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NEWER METHODS OF ARYLATION*

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1. INTRODUCTION

The arylation—replacement of a group by an aryl residue—of organic compounds is an important reaction which continues to attract considerable attention as milder, more selective methods are developed. This review will be limited to a survey of some of the newer methods of replacing *hydrogen* by aryl, with strong emphasis on the methods developed in the authors' laboratories.

One of the most common and useful reagents for effecting arylation of a variety of substrates is the aryldiazonium salt. The Meerwein arylation of activated alkenes,[1] and the Gomberg–Bachmann–Hey reaction with arenes (and variations on this theme, e.g. decomposition of *N*-nitrosoacetanilides),[2] and the copper- or pyridine-catalyzed intramolecular version thereof (Pschorr cyclization)[3] involve radical processes. On the other hand, thermal decomposition of diazonium salts in arenes (or the intramolecular version thereof) involves arylation via a cationic species.[3a,4] Diaroyl peroxides have also been used extensively as sources of aryl radicals in homolytic aromatic substitutions.[2a,5] Another free-radical arylation method consists of the photolysis of aryl iodides in aromatic solvents (or the corresponding intramolecular reaction).[6] Photolysis of arylthallium bis(trifluoroacetates) in an aromatic solvent similarly produces an unsymmetrical biaryl.[7] Nucleophilic arylation of six-membered heteroaromatic nitrogen compounds can be carried out readily with aryllithiums.[8] Diaryliodonium salts have been used extensively to effect arylations, e.g. *O*-arylation of pyridine 1-oxides,[9] of α- and γ-active methylene groups in β-dicarbonyl compounds,[10] of alkyl phenyl sulfides,[11] of tetrazolopyridines,[12] of unsaturated compounds,[13] of aminoacids,[14] and of *N*-hydroxyphthalimide,[15] to name but a few.

Among the more recent methods developed must be mentioned the Heck arylation, the use of

* Submitted in honor of Prof. E. C. Taylor's 65th birthday.

aryllead triacetates, a number of pentavalent bismuth reagents, some aryltin reagents, arylnitrenium ions, and some aryloxypyridinium salts which give arylated pyridines intramolecularly via a 1,2-dihydro intermediate. It is with these methods that we shall be concerned in this review. The use of Ar_3BiX_2 and $ArPdL_2X$ reagents has probably received the most attention. Since arylpalladium intermediates have been reviewed quite extensively their chemistry will only be summarized briefly here as it applies to the present context.

2. ARYLATION USING ORGANOBISMUTH REAGENTS

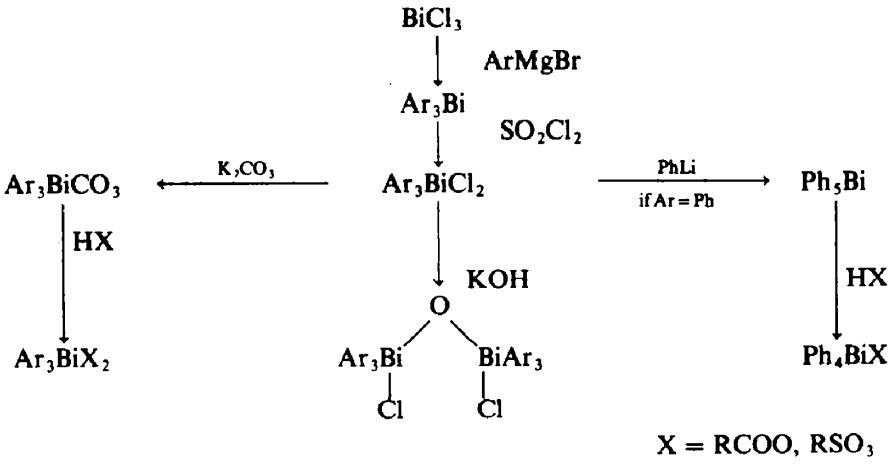
Organobismuth derivatives have been known for a long time.[16] With an electronic configuration of $[Xe]4p^{14}5d^{10}6s^26p^3$, bismuth has all its lower-energy orbitals filled, leaving five electrons in non-equivalent outer orbitals. The participation of the two s electrons leads to two possible valencies: Bi(III) and Bi(V). As expected, two series of organic compounds exist: the trivalent derivatives with a pair of non-bonded s electrons, and the pentavalent derivatives.[17]

Although a wide array of methods lead to organobismuth compounds,[17,18] the most general pathways for their synthesis involve the reaction of a Grignard reagent with $BiCl_3$ (Scheme 1). Thus reaction of phenylmagnesium bromide afforded Ph_3Bi, which upon oxidation with SO_2Cl_2 gave Ph_3BiCl_2, the pivotal compound from which the other tri-, tetra-, and penta-phenylbismuth compounds are derived.[19–22]

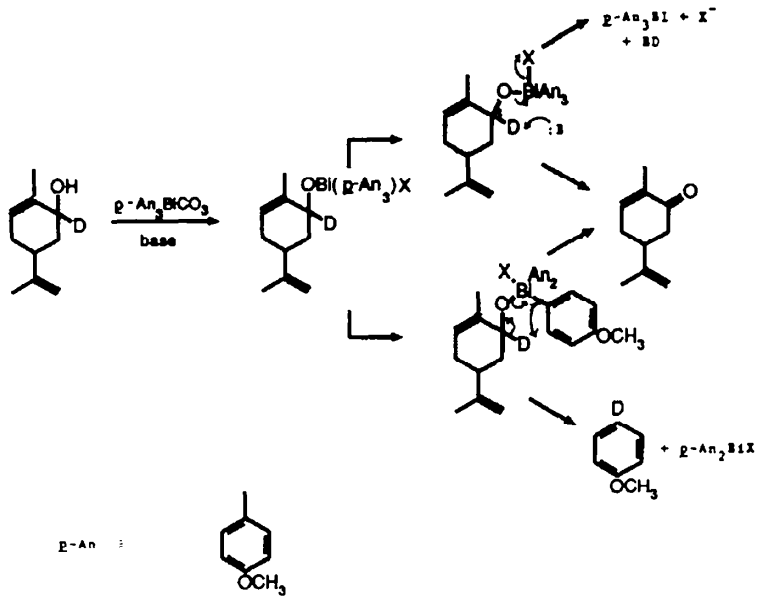
2.1. *Oxidations*

Arylbismuth reagents of the type Ph_3BiX_2 are mild and high yielding oxidizing agents for a range of primary, secondary, benzylic and particularly allylic alcohols.[19,21,23–27] As discussed in Section 2.3, they can also act as *O*-phenylating agents, and, therefore, a brief discussion of oxidation reactions is warranted so as to define in which situations these will take place. A great selectivity was observed with two members of this family, μ-oxo bis(chlorotriphenylbismuth) and triphenylbismuth carbonate, towards the oxidation of such alcohols even in the presence of other sensitive functions such as indole, pyrrole, thiols, and selenides.[19,23,24] Arylbismuth reagents of the type Ph_4BiX have also been shown to oxidize alcohols to the corresponding carbonyl compounds under basic conditions.[28] Similarly, Ph_5Bi[29] acts as an oxidant of the hydroxyl group.[30,31] Mechanistically, these oxidations proceed via a pentavalent Bi(V) intermediate, prone to reductive elimination. Two pathways were detected in the oxidation of (D)-deuteriocarveol to carvone by tri-*p*-methoxyphenylbismuth carbonate. *p*-Deuterioanisole and tri-*p*-methoxyphenylbismuth were formed during the reductive elimination (Scheme 2).[19,32] The existence of Bi(V) intermediates possessing a covalent Bi—O bond was conclusively shown by a series of ^{1}H-NMR experiments.[28]

Triphenylbismuth carbonate is a stoichiometric 1,2-glycol cleaving agent[19] as is triphenylbismuth diacetate for 1,2-glycolstannylenes.[33] Triphenylbismuth is formed quantitatively. This reaction can



Scheme 1.



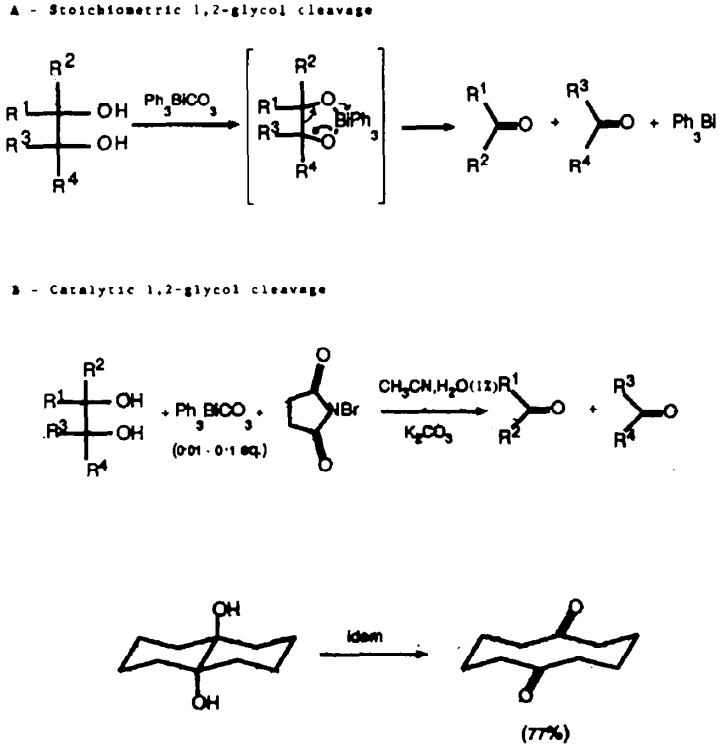
Scheme 2.

be carried out catalytically using *N*-bromosuccinimide as reoxidant, in the presence of K_2CO_3 and a trace of water, in acetonitrile (Scheme 3).[34,35]

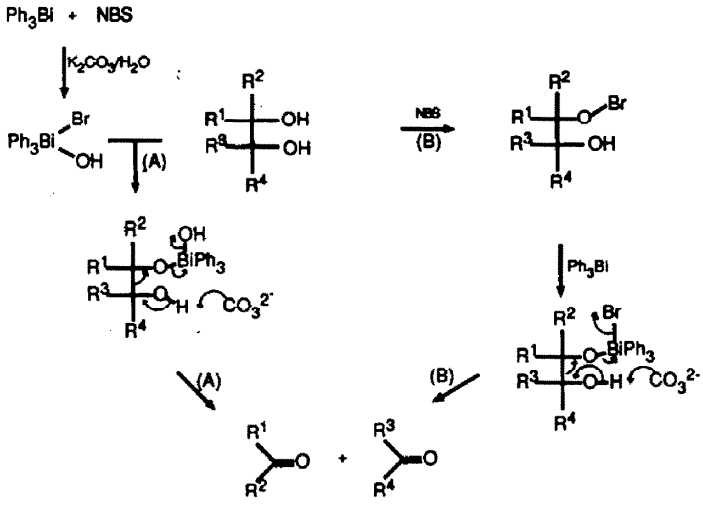
The catalytic reaction was explained as involving the formation of a glycol hypobromite, which oxidizes Ph_3Bi to a pentavalent Bi species (Scheme 4B). A pentavalent Bi derivative formed *in situ* and acting as the oxidant of the glycol is not involved (Scheme 4A).

2.2. *Arylation of phenols, enols, and various anions*

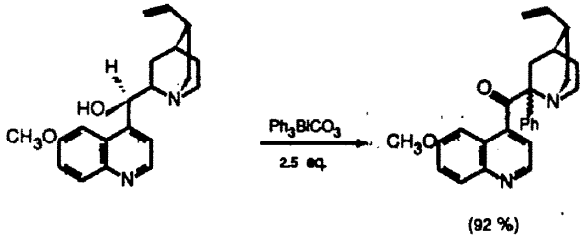
Oxidation of quinine to quininone has remained a classical problem for many years. A modest yield (34%) of quininone was obtained when the oxidation of quinine was performed with one



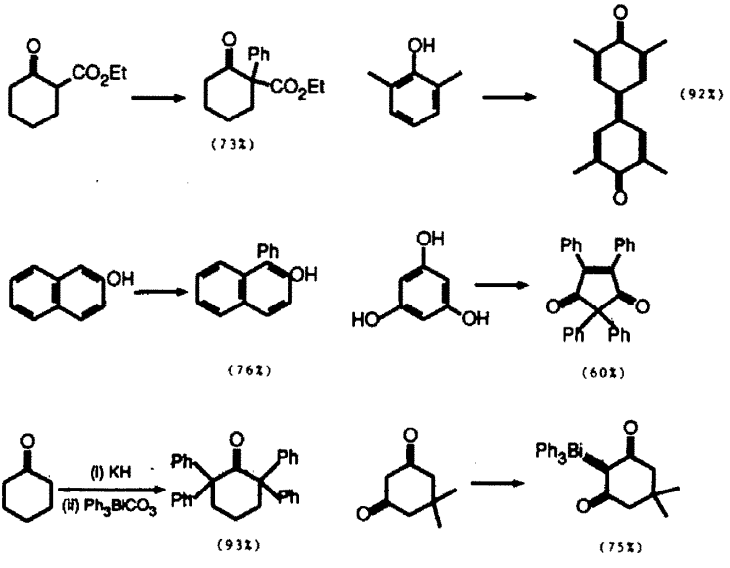
Scheme 3.



Scheme 4.



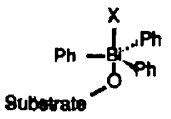
Scheme 5.



