State of The Art on Chemistry and Applications of Organoarsenic Compounds

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Abstract

Organoarsenic compounds have been known for over 200 years and in that time have given insight into important theoretical topics in chemistry from valency to aromaticity. They have also proved to have beneficial pharmacological effects. Organoarsenic compounds are produced industrially with uses as insecticides, herbicides, and fungicides. In general these applications are declining in step with growing concerns about their impact on the environment and human health. The parent compound is arsine. Despite their toxicity, organoarsenic biomolecules are well known.

Keywords: Organoarsenic, Arsonium Ylide, Synthesis, Reactions, Applications

Introduction

Organoarsenic chemistry played a prominent role in the history of the field of chemistry. It is the chemistry of compounds containing a chemical bond between arsenic and carbon. In organic arsenic compounds arsenic combines easily with carbon to form a wide variety of organic compounds with one or more As-C bonds. There are many known organoarsenic compounds used in agriculture as plant protection agents [1]. For wood preservatives, arsenic compounds are used solely in compound preparations. Organoarsenic compounds can be grouped into aliphatic organoarsenic compounds and aromatic organoarsenic compounds.

Aliphatic Organoarsenic Compounds

This class of compounds is still used as herbicides and fungicides in rice, cotton, fruit, and coffee plantations, particularly in Eastern Asia. The three main aliphatic organoarsenic compounds are described below.
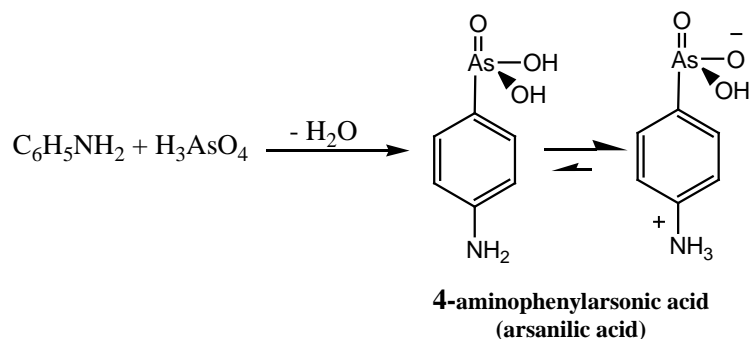
Methanearsonic Acid

Salts of methanearsonic acid, particularly the iron ammonium salt, Neoasozin, are used as a fungicide in rice growing. The sodium, ammonium, and diethanolammonium salts are used as herbicides in cotton growing [1].
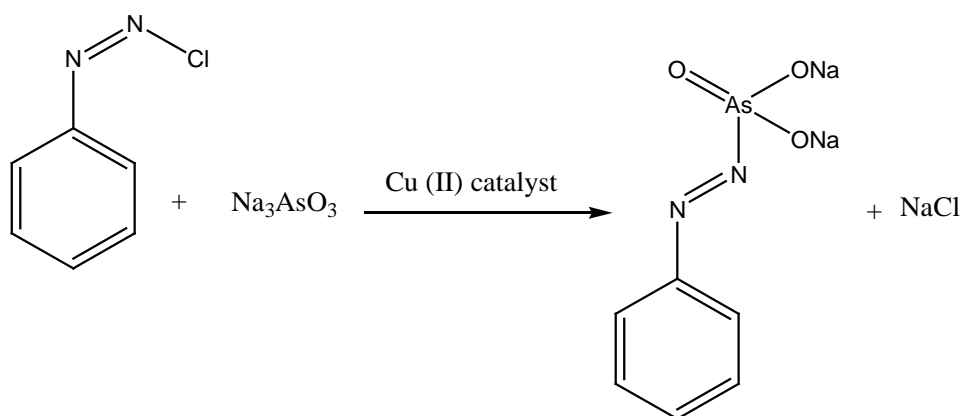
Dimethylarsinic acid

Dimethylarsinic acid, also called Ansar 160, is used as a total herbicide and desiccant. Generally, it is produced by reaction of methyl halide with a salt of arsenous acid [1].

Aromatic Organoarsenic Compounds

There are two classic methods of preparing aromatic organoarsenic compounds. In one method, aniline is reacted with arsenic acid at 392ºF as seen in the sulfonation of organic compounds:

$$C_6H_5NH_2 + H_3AsO_4 \xrightarrow{\text{- } H_2O}$$

4-aminophenylarsonic acid
(arsanilic acid)

In the other method, diazo compounds are reacted with sodium arsenate (III):

$$+ \quad Na_3AsO_3 \xrightarrow{\text{Cu (II) catalyst}} \quad + \text{ NaCl}$$

Of the two methods, the second method has proven to be the most commercially important in producing arsonic acids. In a more modern process, arsenic acid complexed with EDTA is added at 266ºF to a solution of excess aniline in perchloroethylene. The water of reaction and any unreacted aniline are separated off, and the bis(4-aminophenyl)arsinic acid intermediate is converted by acidic hydrolysis into arsanilic acid.

Arsonic acids are used in various industrial applications. For example, they have been used as corrosion inhibitors for iron and steel, and as additives for motor fuel, agricultural bactericides, herbicides, and fungicides.

The primary use of the arsonic acids was in their supplementary processing to arsenobenzenes and "arsenic oxides" by reduction with SO_2, phosphorus trichloride, sodium dithionite, phosphorous acid, or tin (II) chloride. Reduction with zinc dust and hydrochloric acid yields the arsines, which are reoxidized in air (e.g., phenylarsine is rapidly oxidized in air to form the arseno compound, $C_6H_5As_n$). Additional uptake of oxygen is considerably slower unless catalyzed (e.g., by iron) [1].

Arsenic oxides are relatively stable. All arsenic oxide compounds are oxidized to arsenic derivatives by strong oxidants, including hydrogen peroxide, halogens, and Chloramine-T (sodium *p*-toluenechlorosulfonamide). The aromatic arsonic acids are dibasic. Aqueous solutions of the monosodium salts are neutral to mildly acidic, whereas those of the disodium salts are slightly alkaline (pH of 8 to 9).

 Magnesium and calcium salts are typically soluble in cold water, but upon heating, they precipitate to practically insoluble deposits. Because magnesium and calcium salts are soluble in cold water, they can be used to separate arsonic salts from cold solutions. Arsonic acids generally crystallize well, and their stability depends on the substituents on the benzene ring. Some form azo dyes that contain both arsonic acid and sulfonic acid groups, and are used in the analysis of metals.


Aromatic Arsenobenzenes

Aromatic arseno compounds have amino or hydroxyl groups and are soluble in acids and alkalis. Aromatic arseno compounds become soluble in water with the addition of a formaldehyde sulfoxylate or formaldehyde hydrogen sulfite into the amino group [1].

Synthesis and classification

Arsenic typically occurs in the oxidation states (III) and (V), illustrated by the halides AsX_3 (X = F, Cl, Br, I) and AsF_5. Correspondingly, organoarsenic compounds are commonly found in these two oxidation states [2].

Organoarsenic (I) chemistry and uses

Organoarsenic compounds are found in oxidation state (I) [2], e.g. antisyphylic drugs as Salvarsin and Neosalvarsan; these are reprehensive of this class at this compound typically feature three bonds to As but only As-As single bond.
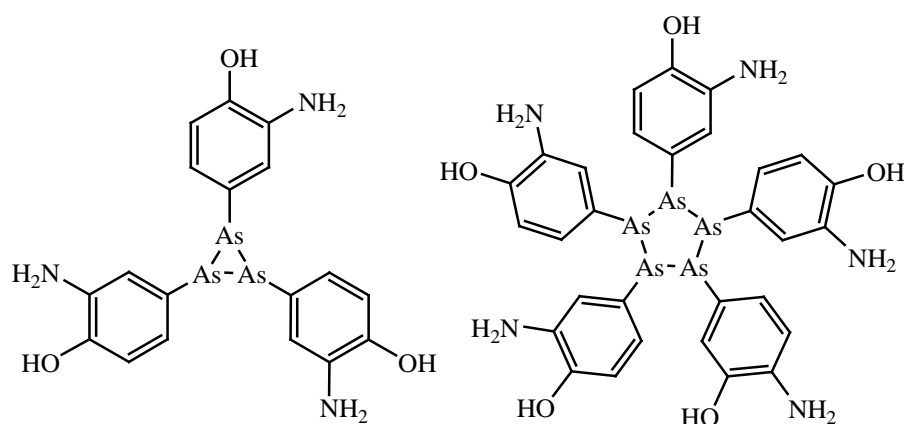
Organoarsenic (V) chemistry and uses

Arsenic (V) compounds typically feature the functional groups $RAsO(OH)_2$ or $R_2AsO(OH)$ (R = alkyl or aryl). Cacodylic acid, with the formula $(CH_3)_2AsO_2H$, figures prominently throughout the chemistry of organoarsenic compounds. In contrast, the dimethylphosphonic acid is less significant in the corresponding chemistry of phosphorus. Cacodylic acid arises from the methylation of arsenic (III) oxide. Phenylarsonic acids can be accessed by the reaction of arsenic acid with anilines, the so-called Bechamp reaction.
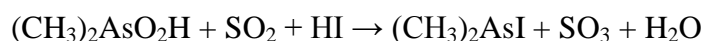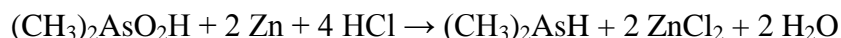
The monomethylated acid, methanearsonic acid ($CH_3AsO(OH)_2$), is a precursor to fungicides (tradename Neoasozin) in the cultivation of rice and cotton. Derivatives of phenylarsonic acid ($C_6H_5AsO(OH)_2$) are used as feed additives for livestock, including 4-hydroxy-3-nitrobenzenearsonic acid (3-NHPAA or Roxarsone), ureidophenylarsonic acid, and *p*-arsanilic acid. These applications are controversial as they introduce soluble forms of arsenic into the environment.

Compounds of arsenic (V) containing *only* organic ligands are rare, the pre-eminent member being the pentaphenyl derivative $As(C_6H_5)_5$ [2].
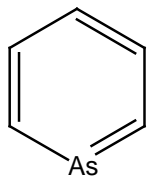
Organoarsenic (III) chemistry and uses

Most such compounds are prepared by alkylation of $AsCl_3$ and its derivatives using organolithium and Grignard reagents [2]. For example, the series trimethylarsine ($(CH_3)_3As$), dimethylarsenic chloride ($(CH_3)_2AsCl$), and methylarsenic dichloride (CH_3AsCl_2) is known. Reduction of the chloride derivatives with hydride reducing reagents affords the corresponding hydrides, such as dimethylarsine ($(CH_3)_2AsH$) and methylarsine (CH_3AsH_2). Similar manipulations apply to other organoarsenic chloride compounds.
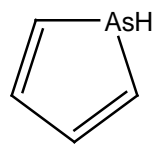
An important route to dimethylarsenic compounds begin with reduction of cacodylic acid (see above):

$$(CH_3)_2AsO_2H + 2\ Zn + 4\ HCl \rightarrow (CH_3)_2AsH + 2\ ZnCl_2 + 2\ H_2O$$

$$(CH_3)_2AsO_2H + SO_2 + HI \rightarrow (CH_3)_2AsI + SO_3 + H_2O$$

A variety of heterocycles containing arsenic (III) are known. These include arsole, the arsenic analogue of pyrrole, and arsabenzene, the arsenic analogue of pyridine

(Arsabenzene, arsinine)   **Arsole**

Symmetrical organoarsenic(III) compounds, e.g. trimethylarsine and triphenylarsine, are commonly used as ligands in coordination chemistry. They behave like phosphine ligands, but are less basic. The diarsine $C_6H_4(As(CH_3)_2)_2$, known as diars, is a chelating ligand. Thorin is an indicator for several metals.

