

Bismuth(V) reagents in organic synthesis

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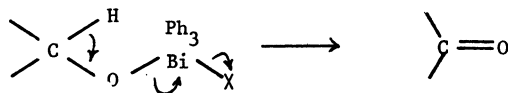
Abstract - The concept that the valency change from Bi^V to Bi^{III} could be harnessed to produce a family of selective oxidants was shown to be correct. However, completely unexpected was the efficiency of Bi^V reagents in carrying out arylations on oxygen, carbon and nitrogen. The new arylation procedures permit the synthesis under very mild conditions of compounds only available otherwise by indirect routes. In general, these arylation reactions do not involve radical intermediate, but are rather examples of reductive elimination.

The Chemistry of Natural Products has always been associated with major advances in Organic Chemistry from its origin up to the present time. Major objectives of Natural Product Chemistry have been first the determination of structure, and then synthesis. Due to the development of powerful physical methods, the structural analysis of natural products is now a relatively trivial matter. The synthesis of natural products however has remained an active field, always requiring new synthetic methods. As we argued some years ago, the invention of new synthetic methods takes place through conception, or misconception, or by accident (ref. 1).

We will examine some of our work which resulted from the combination of the first and third concept, i.e. application of a conceptually devised reaction to the Chemistry of Natural Products which led to an accident and the development of a family of unusual arylation reactions.

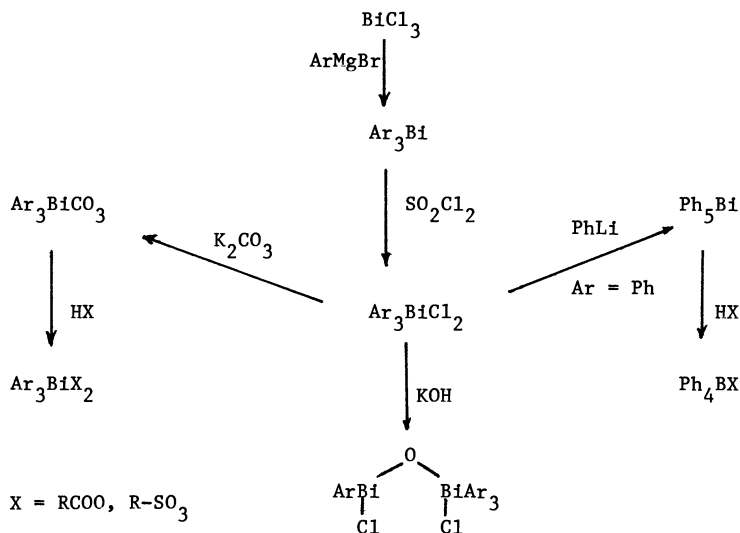
Mild and selective oxidation of polyfunctional substrates remains a major goal for organic chemists. Metal and metalloid oxides have been used for a long time. However, reactions can be more or less selective, and recycling of the oxidant, thus giving a catalytic system, is rarely seen. The reactivity of metalloids like selenium, tellurium or bismuth is improved through using covalently bonded substituted derivatives. Thus the chemistry of "organo-metalloid" compounds (ref. 2) has grown into an active field. Some such examples can be found in the chemistry of selenium (ref. 3), tellurium (ref. 4), iodine (ref. 5) to name only a few. Among borderline organo-metalloid derivatives, in the group VA, organobismuth derivatives have been known for a long time (ref. 6). With an electronic configuration $[\text{Xe}] 4p^4 5d^{10} 6s^2 6p^3$, 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. The Bi(V) → Bi(III) change led to the conception of an oxidation reaction (Scheme 1), which might moreover be developed into a catalytic reaction, as in the group VI elements.

Scheme 1. Conception of the Oxidation Mechanism



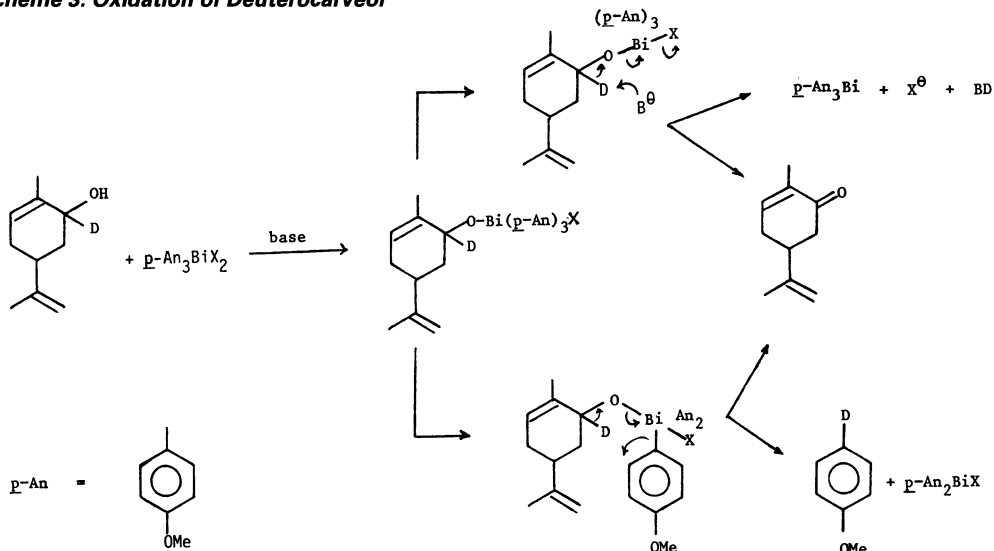
Although a wide array of methods lead to organobismuth compounds (refs. 7, 8), the most general pathways for their synthesis involve the reaction of a Grignard reagent with BiCl_3 (Scheme 2). Thus, reaction of phenylmagnesium bromide afforded Ph_3Bi , which upon oxidation gave Ph_3BiCl_2 , the pivotal compound from which the other tri-, tetra-, and penta-phenylbismuth are derived (refs. 9, 10, 11, 12).

