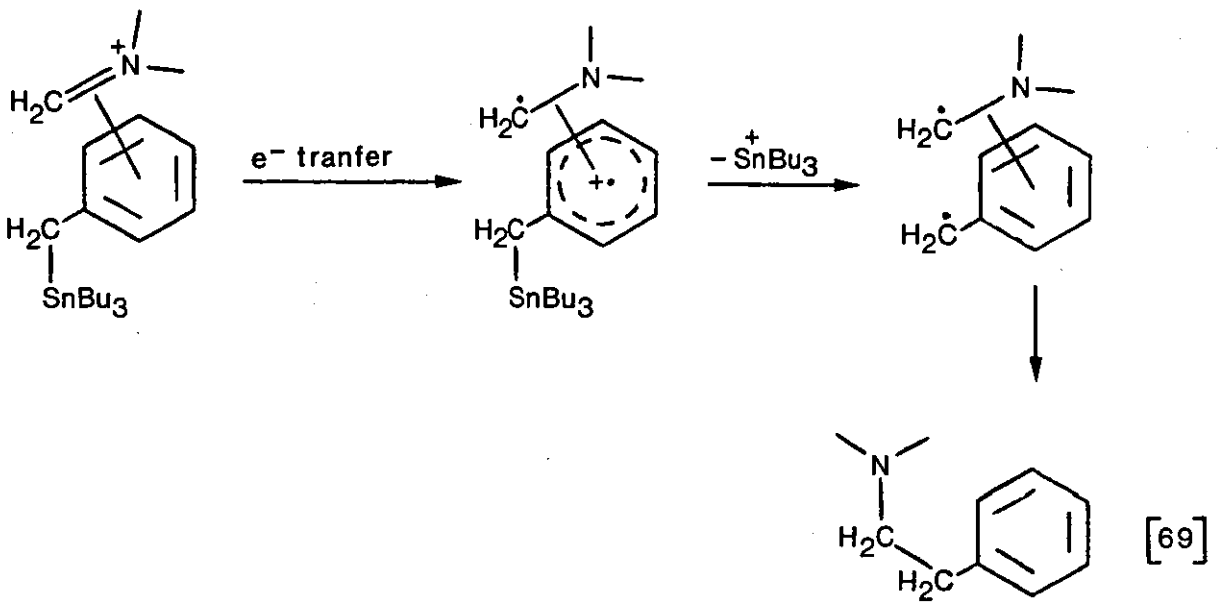
The reaction required heating under reflux in dichloromethane and proceeded at a similar rate to the aminomethylation of phenyltributylstannane. The addition of fluoride ion did not have any catalytic effect.

Electrophilic cleavage of benzyl-tin bonds is not unprecedented, but generally occurs far less readily than aryl-tin cleavage. Highly reactive electrophiles, such as acids[120] and mercuric chloride,[121] react by electrophilic attack at the benzylic carbon. Sulphur dioxide, which is only moderately electrophilic, also reacts[122] with benzylstannanes to yield the insertion product (Equation [68]).

$$PhCH_2SnMe_3 \xrightarrow[30°C]{SO_2,MeOH} PhCH_2SO_2SnMe_3 \quad [68]$$

The mechanism of this reaction is not clear but kinetic studies support a simple S_E2 process. Reaction of the Eschenmoser salt by an electrophilic process seems very unlikely however in view of the weak electrophilicity of the methyleneiminium salt. A more plausible mechanism may be proposed involving initial electron transfer. Allylsilanes

and benzylsilanes are known to react with pyrrolinium salts [123,124] by a photochemical process which is thought to involve electron transfer from the silane to the iminium salt. A similar process might be envisaged for the benzylstannane reaction and a mechanism can be formulated as shown in Equation [69].



[69]

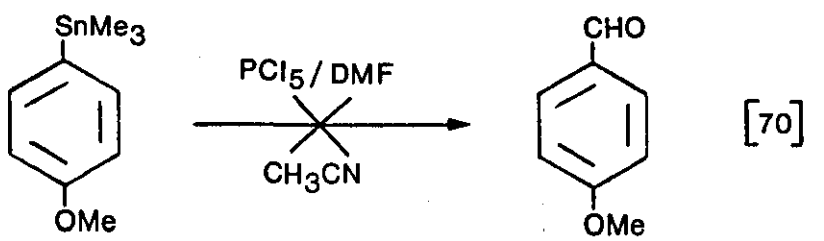
Irradiation with ultraviolet light however, did not improve the yield (45%), while the addition of p-dinitrobenzene did not have any inhibiting effect (43% yield). Obviously more studies need to be carried out before any conclusions can be reached regarding the mechanism of this reaction.

3.2.10 Attempted reaction of the Vilsmeier reagent with aryl-stannanes

The Vilsmeier reaction[125] provides a method for performing

formylation, using a reagent prepared from a phosphorous chloride and a dialkylformamide. Like the Mannich reaction, formylation only occurs with particularly nucleophilic aromatic compounds.

Formylation of aryl-stannanes was attempted using the Vilsmeier reagent prepared from phosphorus pentachloride and N,N-dimethylformamide (DMF), but no reaction occurred - the aryl-stannane was recovered almost quantitatively, (Equation [70]).



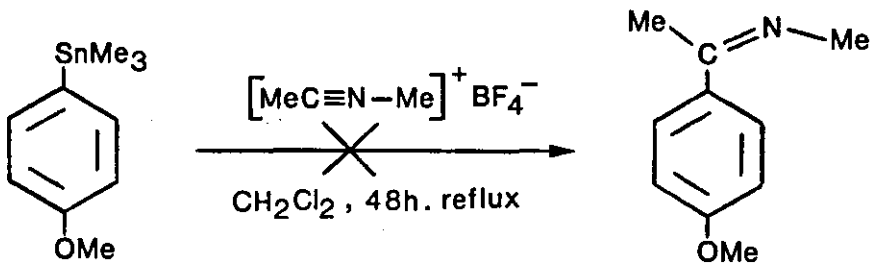
[70]

Formylation is believed to involve chloromethylenedimethyliminium chloride, $[Me_2N{=}CHCl]^+ Cl^-$, as the reactive species. In view of the similarity of this species to that involved in the Mannich reaction, the failure of the formylation reaction is surprising. It would appear that steric interaction between the electrophile and the stannyl group in the transition state, is a decisive factor.

3.2.11 Attempted reaction of nitrilium salts with aryl-stannanes

Nitrilium salts react with activated aromatic compounds, such as m-dimethoxybenzene,[126] to afford the imino deriv-

ative which may be hydrolysed to the ketone. Reaction of N-methylacetonitrilium fluoroborate was attempted with several aryl-stannanes but in all cases reaction failed to occur (Equation [71]).



(89)

[71]

CHAPTER 4

EXPERIMENTAL

All solvents were dried and distilled by conventional methods.

Melting points were recorded using a Kofler hot-stage apparatus and are uncorrected.

Infra-red spectra were recorded using a Perkin-Elmer 177 grating spectrophotometer.

Proton magnetic resonance spectra were recorded at 90 MHz, unless otherwise stated, on a Perkin-Elmer R32 spectrometer. 60 MHz spectra were recorded on a Varian EM360A spectrometer. Chemical shifts are quoted relative to tetramethylsilane as internal standard.

Carbon magnetic resonance spectra were recorded at 20.1 MHz on a Bruker WP80 spectrometer.