Trimethylarsine   **Arsenobetaine**   **Thorin**
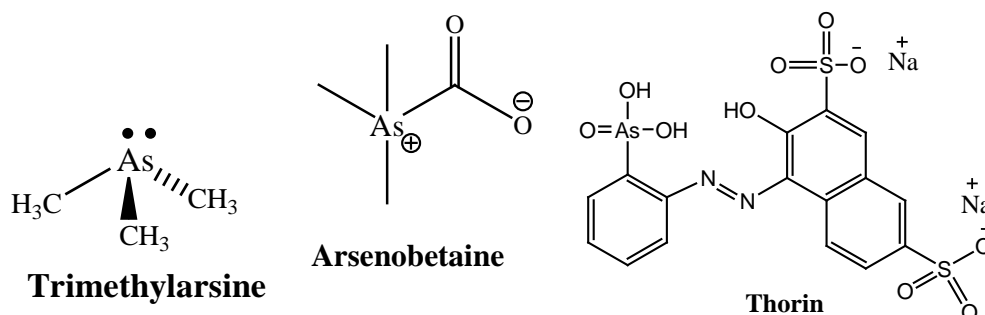
Organoarsenic Compounds in nature

As arsenic is toxic to most life forms and it occurs in elevated concentration in some areas, several detoxification strategies have evolved. Inorganic arsenic and its compounds, upon entering the food chain, are progressively metabolized to a less toxic form of arsenic through a process of methylation [3]. Organoarsenic compounds arise *via* biomethylation of inorganic arsenic compounds [4] *via* processes mediated by enzymes related to vitamin B_{12} [5].

$$(H_3C)_2\overset{\overset{\displaystyle O}{\|}}{As}$$
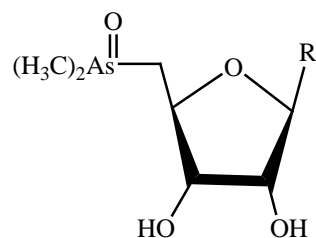
S- Oxarsenosugar

(Source of methyl groups in many biogenic arsenic compounds)

For example the mold *Scopulariopsis brevicaulis* produce significant amounts of trimethylarsine if inorganic arsenic is present [6]. The organic compound arsenobetaine, a betaine, is found in some marine foods such as fish and algae, and also in mushrooms in larger concentrations. The average person's intake is about 10-50 µg/day. Values about 1000 µg are not unusual following consumption of fish or mushrooms; however, there is little danger in eating fish since this arsenic compound is nearly non-toxic [7]. Arsenobetaine was first identified in the Western rock lobster [8,9].

In mammals, methylation occurs in the liver by methyltransferases, the products being the $(CH_3)_2AsOH$ (dimethylarsinous acid) and $(CH_3)_2As(O)OH$ (dimethylarsinic acid), which have the oxidation states As(III) and As(V), respectively [10]. Although the mechanism of the methylation of arsenic in humans has not been elucidated, the source of methyl is methionine, which suggests a role of S-adenosyl methionine [11]. Exposures to toxic doses begin when the liver's methylation capacity is exceeded or inhibited.

Carbohydrates bound to arsenic, collectively known as arsenosugars, are found especially in seaweeds. Arsenic containing lipids are also known [12].Although arsenic and its compounds are

toxic for humans, one of the first synthetic antibiotics was Salvarsan (the use of which has long been discontinued). The only polyarsenic compound isolated from a natural source is arsenicin A

Organoarsenic Compounds in Organic Synthesis

In the field of organic synthesis, organoarsines have found wide application. They, especially triphenylarsine [13] have been found to be useful as a metal ligand in a range of palladium-catalyzed cross-coupling reactions between organohalides and organostannanes [14] or organoboronic acids [15]. They can also be used for the preparation of arsonium ylides (alkylidenearsoranes) that are more nucleophilic than their phosphonium counterparts [16-19].

**more significant
contribution**
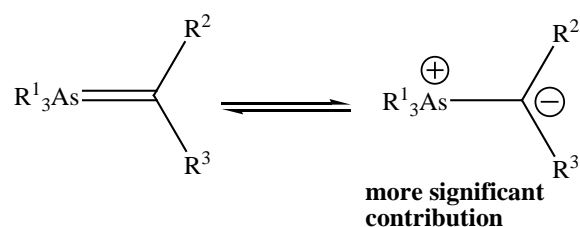
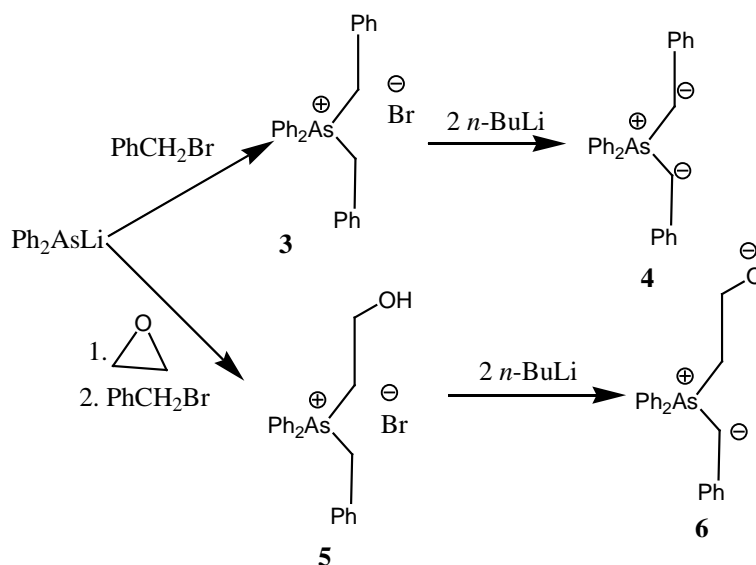## Synthesis of arsonium salts and ylides

The methods for the preparation of arsonium ylides [17] include: (1) deprotonation of an arsonium salt, (2) methods involving arsine dihalides, arsine oxides or diazo compounds, (3) transylidation and (4) reverse Wittig processes. It was noted that the salt method in which an arsonium salt (obtained by the reaction of an organosulfonate or halide with a tertiary arsine) is treated with a suitable base to provide the ylide, has been the most widely used for arsonium ylide generation in recent years. A variation for arsonium salt synthesis has been reported by Mioskowski *et al*. [20] that utilizes *t*-butyl chloride and aluminum chloride (Scheme 1).

t-**BuCl/AlCl₃**

Ph₂As ⟍⟍⟍⟍⟍⟍⟍⟍

1

Ph₂As⊕ ⟍⟍⟍⟍⟍⟍⟍⟍

⊖
Cl   **2, (55%)**
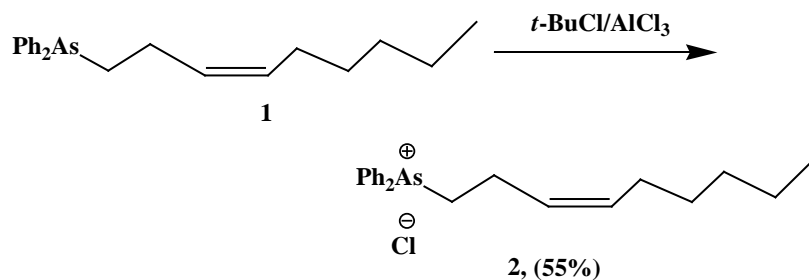
Scheme 1

They prepared **2** from the alkyldiphenylarsine **1** as an intermediate in their synthesis of (G)-hepoxilin A₃ [20]. In this synthesis, the use of an arsonium ylide was essential because it was used to convert an aldehyde group into an epoxide moiety in the penultimate step of the synthesis.

At approximately the same time, this group also reported the synthesis of ylide **4**, [21] which they described as the first ylide-anion, together with δ-oxido benzyl ylide **6** [22] (Scheme 2). Lithium diphenylarsenide, which was freshly prepared from diphenylarsine and lithium in THF, was reacted with benzyl bromide or ethylene oxide followed by benzyl bromide to afford **3** and **5**, respectively. When condensed with aldehydes such as hexanal, these ylides afforded trans-alkenes with a very high stereoselectivity (99:1) that was greater than that observed with the corresponding phosphonium ylides
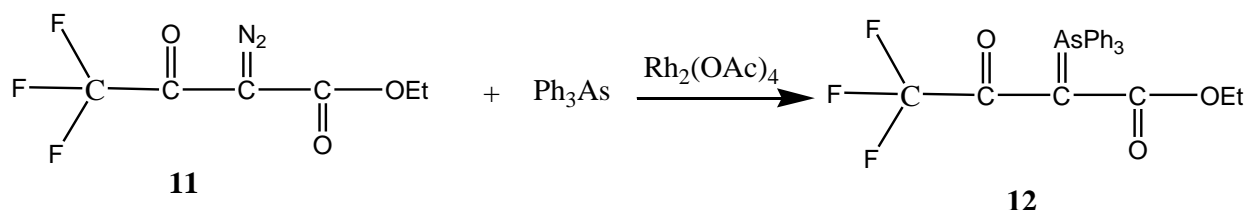
Scheme 2

The asymmetric Wittig reaction using chiral arsonium ylides has been described by Dai *et al*.

[23] Thus, they reported the first synthesis of chiral arsonium salts **9** and **10**, which were

obtained from triphenylarsine and chiral menthol-derived esters **8** (Scheme 3) [23].
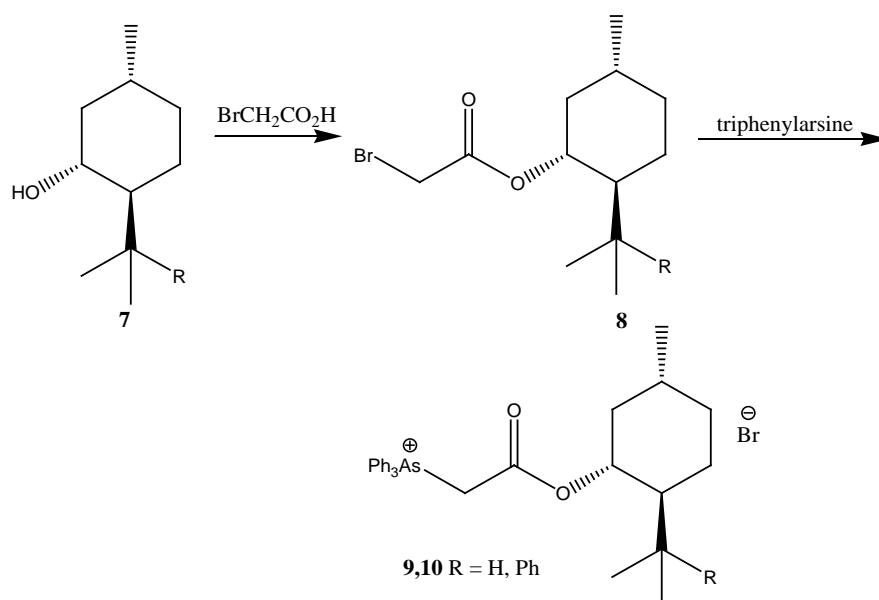
Scheme 3

Ethyl 2-diazo-4,4,4-trifluoro-3-oxobutanoate **11** reacted readily with triphenylarsine under mild reaction conditions in the presence of catalytic $Rh_2(OAc)_4$ affording to the corresponding *trans*-ethyl 4,4,4-trifluoro-3-oxo-2-(triphenyl-λ^5-arsorane)butanoate **12**. All the ylide products obtained are fairly stable due to the strong electron-withdrawing properties of the fluorine atom (Scheme 4) [24].