Scheme 2. Preparation of Arylbismuth(V) Compounds



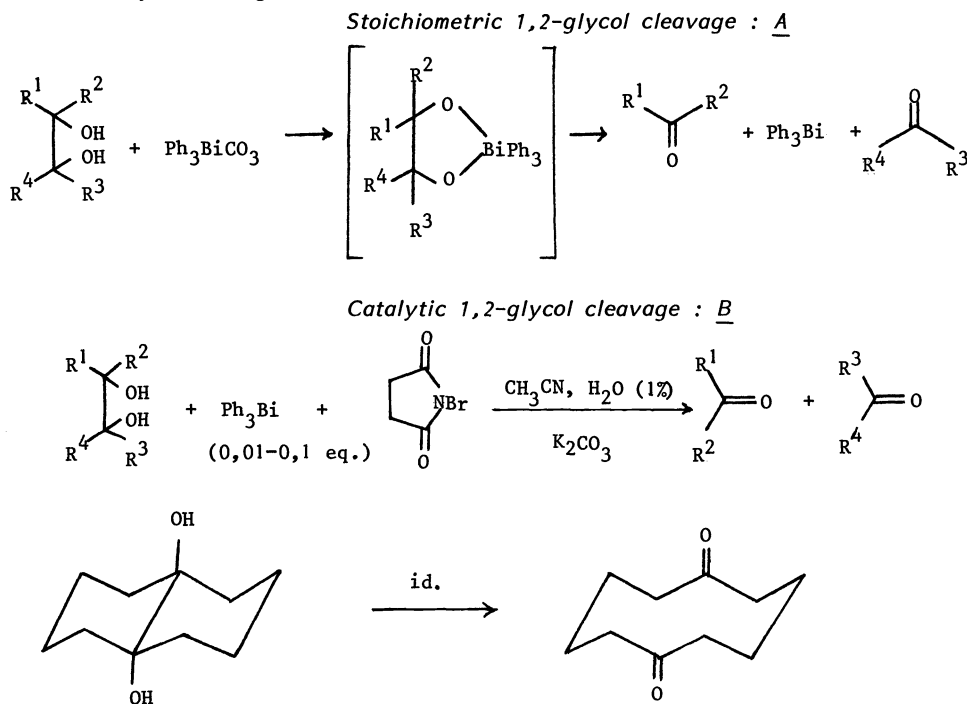
Arylbismuth reagents of the type Ph_3BiX_2 are mild and high yielding oxidising agents for a range of primary, secondary, benzylic, and particularly allylic alcohols. A great selectivity was observed with two members of this family, μ -oxo-bis(chlorotriphenylbismuth) and triphenylbismuth carbonate towards indole, pyrrole, thiols, and selenides (ref. 9). Recently arylbismuth reagents of the type Ph_4BiX have also been shown to oxidise alcohols to the corresponding carbonyl compounds under basic conditions (ref. 13). Similarly, Ph_5Bi acts as an oxidant of the hydroxyl group (refs. 14, 15). Mechanistically, these oxidation reactions 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 (ref. 9) (Scheme 3). Thus, development of the conceptually attractive catalytic cycle was excluded. The existence of the Bi(V) intermediate possessing a covalent Bi-O bond was conclusively shown by a series of $^1\text{H-n.m.r.}$ experiments (ref. 13).

Scheme 3. Oxidation of Deuterocarveol



Triphenylbismuth carbonate is a stoichiometric 1,2-glycol cleaving reagent. The yield of triphenylbismuth was quantitative (ref. 9). A catalytic process was possible. Thus, it was realised with *N*-bromosuccinimide as reoxidant, in the presence of K_2CO_3 , a trace of water in acetonitrile (refs. 16, 17). Yields are similar or better than those obtained with lead tetraacetate and periodic acid.