Mass spectra were recorded at high resolution on a Kratos MS80 mass spectrometer using a DS-55 data system.

Analysis by gas-liquid chromatography

The following columns and instruments were used:

(i)	Column:	10% Carbowax 20M
	Support:	Chromosorb W
	Carrier gas:	nitrogen
	Detector:	FID
	Chromatograph:	PYE series 104

This column was used for analysis of the phenolic products obtained from o-xylene, m-xylene, mesitylene (temp. 175°C),

and naphthalene (temp. 220°C). Also the lactones obtained from the Baeyer-Villiger oxidations were analysed using this column at 160°C.

(ii) Column: Carbopack C
Carrier gas: nitrogen
Temperature: 175°C
Detector: FID
Chromatograph: PYE series 104

This column was able to separate m- and p-cresol and was used to analyse the phenolic products obtained from toluene and from the aryl-metal compounds.

(iii) Column: 25QC2 FFAP 12m capillary
Carrier gas: helium + nitrogen
Temperature program: 90°C for 2 mins.
90 – 170°C at 4°C/min.
Hold at 170°C
Detector: FID
Chromatograph: PYE series 104

This column was able to separate 2,4- and 2,5-xylenol and was used for analysis of the products from hydroxylation of p-xylene.

(iv)	Column:	BP1 12m capillary
	Carrier gas:	helium
	Temperature:	100°C
	Detector:	FID
	Chromatograph:	Carlo Erba Strumentazione, Fractovap series 2150

This non-polar column was used for analysis of the hydroxylation products obtained using triphenylsilylhydroperoxide. The column allowed separation of phenol and o-cresol which was not possible on the polar columns.

(v)	Column:	5% Bentone
	Support:	Chromosorb W
	Carrier gas:	nitrogen
	Detector:	FID
	Chromatograph:	PYE series 104

This column was used for analysis of the neutral organic material (recovered aromatic compounds) from the hydroxylation reactions.

Components were identified by comparison of retention times with those of authentic standards and the identification was confirmed by 'spiking' with the standard.

The yield of a component was determined by addition of a suitable internal standard to the sample and comparison of the peak integration with standard solutions of the authentic material.

4.1 PREPARATION OF THE PEROXIDE ADDUCTS

The hydrogen peroxide and t-butylhydroperoxide adducts were prepared by the literature methods. The active oxygen content of the adducts was determined by iodometric titration [127] and in all cases was >98%.

4.1.1 Triphenylphosphine oxide - hydrogen peroxide adduct[55] - $(Ph_3PO)_2.H_2O_2$

30% aqueous hydrogen peroxide (0.1 mole, 11.3g) was added dropwise to a solution of triphenylphosphine (13.1g, 0.05 mole) in diethyl ether (100 mls) at 0°C. The white, crystalline solid which immediately formed was filtered off, washed with ether, and dried *in vacuo* over calcium chloride. Yield of the adduct was 14.0g, 92%. M.pt 130-132°C. (Lit.[55] 132 - 133°C).

I.R.(nujol mull) ν_{max}/cm^{-1} 1180 (P = O)

4.1.2 Urea-hydrogen peroxide adduct

This adduct was prepared as described in the literature,[51] by crystallisation from a saturated solution of urea in 30% hydrogen peroxide. Yield was 91%.

M.pt : decomposed before melting

I.R. (nujol mull) ν_{max}/cm^{-1} 3340 (N-H), 1675 (C=O), 1365 (O - O).

4.1.3 1,4-Diazabicyclo[2.2.2]octane - hydrogen peroxide adduct - $DABCO(H_2O_2)_2$

This was prepared by addition of 86% hydrogen peroxide to a solution of DABCO in ether, as described by Oswald and Guertin.[46] The adduct precipitated as a white crystalline solid. Yield, 93%.

M.pt 110-112°C (decomposed).

I.R. (nujol mull) ν_{max}/cm^{-1} 3060 (O - H), 2760 (O - H), 940, 910, 860.

4.1.4 DABCO dioxide - hydrogen peroxide adduct - $DABCO(O.H_2O_2)_2$

Prepared by the literature procedure.[46] Yield, 58%.

M.pt 124°C (decomposed).

I.R. (nujol mull) ν_{max}/cm^{-1} 3120, 2790, 945, 800.

4.1.5 Sodium carbonate - hydrogen peroxide adduct - $Na_2CO_3.1\frac{1}{2}H_2O_2$

This adduct was obtained by precipitation from a solution of sodium carbonate in 15% aqueous hydrogen peroxide, by the method of Jones and Griffith.[53] Yield, 79%.

I.R. (nujol mull) ν_{max}/cm^{-1} 2490, 1550, 1430, 985, 960, 855.

4.1.6 Dicyclohexylamine - hydrogen peroxide adduct - $[(C_6H_{11})_2NH]_2.H_2O_2$

Prepared from dicyclohexylamine and 30% hydrogen peroxide by the literature procedure.[57]

M.pt 88 - 90°C (Lit.[57] 88 - 90°C).

4.1.7 DABCO-t-butylhydroperoxide adduct - DABCO(t-BuOOH)$_2$

Prepared by addition of 70% t-butylhydroperoxide to DABCO in toluene, by the method of Oswald.[128]

M.pt 71 - 73°C (Lit.[128] 73 - 74°C).

I.R. (nujol mull) ν_{max}/cm^{-1} 1355, 1320, 1060, 1000, 835 (O - O)

$\delta_H(CDCl_3)$/ppm 1.25(s,18H), 2.75(s,12H)

4.2 PREPARATION OF TRIPHENYLSILYLHYDROPEROXIDE

(i) Preparation of triphenylsilyl chloride[129]

Freshly cut pieces of lithium (9.1g, 1.30 mole) were placed in dry diethyl ether (140 mls) in a 3-necked, 1 litre flask fitted with a pressure-equalizing dropping funnel and condenser, and supplied with a static pressure of dry argon. Bromobenzene (94.2g, 0.6 mole) in dry diethyl ether (100mls) was then added dropwise, at such a rate as to maintain gentle reflux. After complete addition, a further 100 mls of ether was added and the mixture was heated under reflux for 1 hour.

The pale yellow solid (LiBr) was removed by filtration through a plug of glass wool, under an atmosphere of dry nitrogen. The brown solution of phenyllithium was placed in a 500 ml pressure-equalizing dropping funnel and was diluted to 500 mls with ether. A 2 ml sample of this solution was removed and was hydrolysed by addition of water. The liberated lithium hydroxide was determined by titration with a standard solution of hydrochloric acid. This was repeated and from the mean titre the yield of phenyllithium was 0.345 moles, 58%.

The phenyllithium solution was then added dropwise, over a 2 hour period, to 0.33 equivalents of silicon tetrachloride (19.55g, 0.115 mole) in dry diethyl ether (100 mls) with stirring at 0°C, under a dry nitrogen atmosphere.

After stirring for 16 hours at room temperature and for a further 1 hour at reflux, the solid material (LiCl) was filtered off and the ether was removed from the filtrate, in vacuo, to obtain a brown, resinous solid. This crude material was extracted with hot benzene, and the brown solid obtained upon removal of the benzene from the extracts was crystallised from petroleum ether (40/60°). A second recrystallisation from petroleum ether yielded pure triphenylsilyl chloride as pale yellow crystals (10.6g, 31%).

M.pt 98 - 100°C. (Lit.[129] 104°C).