Scheme 6.

molar equivalent of Ph_3BiCO_3. However, when two molar equivalents of Ph_3BiCO_3 were used, the major product was a mixture of diastereoisomeric α-phenylated quininones (Scheme 5).[32]

Subsequently, a variety of other enolizable compounds were shown to be smoothly α-phenylated by Ph_3BiCO_3.[31,32,36-38] Unexpected products were, however, formed with a number of substrates such as 2,6-dimethylphenol, phloroglucinol, and dimedone (Scheme 6).[31,37] A covalently bonded Bi—O-substrate intermediate (**1**) was proposed to explain all of these phenylations.



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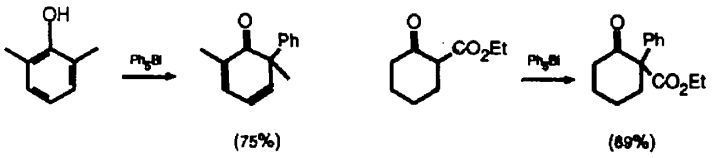
The influence of the fifth substituent X on the course of the phenylation process was examined. Ph_5Bi was shown to be a more selective phenylating agent for enols and phenols under neutral conditions (Scheme 7).[30,31] Among the phenols studied, 4-nitrophenol was found to react with Ph_5Bi to give the 4-nitrodiphenylether by *O*-phenylation.[31] From the point of view of mechanism (*O*- vs *C*-phenylation), this observation was misleading since it led to the postulate that the breakdown of the pentavalent Bi(V) intermediate was controlled by the nature of the fifth ligand, an electron-withdrawing group favoring *O*-phenylation and an electron-donating group favoring *C*-phenylation,[39] and both processes (*O*- and *C*-phenylation) proceeding via a common Bi(V) intermediate (**2**) (Scheme 8).

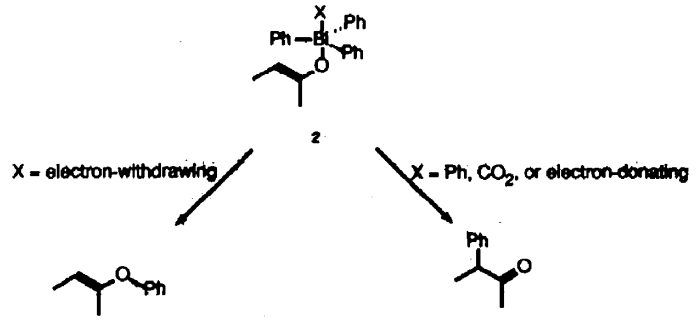
Some apparent support for this proposal came from the observation that a variety of enolizable substrates were phenylated with tetraphenylbismuth esters. *O*-Phenylation of 2-naphthol (**3**) occurred in high yield under neutral and acidic conditions, and *C*-phenylation under basic conditions (Table 1 and Scheme 9).[22,39,40] The proposal was disproved, however, when the formation and decomposition of the postulated intermediate was studied. Reaction of 2-naphthol with $Ph_3Bi(OCOCF_3)_2$ under basic conditions would be expected to occur via the same Bi(V) intermediate. Only the *C*-phenyl derivative (**4**) was obtained in this case, however.[22] The *C*-phenylation reaction is a fast, room temperature reaction, whereas the reaction under neutral or acidic conditions is slow and requires heating.

O-Phenylation by tetraphenylbismuth esters is now proposed to follow an aromatic S_N2-type pathway involving nucleophilic attack by the phenol at the Bi-hearing aromatic carbon.[22] A partial positive charge on the *ipso* carbon of that phenyl ring results from the presence of the electron-withdrawing substituent borne by the Bi atom. This charge is sufficient to induce attack by the lone pair of electrons on the phenolic oxygen leading to the *O*-phenyl ether (Scheme 10). Although the bimolecular kinetics of the reaction[41] would also be compatible with a transient 6-, or even 7-coordinated bismuth intermediate, this would be much more likely under basic, rather than neutral or acidic, conditions.

Under basic conditions, tetraphenylbismuth esters are among the best and most selective reagents for *ortho* or α-*C*-phenylation of a wide range of substrates such as phenols, enols, ketones, and β-

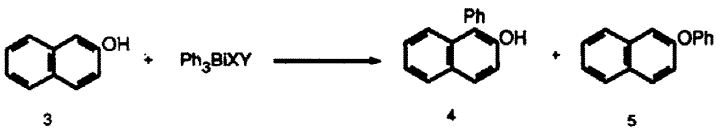


Scheme 7.



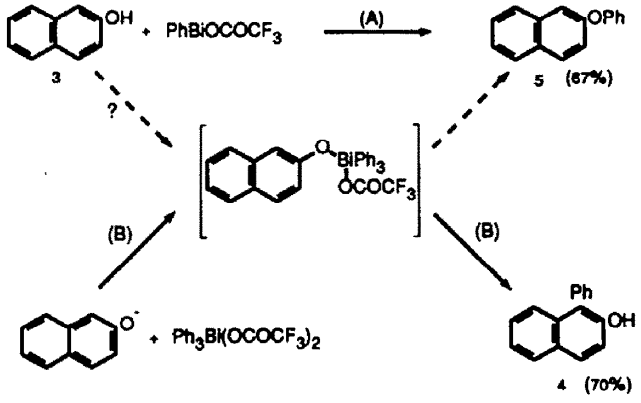
Scheme 8.

Table 1. O- and C-phenylation of 2-naphthol (3)



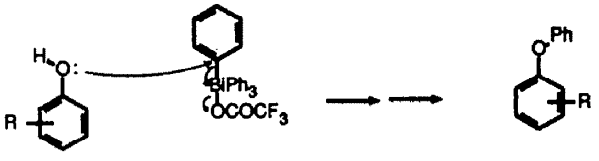
X	Y	pH	(4)(%)	(5)(%)	ref.
Ph	Ph	-	61	-	31
Ph	$OCOCF_3$	-	9	67	39
Ph	$OCOCF_3$	a	-	91	39
Ph	$OCOCF_3$	b	94	-	39
$OCOCF_3$	$OCOCF_3$	b	70	-	22
Cl	Cl	b	90	-	22

[a]Addition of trichloroacetic acid (0.6 equiv.). [b]Preformed anion using tetramethyl-2-t-butylguanidine.[42]



(A) Neutral or Acidic Conditions.
(B) Basic Conditions.

Scheme 9.



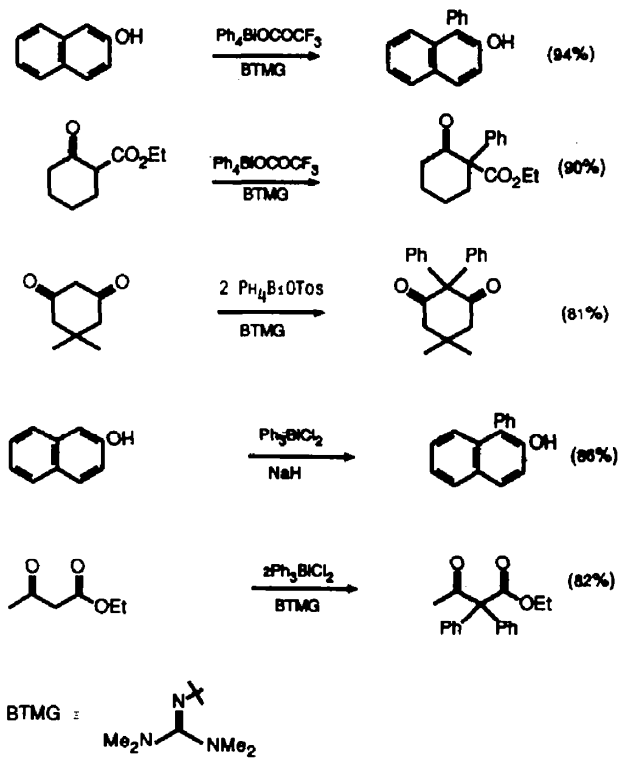
Scheme 10.

diketones.[22,37-39] Finally, it was found that the pivotal bismuth compound, Ph_3BiCl_2, was itself a good, high yielding reagent for *ortho* (or α-) *C*-phenylation in the presence of a suitable base (Scheme 11).[22,37]

The nature of the substituents on the phenol appears to govern the regioselectivity of the reaction with Ph_3BiCl_2 under basic conditions. Phenols bearing electron-withdrawing substituents are predominantly or selectively *O*-phenylated. Phenols bearing electron-donating substituents were mostly *ortho*-*C*-phenylated. Other decomposition pathways are sometimes involved (Scheme 12).[43]

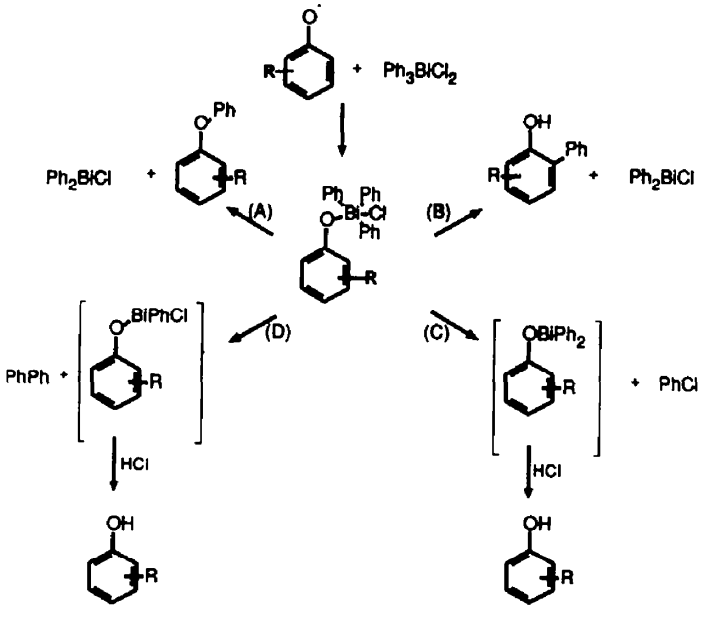
Different stabilized anions other than the aforementioned enolates have also been phenylated, such as nitroalkanes, thiols, sulphinic acids, indoles, and esters (Scheme 13).[37]

In the *C*-phenylation process (as compared with *O*-phenylation with Ph_4BiX under neutral conditions), the existence of covalently bonded Bi(V) intermediate was postulated and later detected



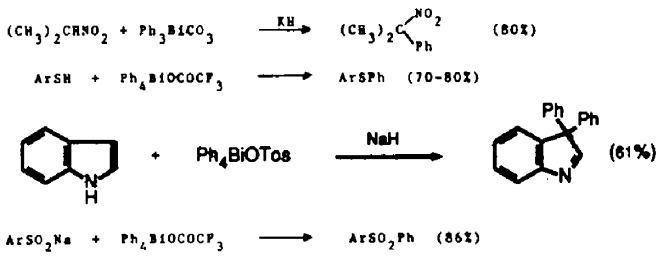
Scheme 11.

by physical methods. ^{1}H-NMR monitoring of the reaction of 3,5-di-*t*-butylphenol (**6**) with Ph_3BiCl_2 or $Ph_3Bi(OCOCF_3)_2$ under basic conditions or with Ph_5Bi indicated the formation of an intermediate (**7**). Two such intermediates have been isolated and their structures assigned. Their controlled thermal degradation led to 4,6-di-*t*-butyl-2-hydroxybiphenyl (**8**) (Scheme 14).[22]

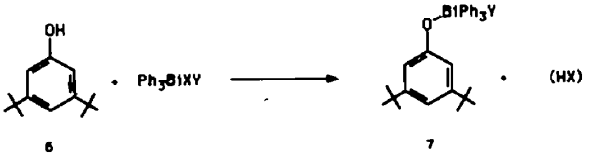


(A) O-phenylation; (B) ortho-C-phenylation; (C) α-Elimination of PhCl; (D) α-Elimination of biphenyl.

Scheme 12.



Scheme 13.

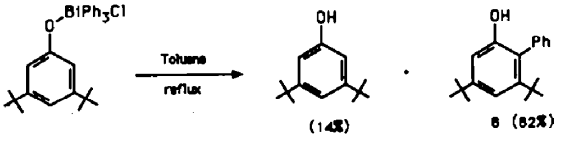


1. ^{1}H N.M.R.

	δ ortho-H	δ para-H
6	6.66	6.97
6 + TMG	6.67	6.82
6 + TMG + Ph_3BiCl_2	6.10	6.50
6 + TMG + $Ph_3Bi(OCOCF_3)$	6.13	6.46
6 + Ph_5Bi	6.15	6.47

(TMG = N,N'-tetramethylguanidine)

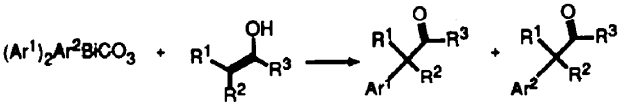
2. Isolation and Chemical Decomposition:



Scheme 14.