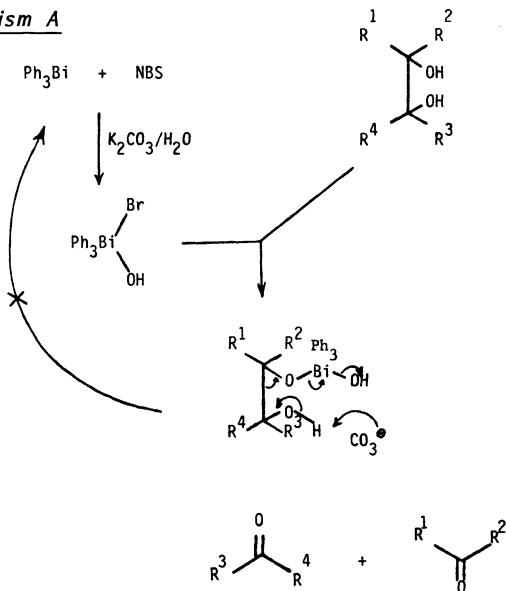
Scheme 4. 1,2-Glycol Cleavage



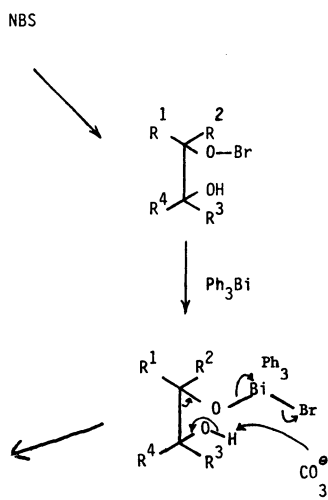
From the mechanistic point of view, it must be noted that a rigid diol such as *trans*-decalin-9,10-diol was cleaved in the catalytic system, but not in the stoichiometric. The corresponding *cis*-diol was cleaved at a similar rate. In the stoichiometric reaction, a cyclic intermediate is formed. The catalytic reaction was explained by formation of a glycolhypobromite, acting as an oxidant of Ph_3Bi to a pentavalent Bi species (Scheme 5B). An *in situ* formed pentavalent Bi derivative acting as oxidant of the glycol is not involved (Scheme 5A).

Scheme 5. Mechanism of the Catalytic Glycol Cleavage

Mechanism A

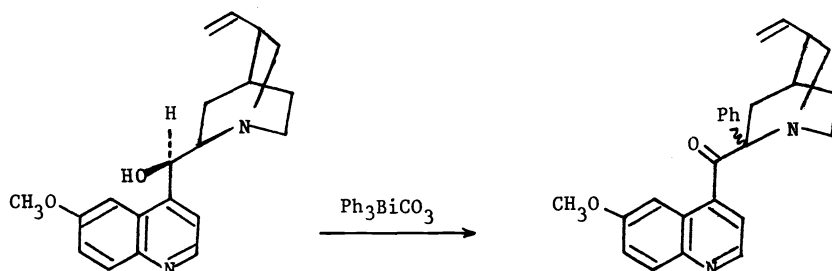


Mechanism B



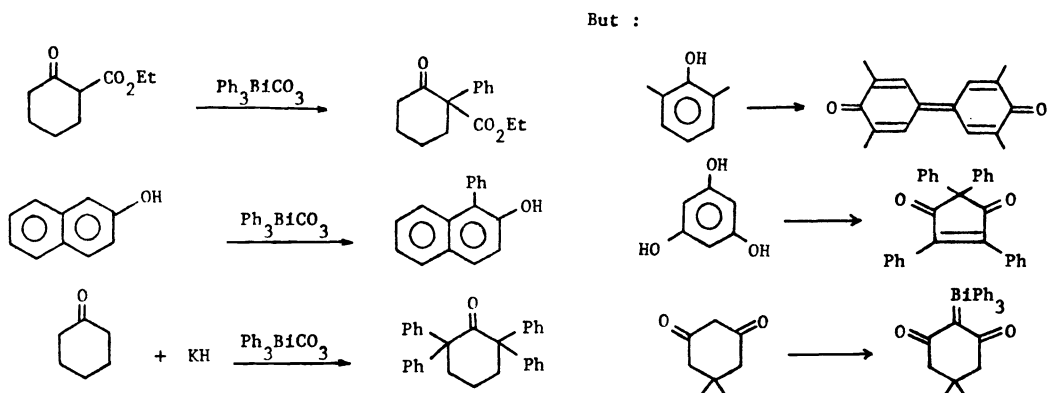
And then occurred the seminal accident ! Oxidation of quinine to quinone has remained a classical problem for many years. We decided to apply our mild oxidising system to quinine (ref. 18). When the oxidation of quinine was performed with one molar equivalent of Ph_3BiCO_3 , a modest yield of quinone (34%) was obtained. However, when two molar equivalents of Ph_3BiCO_3 were used, the major product was now a diastereo-isomeric mixture of α -phenylated quinones (Scheme 6).