I.R.(CCl_4) ν_{max}/cm^{-1} 3070, 1485, 1430, 1190, 1120, 1030, 1000, 690.

The infra-red spectrum was in good agreement with the data quoted in the literature.[130]

(ii) Preparation of triphenylsilylhydroperoxide[63]

To a stirred solution of triphenylsilyl chloride (8.0g, 0.027 mole) in anhydrous ether (300 mls) was added 94% hydrogen peroxide (8 mls) at 0°C. After 2 - 3 minutes stirring, anhydrous ammonia was bubbled rapidly into the reaction mixture for 60 seconds. The reaction was then immediately quenched by adding distilled water (100 mls). The ether layer was separated, washed four times with 50 ml portions of water, and dried over anhydrous magnesium sulphate. Removal of the solvent in vacuo yielded a white

residue which was dissolved in hot carbon tetrachloride and crystallized by cooling to -20°C. A second recrystallization from petroleum ether gave triphenylsilylhydroperoxide (6.0g, 76%) as a colourless, crystalline solid.

M.pt 108 - 110°C. (Lit.[63] 110 - 112°C).

I.R. (nujol mull) ν_{max}/cm^{-1} 3360 (O - H), 1430, 1120, 865 (O - O).

$\delta_H(CDCl_3)$/ppm 8.20(br.s,1H), 7.30-7.75(m,15H).

The active oxygen content of the solid was only 82% of the theoretical value and could not be improved by further recrystallization. The presence of some bis(triphenylsilyl) peroxide could perhaps account for this, although the melting point was reasonably sharp.

Note

Care should be taken during this procedure to ensure that the hydrogen peroxide is destroyed by washing the ether phase thoroughly with sodium sulphite solution before concentrating.

4.3 AROMATIC HYDROXYLATION

4.3.1 General procedure (e.g. hydroxylation using urea-$H_2O_2/AlCl_3$)

All reactions were performed under a static pressure of dry nitrogen.

Aluminium chloride (1.32g, 0.10 mole) was added to a solution of the aromatic hydrocarbon (20 mls) in dichloromethane (20 mls) with ice-bath cooling. The urea-H_2O_2 adduct (0.47g, 0.005 mole) was then added portionwise at 0°C and the suspension was stirred for 2 hours at 0°C, and for 24 hours at room temperature. Dilute aqueous hydrochloric acid (40 mls) was then added, with cooling. The mixture was separated and the aqueous layer was extracted with dichloromethane. (Titration of the aqueous phase showed that generally only a trace of peroxide remained). The combined organic phase was then washed with water (40 mls) and was extracted with 10% sodium hydroxide solution by heating under reflux for 30 mins. After cooling, the two layers were separated and the organic phase was washed with some water. The combined aqueous phase was then extracted with ether (2 x 25mls) and was acidified by dropwise addition of concentrated hydrochloric acid, with cooling. A milky precipitate was obtained which was extracted into diethyl ether (4 x 25 mls). The combined ether extracts were washed with water and dried over anhydrous $MgSO_4$. Removal of the ether *in vacuo* gave a brown phenolic residue which was analysed by gas chromatography (GLC).

Hydroxylations using the other insoluble hydrogen peroxide adducts (i.e. the DABCO, DABCO dioxide, and sodium carbonate adducts), with various Lewis acid catalysts were carried out using the same procedure.

A 1:2 H_2O_2/Lewis acid ratio was normally used.

Boron trifluoride was used in its etherate form.

The $(Ph_3PO)_2.H_2O_2$ and DABCO(t-BuOOH)$_2$ adducts are soluble in dichloromethane. Reactions using these reagents were performed by dropwise addition of the adduct (0.005 mole) in dichloromethane (20 mls) to a suspension of aluminium chloride in the aromatic hydrocarbon (20 mls). The reactions in this case were worked-up after approximately 2 hours at 0°C and 6 hours at room temperature.

4.3.2 Hydroxylation of the isomeric xylenols using $(Ph_3PO)_2.H_2O_2/AlCl_3$

Each of the xylenol isomers was subjected to the hydroxylating conditions in order to establish which isomers the chlorinated phenolic products were derived from in the xylene hydroxylations.

To a solution of the xylenol (0.61g, 0.005 mole) in dichloromethane (15 mls) was added aluminium chloride (0.01 mole). The triphenylphosphine oxide adduct (0.005 mole) in

dichloromethane (20 mls) was then added dropwise at 0°C. After stirring for 8 hours the phenolic products were isolated in the usual way. GLC analysis, using the Carbowax column, showed that mainly polyhydroxylated products were obtained, but chlorinated xylenol derivatives were also present, and these corresponded to the chlorinated products formed in the xylene hydroxylations.

4.3.3 Hydroxylation of naphthalene

Hydroxylation was carried out using a solution of naphthalene in dichloromethane, by the normal procedure using the peroxide adducts. Hydroxylation using t-butylhydroperoxide was performed using an anhydrous solution of the peroxide in dichloromethane, prepared by azeotropic distillation.[131]

4.3.4 Hydroxylation of mesitylene using trifluoroperoxyacetic acid

Trifluoroperoxyacetic acid was prepared by addition of trifluoroacetic anhydride (1.26g, 0.006 mole) in dichloromethane (5 mls) to a solution of the triphenylphosphine oxide - hydrogen peroxide adduct (3.04g, 0.005 mole) in dichloromethane (10 mls) at 0°C. The solution was stirred for 30 minutes and then was placed in a dropping funnel and added dropwise to a stirred mixture of mesitylene (10 mls)

and boron trifluoride etherate (0.01 mole) with ice-bath cooling. The reaction mixture was stirred for 30 minutes at 0°C and for a further 6 hours at room temperature. Dilute hydrochloric acid (40 mls) was then added and the organic phase separated and washed with dilute sodium bicarbonate solution. The organic phase was then extracted with 10% sodium hydroxide solution, as described previously, to obtain the phenolic products.

Hydroxylation of mesitylene was also performed using a solution of the urea-H_2O_2 adduct (0.005 mole) in trifluoroacetic acid (2.3g, 0.02 mole) and dichloromethane (10 mls).

4.3.5 Hydroxylation using triphenylsilylhydroperoxide

Triphenylsilylhydroperoxide (0.002 mole) in dichloromethane (10 mls) was added dropwise to a stirred mixture of aluminium chloride (0.53g, 0.004 mole) and the aromatic hydrocarbon (10 mls) at 0°C. After stirring for 24 hours at room temperature, dilute hydrochloric acid was added and the phenolic products were isolated by alkaline extraction.

4.4 BAEYER-VILLIGER OXIDATIONS

(i) Oxidation using the hydrogen peroxide adducts

The hydrogen peroxide adduct (0.005 mole) was added to a stirred mixture of cyclopentanone (0.42g, 0.005 mole) and boron trifluoride etherate (1.42g, 0.01 mole) in dichloromethane (20 mls), at 0°C. Stirring was continued for 24 hours at room temperature. Saturated sodium bicarbonate solution (20 mls) was then added and the aqueous phase was separated and extracted with dichloromethane (2 x 20 mls). The combined organic phase was then washed with water and dried over anhydrous magnesium sulphate. The solvent was removed under vacuo and the crude material analysed by gas chromatography. An internal standard (ε-caprolactone) was added and the yield was determined by comparison with standard solutions of the lactones.