Scheme 4

The reaction of electron-deficient cyclopropane derivatives, *cis*-1-methoxycarbonyl-2-aryl-6,6-dimethyl-5,7-dioxospiro[2,5]octa-4,8-diones **13** with methoxycarbonylmethylene-triphenylarsorane (**14a**) and benzoylmethylenetriphenylarsorane (**14b**) was found to form methyl (2*R*,3*R*)-5-[3-methoxy-3-oxo-2-triphenylarsoranylidene))propanoyl]-3-pentyl-6-oxotetrahydro-2*H*-pyran-2,4-dicarboxylate (**15**) and *trans*-5-[2′-methoxycarbonyl-2′-(triphenylarsoranylidene)acetyl]-6-oxo-3-phenyl-tetrahydro-pyran-2,4-dicarboxylic acid dimethyl esters (**16**) respectively with high stereoselectivity (Scheme 5) [25].
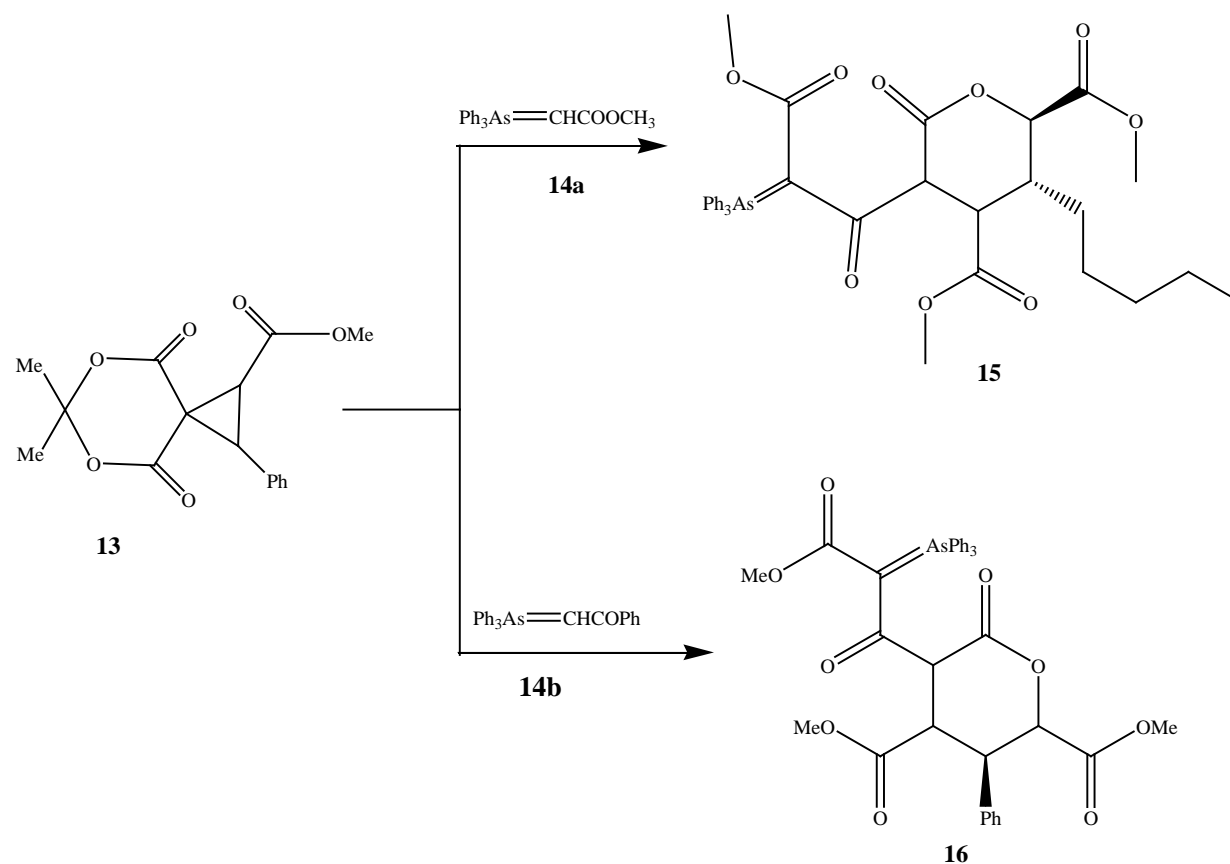
Scheme 5

A series of stable fluorine-containing arsonium ylides are simply synthesized from perfluoroalkanesulfonyl diazocarbonyl compounds in the presence of rhodium catalyst. The ylide products **17a-e** are fairly stable due to the strong electron-withdrawing properties of perfluoroalkanesulfonyl group and carbonyl group. They are fully confirmed by spectral methods (Scheme 6) [26].
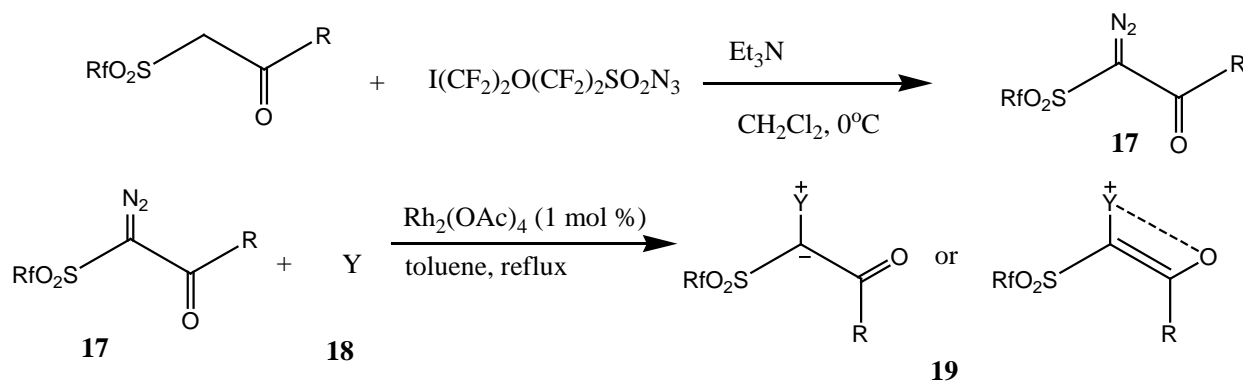
Table (1) Reaction results of perfluoroalkanesulfonyl diazocarbonyl compounds 17 with 18

| Entry	17	R_f	R	18(Y)	Product	Yield(%)	m.p.(^{o}C)
1	a	ClC_4F_8	CH_3	Ph_3As	19a	28	205-207
2	b	ClC_4F_8	Ph	Ph_3As	19b	96	196-198
3	c	CF_3	CH_3	Ph_3As	19c	65	156-158
4	d	CF_3	Ph	Ph_3As	19d	60	197-199
5	e	CF_3	OC_2H_5	Ph_3As	19e	32	151-153

Scheme 6

Non-cross-linked polystyrene-supported (carbomethoxymethyl)triphenylarsonium bromide (**21**) and benzyltriphenylarsonium iodide (**22**) were synthesized. They showed similar reactivities compared with the free arsonium salts in the arsa-Wittig reaction. The use of the polymer-supported reagents facilitated product purification and rendered the organoarsenic reagents easily separable and recyclable (Scheme 7) [27].
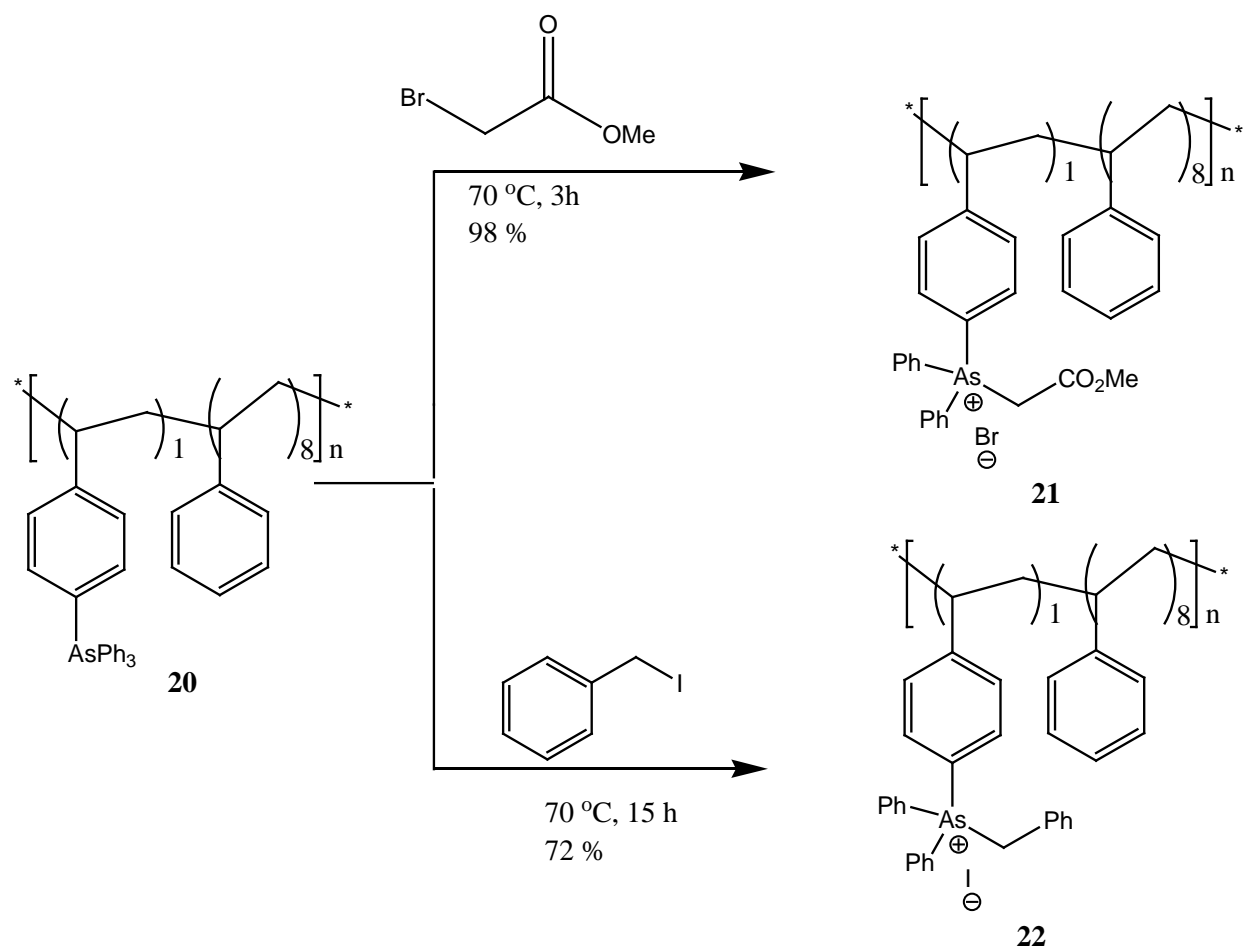
Scheme 7

A novel C_3-symmetric arsine have been synthesized from *p*-arsanilic acid in three steps. It was employed in the one-pot cyclopropanation of olefins with carbonyl-stabilized arsonium ylides formed in situ from methyl bromoacetate in the presence of NaHCO$_3$. This new arsine demonstrates good stereoselectivity and activity in the one-pot cyclopropanation of arylidenemalononitrile (Scheme 8) [28].

23a-23m   **24a-24m**
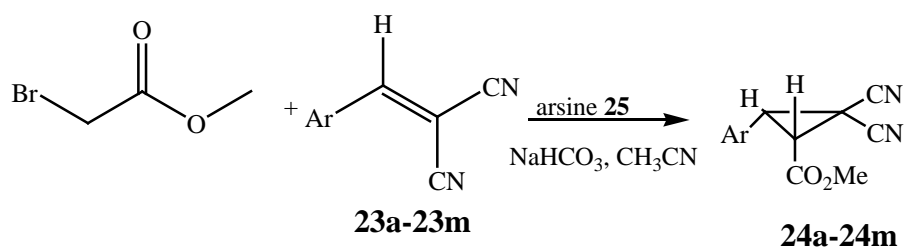
Ar = Ph; 4-CH$_3$-C$_6$H$_4$; 3,4-(CH$_3$)$_2$-C$_6$H$_3$; 4-OCH$_3$-C$_6$H$_4$; 3,4-OCH$_2$OC$_6$H$_3$;
   3,4-(OCH$_3$)$_2$-C$_6$H$_3$; 4-Cl-C$_6$H$_4$; 3-Cl-C$_6$H$_4$;2-Cl-C$_6$H$_4$;
   3,4-(Cl)$_2$-C$_6$H$_4$; 4-F-C$_6$H$_4$;4-Br-C$_6$H$_4$; 4-NO$_2$-C$_6$H$_4$.
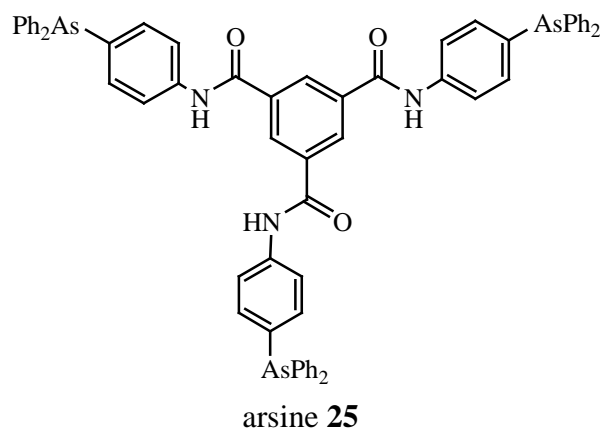
arsine **25**

Scheme 8

2-Diazo(fluoroalkyl)acetoacetates reacted readily with triphenylarsine under mild reaction conditions affording to the corresponding stable ylides in good to excellent yield (Scheme 9) [29].