Scheme 6. Quinine Oxidation by Ph_3BiCO_3



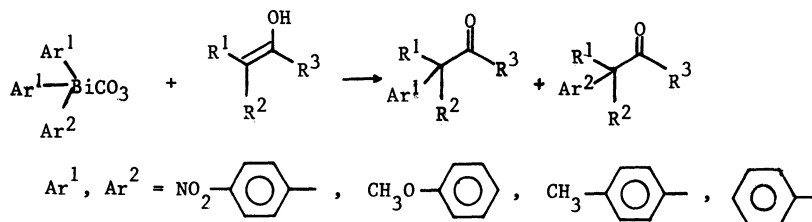
Subsequently a variety of other enolizable compounds were shown to be smoothly α -phenylated by Ph_3BiCO_3 (Scheme 7).

Scheme 7. Reactions of Ph_3BiCO_3

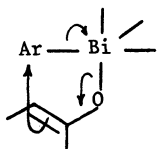
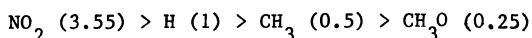


Ph_3BiCO_3 gave unusual products with a number of substrates such as 2,6-dimethylphenol, phloroglucinol, and dimedone (refs. 11, 19, 20). All the phenylation reactions were explained by the intermediacy of a covalently bonded Bi-O-substrate species. Reductive elimination resulted in intramolecular arylation, a process strongly dependent upon the nature of the aryl substituents on the bismuth. Studies of the relative migratory aptitudes proved that the reductive elimination is neither cationic, nor radical, but non-synchronously concerted (ref. 21) (Scheme 8).

Scheme 8. Mechanism of Reductive Elimination

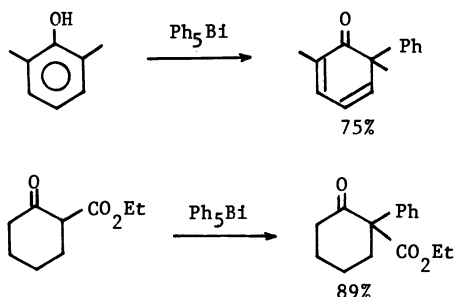


Relative migratory aptitude :

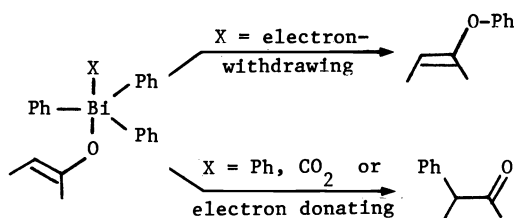


The influence of the fourth ligand on the course of the phenylation process was examined. Ph_5Bi was shown to be a more selective phenylating agent for ketones, enols, phenols under neutral conditions (refs. 11, 20) (Scheme 9).

Scheme 9



Scheme 10. Postulated Influence of the Ligand X on the Regioselectivity

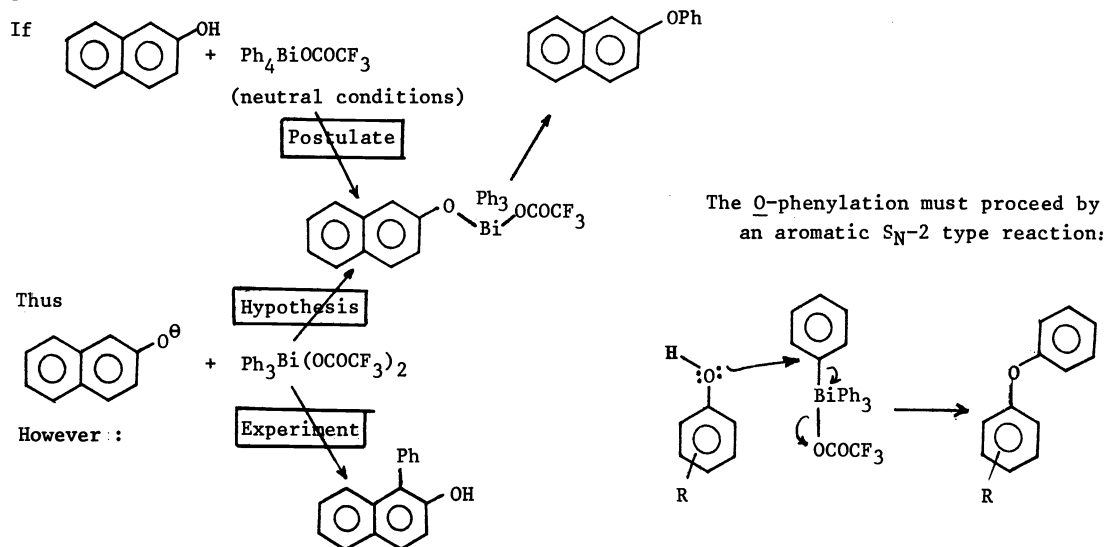


Amongst the phenols studied, *p*-nitrophenol reacted with Ph_5Bi to give the 4-nitrodiphenyl ether by O-phenylation. Mechanistically this was a misleading observation since it led us to postulate that the breakdown of the pentavalent Bi(V) intermediate was controlled by the nature of this fourth ligand, with an electron-withdrawing group favouring O-phenylation and an electron-donating group favouring C-phenylation. Therefore, both processes (O- and C-phenylation) should proceed via a common Bi(V) intermediate (Scheme 10).