(ii) Oxidation using trifluoroperoxyacetic acid

Trifluoroperoxyacetic acid was prepared from the $(Ph_3PO)_2 . H_2O_2$ adduct (0.005 mole) and trifluoroacetic anhydride, as described previously, (4.3.4), and was added dropwise to a solution of the ketone (0.004 mole) in dichloromethane (15 mls) at 0°C. After stirring for 4 hours at room temperature, saturated sodium bicarbonate solution was added and the organic phase was separated and washed several times with water. The organic phase was dried and the solvent removed to afford the crude product which was analysed by GLC to determine the yield of lactone.

4.5 PREPARATION OF THE ARYL-METAL COMPOUNDS

4.5.1 Preparation of the Tin Compounds

(i) p-Tolyltributylstannane

p-Tolylmagnesium bromide was prepared from p-bromotoluene (42.8g, 0.25 mole) and magnesium (6.7g, 0.28 mole) in sodium-dried diethyl ether (150 mls). Tributyltin chloride (48.7g, 0.15 mole) in ether (50 mls) was then added dropwise, maintaining a steady reflux. After complete addition the mixture was heated under reflux for a further 6 hours. The reaction mixture was then quenched with a saturated ammonium chloride solution (200 mls) and the organic phase was separated, washed with water and dried over anhydrous magnesium sulphate. Removal of the solvent gave a yellow oil which was shown by its ^{1}H NMR spectrum to contain some unreacted tributyltin chloride. This was removed by treating a solution of the crude material in ether, with a saturated solution of potassium fluoride in ethanol. The precipitated material (tributyltin fluoride) was filtered off and the solvent was removed from the filtrate to obtain the crude product. Fractional distillation of this liquid afforded p-tolyltributylstannane (29.5g, 52%) at 138 - 144°C/0.1 mmHg. (Lit.[84] 155 - 160°C/0.2 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3030, 2960, 2930, 2880, 1460, 1075, 795.

$\delta_H(CDCl_3)$/ppm 7.00-7.28 (ABq, 4H, J_{AB} = 9Hz), 2.25(s,3H), 0.70-1.70 (m,27H).

(ii) m-Tolyltributylstannane

This was prepared from m-bromotoluene by the procedure described for p-tolyltributylstannane. Fractionation gave m-tolyltributylstannane[132] (57% yield) at 122 - 126°C/0.1 mmHg.

I.R. (liquid film) ν_{max}/cm^{-1} 3040, 3020, 2960, 2925, 2860, 1460, 1070, 770, 700.

$\delta_H(CDCl_3)$/ppm 6.90-7.30(m,4H), 2.28(s,3H), 0.70-1.70(m,27H)

(iii) o-Tolyltributylstannane

Prepared from o-bromotoluene. Fractionation gave o-tolyltributylstannane[132] (68%) at 144 - 146°C/0.5 mmHg.

I.R. (liquid film) ν_{max}/cm^{-1} 3030, 2960, 2930, 2880, 2860, 1460, 1075, 745.

$\delta_H(CDCl_3)$/ppm 6.80-7.50 (m,4H), 2.34(s,3H), 0.70-1.75(m,27H).

(iv) Phenyltributylstannane

Prepared from bromobenzene by the procedure described for p-tolyltributylstannane. Fractionation gave phenyltributylstannane (64%) at 152 - 155°C/1.3 mmHg. (Lit.[133] 139°C/0.6 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3070, 2965, 2935, 2860, 1460, 1080, 730, 705.

$\delta_H(CDCl_3)$/ppm 7.10-7.50 (m,5H), 0.70-1.70 (m,27H).

(v) p-Methoxyphenyltributylstannane

p-Methoxyphenylmagnesium bromide was reacted with tributyltin chloride, as described for the preparation of p-tolyltributylstannane, and the mixture was heated under reflux for 6 hours. Work-up, by the same procedure, gave a yellow oil which was fractionated to obtain p-methoxyphenyltributylstannane (48%) at 164 - 168° C/1.0 mmHg. (Lit.[84] 158 - 160°C/0.5 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 2960, 2930, 2870, 2850, 1590, 1495, 1460, 1075, 810.

$\delta_H(CDCl_3)$/ppm 6.70-7.35 (ABq, 4H, J_{AB} = 8Hz), 3.75(s,3H), 0.70-1.70 (m,27H).

(vi) o-Methoxyphenyltributylstannane

Prepared from o-bromoanisole. Fractionation gave o-methoxyphenyltributylstannane (60%) at 140 - 145°C/0.3 mmHg. (Lit.[134] 141 - 143°C/0.2 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3050, 2960, 2925, 2860, 1580, 1460, 1080, 755.

$\delta_H(CDCl_3)$/ppm 6.65-7.45 (m,4H), 3.65(s,3H), 0.70-1.70 (m,27H).

(vii) p-Tolyltrimethylstannane

Trimethyltin chloride (4.0g, 0.02 mole) in ether (10 mls) was added to p-tolylmagnesium bromide [prepared from p-bromotoluene (6.84g, 0.04 mole)] in ether (40 mls). The mixture was then heated under reflux for 6 hours, and the reaction then worked up in the usual way to obtain the crude product. Fractionation gave p-tolyltrimethylstannane (3.7g, 73%) at 60 - 65°C/0.4 mmHg. (Lit.[135] 69°C/1.2mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3040, 2980, 2930, 1600, 1490, 1075, 795.

$\delta_H(CDCl_3)$/ppm 6.85-7.30 (ABq, 4H, J_{AB} = 7 Hz), 2.22(s,3H), 0.25(s,9H).

(viii) o-Tolyltrimethylstannane

Prepared from o-bromotoluene. Fractionation gave o-tolyltrimethylstannane (3.8g, 74%) at 64 - 68°C/0.5 mmHg. (Lit.[136] 90°C/7 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3060, 2960, 2930, 1590, 1460, 1075, 750.

$\delta_H(CDCl_3)$/ppm 6.90-7.45 (m,4H), 2.35 (s,3H), 0.30 (s,9H).

(ix) m-Tolyltrimethylstannane

Prepared from m-bromotoluene. Fractionation gave m-tolyltrimethylstannane (3.3g, 65%) at 76 - 78°C/1.6 mmHg. (Lit.[135] 55°C/0.9 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3040, 3020, 2960, 2930, 1580, 1460, 1075, 770, 700.

$\delta_H(CDCl_3)$/ppm 6.95-7.30 (m,4H), 2.30 (s,3H), 0.27 (s,9H).

(x) Phenyltrimethylstannane

Prepared from bromobenzene. Fractionation gave phenyltrimethylstannane (75% yield) at 80 - 84°C/10 mmHg. (Lit.[135] 198°C/750 mmHg).

$\delta_H(CDCl_3)$/ppm 7.00-7.50 (m,5H), 0.25 (s,9H).

(xi) p-Methoxyphenyltrimethylstannane

Prepared from p-bromoanisole. Fractionation gave p-methoxyphenyltrimethylstannane (50% yield) at 103 - 104°C/3.5 mm Hg. (Lit.[135] 102°C/3.5 mm Hg).

I.R. (liquid film) ν_{max}/cm^{-1} 3040, 2960, 2930, 1590, 1490, 1075, 800.

$\delta_H(CDCl_3)$/ppm 6.70-7.40 (ABq, 4H, J_{AB} = 9 Hz), 3.65 (s,3H), 0.25 (s,9H).