Studies of the relative migratory aptitudes of aryl groups have shown that the *C*-phenylation reaction is not an ionic process, and that the intermediate is unlikely to undergo reductive elimination by a free-radical pathway, but rather does so by a non-synchronous concerted mechanism (Scheme 15).[44] A combination of ESR spectroscopy (qualitative and quantitative) and quantitative chemical trapping experiments eliminated completely a possible free-radical pathway for these reactions (Scheme 16).[45]

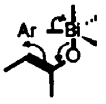
The occurrence of a cage-radical mechanism was not detected in the reaction of Ph_5Bi with a phenol (**9**) bearing an internal radical trap (Scheme 17).[46]



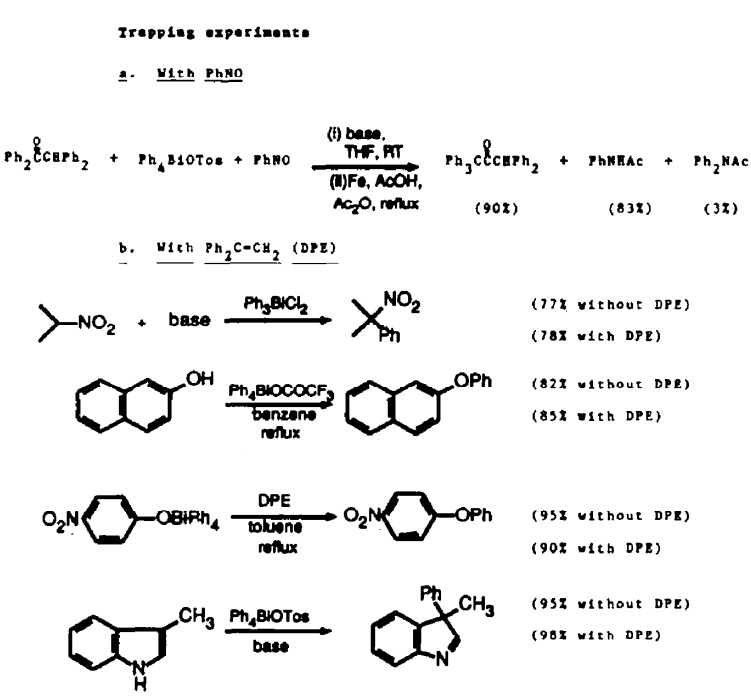
(Ar^1,Ar^2 = p-$NO_2C_6H_4$, p-$CH_3OC_6H_4$, p-$CH_3C_6H_4$, C_6H_5)

Relative migratory aptitudes:

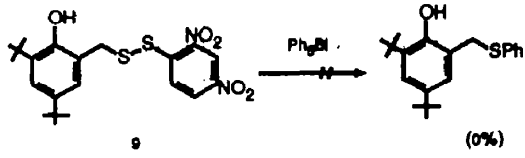
NO_2 (3.55) > H (1) > CH_3 (0.5) > CH_3O (0.25)



Scheme 15.



Scheme 16.



Scheme 17.

2.3. *Phenylation of alcohols and amines*

The pH-dependent behavior of phenols and enols towards tetraphenylbismuth trifluoroacetate was also observed in the reaction with alcohols. Thus, whereas under basic conditions primary and secondary alcohols are oxidized by $Ph_4BiOCOCF_3$, via a covalent Bi—O intermediate, the *O*-phenyl ethers are obtained under neutral conditions by an aromatic S_N2-type displacement (Schemes 10 and 18).[28]

a. Under neutral conditions:

$$RCH_2OH + Ph_4BiOCOCF_3 \xrightarrow[\text{or toluene/reflux}]{\text{benzene/reflux}} RCH_2OPh \qquad (70\%)$$

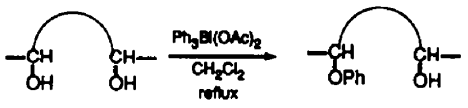
$$CH_3CH(OH)CH_3 + Ph_4BiOCOCF_3 \xrightarrow{\text{benzene/reflux}} (CH_3)_2CHOPh \qquad (30\%)$$

b. Under basic conditions:

$$R^1CH(OH)R^2 + Ph_4BiX \xrightarrow[\text{base}]{\text{R.T.}} R^1\overset{\overset{O}{\|}}{C}R^2 \qquad (85\text{–}90\%)$$

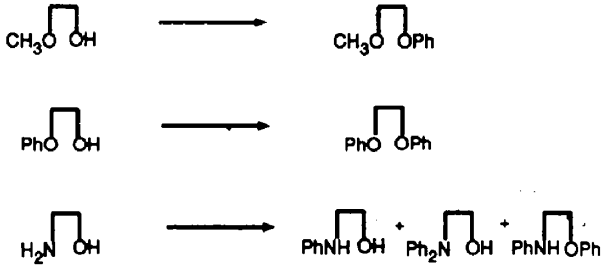
Scheme 18.

Within the framework of a comparative study of various oxidants towards glycols and glycolstannylenes, David and Thieffry[33] discovered a selective mono-*O*-phenylation of diols by reaction with triphenylbismuth diacetate in CH_2Cl_2. Good to excellent yields were obtained with *bis*-primary and *bis*-secondary vicinal diols. The reaction rate decreased with increasing chain length



[α-,β-,γ-, or δ-glycols (with axial preference); induction time, solvent (CH_2Cl_2), light-catalysed]

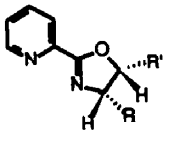
Other substrates:



Scheme 19.

between the two hydroxyl functions up to six carbons, but yields were good. An axial preference was observed in conformationally rigid molecules. An induction period (~2 h) was always observed.[47] The reaction was, moreover, photochemically activated, solvent selective and efficient only with $Ph_3Bi(OAc)_2$. Ether-alcohols and amino-alcohols were also phenylated (Scheme 19).[48]

At the same time, Dodonov and coworkers discovered that simple aliphatic alcohols were slowly *O*-phenylated when treated with $Ph_3Bi(OAc)_2$ in the presence of copper salts but in the absence of solvent.[49] In the glycol *O*-phenylation reaction, addition of a catalytic amount of a copper salt, such as $Cu(OAc)_2$, increased the reaction rate considerably and suppressed the induction period and solvent selectivity (Table 2). Optical inductions were observed in the presence of a chiral pyridine oxazoline ligand (**10**).[50] The highest *ee* (30.2%) was observed when R = (*S*)—CHMeEt and R′=H,



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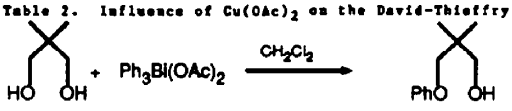
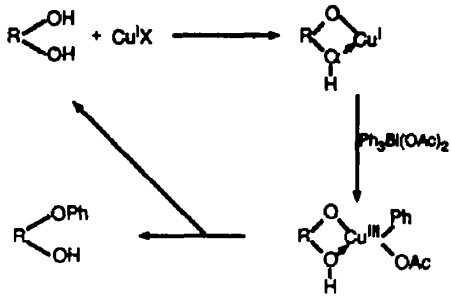
but the yields were considerably lower when the copper catalysts were complexed with the 2-pyridyloxazoline than in the other cases. Although a free radical mechanism was proposed for the copper-catalyzed reaction,[51] a more likely mechanism may involve catalysis by copper(I) through oxidative addition of Ph and OAc, followed by transfer to the hydroxyl function (Scheme 20).[48]

Table 2. Influence of $Cu(OAc)_2$ on the David-Thieffry Reaction

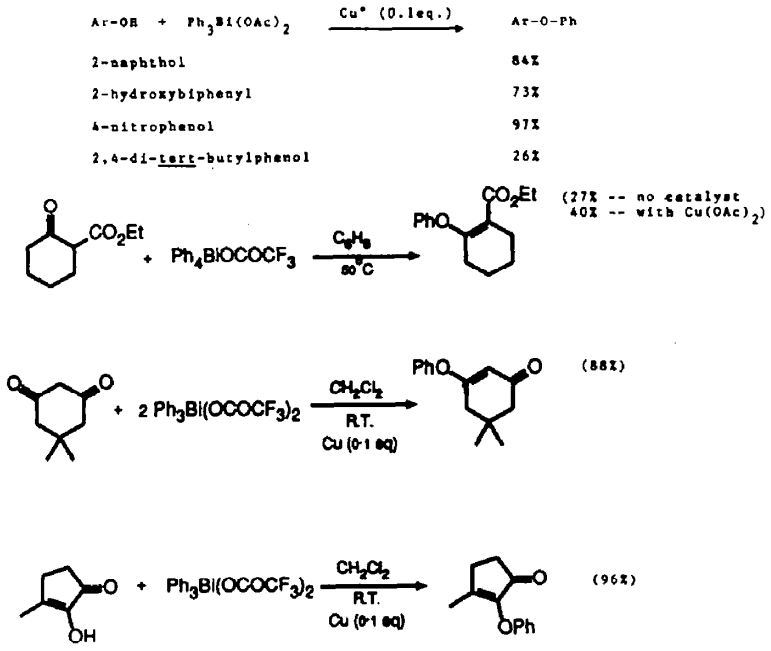


$Cu(OAc)_2$ (eq.)	Temp.	Conditions	Induction Time (h)	Reaction Time (h)	O-Phenyl ether(%)
0	reflux	a	2	4	91
10^{-4}	reflux	a	0	0.25	82
0.1	reflux	b	0	0.25	78
0.1	20 C	b	0	1	82

[a]Ambient light. [b]In the absence of light.



Scheme 20.



Scheme 21.

Copper-catalysis was extended to the phenylation of other substrates, such as phenols and enols (Scheme 21).[51,52]

In an exciting new development, it has been found that aliphatic and aromatic primary and secondary amines are mono- or di-*N*-phenylated by $Ph_3Bi(OAc)_2$ under copper catalysis in a mild, selective and high yielding reaction (Table 3).[53,54]

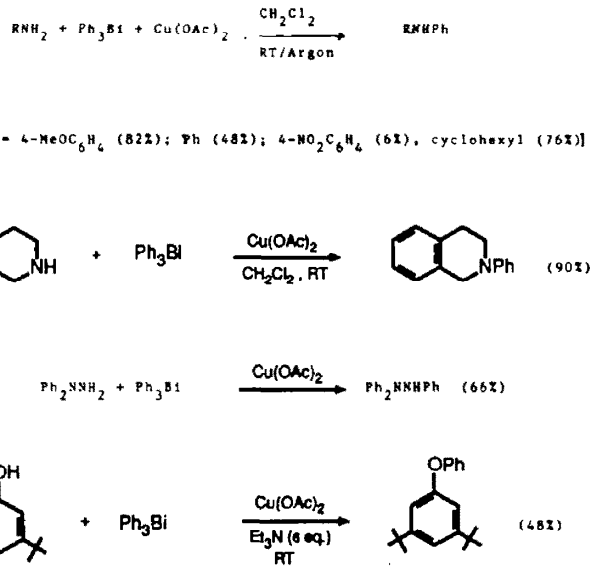
Triphenylbismuth itself can act as a phenylating agent of alcohols and amines in the presence of $Cu(OAc)_2$.[55,56] Only copper(II) acylates are efficient, and a stoichiometric amount is required.

Table 3. Copper-catalyzed *N*-arylation of amines

$$R{-}NH_2 + Ph_3Bi(OAc)_2 \xrightarrow{Cu^{\circ}(0.1\,eq.)} \underset{\underline{B}}{R{-}NH{-}Ph} + \underset{\underline{C}}{R{-}NPh_2}$$
(A)

R	A (eq.)	B (%)	C (%)
n-C_4H_9	1.1	60	20
	2.2	—	70
4-$CH_3OC_6H_4$	1.02	91	—
	3.3	28	68
4-$O_2NC_6H_4$	1.02	23	—
	2.2	90	—

One example each of a hydrazine and a hydrazone were also *N*-phenylated. Phenols were *O*-phenylated only in the presence of excess triethylamine. The proposed mechanism involves an *in*



situ oxidation of Ph_3Bi by $Cu(OAc)_2$, followed by a copper(I)-catalyzed aryl transfer (Scheme 22).[56] Radical traps, e.g. $Ph_2C{=}CH_2$ do not change the yields.

$$[Cu(OAc)_2,\ m\ RNH_2] + Ph_3Bi \longrightarrow Ph_3Bi(OAc)_2 + Cu^{I}OAc,\ n\ RNH_2$$

$$Ph_3Bi(OAc)_2 + R{-}NH_2 + Cu^{I}X \rightarrow \begin{array}{c} R{-}NH_2 \\ | \\ Cu{-}X \\ / \quad \backslash \\ AcO \quad Ph \end{array} \rightarrow R{-}NH{-}Ph + Cu^{I}X$$

Scheme 22.

Aliphatic alcohols (neat) are reported to be *O*-phenylated slowly by Ph_3Bi and $Cu(OAc)_2$ the reaction being improved by the presence of oxygen.[56]

$$Alk{-}OH + Ph_3Bi \xrightarrow[O_2]{Cu(OAc)_2,\ \text{slow}} Alk{-}OPh$$

In summary, arylbismuth compounds are proving to be very versatile and convenient reagents for the arylation of a variety of organic molecules. By a choice of the right reagent and reaction conditions, phenols can either be *O*- or *ortho*-phenylated, enols can be *O*- or α-monophenylated or α,α-diphenylated, alcohols may be oxidized or *O*-phenylated, and aromatic and aliphatic amines may be *N*-phenylated (*N*,*N*-diphenylated if the amine is primary and two equivalents of bismuth reagents are used). Hydrazines and hydrazones may also be *N*-phenylated. At present, one limitation of the procedure is when an expensive aryl halide (to get the arylbismuth derivative) has to be used, since at least two equivalents of Ar are 'lost' from, say, Ar_3BiX_2, only one being utilized. (Dismutation of Ph_2BiX to Ph_3Bi[17,18] improves matters somewhat in those cases where the latter is used). This is not a problem with the readily available simple aryl halides where it may be the method of choice for achieving arylation.