This proposal seemed pertinent when a variety of enolizable substrates were phenylated with tetraphenylbismuth esters. O-phenylation of 2-naphthol occurred in high yield under neutral and acidic conditions. However this proposal was disproved when the synthesis and evolution of the postulated intermediate was studied. Reaction of 2-naphthol with $\text{Ph}_3\text{Bi}(\text{OCOCF}_3)$ under basic conditions would be expected to occur via the same Bi(V) intermediate. However, only the C-phenyl derivative was obtained. So, such an intermediate was not involved (Scheme 11).

We consider that the O-phenylation by tetraphenylbismuth esters follows an aromatic $\text{S}_{\text{N}}2$ type pathway (ref. 11). A positive charge on the ipso carbon of the 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, triphenylbismuth and acetic acid. The formation of benzene during the O-phenylation is explained by the acid produced in the reaction interacting with Ph_3Bi to give Ph_2BiX and benzene (ref. 22). Of course, the bimolecular kinetics of the reaction would also be compatible with a transitory six, or even seven co-ordinate bismuth intermediate. However, we discount this possibility which would be much more likely under basic, rather than neutral or acidic conditions. Under basic conditions, tetraphenylbismuth esters are one of the best and most selective reagents

Scheme 11

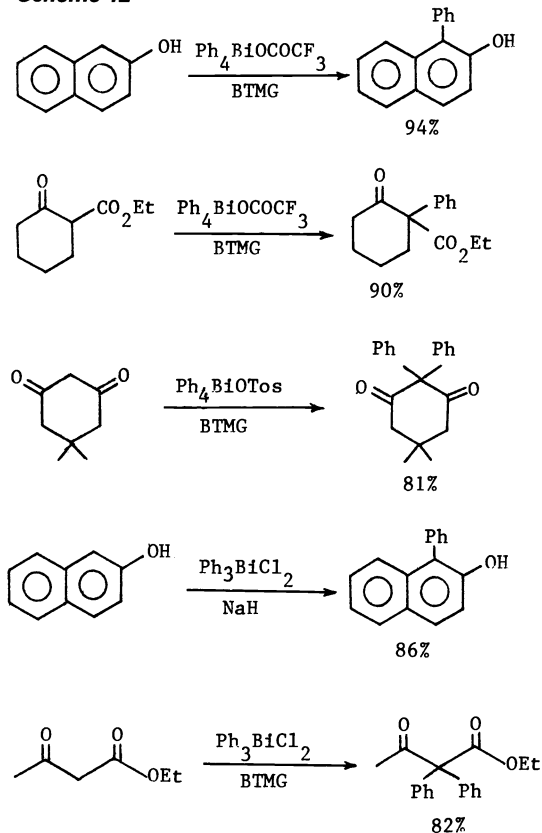


for ortho \underline{C} -phenylation of a wide range of substrates, such as phenols, enols, ketones, β -diketones.

Finally we discovered that the pivotal bismuth compound, Ph_3BiCl_2 , was itself a good, high yielding reagent for these ortho \underline{C} -phenylation reactions (Scheme 12) in presence of a suitable base.

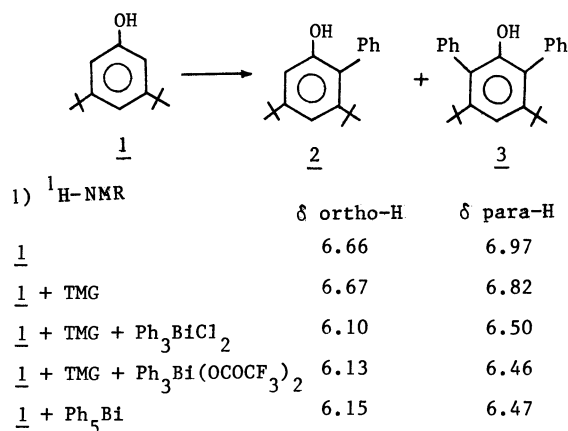
In the \underline{C} -phenylation process, the existence of a covalently bonded Bi(V) intermediate was postulated and later detected by physical methods: $^1\text{H-NMR}$ monitoring of the reaction of 3,5-di-*tert*-butylphenol with Ph_3BiCl_2 or $\text{Ph}_3\text{Bi}(\text{OCOCF}_3)_2$ under basic conditions, or with Ph_3Bi indicated the formation of an intermediate. Two such intermediates were then isolated, their structures assigned. Their controlled thermal degradation led to 3,5-di-*tert*-butyl 2-phenylphenol (Scheme 13).