(xii) 1-Naphthyltributylstannane

The Grignard reagent was prepared from 1-bromonaphthalene (41.4g, 0.20 mole) by the usual procedure. Tributyltin chloride (48.7g, 0.15 mole) in ether (40 mls) was then added dropwise at 0°C and the mixture was heated under reflux for 16 hours. Work-up in the usual way gave an orange oil. Naphthalene (5.2g) was removed from this liquid by sublimation at reduced pressure and the residual oil was fractionated to obtain 1-naphthyltributylstannane[137] (31.8g, 51%) at 170 - 175°C/0.1 mmHg.

I.R. (liquid film) ν_{max}/cm^{-1} 3050, 2960, 2925, 2875, 2855, 1505, 1460, 1075, 790, 775.

$\delta_H(CDCl_3)$/ppm 7.10-7.80 (m,7H), 0.65-1.70 (m,27H).

(xiii) p-Phenylenebis(tributylstannane) (81)

The *in situ* Grignard method[138] was used. p-Dibromobenzene (11.8g, 0.05 mole) in tetrahydrofuran (100 mls) was added dropwise to a mixture of tributyltin chloride (39.0g, 0.12 mole) and magnesium (2.64g, 0.11 mole) in tetrahydrofuran (50 mls). (A few drops of 1,2-dibromoethane was added to initiate the reaction). After complete addition the dark solution was heated to 50°C for 6 hours. Saturated ammonium chloride solution (150 mls) was then added and the organic phase separated, washed with water, and dried over anhydrous magnesium sulphate. Removal of the solvent gave a colourless liquid (31.5g) which was treated with a saturated solution of potassium fluoride (as described in the p-tolyltributylstannane preparation) to remove unreacted tributyltin chloride. Fractionation gave p-phenylenebis-(tributylstannane)[139] (16.7g, 51%) as a colourless liquid at 230°C/0.2 mmHg.

I.R. (liquid film) ν_{max}/cm^{-1} 3040, 2960, 2930, 2870, 2850, 1460, 1070, 785.

$\delta_H(CDCl_3)$/ppm 7.30 (s,4H), 0.75-1.80 (m,54H).

(xiv) Benzyltributylstannane

Benzylmagnesium bromide was prepared from benzylbromide (0.17 mole). Tributyltin chloride (0.10 mole) in ether (35 mls) was then added dropwise, and the mixture was heated under reflux for 16 hours. Water (100 mls) was

added and the organic phase was separated, washed with water and dried. Removal of the ether gave a pale yellow liquid which was fractionated to give benzyltributylstannane (26.5g, 69.5%) at 150 - 152°C/0.5 mmHg. (Lit.[140] 192 - 194°C/24 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3060, 3030, 2975, 2945, 2820, 2770, 1450, 1030, 735, 695.

$\delta_H(CDCl_3)$/ppm 6.95 (s,5H), 2.25 (s,2H), 0.60-1.80 (m,27H).

(xv) 3-Thienyltrimethylstannane

A 15% solution of butyllithium (0.038 mole) in hexane was added dropwise to a stirred solution of 3-bromothiophene (6.86g, 0.04 mole) in diethyl ether (40 mls) at -78°C, under a static pressure of dry nitrogen. The mixture was stirred for 30 min. at -78°C and trimethyltin chloride (7.0g, 0.035 mole) in ether (20 mls) was then added dropwise at this temperature. Stirring was continued for 10 hours at -78°C and for a further 2 hours at room temperature. Water (100 mls) was then added and the organic phase was separated, washed with water, and dried over anhydrous magnesium sulphate. Removal of the solvent, in vacuo, gave a brown liquid (8.6g) which was distilled twice using a Kugelröhr apparatus, to obtain 3-thienyltrimethylstannane[141] (4.8g, 56%) at 90 - 92°C/6 mmHg.

I.R. (liquid film) ν_{max}/cm^{-1} 3060, 2980, 2910, 1365, 1200, 1080, 845, 760.

$\delta_H(CDCl_3)$/ppm 6.90-7.30 (m,3H), 0.27 (s,9H).

(xvi) Preparation of 2-(4-trimethylstannylphenoxy)tetrahydropyran (85)

(a) Preparation of 2-(4-bromophenoxy)tetrahydropyran (87)

This was prepared according to the general procedure reported by Prelog.[142]

A saturated solution of hydrogen chloride in ethyl acetate (7 mls) was added to a stirred solution of p-bromophenol (20.76g, 0.12 mole) in ethyl acetate (130 mls). Dihydropyran (40 mls) was then added and the solution was stirred for 24 hours at room temperature. Sodium hydroxide solution (2%, 50mls) was then added. The organic phase was separated and was washed with sodium dithionate solution (50 mls), 2% sodium hydroxide solution (2 x 50 mls), water (2 x 50 mls) and finally with saturated sodium chloride solution (50 mls). The organic phase was then dried over anhydrous magnesium sulphate and the solvent was removed in vacuo, to obtain a yellow liquid. Distillation gave 2-(4-bromophenoxy)tetrahydropyran[143] (22.8g, 74%) at 122 - 124°C /0.35 mmHg as a colourless liquid which crystallised on cooling; m.pt 43 - 44°C.

I.R. (nujol mull) ν_{max}/cm^{-1} 1590, 1580, 1485, 1440, 1235, 965, 920, 875, 820.

$\delta_H(CDCl_3)$/ppm 6.82-7.36 (ABq,4H,J_{AB} = 9Hz), 5.32 (t,1H), 3.45-4.02 (m,2H), 1.40-2.20 (m,6H).

$\delta_C(CDCl_3)$/ppm 156.4(s), 132.3(d), 118.5(d), 113.9(s), 96.6(d), 62.0(t), 30.3(t), 25.1(t), 18.7(t)

(b) Conversion to stannyl derivative (85)

Butyllithium (15% in hexane, 0.019 mole) was added to 2-(4-bromophenoxy)tetrahydropyran (4.9g 0.019 mole) in dry ether (50 mls), at -78°C, under a static pressure of dry nitrogen. The mixture was stirred at -78°C for 2 hours and then for a further 1 hour at 0°C. Trimethyltin chloride (3.8g, 0.019 mole) in ether (10 mls) was then added dropwise at 0°C. Stirring was continued at this temperature for 6 hours and then for 16 hours at reflux. Water (50 mls) was then added to the cooled mixture and the organic phase was separated, washed with water and dried over anhydrous magnesium sulphate. Removal of the solvent gave the crude product as a yellow liquid which was fractionated to obtain 2-(4-trimethylstannylphenoxy)tetrahydropyran (3.6g, 56%) at 170 - 176°C/1.0 mmHg.

I.R. (liquid film) ν_{max}/cm^{-1} 3020, 2945, 2880, 1455, 1220, 1200, 1040, 965, 770.

$\delta_H(CDCl_3)$/ppm 6.75-7.30 (ABq, 4H, J_{AB} = 8Hz), 5.25 (t,1H), 3.40-4.00 (m,2H), 1.40-2.20 (m,6H), 0.30 (s,9H)

M.S. m/e (M^+) 342.0618, 340.0613, and 338.0617;
$C_{14}H_{22}O_2Sn$ requires 342.0642, 340.0640, and 338.0642.