26   **27**
X = F, Br; Y = Ph$_3$As
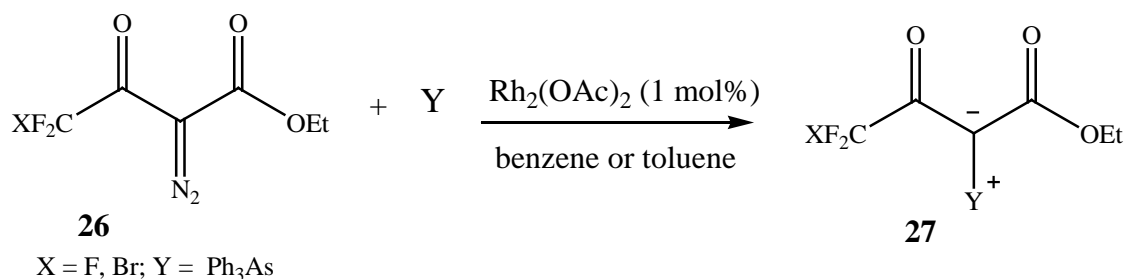
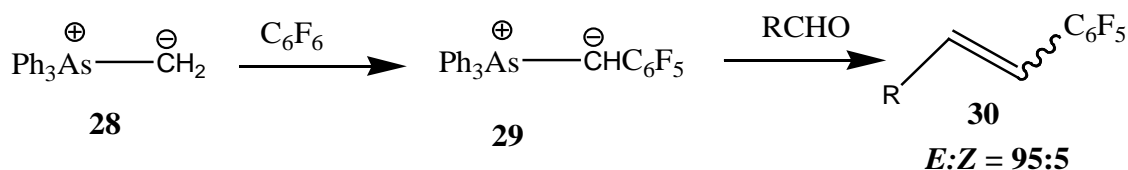**Scheme 9**

Synthetic applications of arsonium ylides

Due to the increased Zwitterionic nature of the As–C bond in these ylides, compared to the corresponding phosphonium ylides, arsonium ylides are stronger nucleophiles and they participate in a wide range of addition and substitution reactions, most of which involve electrophilic carbonyl compounds.

Alkene synthesis

As with their phosphonium counterparts, arsonium ylides can add to aldehydes and ketones in Wittig reactions to form alkenes that are accompanied by the formation of an arsine oxide.

Unconjugated alkene synthesis

It has been reported that reaction of the ylide **29**, generated *in situ* by the reaction of **28** with hexafluorobenzene, with a wide range of aromatic aldehydes afforded good to excellent yields (83–94%) of pentafluorophenylalkenes **30** (Scheme 10) [30].The authors reported that most products were formed with a predominantly *E* stereochemistry and that even the worst case afforded an *E/Z* ratio of 95:5.

$$\overset{\oplus}{Ph_3As}\text{——}\overset{\ominus}{CH_2} \xrightarrow{C_6F_6} \overset{\oplus}{Ph_3As}\text{——}\overset{\ominus}{CH}C_6F_5 \xrightarrow{RCHO} \underset{\underset{\textbf{30}}{R}}{\diagup\diagdown} C_6F_5$$

28   **29**

E:Z = 95:5

R = -Ph, -CH=CHPh, -C$_6$H$_4$-*o*-Cl, -C$_6$H$_4$-*p*-Cl, -C$_6$H$_4$-*p*-F, -C$_6$H$_4$-*p*-NO$_2$,-C$_6$H$_3$-2,4-Cl$_2$,-C$_6$H$_4$-*p*-Br, -C$_6$H$_4$-*p*-Me
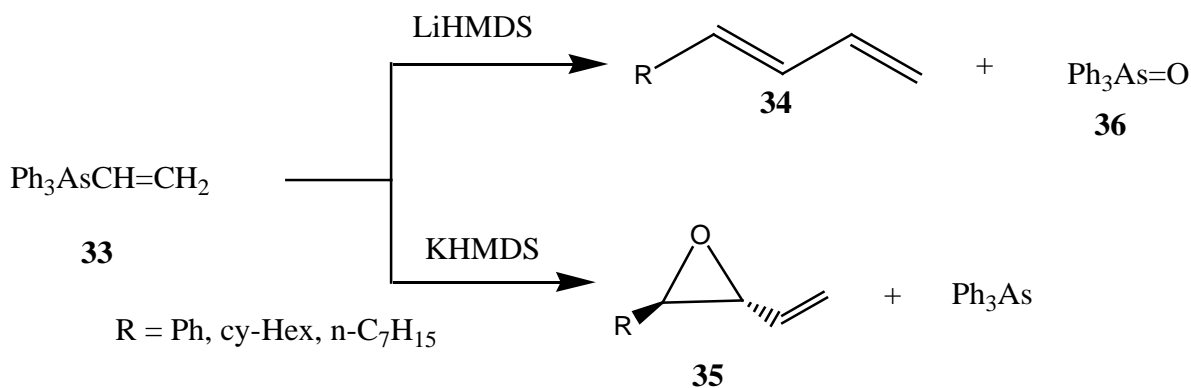
Scheme 10

Also, it has been reported that an alternative preparation of trans alkenes **32** through an Rh(II)-catalyzed reaction of aldehydes with pentafluorobenzaldehyde tosylhydrazones **31** in the presence of triphenyl arsine. During the reaction, arsonium ylide is assumed to be generated in situ through similar carbine transfer with subsequent Wittig-type reaction (Scheme 11) [31].
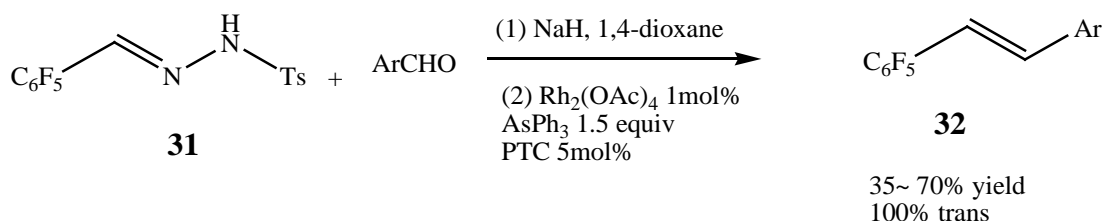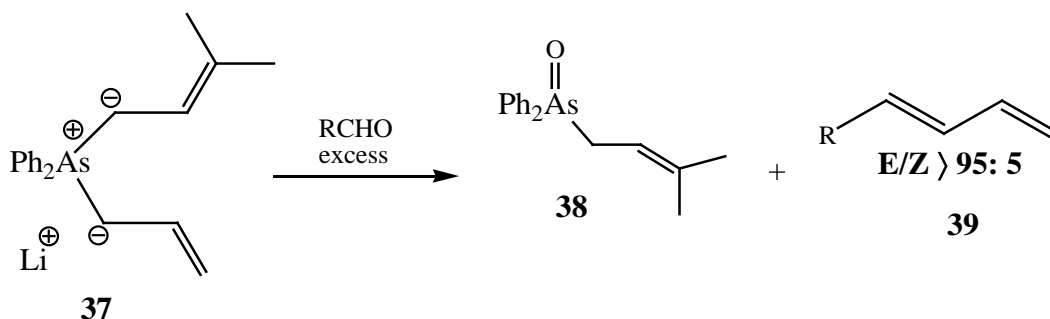

Scheme 11

1,3-Diene synthesis

It is known that the reaction of semi-stabilized arsonium ylides with carbonyl compounds results in a mixture of olefin and epoxide products [32]. Hsi and Koreeda reported that the selectivity for the formation of either olefins **34** or epoxides **35** are dependent upon the choice of base used for the generation of the arsonium ylide **30** (Scheme 12) [33]. Deprotonation of **33** with either Lithium bis(trimethylsilyl)amide (commonly abbreviated as LiHMDS, LithiumHexa MethylDiSilazide) or Potassium bis(trimethylsilyl)amide (commonly abbreviated as KHMDS, Potassium(K) HexaMethylDiSilazide), followed by the addition of the aldehyde, resulted in virtually exclusive olefin **33** or epoxide **35**, respectively (Scheme 12).
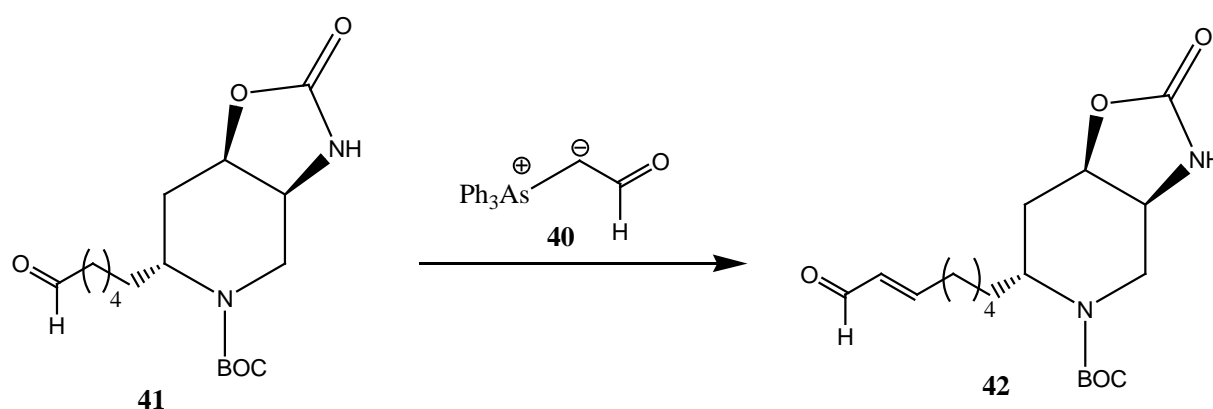
Scheme 12

A study of the reactivity of semi-stabilised arsonium ylide anions in olefination reactions is presented. The different ylide anions are generated by the addition of *n*-BuLi to various arsonium halide derivatives: [Ph(2)As(R)R'](+)X(-), **37** where R and R' are methyl, allyl, prenyl or benzyl groups. By using diallyldiphenylarsonium bromide (R=R'=allyl) an olefination protocol was optimised allowing the efficient transformation of aliphatic aldehydes into terminal 1,3-dienes with a high selectivity for the *E* isomer (*E/Z* ratios ranging from 90:10 to 97:3) **39**. The olefination reactions of aldehydes with dissymmetric arsonium halides (R not equal R') are very chemoselective; with arsonium ylide anions the benzyl moiety is more reactive than the allyl moiety which is much more reactive than phenyl and methyl groups (Scheme 13) [34].
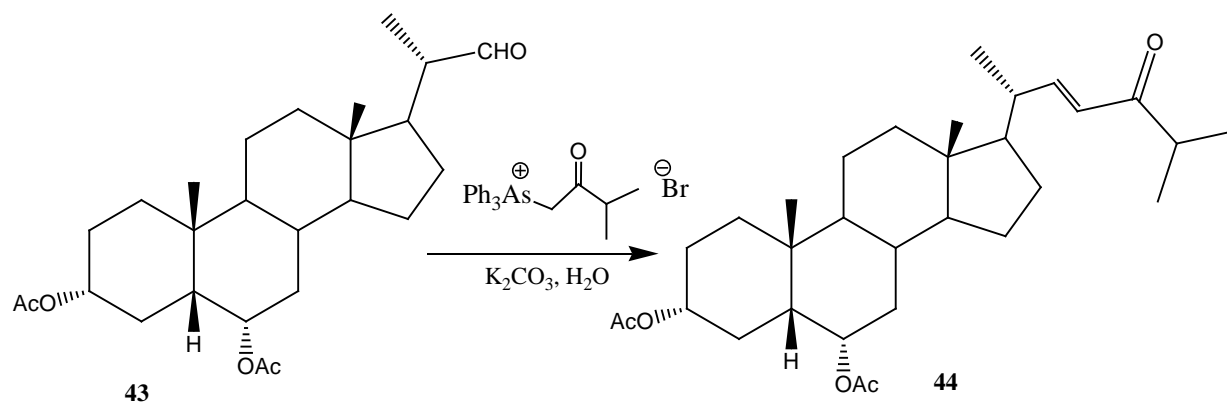

Scheme 13

α,β -Alkenal synthesis.