3. ARYLATIONS USING ORGANOLEAD(IV) REAGENTS

The use of aryllead triacetates as arylating agents has been pioneered by Pinhey and his co-workers. Phenyllead triacetate was first prepared by Kocheshkov in 1952.[58] The synthesis of aryllead(IV) tricarboxylates was improved by Pinhey[59] but still suffered from two main disadvantages:

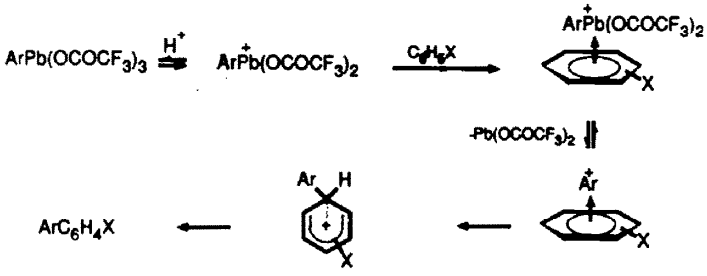
(i) the separation of the aryllead triacetate $Ar_2Hg + Pb(OAc)_4 \rightarrow ArPb(OAc)_3 + ArHgOAc$ from arylmercury acetate was difficult; (ii) one aryl residue was lost as the mercuriacetate, a serious handicap with less readily available aromatics. The formation of $ArPb(OCOCH_3)_3$ has now been improved considerably and involves the following sequence:[60]

$$ArX \longrightarrow ArMgX \xrightarrow{n\text{-}Bu_3SnCl} ArSnBu_3 \xrightarrow[\substack{CHCl_3/40^\circ C \\ \text{cat. } Hg(OCOCF_3)_2}]{Pb(OAc)_4} ArPb(OAc)_3 + Bu_3SnOAc$$

Yields are good with either electron-withdrawing or -donor groups in the aromatic ring. An alternate method which avoids the separation of ArHgOAc is the generation and use *in situ* of $ArPb(OAc)_3$ from Ar_2Hg.[61] This does not avoid, however, the 'loss' of one aryl residue, as discussed above.

Aryllead(IV) tricarboxylates arylate aromatic rings.[62] The yields vary from 88% for mesitylene, to 2% for benzene and toluene to zero for nitrobenzene. The solvent of choice is trifluoroacetic acid. The yields from benzene (38%) and toluene (58%) are improved considerably when $AlCl_3$ or $Al(OCOCF_2CF_2CF_3)_3$ are used as the catalyst in the absence of solvent. When only a slight excess of aromatic substrate over $ArPb(OCOCH_3)_3$ is used in the absence of CF_3CO_2H an appreciable amount of terphenyls is formed. Some representative results are summarized in Table 4.

On the basis of the effects of substituents in the substrate upon reactivities and orientation, it was proposed that, with good π-donors and CF_3CO_2H as solvent, attack by a cationic species was taking place, but that no *free* aryl cations were involved as intermediates (Scheme 23). As the π-



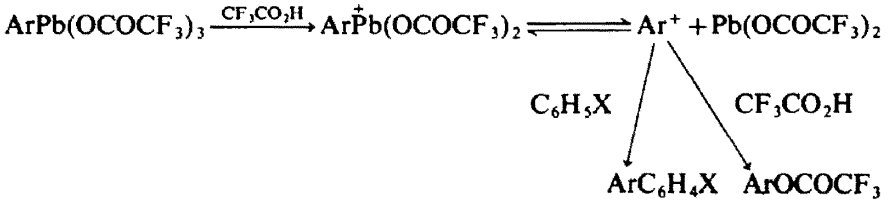
Scheme 23.

Table 4. Some aromatic arylation using $ArPb(OAc)_3$

$ArPb(OAc)_3$	Substrate	Conditions	Time (h)	Products: Biaryls (% yields; isomer ratios)	Products: ArH (%)	Products: Other (%)
Ar = 4-MeC_6H_4	C_6H_6	A	24	30		4-$CH_3C_6H_4OCOCF_3$ (33)
4-MeC_6H_4	C_6H_6	C	24	2		
C_6H_5	$C_6H_5CH_3$	B	72	56 ($o:m:p$ = 56:23:21)		
4-FC_6H_4	$C_6H_5CH_3$	C	120	2 ($o:m:p$ = 56:14:30)	19	
4-FC_6H_4	Mesitylene	C	24	88		
4-FC_6H_4	Mesitylene	D	24	50	14	2,4-Di-*p*-fluorophenyl-1,3,5-trimethylbenzene (4)
4-FC_6H_4	Pentamethylbenzene	C	0.3	80		
4-FC_6H_4	Durene	C	8	67	10	
4-FC_6H_4	*p*-Xylene	C	72	64	32	2,4-Dimethylphenyl trifluoroacetate (4)
C_6H_5	$C_6H_5OCH_3$	C	0.1	15 ($o:m:p$ = 63.3:0.6:36.1)		
C_6H_5	$C_6H_5OCH_3$	E	120	32 ($o:m:p$ = 47.2:0.4:52.4)		
C_6H_5	Naphthalene	C	0.1	20 (1-Phenylnaphthalene)		
C_6H_5	Naphthalene	A	0.1	25 (1- and 2-Phenyl-, 8:92)		

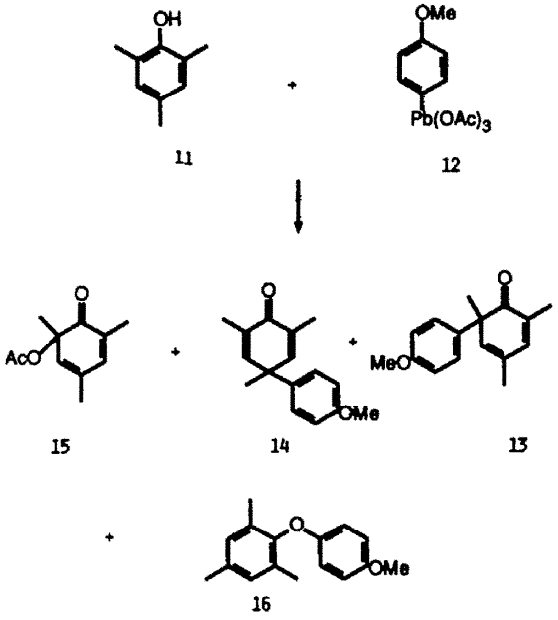
A: $ArPb(OAc)_3$ (2×10^{-4} mol), substrate (4×10^{-2} mol), $Al(OCOCF_3)_3$ (16×10^{-4} mol), R.T. B: Same as A but using $Al(OCOCF_2CF_2CF_3)_3$ as catalyst. C: CF_3CO_2H (4 ml) added to $ArPb(OAc)_3$ (0.2 mmol) and substrate (1.0 mmol), R.T. D: CF_3CO_2H (4.0 ml) added to $ArPb(OAc)_3$ (0.2 mmol). E: Cl_2CHCO_2H (4.0 ml) added to $ArPb(OAc)_3$ (0.2 mmol) and substrate (1.0 mmol).

donor ability of the substrate decreases, its ability to assist Pb—C cleavage diminishes leading eventually to formation of aryl trifluoroacetate mainly. In such cases, it was thought likely that free aryl cations were produced that reacted indiscriminately with available nucleophiles (Scheme 24):



Scheme 24.

Aryllead(IV) triacetates (aryl = *p*-methoxyphenyl was extensively studied) react with phenols to give mainly products of *C*-arylation.[63] Unlike the situation with the arylbismuth(V) compounds, only one case of *O*-arylation was reported, namely in the reaction of 2-hydroxymesitylene (**11**) with 4-methoxyphenyllead triacetate (**12**) in chloroform at room temperature. The cyclohexadienones **13** (64%) and **14** (16%), together with **15** and **16** (**15**+**16** < 5%) were obtained. Another case of *O*-arylated product, that from the reaction of 4-methoxyphenol with **12** (Table 5) is ambiguous in that the origin of the second 4-$CH_3OC_6H_4$ group is not clear, i.e. either from **12** in which case *O*-arylation has occurred, or from a second molecule of 4-$CH_3OC_6H_4OH$. Yields of *C*-arylated products improved by the addition of one equivalent of pyridine to the reaction mixture (no **15** or **16** detected from **11** and **12**). Selected examples of *C*-arylation are listed in Table 5.



It is clear that with methylated phenols, the reaction only proceeds in high yield when both *ortho* positions are substituted, while the reaction fails with phenols bearing only electron-withdrawing groups. There is a marked preference for *ortho* arylation and a preference for attack *ipso* to a methoxyl group compared with methyl groups. Attack *para* to the hydroxyl group does take place in favorable cases, however, in marked contrast to the corresponding arylbismuth reactions, which are thus more selective.

The mechanism has not been established, but NMR evidence for a complex (**19**) between the

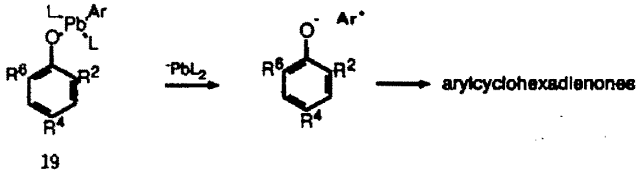
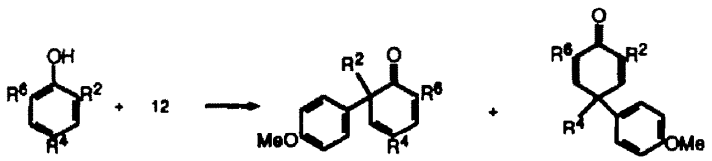


Table 5. Reaction of *p*-methoxyphenyllead triacetate with phenols in the presence of pyridine[63]



17 18

Phenol			17 (%)	18 (%)	Anisole (%)	Other (%)
R^2	R^4	R^6				
H	CH_3	H	—	—	12	$MeOC_6H_4OH$ (1%)
CH_3	H	H	5–10		5	
CH_3	H	CH_3	75–90	—	3	4'-Methoxy-2,4-dimethyl-3-hydroxybiphenyl (1–2%)
CH_3	H	CH_3[a]	40	—	3	
CH_3	CH_3	H	18	5[b,c]	3	
CH_3	CH_3	CH_3	75	20	1–3	
CH_3	CH_3	*t*-Bu	65	5–7[c]		No attact at C_6
t-Bu	CH_3	*t*-Bu	—	30	31	
t-Bu	*t*-Bu	*t*-Bu	—	—	23	
OCH_3	—	—	48	—	6	
—	OCH_3	—	—	—	29	$(4\text{-}MeOC_6H_4)O$ (34%)
Cl	—	Cl	—	—	—	No reaction
Cl	NO_2	Cl	—	—	—	No reaction
3,4,5-Trimethylphenol			—	12	4	4'-Methoxy-2-hydroxy-4,5,6-trimethylbiphenyl (22%)
2-Methyl-1-naphthol			56	—	13	

[a] No pyridine.
[b] Approximate yield.
[c] Product not isolated.

phenol with aryllead compound has been obtained from the reaction of 4-methoxyphenyllead triacetate and 2,6-dichloro-4-nitrophenol.[63] The reaction is catalyzed by excess phenol which suggested[63] also that an intermediate such as **19** was involved. A note of caution needs to be sounded here since, as pointed out above, the observation of a similar complex between 4-nitrophenol and Ph_3Bi was misleading as to the mechanism of *O- vs C*-phenylation.[39] It was proposed[63] that **19** could break down to phenoxide ion and aryl cation which could then combine. *Some* intramolecular arylation (cf. Scheme 15) could also account for the predominant *ortho*-arylation, for example with 2,4,6-trimethylphenol. The role of pyridine has been discussed: a possible catalyst, as an inhibitor of a side-reaction, or as a base to trap acetic acid. Evidence has been found that it complexes with *p*-methoxyphenyllead triacetate (**12**), so that such a complex might be involved in these reactions. Finally, a radical process (Scheme 25) was not excluded,[63] but is improbable.[45]

In contrast to the behavior with 5-valent bismuth reagents, phenols were not phenylated by Ph_xPbX_{4-x} ($x = 1$–4) in the presence of $Cu(OAc)_2$ in CH_2Cl_2.[64]

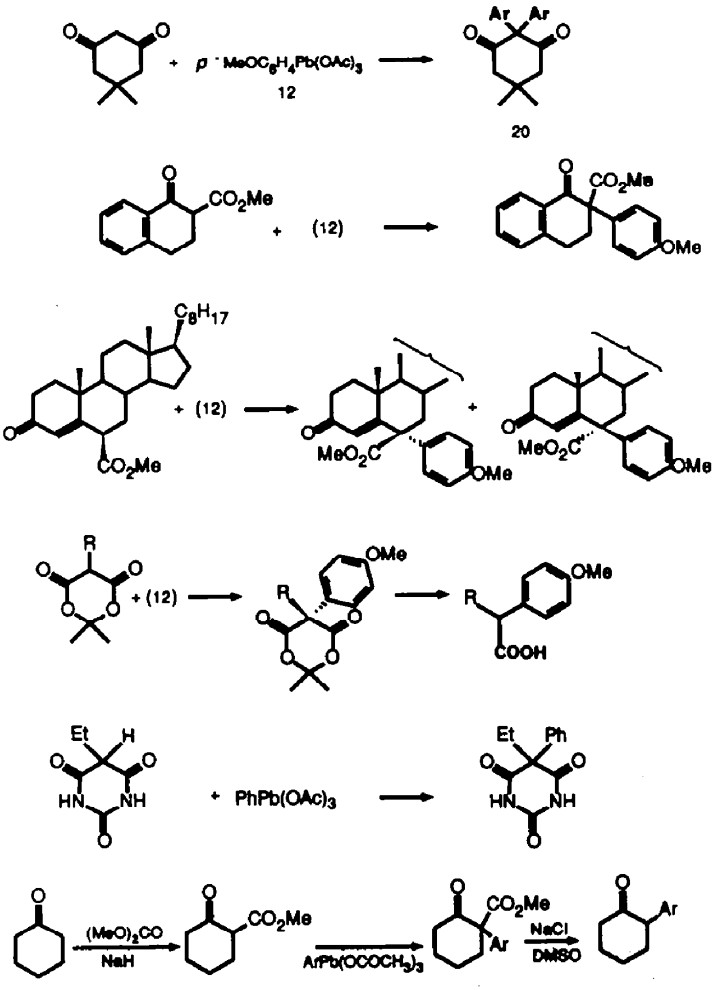
β-Diketones,[65] *β*-keto esters,[66] and malonic ester derivatives (except for malonic ester and Meldrum's acid themselves which give very low yields)[67] are readily α-arylated. Thus, dimedone gives 2,2-bis-*p*-methoxyphenyl-5,5-dimethylcyclohexan-1,3-dione (**21**) with *p*-methoxyphenyllead triacetate (**12**) in chloroform containing pyridine at 40°C. Other examples are also given in Scheme 26. Aryllead triacetates, produced *in situ* by mercury–lead exchange,[61,68] may be used to arylate *β*-keto esters. Vinylogous *β*-keto-esters undergo regiospecific arylation with aryllead triacetates at C_1,

$$Ar'O^- + ArPbX_3 \longrightarrow Ar'O^{\bullet} + [ArPbX_3]^{\bullet -} \longrightarrow Ar^{\bullet} + PbX_2 + X^-$$

$$\downarrow$$

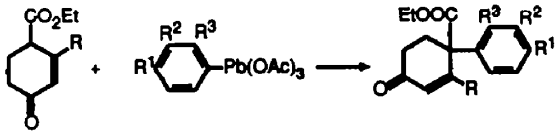
products

Scheme 25.