4.5.2 Preparation of the Aryl-silanes

(i) p-Tolyltrimethylsilane

Trimethylsilyl chloride (16.3g, 0.15 mole) in dry ether (20 mls) was added dropwise to a stirred solution of p-tolylmagnesium bromide (prepared from p-bromotoluene, 0.15 mole) in ether (100 mls), at room temperature, under a static pressure of dry nitrogen. The mixture was then heated under reflux for 4 hours. After cooling, the reaction was quenched with a saturated solution of ammonium chloride (100 mls) and the organic phase was separated, washed with water, and dried over anhydrous magnesium sulphate. Removal of the solvent gave a yellow liquid which was fractionated to obtain p-tolyltrimethylsilane (17.7g, 72%) at 104 - 105°C/60 mmHg. (Lit.[144] 80°C/35 mmHg).

$\delta_H(CDCl_3)$/ppm 6.80-7.40 (m,4H), 2.20 (s,3H), 0.20 (s,9H)

(ii) p-Methoxyphenyltrimethylsilane

Prepared from p-bromoanisole. Fractionation gave p-methoxyphenyltrimethylsilane (62% yield) at 89 - 94°C/2 mmHg. (Lit.[145] 80°C/6 mmHg).

$\underline{\delta_H}(CDCl_3)$/ppm 6.60-7.40 (ABq, 4H, J_{AB} = 8Hz),
3.70 (s,3H), 0.22 (s,9H).

(iii) o-Methoxyphenyltrimethylsilane

Prepared from o-bromoanisole. Fractionation gave o-methoxyphenyltrimethylsilane (49% yield) at 70 - 74°C/2 mmHg. (Lit.[145] 205 - 206°C/733 mmHg).

$\underline{\delta_H}(CDCl_3)$/ppm 6.60-7.40 (m,4H), 3.65 (s,3H), 0.25 (s,9H)

4.5.3 Preparation of the Aryl-mercury Compounds

(i) 2,4-Dimethylphenylmercuric acetate

This was prepared by the method described in the literature,[116] involving direct mercuration of m-xylene by reaction with mercuric acetate. 2,4-Dimethylphenylmercuric acetate was obtained as a white solid (4.6g, 51%) after recrystallization from ethanol, m.pt 125 - 127°C. (Lit.[116] 126 - 127°C).

(ii) p-Tolylmercuric bromide

This was prepared by the general procedure described by Nesmeyanov.[146] p-Tolylmagnesium bromide was prepared from p-bromotoluene (8.55g, 0.05 mole) in dry ether (30 mls) in the usual way. Mercuric bromide (18.0g, 0.05 mole) was then added in small portions to the stirred Grignard re-

agent at 0°C. After stirring at room temperature for 1 hour, the mixture was heated under reflux for a further 4 hours. The ether was then decanted off and the residue was boiled three times with 50 ml portions of 1% hydrochloric acid to removed unreacted mercuric bromide. The crude solid was then washed with hot water, ethanol, and ether and was dried at 100°C. Recrystallization from pyridine and cleaning with decolourising charcoal, gave p-tolylmercuric bromide (5.8g, 31%) as colourless platelet crystals, m.pt 229°C. (Lit.[147] 231°C).

4.5.4 Preparation of Dipotassium p-tolylpentafluorosilicate

This was prepared from p-tolyltrichlorosilane by the general procedure described by Tamao and co-workers.[117] p-Tolyltrichlorosilane was prepared by the following procedure adapted from the method of Lewis.[148]

p-Tolylmagnesium bromide was prepared from p-bromotoluene (0.15 mole) in the usual way. The solution was then filtered, under dry nitrogen, through a plug of glass wool and was added dropwise to a solution of silicon tetrachloride (0.22 mole) in benzene (40 mls), under dry nitrogen, at 0°C. The mixture was then stirred for 12 hours at room temperature. Magnesium salts were filtered off and the solvent was removed under vacuo. The dark brown liquid was distilled to obtain p-tolyltrichlorosilane (11.8g, 35%) as a colourless liquid, b.pt 95 - 98°C/5.5 mmHg. (Lit.[149] 65°C /1-1.2 mmHg).

p-Tolyltrichlorosilane (11.3g, 0.05 mole) was added dropwise to a stirred solution of anhydrous potassium fluoride (52.3g, 0.9 mole) in distilled water (100 mls), at 0°C. The white precipitate was filtered off, washed successively with water, ethanol and ether, and was dried *in vacuo* over calcium chloride. Dipotassium p-tolylpentafluorosilicate [150] was obtained as a white solid which was insoluble in all organic solvents. The overall yield (from p-bromotoluene) was 10.5g, 24%.

4.6 HYDROXYLATION OF ARYL-METAL COMPOUNDS

4.6.1 Hydroxylation of the tin, silicon and mercury derivatives

(i) Using the peroxide adducts catalysed by aluminium chloride

The peroxide adduct (0.005 mole) was added to a stirred mixture of the aryl-metal compound (0.005 mole) and aluminium chloride (0.01 mole) in dichloromethane (20 mls) at 0°C. Stirring was continued for 24 hours at room temperature and dilute hydrochloric acid solution (20 mls) was then added. The phenolic products were isolated from the organic phase by alkaline extraction, as described previously (4.3.1). The yield and isomer distribution of the products was determined by GLC analysis.

(ii) Using t-butylhydroperoxide catalysed by aluminium chloride

t-Butylhydroperoxide was used as an anhydrous solution in dichloromethane, prepared by azeotropic distillation. The reaction was performed as described using the peroxide adducts. The mixture was stirred at room temperature for 6 hours and the phenolic products then extracted in the usual way.

(iii) Using t-butylperbenzoate catalysed by aluminium chloride

t-Butylperbenzoate (0.39g, 0.002 mole) in dichloromethane (10 mls) was added dropwise to a stirred mixture of the aryl-metal compound (0.004 mole) and aluminium chloride (1.52g, 0.004 mole) in dichloromethane (10 mls) at 0°C. Stirring was continued for 24 hours at room temperature and sodium sulphite solution was then added. The phenolic products were isolated by alkaline extraction and were analysed by GLC.

(iv) Using triphenylsilylhydroperoxide catalysed by aluminium chloride

Triphenylsilylhydroperoxide (0.002 mole) in dichloromethane (10 mls) was added dropwise to a stirred mixture of aluminium chloride (1.52g, 0.004 mole) and the aryl-metal compound (0.004 mole) in dichloromethane (10 mls) at 0°C. After stirring for 24 hours, dilute hydrochloric acid was added and the phenolic products were isolated by alkaline extraction and analysed by GLC using a BP1 capillary column.

(v) Using m-chloroperbenzoic acid

m-Chloroperbenzoic acid (0.008 mole) in dichloromethane (20 mls) was added dropwise to a stirred solution of the aryl-metal compound in dichloromethane (10 mls) at 0°C. The solution was stirred at room temperature for 24 hours. Sod-

ium bicarbonate solution (10%, 20 mls) was then added and the aqueous phase was separated and extracted with dichloromethane. The combined organic phase was washed with sodium bicarbonate solution (2 x 20 mls) and was then extracted with 10% sodium hydroxide solution to obtain the phenolic products by the usual procedure.

4.6.2 Hydroxylation of aryl-Grignard reagents

The reactions were performed under a static pressure of dry nitrogen. The Grignard reagent was prepared from the aryl bromide (0.02 mole) in dry ether (25 mls) by the usual procedure. The peroxide (0.01 mole) was then added portionwise at 0°C and the mixture was stirred for 2 hours at 0°C, and then at room temperature for 24 hours (4 hours using t-butylhydroperoxide). Dilute hydrochloric acid solution (20 mls) was then added and the phenolic products isolated by extraction in the usual way.