The facile formyl olefination of aldehydes by means of formylmethyltriphenylarsonium bromide **40** is described and they reported that the use of an arsonium ylide allowed the reaction to occur under much more milder conditions than with the corresponding phosphorus ylide [35]. This method is [36]in the synthesis of an intermediate of pseudodistomin B triacetate [21]. Treatment of aldehyde **41** with **40** afforded the desired formyl-olefination product **42** in 73% yield (Scheme 14).

Scheme 14

α,β-Alkenone synthesis.

An efficient and highly stereoselective synthesis of (*E*)-enones is reported by the reaction of aldehydes with arsonium bromides and potassium carbonate with a trace of water at room temperature [37]. Using this method, the key intermediate **44** for the synthesis of brassinosteroid (a class of polyhydroxysteroids that have been recognized as a sixth class of plant hormones) are prepared from the aldehyde **43** (Scheme 15).

Scheme 15

β,γ-Disubstituted butyrolactones **48** have been produced effectively and steroeselectively from arsonium ylides **45** generated *in situ* and substituted olefins **46**. The transformation could be realized in one-pot or in two steps, which depended on the electronic properties of the olefins. With the adjustment of the solvent and in the presence of EtOH, α,β,γ -trisubstituted butyrolactones **49** have been also obtained in high yield from arsonium ylides and substituted olefins (Scheme 16) [38].
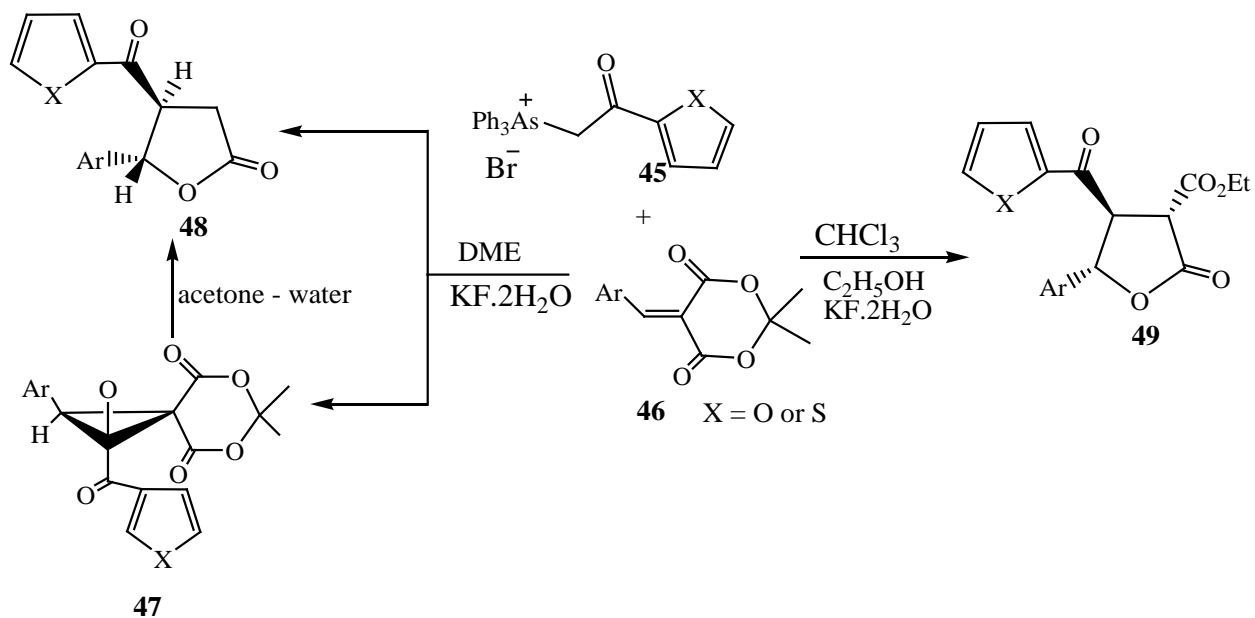
Scheme 16

α,β-Alkenoate synthesis.

 α-Halo-α,β-unsaturated compounds are useful intermediates in organic synthesis. for example α-iodo-unsaturated esters, ketones and nitriles **52** could be synthesized under mild conditions using readily available arsonium salts **50** in a one-pot procedure (Scheme 17) [39].
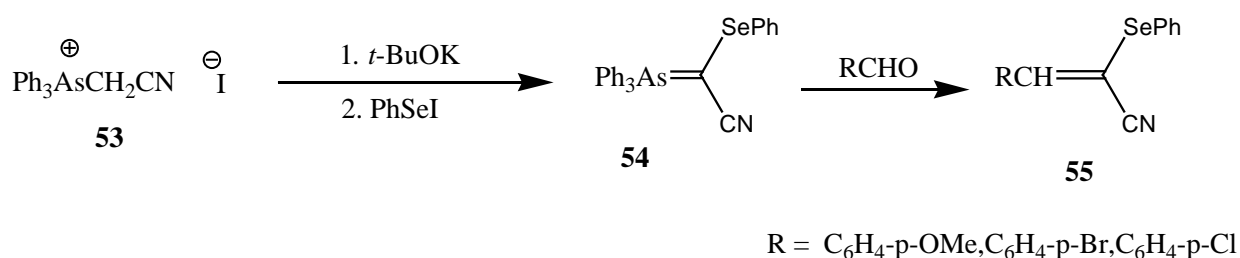
$$\overset{\oplus}{Ph_3As}CH_2R^1\overset{\ominus}{Br} \xrightarrow{K_2CO_3, \, I} \overset{\oplus}{Ph_3As}CH_2IR^1 \overset{\ominus}{I} \xrightarrow[R^2CHO]{K_2CO_3} R^2CH=CR^1I$$

50   **51**   **52**

$R^1 = CO_2Me, COMe, CN$
$R^2 = Ph, C_6H_4$-p -NO_2, C_6H_4-p -Cl, C_6H_4-p -OMe,CH=CHPh
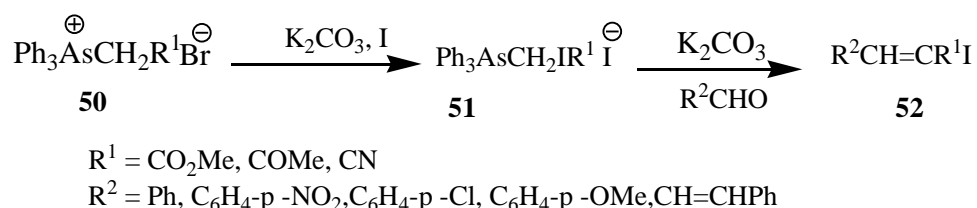
Scheme 17

α,β-Alkenitrile synthesis

The salt **53** was treated sequentially with a base and phenylselenenyl iodide to produce ylide **54**, which was found to be very unstable in air and water. Thus, after filtration under nitrogen, **54** was used directly in Wittig reactions with aromatic aldehydes to afford the α-Phenylseleno-α,β-unsaturated nitriles **55** in good yields (Scheme 18) [40].

$$\overset{\oplus}{Ph_3As}CH_2CN \quad \overset{\ominus}{I} \xrightarrow[\text{2. PhSeI}]{\text{1. } t\text{-BuOK}} Ph_3As=\overset{SePh}{\underset{CN}{\big|}} \xrightarrow{RCHO} RCH=\overset{SePh}{\underset{CN}{\big|}}$$

53   **54**   **55**

$R = \; C_6H_4$-p-OMe,C_6H_4-p-Br,C_6H_4-p-Cl

Scheme 18

2,4-Diene carbonyl compound synthesis

The use of the highly reactive arsorane **56** as an isoprenoid reagent reported to synthesize abscisic acid ester analogs [41]. This method gave only two isomeric products **57**, and **58**, while

the corresponding phosphonium ylide afforded four geometric isomers (Scheme 19). A similar strategy is used in the synthesis of pear ester with ylide **56** [42]. Finally, this method used in the synthesis of (+)-azimic acid [38].
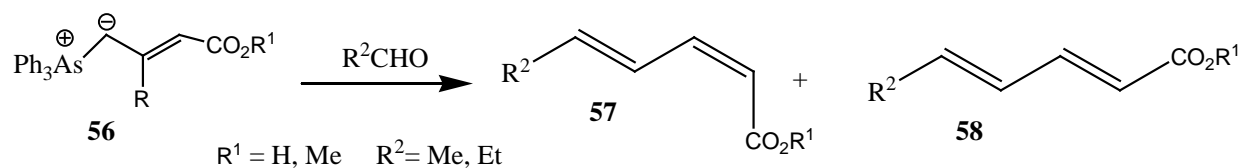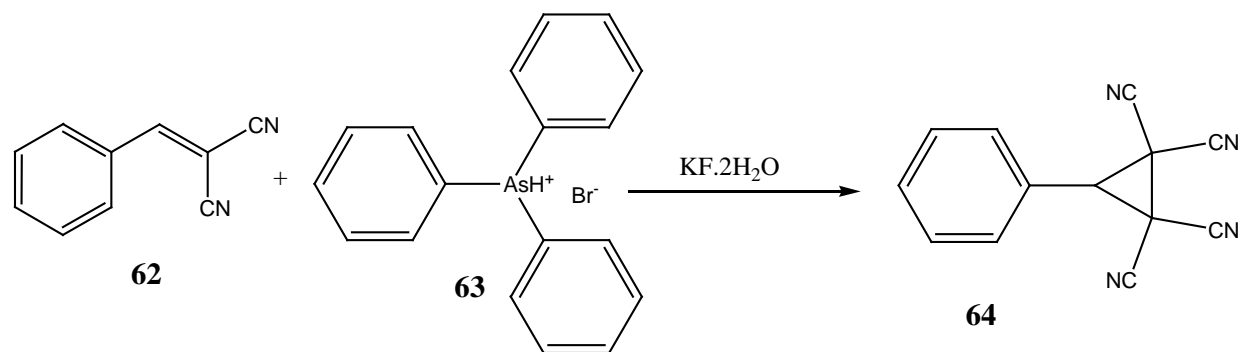