Scheme 12

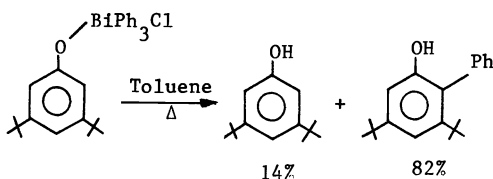


BTMG =

\underline{N} -*tert*-butyl \underline{N}' , \underline{N}'' -tetramethylguanidine

Scheme 13. Bi(V) Intermediates:
Synthesis and Decomposition

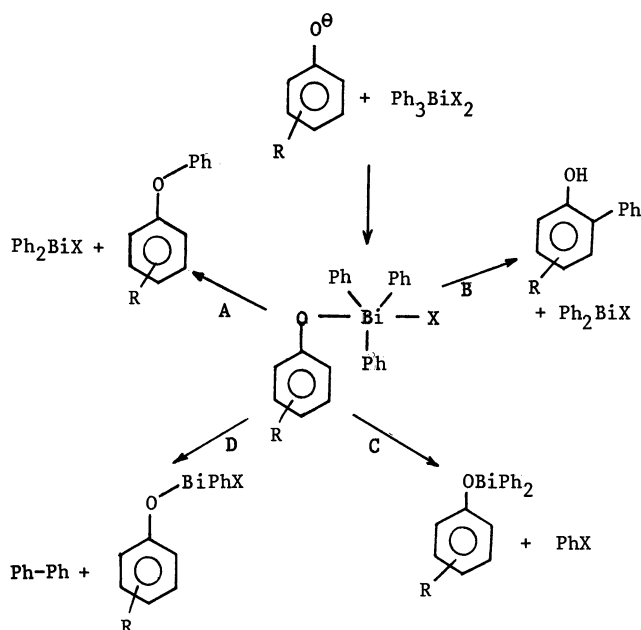
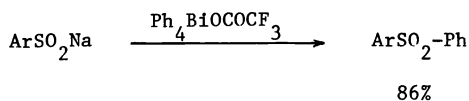
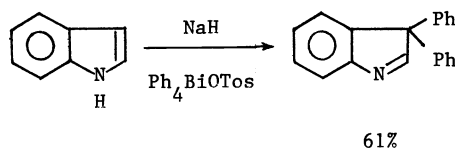
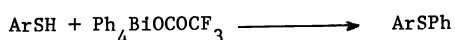
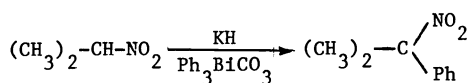
2) Isolation and Chemical Decomposition :



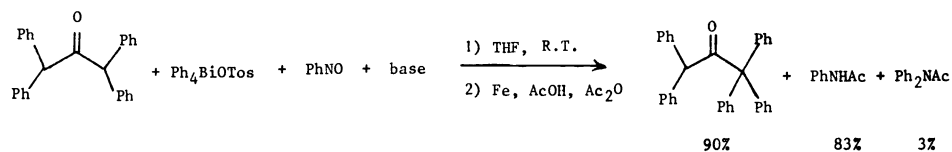
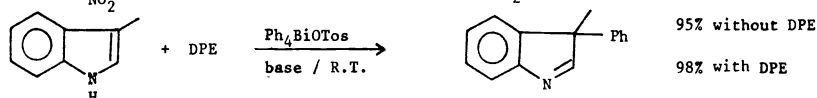
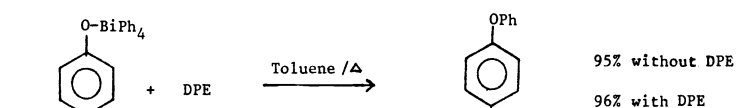
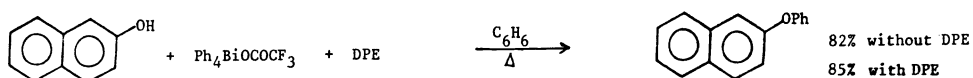
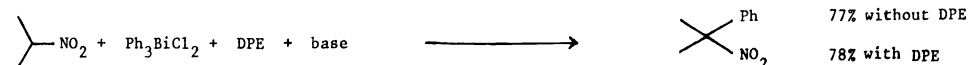
The nature of the substituents on the phenol appeared to govern the regioselectivity of the reaction (ref. 23). When a series of phenols were reacted with Ph_3BiCl_2 under basic conditions, a Bi(V) intermediate was formed and decomposed. Phenols bearing electron-withdrawing substituents were predominantly or selectively \underline{O} -phenylated. Phenols bearing electron-donating substituents were mostly \underline{C} -phenylated. Other decomposition pathways are sometimes involved (Scheme 14).