4.6.3 Hydroxylation of p-tolyltrimethylsilane using deuterio-t-butylhydroperoxide catalysed by aluminium chloride

Deuterio-t-butylhydroperoxide was prepared by mixing an excess of deuterium oxide (D_2O) with an anhydrous solution of t-butylhydroperoxide in dichloromethane. The D_2O was then removed by azeotropic distillation using thoroughly

dried apparatus. This procedure was repeated twice. Analysis of the t-butylhydroperoxide solution by ^{1}H NMR showed that about 90% incorporation of deuterium had been effected.

Hydroxylation of p-tolyltrimethylsilane was carried out in the usual way using the deuterated solution in the presence of aluminium chloride. All apparatus was washed out with D_2O and thoroughly dried before use. After stirring for 6 hours at room temperature, the phenolic products were isolated and the GLC-mass spectrum was recorded using a BP17 column at 140°C.

The mass spectra of the cresol isomers were identical to authentic standards and there was no indication of any deuterated cresols being present.

4.7 MANNICH REACTIONS

4.7.1 Reaction of N,N-Dimethyl(methylene)iminium chloride with Aryl-stannanes

4.7.1.1 General procedure

The iminium salt was prepared immediately before use. All procedures were carried out under a dry nitrogen atmosphere, using anhydrous solvents.

Acetyl chloride (1.18g, 0.015 mole) in dry diethyl ether (5 mls) was added dropwise to a stirred solution of bis(dimethylamino)methane[151] (1.53g, 0.015 mole) in ether (10 mls) at 0°C. After stirring for 20 minutes, the solvent was removed by use of a filter stick, and the salt was washed with several portions of dry ether. Dichloromethane (20 mls) was then added to the iminium salt, and the aryl-stannane (0.01 mole) in dichloromethane (10 mls) was added dropwise with ice-bath cooling. The mixture was stirred for the required period at the specified temperature and was then terminated by addition of 4N sodium hydroxide solution (20 mls). The two layers were separated, the aqueous phase was extracted with dichloromethane and the combined organic phase was washed with 4N sodium hydroxide solution. The organic phase was extracted with 2N hydrochloric acid solution (3 x 30 ml portions) and the acidic extracts washed with dichloromethane (20 mls). The acidic aqueous phase was then basified with 4N sodium hydroxide

solution and the milky precipitate which formed was extracted into dichloromethane (4 x 25 ml portions). The combined organic extracts were then washed with sodium hydroxide solution and dried over anhydrous magnesium sulphate. Removal of the solvent, under vacuo, afforded the crude aminomethyl derivative which was purified by distillation using a Kugelröhr apparatus.

4.7.1.2 N,N-Dimethylaminomethyl products

(i) N,N-Dimethylbenzylamine

B.pt 82 - 84°C/20 mmHg (Lit.[112] 178 - 180°C/760 mmHg)

I.R. (liquid film) ν_{max}/cm^{-1} 3085, 3065, 3030, 2980, 2945, 2820, 2770, 1520, 1495, 1455, 1025, 735, 700.

$\delta_H(CDCl_3)$/ppm 7.30 (s,5H), 3.38 (s,2H), 2.23 (s,6H).

(ii) N,N,2-Trimethylbenzylamine

B.pt 76 - 78°C/10 mmHg (Lit.[152] 73 - 75°C/10 mmHg)

I.R. (liquid film) ν_{max}/cm^{-1} 3060, 3020, 2980, 2945, 2820, 2765, 1460, 1020, 740.

$\delta_H(CDCl_3)$/ppm 6.92 (m,4H), 3.22 (s,2H), 2.30 (s,3H), 2.15 (s,6H).

M.S. m/e (M^+) 149.1214; $C_{10}H_{15}N$ requires 149.1204.

(iii) N,N,3-Trimethylbenzylamine

B.pt 102 - 104°C/28 mmHg. (Lit.[153] 70 - 72°C/15 mmHg)

I.R. (liquid film) ν_{max}/cm^{-1} 3025, 2975, 2940, 2815, 2770, 1455, 1030, 780.

$\delta_H(CDCl_3)$/ppm 6.90-7.25 (m,4H), 3.35 (s,2H), 2.32 (s,3H), 2.22 (s,6H).

M.S. m/e (M^+) 149.1202; $C_{10}H_{15}N$ requires 149.1204

(iv) N,N,4-Trimethylbenzylamine

B.pt 102°C/35 mmHg. (Lit.[112] 196 - 198°C/760 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3030, 2940, 2820, 2775, 1460, 1030, 840.

$\delta_H(CDCl_3)$/ppm 7.10 (s,4H), 3.36 (s,2H), 2.33 (s,3H), 2.22 (s,6H).

M.S. m/e (M^+) 149.1194; $C_{10}H_{15}N$ requires 149.1204.

(v) N,N-Dimethyl-2-methoxybenzylamine

B.pt 102 - 104°C/12 mmHg. (Lit.[154] 113°C/20 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3020, 2940, 2825, 2780, 1460, 1035, 750.

$\delta_H(CDCl_3)$/ppm 6.70-7.30 (m,4H), 3.78 (s,3H), 3.43 (s,2H), 2.25 (s,6H).

M.S. m/e (M^+) 165.1150; $C_{10}H_{15}NO$ requires 165.1154

(vi) N,N-Dimethyl-4-methoxybenzylamine

B.pt 122 - 124°C/18 mmHg. (Lit.[155] 110 - 111°C/16 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3040, 2940, 2820, 2770, 1510, 1455, 1040, 860.

$\delta_H(CDCl_3)$/ppm 6.75-7.25 (ABq, 4H, J_{AB} = 9Hz), 3.80 (s,3H), 3.35 (s,2H), 2.20 (s,6H).

M.S. m/e (M^+) 165.1156; $C_{10}H_{15}NO$ requires 165.1154

(vii) 1-(N,N-Dimethylaminomethyl)naphthalene

B.pt 135°C/1.5 mmHg. (Lit.[156] 132 - 134°C/2 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3040, 2970, 2940, 2820, 2765, 1510, 1460, 1015, 790, 775.

$\delta_H(CDCl_3)$/ppm 8.05-8.25 (m,1H), 7.25-7.80 (m,6H), 3.75 (s,2H), 2.26 (s,6H).

M.S. m/e (M^+) 185.1205; $C_{13}H_{15}N$ requires 185.1204.

(viii) 3-(N,N-Dimethylaminomethyl)thiophene (83)

B.pt 85°C/12 mmHg. (Lit.[157] 28 - 32°C/0.12 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 2980, 2940, 2820, 2770, 1455, 1030, 775.

$\delta_H(CDCl_3)$/ppm 6.90-7.25 (m,3H), 3.42 (s,2H), 2.21 (s,6H)

$\delta_c(CDCl_3)$/ppm 139.7(s), 128.5(d), 125.5(d), 122.8(d), 59.0(t), 45.2(q).

M.S. m/e (M^+) 141.0615; $C_7H_{11}NS$ requires 141.0612.

The spectral data are in agreement with values quoted by Gierer:[158]

I.R. ν_{max}/cm^{-1} 2900-2750, 1465, 1025, 775.

$\delta_H(CDCl_3)$/ppm 7.00-7.23 (m,3.2H), 3.42 (s,1.9H), 2.17 (s,5.9H).