Scheme 19

cyclopropanation synthesis

Alkylidene or arylidene malonates **60** react with arsonium allylides **59** and give *trans*-disubstituted cyclopropane-1,1-dicarboxylates **61** with high stereoselectivity in high yields. The mechanism of the cyclopropanation reactions has also been investigated (Scheme 20) [44].
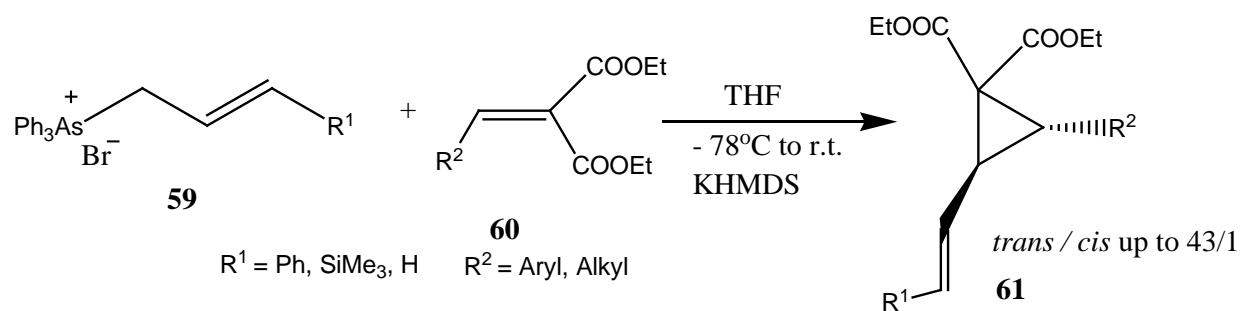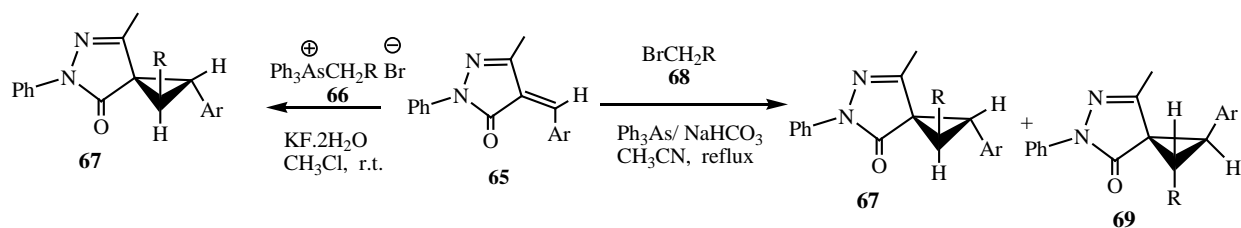

Scheme 20

A facile and efficient methodology for the preparation of 3-aryl-1,1,2,2-tetracyanocyclopropanes **64** is described. Arsonium bromides **63** reacted with benzylidenemalononitrile **62** in the presence of $KF.2H_2O$ to provide 3-phenyl substituted tetracyanocyclopropanes **64** in high yield (Scheme 21) [45].
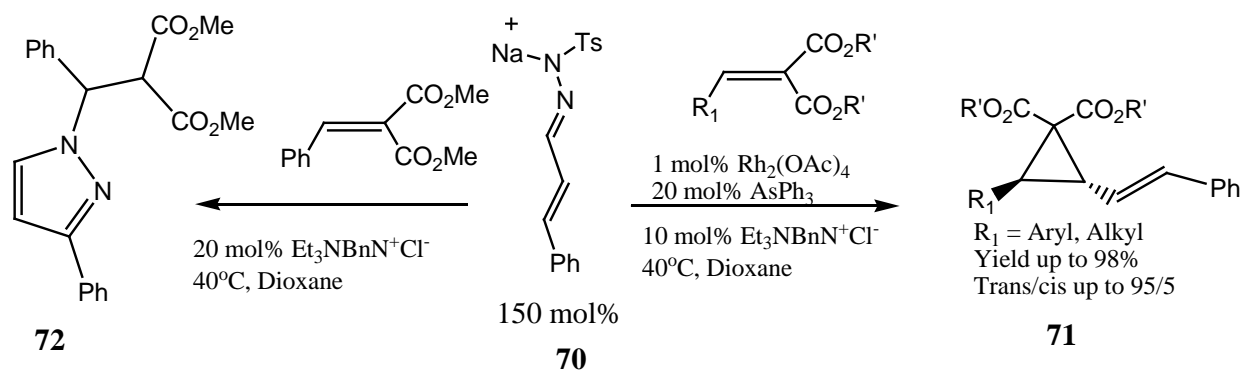
Scheme 21

A highly stereoselective synthesis of *exo*-spiro[cyclopropane-1,4`-pyrazolin-5`-one] **67** from 4-arylidene-3-methyl-1-phenylpyrazolin-5-one **65** and arsonium bromide **66** in the presence of base has been achieved. The triphenylarsine-catalyzed cyclopropanation of 4-arylidene-3-methyl-1-phenylpyrazolin-5-one **65** with bromide in the presence of NaHCO$_3$ has also been studied. Both *exo* and *endo* isomers were formed in this reaction **67, 69** (Scheme 22) [46].
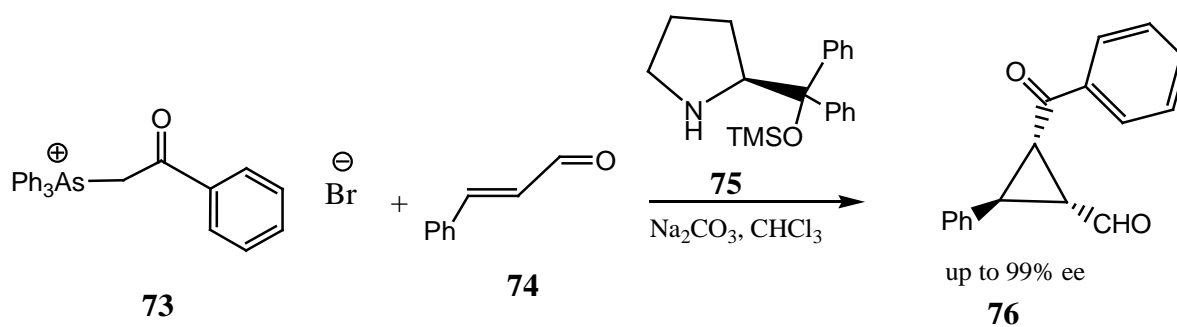

Scheme 22

Under mild conditions, the reaction of alkylidene, arylidene, and heteroarylidene malonates with tosylhydrazone salts **70** in the presence of catalytic amount of Rh$_2$(OAc)$_4$ and triphenylarsine affords trans-2,3-disubstituted cyclopropane 1,1-dicarboxylic esters **71** in high yields and high diastereoselectivities (Scheme 23) [47].

Scheme 23

A novel organocatalytic asymmetric cyclopropanation of α,β-unsaturated aldehydes **74** with arsonium ylides **73** using diphenylprolinol silylether **75** as a catalyst is described. A variety of chiral cyclopropyl aldehydes **76** are obtained in moderate to good yields with up to 99:1 dr (diastereomeric ratio) and 99% ee under simple and mild reaction conditions (Scheme 24) [48].

Scheme 24

A one-pot triphenylarsine-catalyzed synthesis of trans-cyclopropane derivatives **79, 80** is achieved by means of the reaction between acetylenic esters **77** and C–H acids **78** in the presence

of triphenylarsine. This procedure is simple and proceeds under mild reaction conditions. Its

success depends on the choice of solvent, temperature and C–H acid used (Scheme 25) [49].
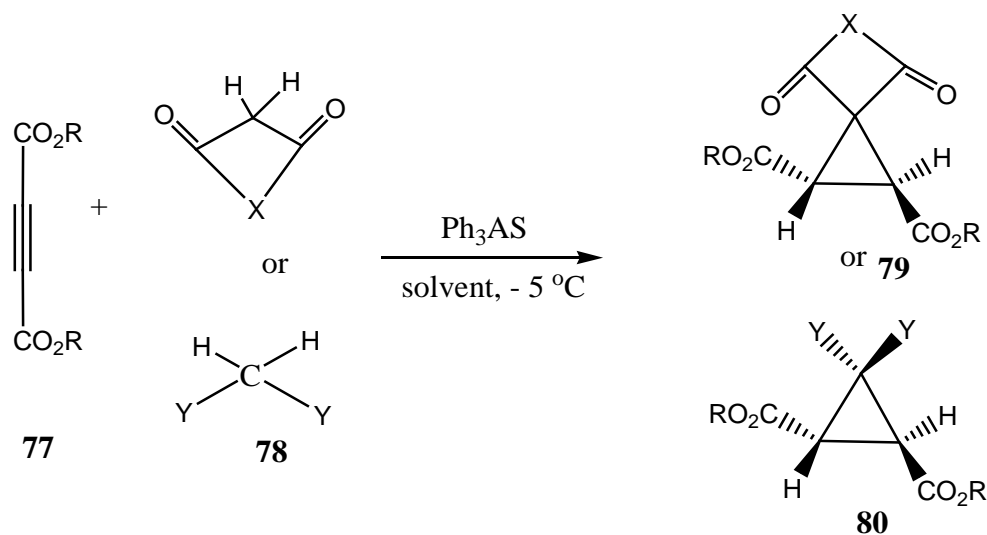
Scheme 25

A novel tandem cyclopropanation/Wittig reaction of α,β-unsaturated aldehydes **82** with arsonium

ylides **81** using a chiral 2-trimethylsilanyloxy-methyl-pyrrolidine-based dendritic catalyst is

described to give compound **83** . Good yields (up to 86%), and high diastereoselectivities (up to

dr = 99:1) and enantioselectivities (up to 99% ee) are obtained under simple and mild reaction

conditions. The catalyst can be recycled without any loss in activity (Scheme 26) [50].
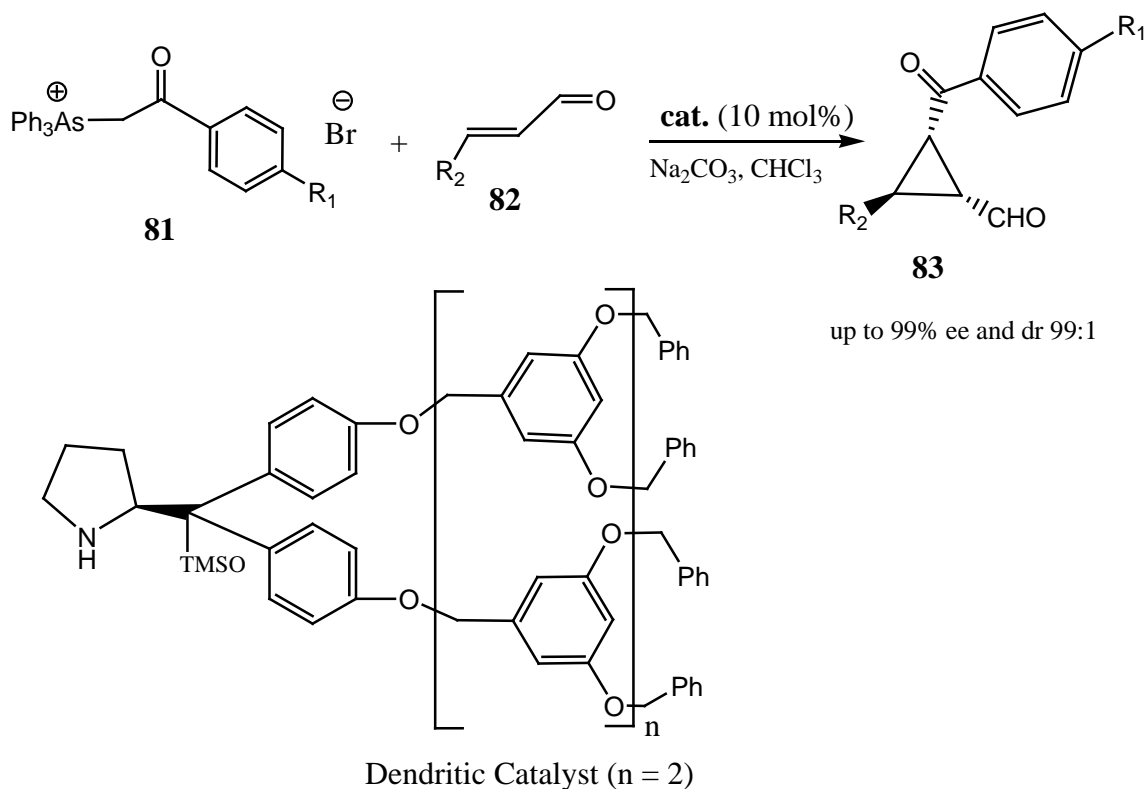
Scheme 26