Different stabilised anions other than the aforementioned enolates have also been phenylated, such as nitroalkanes, thiols, sulphinic acid, indoles and esters (ref. 20) (Scheme 15).

Early mechanistic studies had shown that the \underline{C} -phenylation reaction was not ionic, and that the proposed intermediate was unlikely to be reductively eliminated by a free-radical pathway, but rather by a concerted mechanism. To discard completely the free-radical pathway, further studies were performed. First, the complete absence of

Scheme 14. Various Pathways for the Reductive Elimination of Pentavalent Aryloxybismuth Species**Scheme 15**

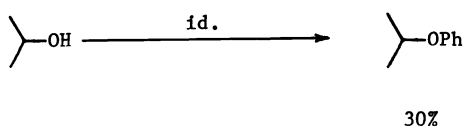
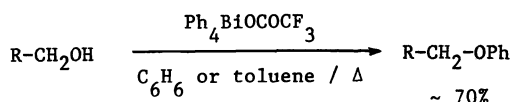
p-phenylated product was noted (ref. 23). A combination of e.s.r. spectrometry (qualitative and then quantitative) and quantitative chemical trapping experiments allowed us to eliminate completely the free radical pathway in these reactions (ref. 24).

Scheme 16. Studies of Free Radical Trapping**1 - With PhNO****2 - With Ph₂C = CH₂ (DPE)**

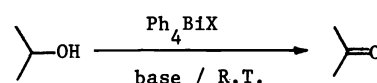
The pH-dependent behaviour of phenols and enols towards tetraphenylbismuth trifluoroacetate was also obtained in the reaction with alcohols. Thus, whereas under basic conditions, primary and secondary alcohols are oxidised by $\text{Ph}_4\text{BiOCOCF}_3$, via a covalent Bi-O intermediate, the *O*-phenyl ethers are obtained under neutral conditions by an aromatic $\text{S}_{\text{N}}2$ type displacement (ref. 13) (Scheme 17) (and see above).

Scheme 17. Reactivity of Alcohols towards Tetraphenylbismuth Esters

a) Under neutral conditions



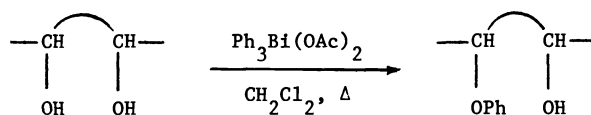
b) Under basic conditions



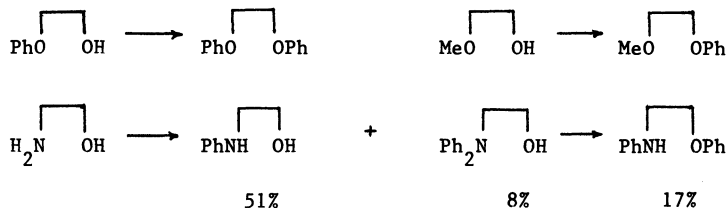
85-90%

In 1981, David and Thieffry, in the frame of a comparative study of various oxidants towards glycols and glycolstannoxanes, discovered accidentally a selective *O*-phenylation of diols by reaction with triphenylbismuth diacetate in CH_2Cl_2 . Good to excellent yields were obtained for *bis*-primary and *bis*-secondary vicinal diols. The reaction rate decreased with the chain length between the two hydroxy functions up to six carbons, but yields were good. In conformationally rigid molecules, axial hydroxy groups were preferentially *O*-phenylated. The kinetics of the reaction was quite unusual as an induction period (~ 2 h) was always noticed (ref. 25). This intriguing behaviour drew our attention, and we were even more puzzled to discover an array of other characteristics, such as bismuth compound selectivity ($\text{Ph}_3\text{Bi}(\text{OAc})_2$), solvent selectivity (only CH_2Cl_2 under reflux) and photochemical activation. But we also found that ether-alcohols and amino-alcohols were easily *O*-phenylated (ref. 26) (Scheme 18).

Scheme 18. David and Thieffry Reaction



- $\alpha, \beta, \gamma, \delta$ glycol with axial preference
- induction time, solvent (CH_2Cl_2), light
- other substrates :

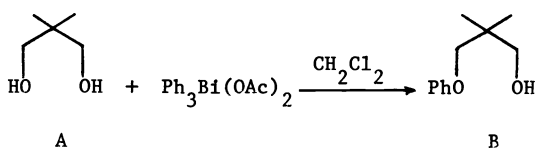


While these studies were in progress, we became aware of the work of Russian chemists in Gorki, who discovered that simple aliphatic alcohols were slowly *O*-phenylated when reacted without solvent with $\text{Ph}_3\text{Bi}(\text{OAc})_2$ in the presence of copper salts (ref. 27).