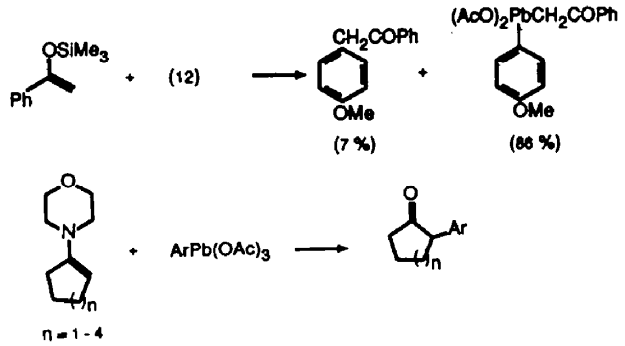


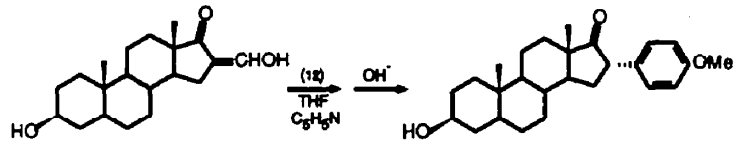
Scheme 26.

and this has been used to provide intermediates for the synthesis of (±)-*o*-methyljoubertiamine, (±)-mesembrine, and (±)-lycoramine[69] (see also Scheme 26).



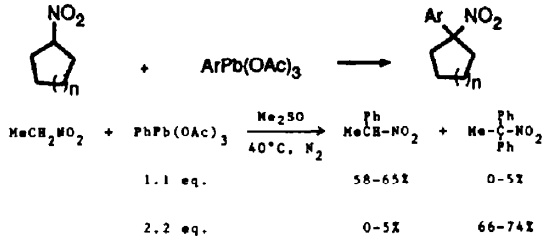
While simple enolizable ketones do not undergo α-arylation under these conditions and silyl enol ethers undergo mainly α-plumbation under the conditions used,[70] enamines[71] and α-hydroxymethylene ketones[72] do arylate. The reaction with enamines is very sensitive to steric effects and is,



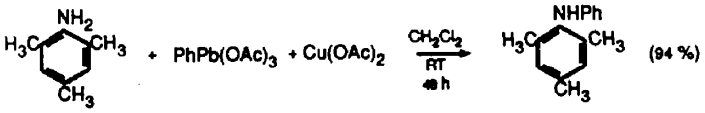


therefore, of limited application. Acetoxylation is the major competing process.[71] Yields are moderate to good in the arylation of α-hydroxymethylene ketones, which makes it a useful alternative to the β-keto ester route[66] as a method of obtaining α-arylated ketones.

Nitroalkanes and nitronate salts in DMSO undergo α-arylation in good yields.[73] The salts react faster. Where there is no steric hindrance, the reaction is quite general, compounds with two α-hydrogens giving either mono- or di-arylated products under controlled conditions. *In situ* generated $ArPb(OAc)_3$ also reacts with nitroalkanes to give the desired α-arylated molecules.[68]



Lastly, copper-catalyzed phenylation of aromatic and aliphatic amines using Ph_xPbX_{4-x} and $Cu(OAc)_2$ has been reported and compared with the analogous reactions using Bi(V) derivatives.[64] $PhPb(OAc)_3$ ($x = 1$) was the most efficient of the lead reagents, and X = acyl was mandatory. Steric hindrance had no significant influence in the case of anilines, e.g.



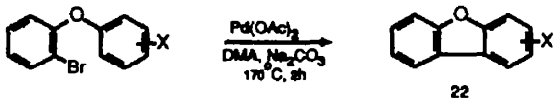
Reaction of $PhPb(OAc)_3$ with aliphatic and alicyclic amines, or with hydrazones gave the corresponding *N*-phenyl derivatives, in poor to modest yield, and indoles are not phenylated under these conditions. Thus the $Ph_3Bi(OAc)_2$ system is much superior in these cases.

4. PALLADIUM-MEDIATED ARYLATIONS

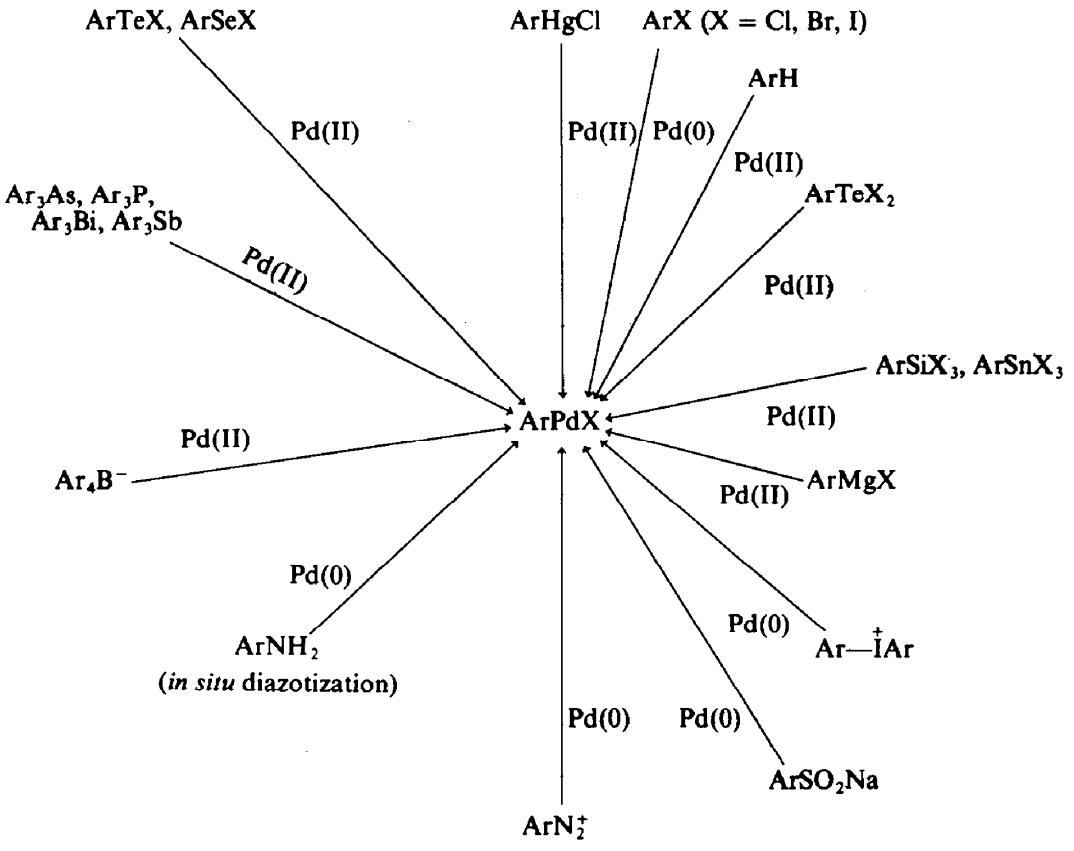
This has probably been the most intensely studied of the arylation methods in recent years and has been reviewed in a number of texts[74] and review articles.[75] Consequently, no detailed treatment will be given here and only the highlights will be mentioned.

Scheme 27 summarizes the many sources of the required arylpalladium intermediates.[74c,d] Transmetallation and direct palladation require the use of a Pd(II) species, while halides and pseudohalides (including ArN_2^+) require a Pd(0) catalyst.

There are very few examples of Pd-catalyzed arylations of aromatic compounds which fall within the scope of our review (replacement of H). Benzo[*b*]furan couples with phenylmercuric acetate or chloride in the presence of Li_2PdCl_4 to give 2-phenylbenzo[*b*]furan (77%).[76] An intramolecular example is the reaction of 2-bromo-X′-substituted diphenyl ethers to give dibenzofurans (**22**) in the presence of $Pd(OAc)_2$ and one equivalent of Na_2CO_3 in dimethylacetamide at 170°C.[77] This reaction is probably not a straightforward arylation but may well involve metallation of the aromatic nucleus followed by displacement of Br.

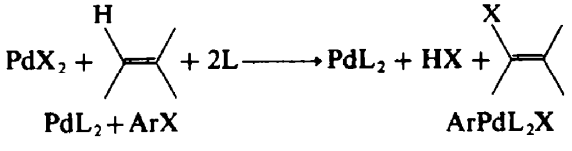


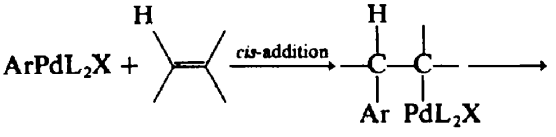
22

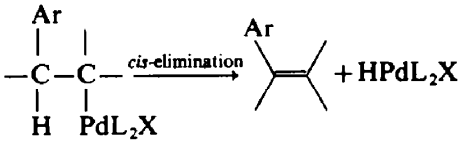


Scheme 27.

On the other hand, arylation of alkenes by arylpalladium intermediates (the Heck reaction) is an extremely useful process. The catalyst usually used with aryl halides is $Pd(OAc)_2$ because of its solubility in organic compounds. It is reduced *in situ* to Pd(0) by an excess of olefin present and is coordinated by added phosphine ligand. Base is added to regenerate PdL_2. A mechanism for the whole sequence is:







$$HPdL_2X + \text{base} \longrightarrow PdL_2 + \text{base } H^+X^-$$

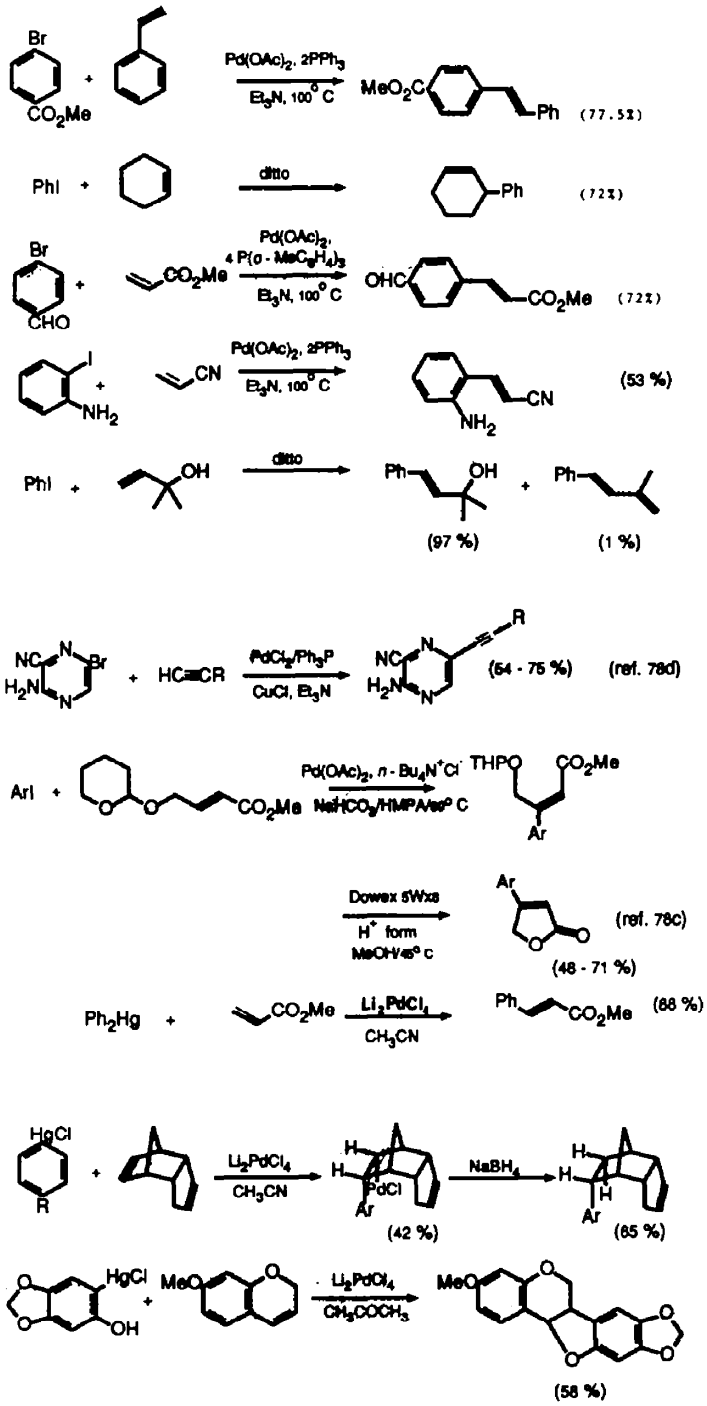
With ArHgX, the catalyst is usually either Li_2PdCl_4, $LiPdCl_3$, or $Li_2Pd(OAc)_2Cl_2$, and a solvent such as acetonitrile, ethanol, or acetone may be used. A catalytic process results when the Pb(0) species formed is reoxidized to Pd(II), usually by $CuCl_2$,[78a] sometimes by $Pb(OAc)_4$.[78b]

Both activated and non-activated alkenes react. If *cis*-elimination of $HPdL_2X$ is difficult, the initially formed adduct may be reduced with $NaBH_4$ to give the product of the formal addition of Ar—H to the double bond. Some examples are given in Scheme 28.