A facile methodology for the preparation of highly functionalized *trans*-1,2-cyclopropanes containing *p*-trifluoromethylphenyl group **3** is described. Arsonium bromides **34** reacted with electron-deficient olefins **84** in the presence of K$_2$CO$_3$to provide **85** stereoselectively in moderate to good yields. This process has been successfully applied to the construction of cyclopropane ring fused pyridazinone derivatives **86** or pyrazole derivatives **87** (Scheme 27) [51].
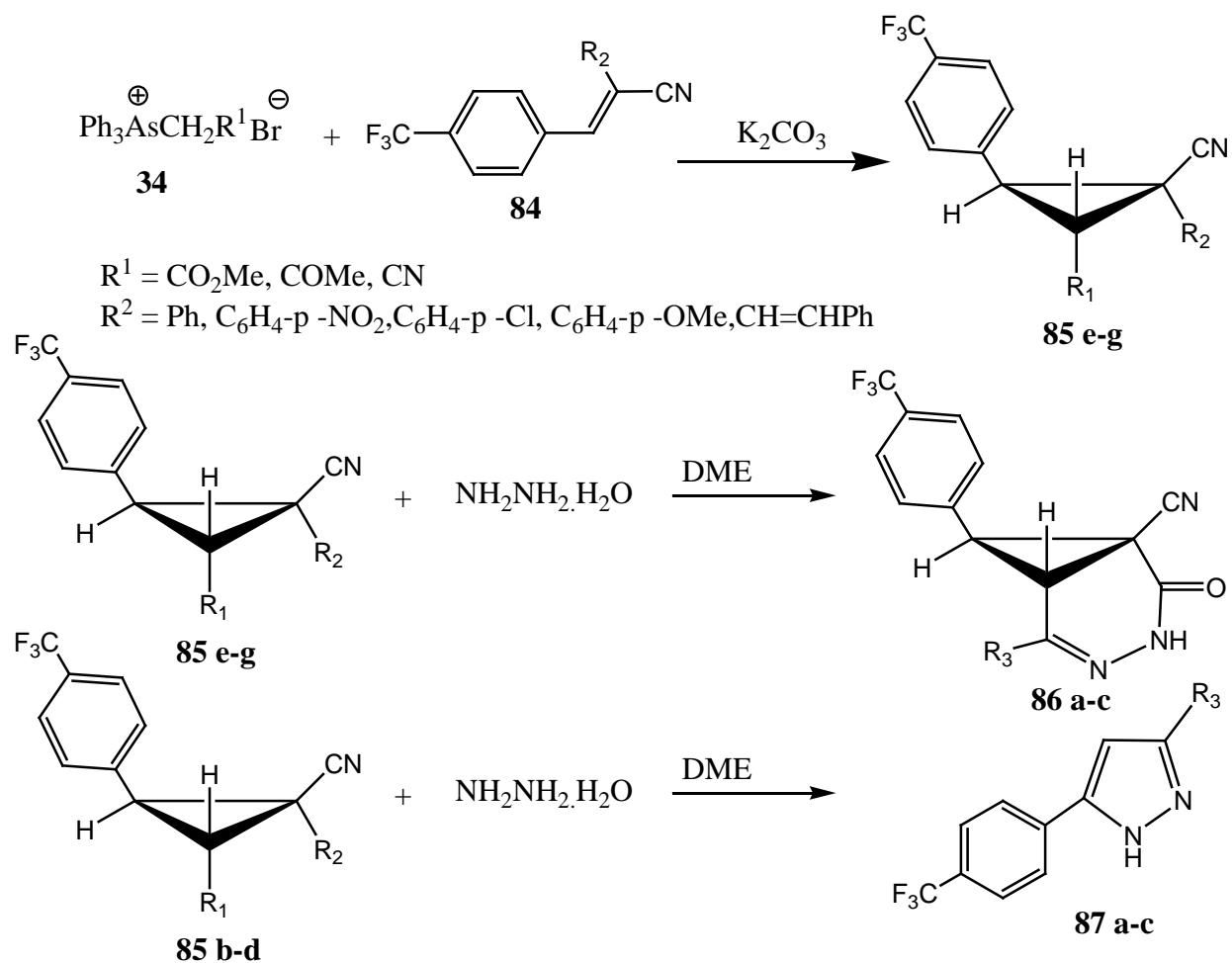
Scheme 27

Arsonium bromides **34** reacted with electron-deficient olefins **88** in the presence of K_2CO_3 to provide *trans*-1,2-cyclopropanes containing *p*-trifluoromethyl phenyl group **89** stereoselectively in moderate to good yields. (Scheme 28) [52].
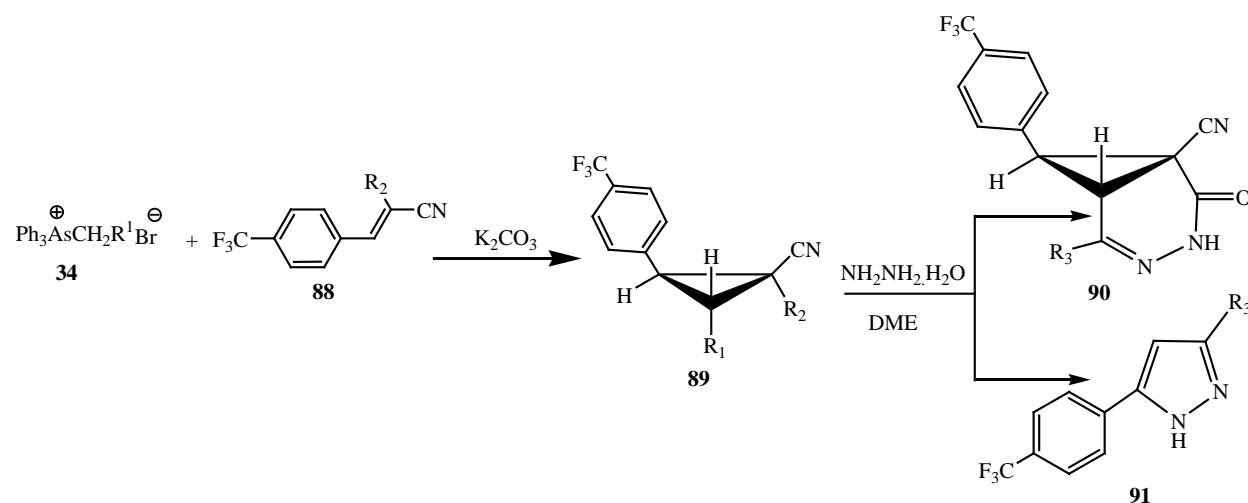
Scheme 28

In the presence of KF·2H$_2$O, furoylmethyltriphenylarsonium bromide (**92a**) or thienoylmethyltriphenylarsonium bromide (**92b**) reacted with 2-[(un)substituted benzylidene]malononitrile (**93**) in chloroform at room temperature to give *trans*-3,3-dicyano-1-furoyl-2-[(un)substituted phenyl]cyclopropane (**94a**) or *trans*-3,3-dicyano-1-thienoyl-2-[(un)substituted phenyl]cyclopropane (**94b**) respectively in good yield with high stereoselectivity (Scheme 29) [53].
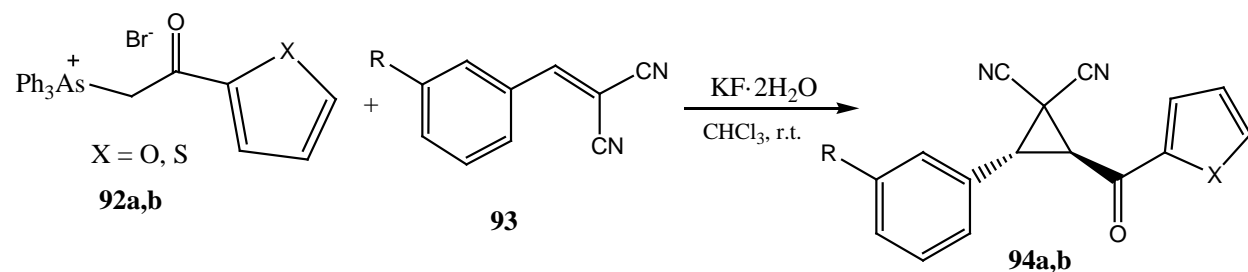
Scheme 29

An efficient and highly stereoselective approach for the preparation of highly functionalized cyclopropyl heterocycles **97a,b** *via* the cyclopropanation of olefines **96** with arsonium salts **95a,b** in the presence of KF.2H$_2$O has been developed (Scheme 30) [54].
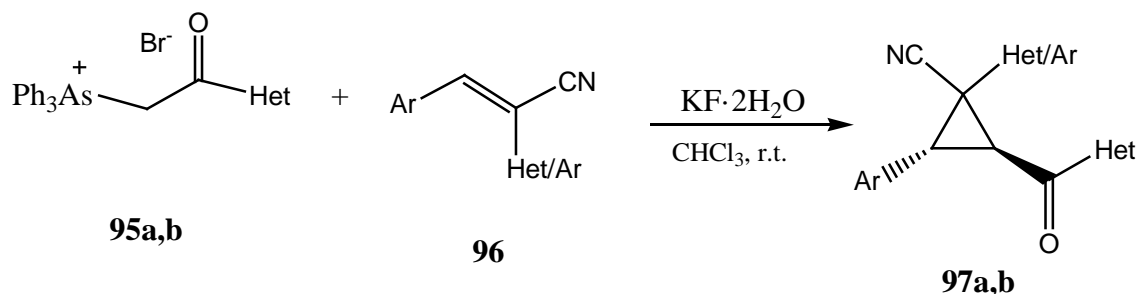
Scheme 30

Heterocycle synthesis

It has been reported that ylides **98a** [55] and **98b** [56] as β-formyl vinyl anion and δ-formyl butadienyl anion equivalents, respectively. Using these ylides, a variety of aldehydes could be homologated by three or five carbons to form the corresponding hydroxyl enals **99** under very mild conditions through a three-step sequence (Scheme 31). The initially formed acetal-containing epoxide is first hydrolyzed, followed by base-induced ring opening.

n = 0, 1
R^1 = OEt, O-i-Pr
R = (CH$_2$)$_{10}$Me, cy-Hex, CH$_2$Ph,
CH$_2$CH(Me)CH$_2$CH$_2$CH=C(Me)$_2$
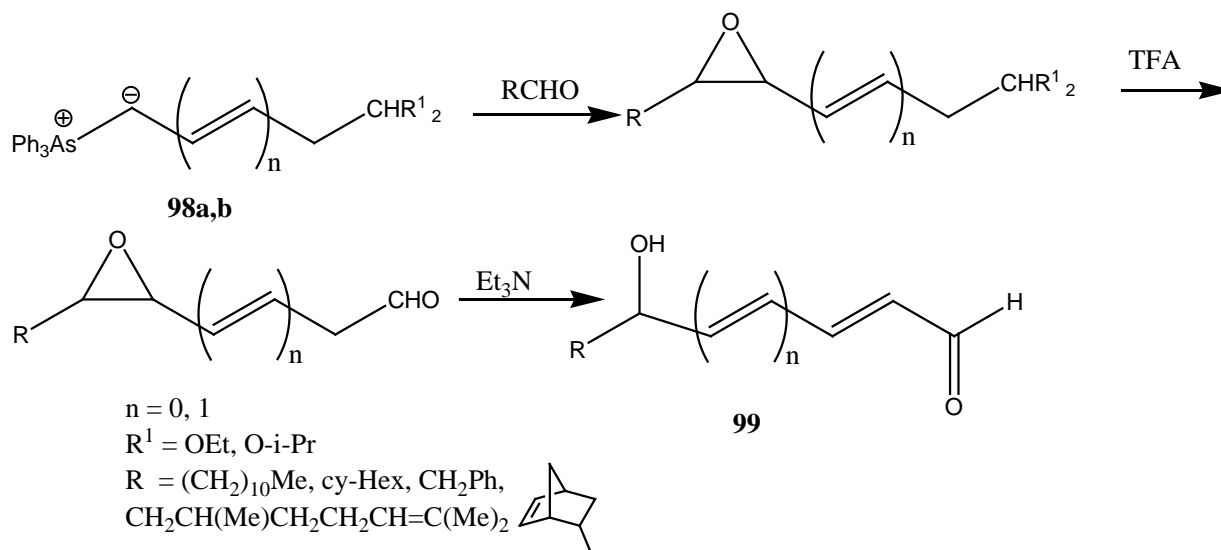
Scheme 31