In the case of the David and Thieffry reaction, addition of a catalytic amount of copper salts, such as $\text{Cu}(\text{OAc})_2$ had a dramatic effect : the reaction rate was considerably increased and most of reaction specificities disappeared : solvent selectivity,

induction period, temperature and light activation (Scheme 19). Although not fully understood, the mechanism seems to imply a reaction between copper and $\text{Ph}_3\text{Bi}(\text{OAc})_2$ to yield a Cu^{I} species which transfers a phenyl to the hydroxy function (Scheme 20).

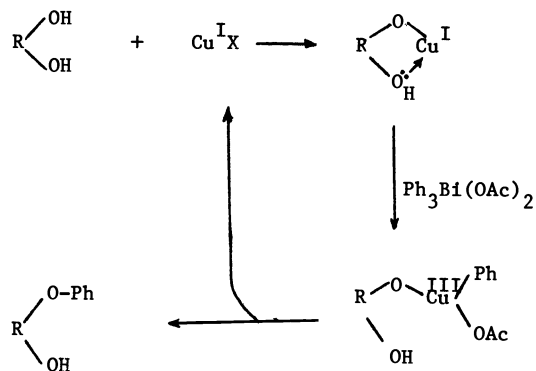
Scheme 19. Influence of $\text{Cu}(\text{OAc})_2$ on the David and Thieffry Reaction



$\text{Cu}(\text{OAc})_2$	Temp.	h ν	Induction Time (h)	Reaction Time (h)	(%) B
0	reflux	a	2	4	91
10^{-4}	reflux	a	0	0,25	82
10^{-1}	reflux	b	0	0,25	78
10^{-1}	20°	b	0	1	82

a) ambient light ; b) in the dark.

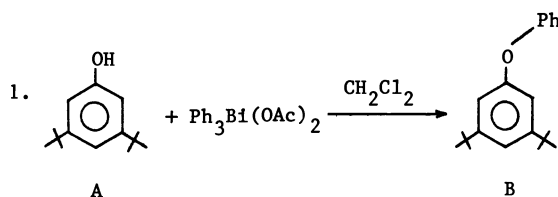
Scheme 20



The catalytic activity of copper salts in this reaction was extended to other substrates such as phenols and enols (ref. 28) (Scheme 21).

The chemoselectivity observed with amino-alcohols led us to develop a mono- or di-phenylation reaction of aliphatic and aromatic amines, under mild, selective and high yielding conditions (refs. 29, 30) (Scheme 22).

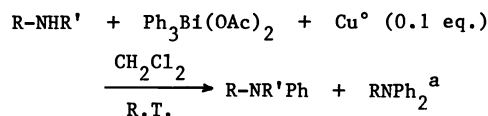
Scheme 21. Copper Catalysed O-Phenylation of Phenols and Enols



Catalyst	Reaction Time (h)	Temp.	A (%)	B (%)
-	23	Ref.	14	86
$\text{Cu}(\text{OAc})_2$	0.1	1 R.T.	15	77
$\text{Cu}(\text{OAc})_2$	0.1	24 R.T.	13	80
Cu°	0.1	4 R.T.	0	90

$\text{ArOH} + \text{Ph}_3\text{Bi}(\text{OAc})_2 \xrightarrow{\text{Cu} (0,1 \text{ eq.})}$	$\text{ArOPh}(\%)$
β -naphthol	84
2-phenyl-phenol	73
4-nitro-phenol	97
2,4-di- <u>tert.</u> -butyl--phenol	26

Scheme 22. Copper Catalysed N-Arylation of Amines



$\text{R} = \text{nBu}, \text{C}_6\text{H}_{11}, \text{C}_6\text{H}_5, \text{CH}_3\text{-C}_6\text{H}_4, \text{NO}_2\text{-C}_6\text{H}_4, \text{CH}_3\text{O-C}_6\text{H}_4$

Some examples

R^-	R'	$\text{Ph}_3\text{Bi}(\text{OAc})_2$	Reaction Time (h)	Yield (%)
Ph	H	1.1	2	96
p-tolyl	H	1.1	0,75	97
p-anisyl	H	1.1	0,25	91
p-anisyl	Ph	2.2	72	78
p-nitroPh	H	2.2	16	90 ^a
o-nitroPh	H	1.1	20	90
mesityl	H	2.2	24	92
mesityl	H	1.1	0,75	95

($\text{Ph}_3\text{Bi}(\text{OCOCF}_3)_2$)

a : diphenyl product if $\text{R} = \text{NO}_2\text{-C}_6\text{H}_4$, $\text{R}' = \text{H}$

This summary on our work on pentavalent organo-bismuth chemistry typically exemplifies the case of an initial rationally designed reaction leading to a series of fruitful accidents, whose developments led to the discovery of other hetero-arylations. Mechanistic studies on these copper catalysed reactions will undoubtedly bring us to other developments and useful applications.

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