Examples of the use of aryl amines (*in situ* diazotization), diazonium salts, and arenes are given in Scheme 29.

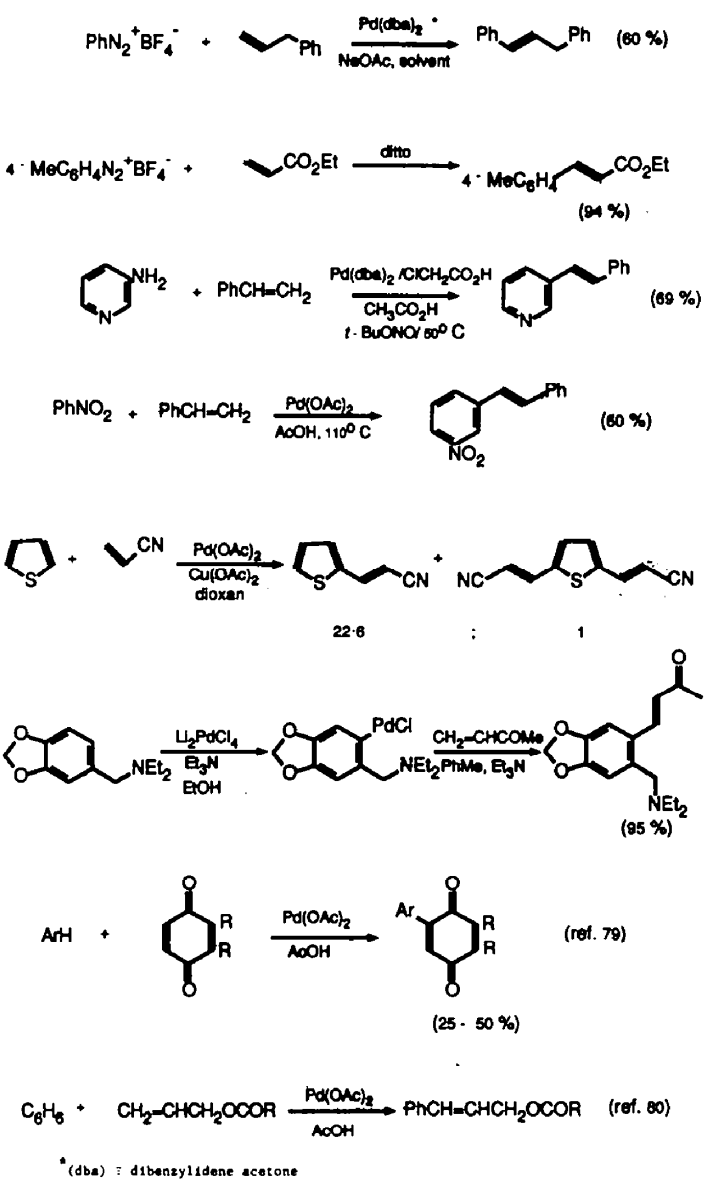
Intramolecular arylation of alkenes provides a powerful synthetic tool (Scheme 30).

Trimethylsilylalkenes may be arylated in the presence of silver nitrate. The latter suppresses



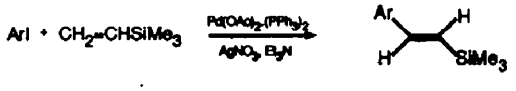
(where a ref. is not given the reaction is taken from ref. 74c)

Scheme 28.

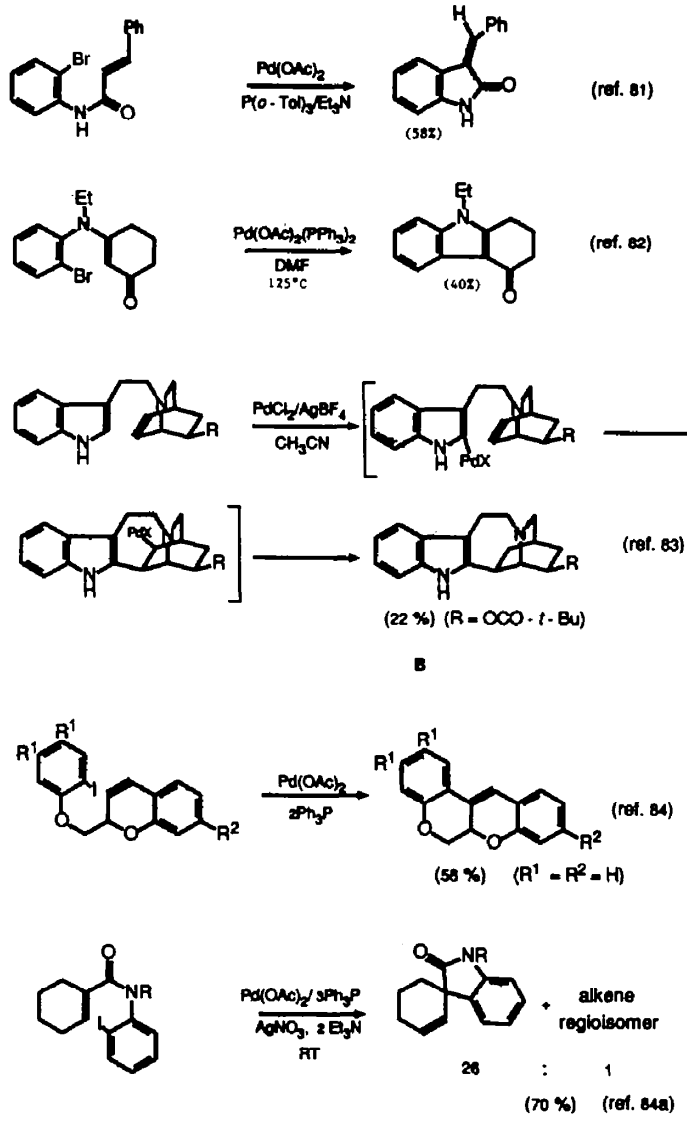


Scheme 29.

elimination of the silyl group and enhances the reaction rate.[85] The stereospecificity of such reactions has been studied in the absence of $AgNO_3$.[85]

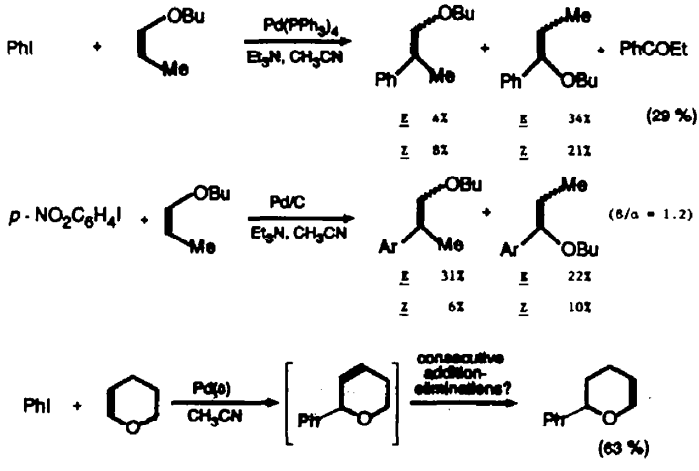


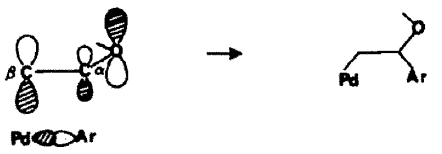
Enol ethers may be arylated regioselectively at the α-[86] or the β-carbon.[87] The regiochemistry is sensitive to (i) the structure of the enol ether, (ii) the arylating agent used, and (iii) the reaction medium and catalyst.[88] Methyl substitution at either α- or β-carbons favors α-arylation, while if the enol ether is part of a ring only α-arylation is observed.[88] Electron-rich aryl systems favor α-arylation, electron-poor aryl β-arylation. Going from X = I to X = Cl in ArX led to a 10-fold increase in the β/α arylation ratio. β-Arylation is favored by use of poorly coordinated Pd catalysts, e.g. $Pd(OAc)_2$ in toluene, while a relatively electron-rich Pd catalyst (Ph_3P ligands, CH_3CN solvent) favors α-arylation.[88]



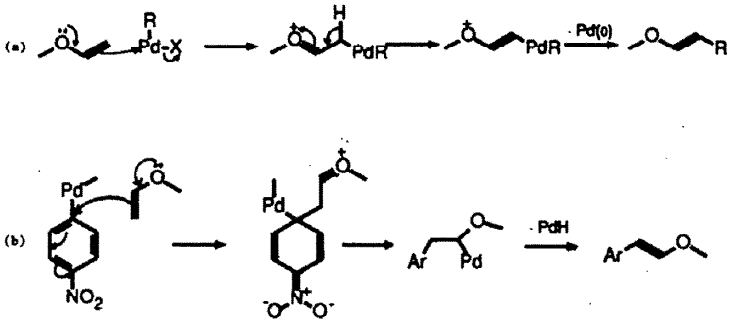
Scheme 30.

α-Arylation was accounted for[88] by assuming that the dominant interaction is that between the highest occupied MO of the enol ether and the antibonding σ^* orbital of aryl-Pd(II): a concerted reaction leads to a *syn*-addition in which the Pd forms a σ-bond with the β-carbon. Two alternatives

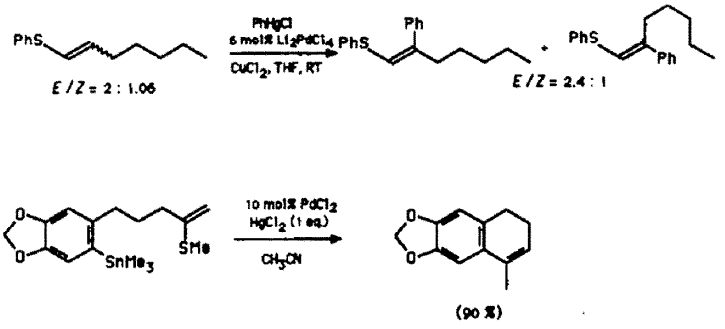




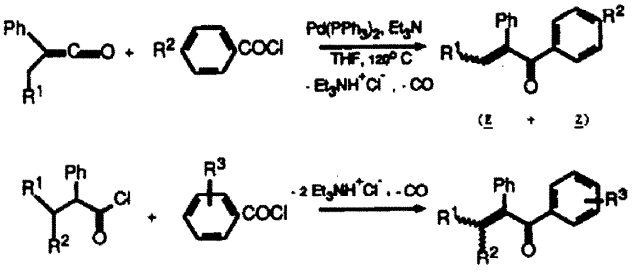
were considered to account for β-arylation.[88] (a) the electron-rich enol ether attacks the poorly coordinated electropositive Pd center or (b) the enol ether attacks the e-deficient aromatic nucleus:



Enol thioethers are arylated regioselectively to the 2-aryl adducts in intermolecular reactions, whereas intramolecular arylation leads to the 1-aryl derivative regioselectively.[88a]



Palladium-catalyzed arylation of alkylphenylketenes with aroyl chlorides (which undergo decarbonylation) and Et_3N yields α,β-unsaturated ketones.[88b] Alternatively, an aroyl chloride may react with an alkylphenylacetyl chloride in the presence of base to give the same products.[88b]

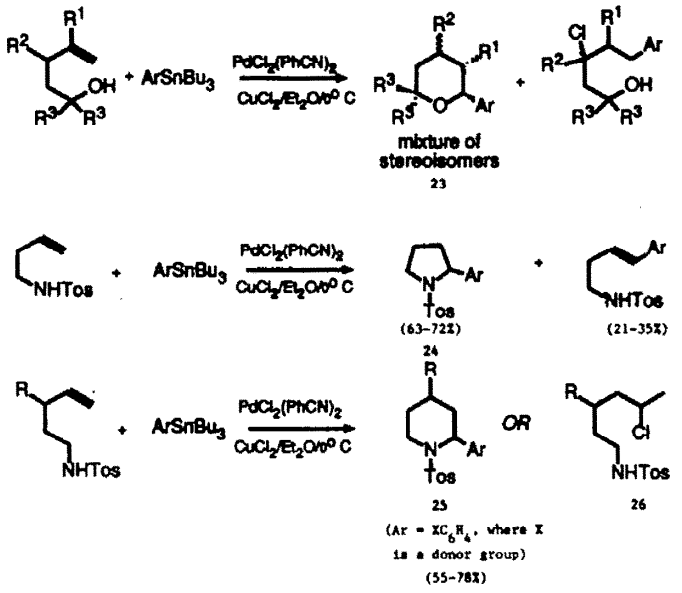


A few recent examples of palladium-catalyzed arylations are worth mentioning:

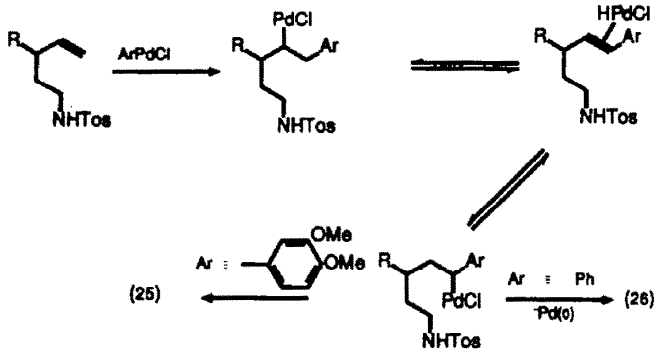
(i) Arylation of malononitrile anions:[89]

$$RCH(CN)_2 \xrightarrow{NaH} R\bar{C}(CN)_2 \xrightarrow[\substack{(cyclooctadiene)PdCl_2\\ Ph_3P,\ THF/N_2/\Delta}]{ArI} ArC(R)(CN)_2$$

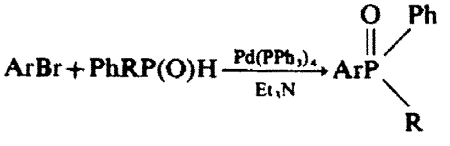
(ii) A slight modification in the Heck reaction conditions (catalytic $PdCl_2(PhCN)_2$, ArHgCl or $ArSn(n\text{-}Bu)_3$, $CuCl_2$ in diethyl ether) alters the reaction pattern from 1,2- to apparent 1,1-addition.[90,91] In this way, 2-aryltetrahydropyrans (**23**),[90] pyrrolidines (**24**) and piperidines (**25**)[91] can be obtained.