(ix) p-Bis(N,N-dimethylaminomethyl)benzene (82)

B.pt 138 - 142°C/8 mmHg. (Lit.[159] 125 - 127°C/5 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3020, 2970, 2940, 2820, 2770, 1610, 1455, 860.

$\delta_H(CDCl_3)$/ppm 7.20 (s,4H), 3.35 (s,4H), 2.22 (s,12H)

M.S. m/e (M^+) 192.1629; $C_{12}H_{20}N_2$ requires 192.1626

(x) 4-(N,N-Dimethylaminomethyl)phenol (86)

B.pt 138 - 140°C/0.8 mmHg. M.pt 86 - 89°C. (Lit.[154] 106°C)

I.R. (CCl_4) $\nu_{max}cm^{-1}$ 3400, 2940, 2780, 1605, 1470, 840.

$\delta_H(CDCl_3)$/ppm 10.00 (s,1H, exchangeable), 6.60-7.20 (ABq, 4H, J_{AB} = 9Hz), 3.55 (s,2H), 2.30 (s,6H).

M.S. m/e (M^+) 151.0995; $C_9H_{13}NO$ requires 151.0997

4.7.1.3 Competition reactions of the Aryl-stannanes with N,N-Dimethyl(methylene)iminium chloride

The methyleneiminium salt was prepared from acetyl chloride (0.001 mole) and bis(dimethylamino)methane (0.001 mole) in ether. A mixture of the aryl-stannanes (0.01 mole of each)

was then added to a suspension of the iminium salt in dichloromethane (20 mls). After heating for the required period, the aminomethyl products were extracted by the usual method, and the ratio of products was determined by GLC analysis using an OV17 column at 100°C.

4.7.2 Reaction of Benzyltributylstannane with N,N-Dimethyl-(methylene)iminium chloride

The procedure was as described for the aryl-stannane reactions. The reaction mixture was heated under reflux for 48 hours and the product, N,N-dimethyl-2-phenylethylamine, was isolated in the usual way and was purified by distillation.

B.pt 76 - 78°C/12 mmHg. (Lit.[160] 66 - 68°C/6 mmHg)

I.R. (liquid film) ν_{max}/cm^{-1} 3060, 3030, 2940, 2820, 2770, 1495, 1460, 1055, 745, 700

$\delta_H(CDCl_3)$/ppm 7.18 (s,5H), 2.40-3.00 (m,4H), 2.30 (s,6H).

M.S. m/e (M^+) 149.1204; $C_{10}H_{15}N$ requires 149.1204.

4.7.3 Reaction of Methylenepiperidinium chloride (79) with o-Methoxyphenyltributylstannane

Dipiperidinomethane was prepared by the literature method.[161] Acetyl chloride (1.18g, 0.015 mole) in ether (5 mls) was added to dipiperidinomethane (2.73g, 0.015 mole) in

ether (20 mls) at 0°C and the mixture was stirred for 20 minutes. The solvent was then removed from the white solid by use of a filter stick, under dry nitrogen, and the iminium salt was washed several times with dry ether. o-Methoxyphenyltributylstannane (3.97g, 0.010 mole) was added to a stirred suspension of the salt in dichloromethane (40 ml) and the mixture was heated under reflux (under a static pressure of dry nitrogen) for 24 hours. The amine product, 2-piperidinomethylanisole (80), was then isolated by acid extraction, as described previously, and was purified by distillation. Yield, 57%.

B.pt 120 - 124°C/0.8 mmHg. (Lit.[111] 91°C/0.03 mmHg).

I.R. (liquid film) ν_{max}/cm^{-1} 3010, 2930, 2850, 2770, 1480, 755.

$\delta_H(CDCl_3)$/ppm 6.60-7.35 (m,4H), 3.68 (s,3H), 3.45 (s,2H), 2.25-2.55 (m,4H), 1.35-1.70 (m,6H).

M.S. m/e (M^+) 205.1472; $C_{13}H_{19}NO$ requires 205.1467.

4.8 ATTEMPTED REACTION OF THE VILSMEIER REAGENT, CHLOROMETHYLENEDIMETHYLIMINIUM CHLORIDE, WITH p-METHOXYPHENYLTRIMETHYLSTANNANE

Chloromethylenedimethyliminium chloride was prepared by the method reported in the literature.[162] Freshly dried and distilled N,N-dimethylformamide (9g) was placed in a flask fitted with a reflux condenser and supplied with a static pressure of dry nitrogen. Phosphorus pentachloride (3.12g, 0.015 mole) was added in small portions, at such a rate that the temperature did not rise above 120°C. After stirring for a further 15 minutes the mixture was cooled to 0°C and the liquid was removed by use of a filter stick. The white crystals of chloromethylenedimethyliminium chloride were washed successively with DMF and anhydrous ether. Dry dichloromethane (25 mls) was then added and p-methoxyphenyltrimethylstannane (2.71g, 0.01 mole) was added dropwise to the stirred suspension at room temperature. The mixture was heated under reflux for 24 hours and was then terminated by addition of water (25 mls). The organic phase was separated, washed with water, and dried over anhydrous magnesium sulphate. Removal of the solvent afforded an orange liquid (2.6g) which was shown by its ^{1}H NMR spectrum to be recovered p-methoxyphenyltrimethylstannane.

The combined aqueous phase was basified by addition of 2N NaOH and was extracted with dichloromethane. The extracts were dried over anhydrous magnesium sulphate and the sol-

vent removed to give a small amount of liquid which was identified as N,N-dimethylformamide.

The attempted reaction of o-methoxyphenyltributylstannane gave similar results. There was no evidence of any formylated products from either of the reactions.

4.9 ATTEMPTED REACTION OF N-METHYLACETONITRILIUM FLUOROBORATE WITH p-METHOXYPHENYLTRIMETHYLSTANNANE

Trimethyloxonium fluoroborate was prepared by the method of Olofson[163] and was converted to N-methylacetonitrilium fluoroborate by the following procedure, as described by Giles.[126]

Trimethyloxonium fluoroborate (2.32g, 0.0157 mole) was added to dry acetonitrile (3.0g, 0.073 mole) under a dry nitrogen atmosphere and the mixture was heated gently until bubbles of dimethyl ether were no longer evolved. Dichloromethane (5 mls) was then added and the solution was cooled to -20°C. N-Methylacetonitrilium fluoroborate crystallized as a colourless solid. The solvent was removed using a filter stick and the solid was washed with dichloromethane. p-Methoxyphenyltrimethylstannane (2.71g, 0.01 mole) in dichloromethane (5 mls) was then added to a suspension of the nitrilium salt in dichloromethane (20 mls) and the mixture was heated under reflux for 2 days. Water (25 mls) was then added and the aqueous layer was separated and extracted with dichloromethane (2 x 20 mls). The combined extracts were dried over magnesium sulphate and the solvent was removed *in vacuo*. Only a trace of material was obtained. This was not identified but there was no indication that any of the expected iminium salt product was present.

The organic phase from the original mixture was dried and the solvent removed *in vacuo* to obtain a colourless liquid

(2.7g). The ^{1}H NMR spectrum indicated that this material was mainly recovered p-methoxyphenyltrimethylstannane, although there was evidence that some protolytic cleavage of the aryl-tin bond had occurred to produce a small amount of anisole and a trimethyltin residue. There was no indication of any of the expected product, i.e. 4-(N-methylacetylimino)methoxybenzene (89) or its hydrofluoroborate.

The attempted reaction of various other aryl-stannanes with this reagent gave similar results.

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