It is proposed[91] that the initially formed 1,2-adduct undergoes elimination of HPdCl followed by readdition to give the 1,1-adduct which either cyclizes or eliminates Pd(0), depending on the nature of Ar.



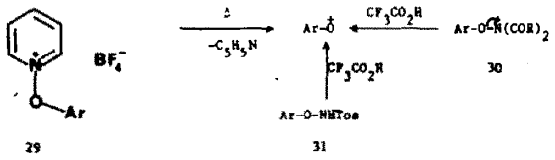
(iii) Phosphine oxides of the type PhRP(O)H[92] and dialkyl ethenyl phosphonates[93] are arylated readily:



(iv) 1,2-Chirality transfer has been reported in the phenylation of (*S*)-(+)-2-methyl-1-butene-3-ol (**27**) leading to (*S*)-(+)(**28**) in 30–50% yield and 27% optical yield:[94]

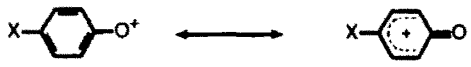
5. ARYLATIONS INVOLVING ARYL-NITRENIUM AND -OXENIUM IONS

Aryloxenium ions may be generated by the thermolysis of *N*-aryloxypyridinium tetrafluoroborates (**29**),[9,95,96] from *N*,*N*-diacetylaryloxyamines (**30**) when heated in the presence of 1 equivalent of trifluoroacetic acid,[9] or from the acid-catalyzed solvolysis of *N*-toluenesulfonyl-*O*-

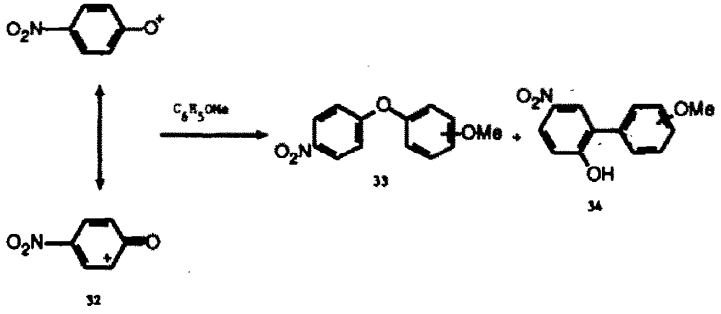


29 31

arylhydroxylamines (**31**).[97] They are of interest from the point of view of phenol oxidation and biosynthetic-type oxidative coupling reactions[98] and, from the present optic, in synthesis. They react with aromatic solvents intermolecularly to form C—O—C and C—C bonds. Waters[99] argued that the positive charge in PhO^+ should be mainly localized on carbon rather than oxygen so that intermolecular coupling should lead to more C—C than C—O—C bond formation, and this has been confirmed by *ab initio* M.O. calculations.[100] It was suggested[95] that electron-withdrawing substituents in the aromatic nucleus should destabilize the positive charge on carbon and lead to an increase in the intermolecular C—O—C/C—C bond formation ratio, which was in fact observed.[95,96]

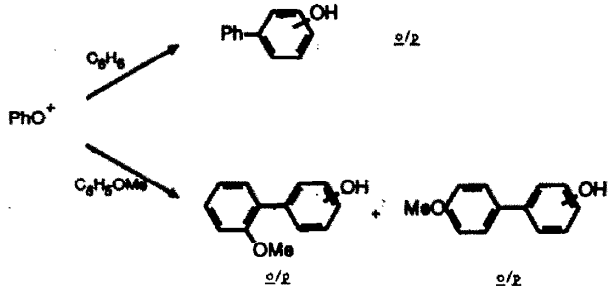


Of interest to the present review is arylation (i.e. C—C bond formation). As predicted, *p*-nitrophenyloxenium ion (**32**) reacts with anisole[9,95] to give mainly products of C—O—C bond formation (**32**)(43.4%)(*o*/*p* = 29:71), together with some C—C bond formation products (**34**)(9.2%)(*o*/*p* = 74:26). Reaction with mesitylene and with 1,3,5-trimethoxybenzene gave



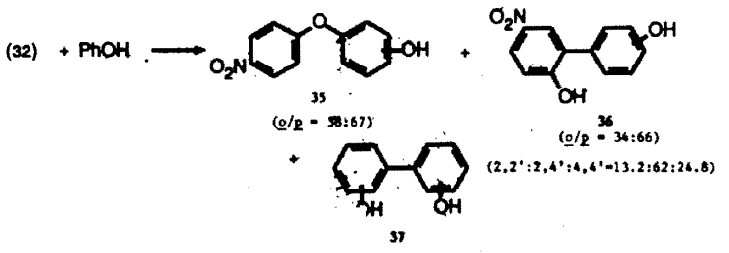
32 33 34

only C—O—C products.[104] Similar results were obtained with *p*-cyano- and *o*-trifluoromethyl-phenyloxenium and anisole.[95] Reaction of *p*-nitrophenyloxenium with benzonitrile does not lead to arylation of the aromatic nucleus: attack takes place instead on the nitrile group.[95] Ion **32** reacts with benzene to give low yields of 4-nitrodiphenyl ether (1.3%) and 2-hydroxy-5-nitrobiphenyl (5.5%), the low yields probably being associated with the insolubility of the starting pyridinium in hot benzene.[102] In contrast, phenyloxenium itself reacts with anisole[95,97] and with benzene[97,102] to give only arylation (C—C) products, in accord with Waters' prediction.[99]

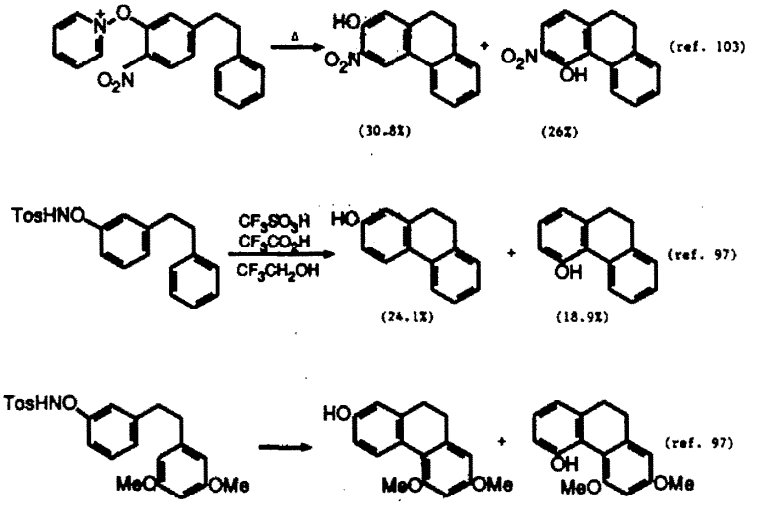


Aryloxenium ions generated from *N*-tosyl-*O*-phenylhydroxylamines behave similarly.[97]

Oxenium ion **32** reacts with phenol to give mainly C—O—C bond formation products **35** (24.6%), together with some arylation products **36** (16.3%) and some dihydroxybiphenyls **37** (25.2%), the latter probably arising by a SET.[102] Only electron-transfer products were observed with *N*,*N*-dimethylaniline and with triphenylamine.[102]

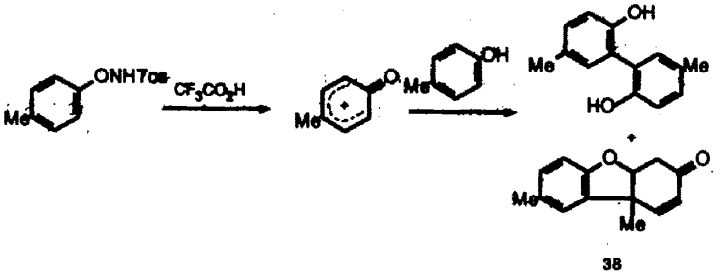


The most interesting applications of aryloxenium ions are intramolecular arylations (remote functionalization). Some examples are given in Scheme 31.

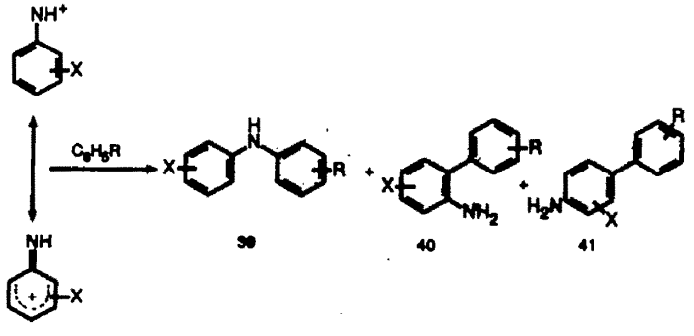


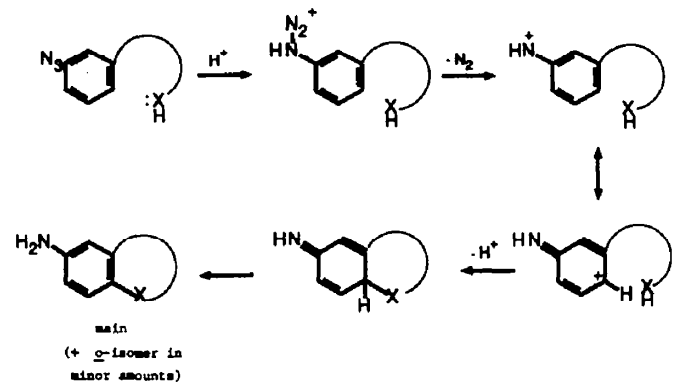
Scheme 31.

Pummerer's ketone **38** was formed (9%) from *o–p* coupling of 4-methylphenyloxenium ion with *p*-cresol.[104]



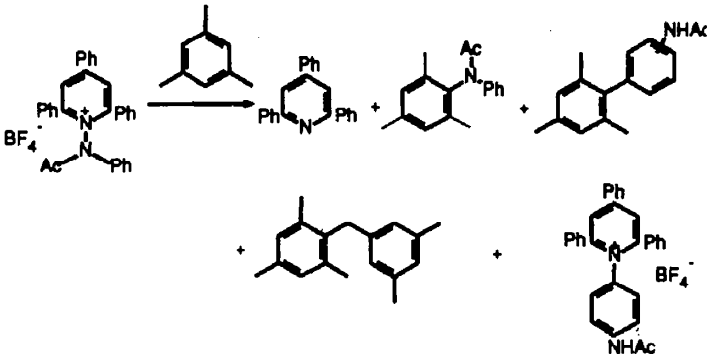
Arylnitrenium ions behave similarly, giving products of C—N—C (**39**) and C—C bond formation (**40** and **41**) in their reactions with arenes.





Scheme 32.

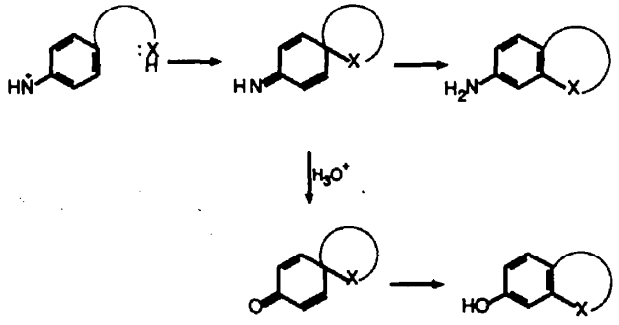
Again, intramolecular arylations (remote functionalization) are the more interesting applications and involve trapping by an internal nucleophile (Scheme 32). If an aryl azide is the source of the nitrenium ion, a strong acid (with a non-nucleophilic counter-ion) is used as the catalyst. *N*-Acetyl-*N*-arylnitrenium ions may be generated thermally under neutral conditions from 1-(*N*-acetyl-*N*-



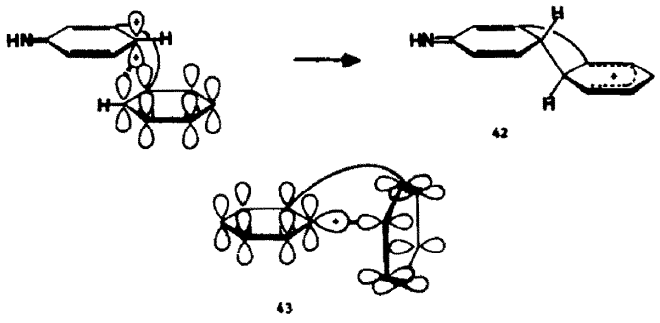
arylamino)-2,4,6-triphenylpyridinium tetrafluoroborates.[105a] Studies are in progress with a view to improving the nature of the leaving group so as to eliminate byproduct formation.

ipso-Substitution has also been achieved (Scheme 33).[106]

These reactions have the potential of leading to interesting polycyclic systems not available by other routes. This is owing to the fact that most of the latter, including the reactions discussed in earlier sections, involve σ-cationic, -radical or other intermediates, while the 'remote functionalization' involving aryl-oxenium or -nitrenium ions go via a π-aryl cation, which requires a different transition state geometry (Scheme 34). They also allow the introduction of desirable substituents at specific positions in aromatic nuclei. The delocalized arylnitrenium ion is a π-cation so that approach of nucleophiles must be in a plane almost perpendicular to the benzene ring (e.g. **42** where the



Scheme 33.

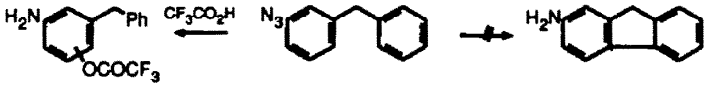


Scheme 34.

nucleophile is an aromatic nucleus). On the other hand, another common method for forming intramolecular C—C bonds, the Pschorr cyclization,[3] in its cationic intermediate form, for example, involves a σ-cation so that approach by the attacking nucleophile (always an aromatic nucleus) is perpendicular to the plane of the benzene ring (**43**). Thus, transition state geometry and steric effects are going to be widely different in both cases, and the new ring size will be a critical factor in whether or not the process is successful in **42** and **43**.

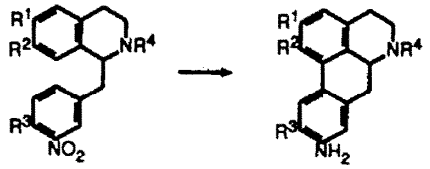
Phenanthrenes, dihydrophenanthrenes,[107] 5- and 6-membered lactones[106,107] (net arylation of carboxylic acid —OH groups) and spiro-lactones,[106] 7-membered rings[108] (including a possible precursor to colchicine), and dihydrophenanthridines and benzochromans[109] can be formed in this way. Occasionally, some *ortho*-product is observed as well. *O*-Arylation of a phenolic group to give a six-membered oxygen heterocycle has been observed.[110] Some examples of these reactions are summarized in Scheme 35.

On the other hand, attempts to prepare 5-membered rings by intramolecular C—C bond formation (as opposed to C—O bond formation) have failed, except where the ring being attacked bears strongly electron-donating substituents; e.g. **44** gives no aminofluorene (**45**).[111] Clearly, the

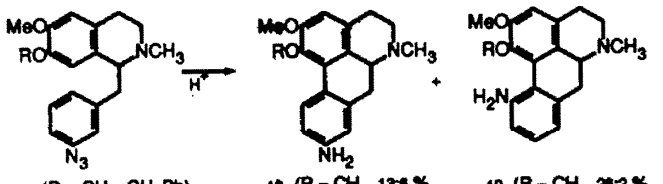


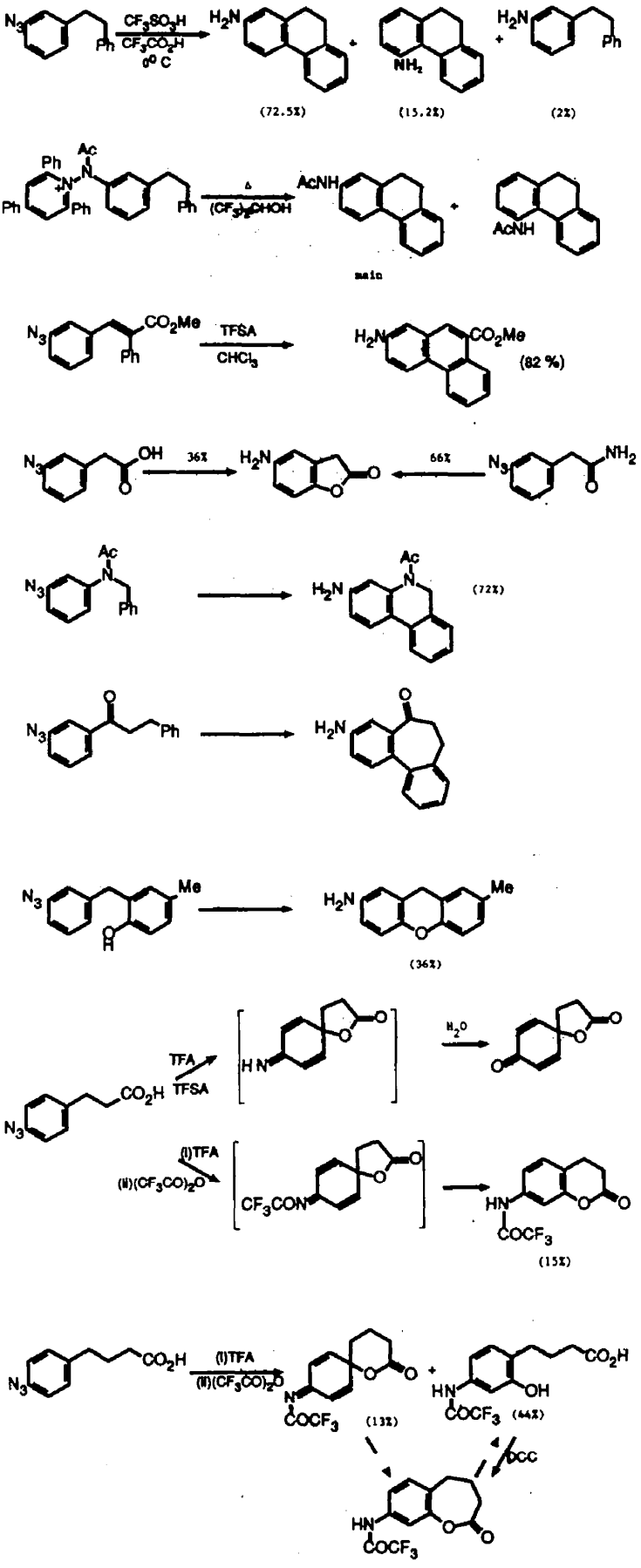
transition state for 5-membered ring formation (attack by a π-cation upon the π-cloud of the adjacent ring) is too strained and, in solution, competing processes are more favorable.

The aporphine ring system may be synthesized readily in this way. For example, reduction of **46** with zinc in trifluoromethanesulfonic acid/trifluoroacetic acid (1 : 1) gave **47**.[112] The reaction



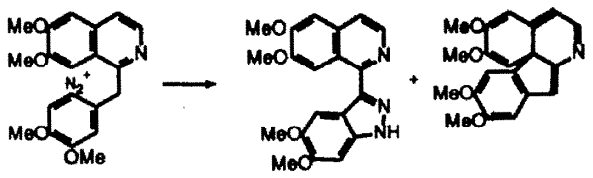
probably involves initial reduction to the hydroxylamine which, with strong acid, yields the nitrenium ion. The azide route also leads to aminoaporphines (**48** and **49**).[113]





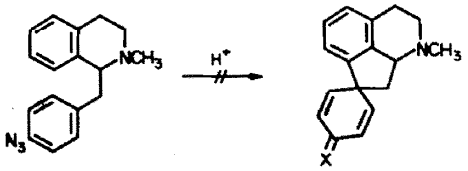
Scheme 35.

The Pschorr cyclization is notable for being strongly subject to steric hindrance by substituents *ortho* to the point of attack. A particularly telling example is the one in which the diazonium salt from 2'-aminopapaverine gives an imidazole and an indenoquinoline rather than the dihydroaporphine.[114]



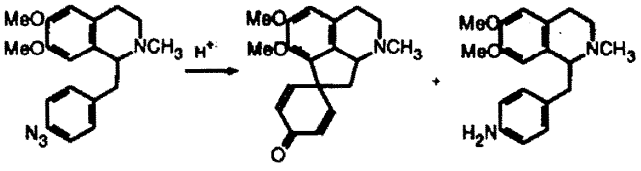
In contrast both **48** and the even more crowded **49** are formed via the nitrenium ion route, clearly illustrating the importance of the difference in transition state geometry.

Attempted cyclization of **50** did not give any of the desired 5-membered ring **51** by *ipso*-attack. Undoubtedly, this reflects the strain in transition state **42**, which allows other pathways to compete



(50) (51)

favorably. When two donor substituents are present in the benzene ring undergoing electrophilic attack, *ipso*-substitution can begin to compete, and some pronuciferine (**53**) is formed in low yield from (**52**), together with some hydrogen-abstraction product (**54**).[113]

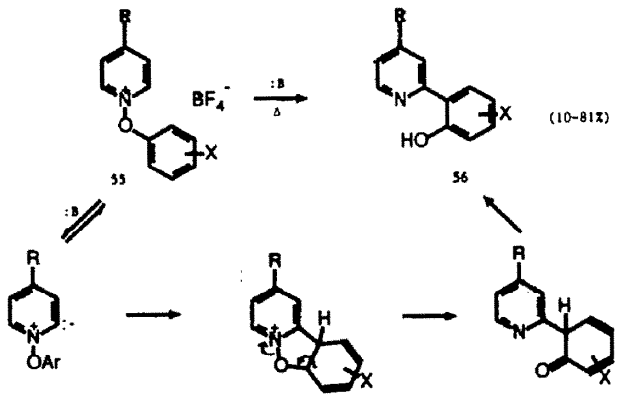


52 53 54

6. MISCELLANEOUS INTRAMOLECULAR ARYLATIONS

To conclude this survey, we describe some intramolecular sigmatropic shifts in 1,2-dihydropyridine derivatives which, effectively, give ring arylated products.

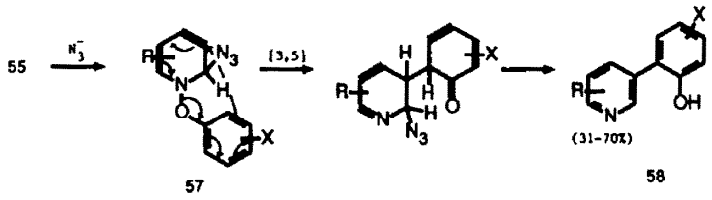
N-Aryloxypyridinium salts (**55**) undergo base-catalyzed rearrangement to give 2-*o*-hydroxyarylpyridines (**56**) (Scheme 36).[115] The pyridinium salts themselves are readily prepared from the



Scheme 36.

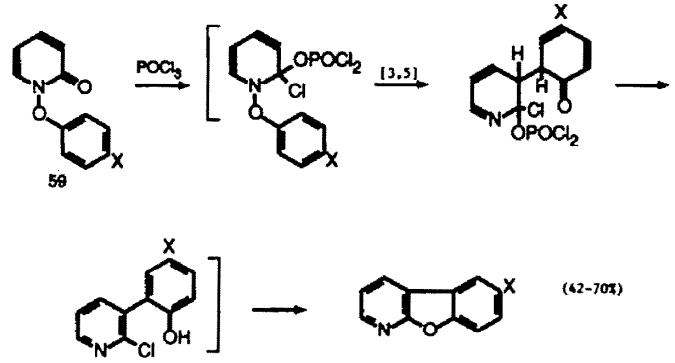
pyridine *N*-oxide and either an arenediazonium tetrafluoroborate bearing electron-withdrawing substituents or a diaryliodonium tetrafluoroborate.

On the other hand, if **55** is treated with a carbon nucleophile e.g. N_3^-, a [3,5]-shift in the presumed 1,2-dihydro intermediate (**57**) leads to 3-*o*-hydroxyarylpyridines (**58**).[116] A possible diradical pathway was shown not to be the route to **58**.



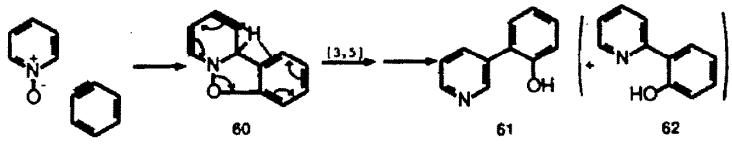
57 58

A similar [3,5]-shift is thought to occur in the intramolecular 3-arylation of *N*-aryloxy-2-pyridones (**59**) with $POCl_3$ or $SOCl_2$.[117]



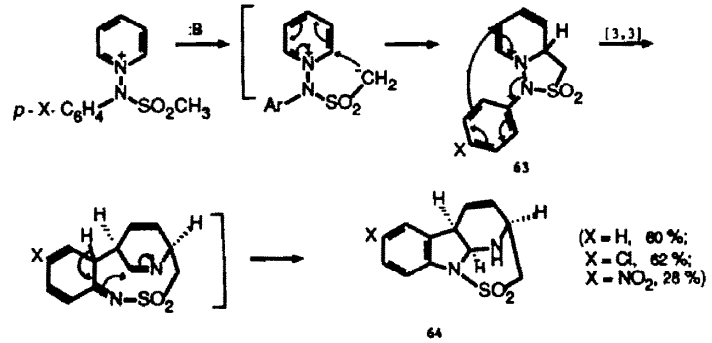
59

The reaction of benzyne with pyridine 1-oxides is thought to yield a 1,2-dihydropyridine 1-oxide (**60**) initially, which undergoes a 3,5-shift to form mainly the 3-*o*-hydroxyphenylpyridine (**61**). Some 2-*o*-hydroxyphenylpyridine (**62**) is also formed in very low yield.[118]



60 61 62

Finally, we mention a recent intramolecular arylation via a 1,2-dihydro-*N*-aryl-*N*-mesylamino-pyridine (**63**) to give, eventually, a bridged hexahydro-α-carboline derivative (**64**).[119]



63 64

In many cases, the scope and extensions of these novel intramolecular arylations to other ring systems remain to be examined.

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