δ-Valerolactone **100** was transformed into β,γ-unsaturated aldehyde **101**, which was subsequently converted into γ-hydroxy-enal **103** by using ylide **102**. Coupling of **103** with the ylide **104** afforded **105**, the methyl ester of hepoxilin A$_3$ (Scheme 32) [20].
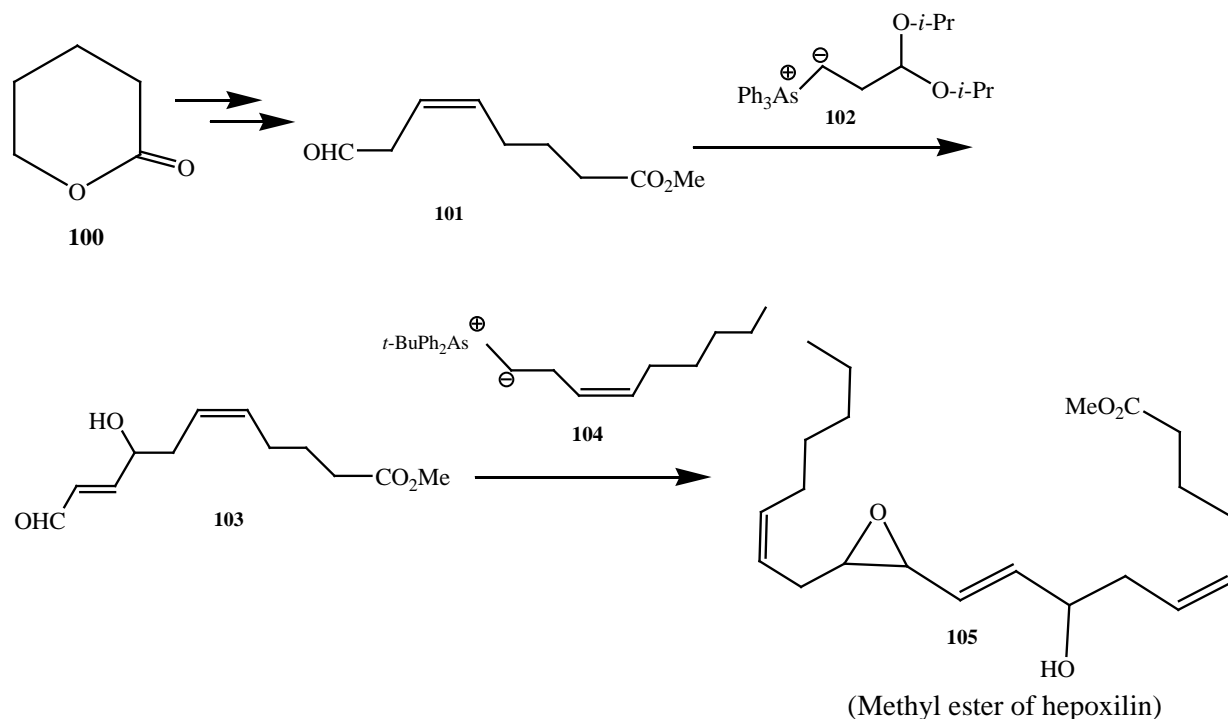
Scheme 32

An efficient approach of highly stereoselective synthesis of novel trifluoromethylated *trans*-4,5-dihydrofuro[2,3-c]pyrazoles **108** has been described. Arsonium bromides **106** reacted smoothly with the electron-deficient alkenes (Z)-4-aryl-1-phenyl-3-(trifluoromethyl)-1H-pyrozol-5(4H)-ones **107** to give *trans*-dihydrofuro[2,3-c]pyrazoles **108** with high stereoselectivity and in good to excellent yields, using CH$_2$Cl$_2$ as solvent and K$_2$CO$_3$ as base (Scheme 33)[57].

R_1= Me, H, Cl, Br, F; R_2 = CO$_2$Me, COMe, COPh, furoyl
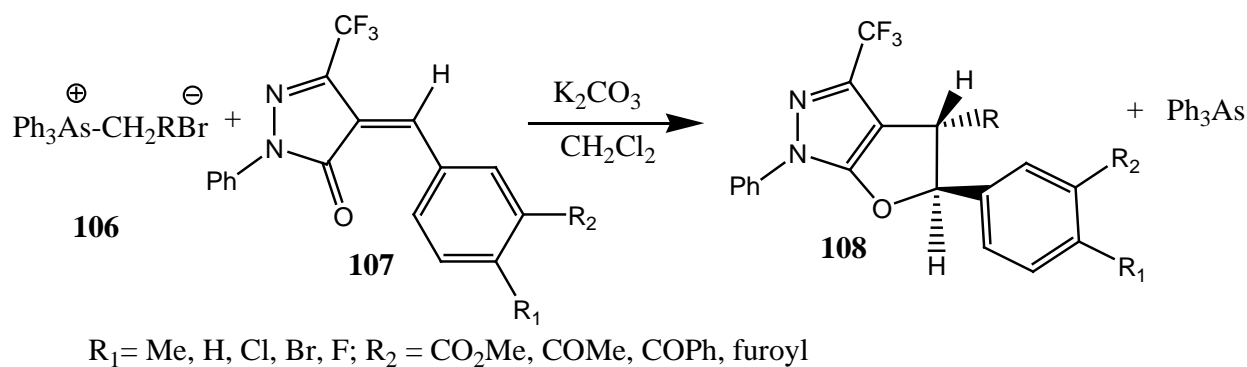
Scheme 33

Semistabilized arsonium ylides **110**, generated in situ from the corresponding arsonium salts **109** in the biphasic system of dichloromethane-50% aqueous sodium hydroxide, reacted smoothly with electron-deficient alkenes **111** to afford trans-1,2-cyclopropane derivatives **112** and **113** respectively with high stereoselectivity. The synthesis of *trans*-1,2-cyclopropane derivatives **112, 113** in the presence of sodium hexamethyl-disilazanide (1.0 M solution in THF) were also studied (Scheme 34)[58].
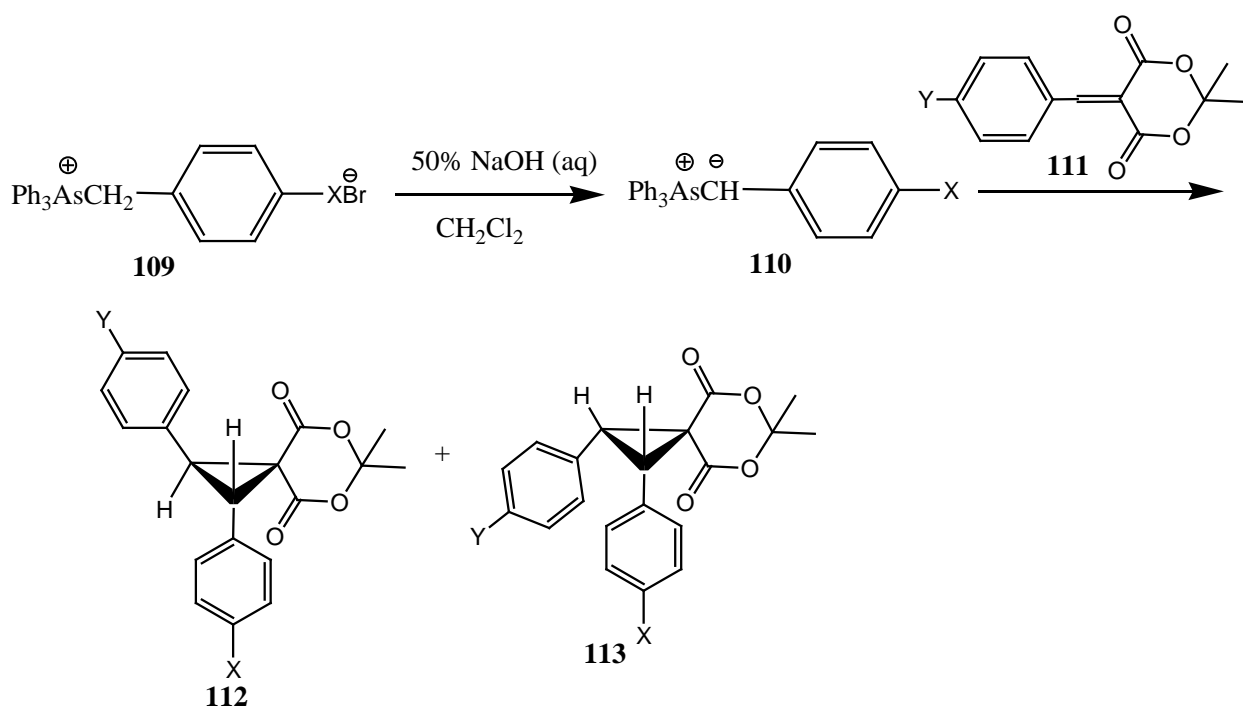
Scheme 34

The reactions of arsonium bromides **106** with (*E*)-α-trifluoromethylsulfonyl-α,β-unsaturated ketones **114** in the presence of Cs_2CO_3 or K_2CO_3 proceeded smoothly under refluxing condition in dichloromethane (DCM) to give the corresponding trifluoromethylated *trans*-2,3-dihydrofurans **115** in good to excellent yields with high stereoselectivity (Scheme 35)[59].

R_1 = Ph, p-Br-Ph
R_2 = Ph, p-F-Ph,p-Me-Ph, p-Br-Ph, o-Cl-Ph, m⁻ Br-Ph, cy-Hexyl, Furyl
R = CN, CO_2Me, COPh, Ph, Vinyl, COMe
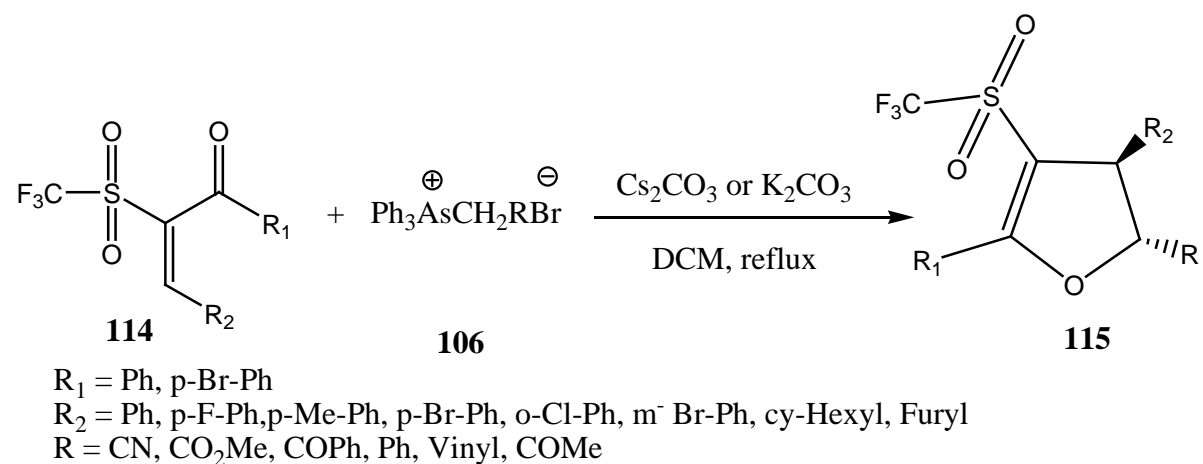
Scheme 35

A one-pot approach for highly stereoselective synthesis of spirocyclopropyl oxindoles **118** with good to excellent yields from the reaction of isatins **117** and arsonium salts **106** in the presence of K_2CO_3 is described (Scheme 36)[60].

R = I, Br, NO_2, CH_3; R' = H, Ph
X = CO_2CH_3, CN
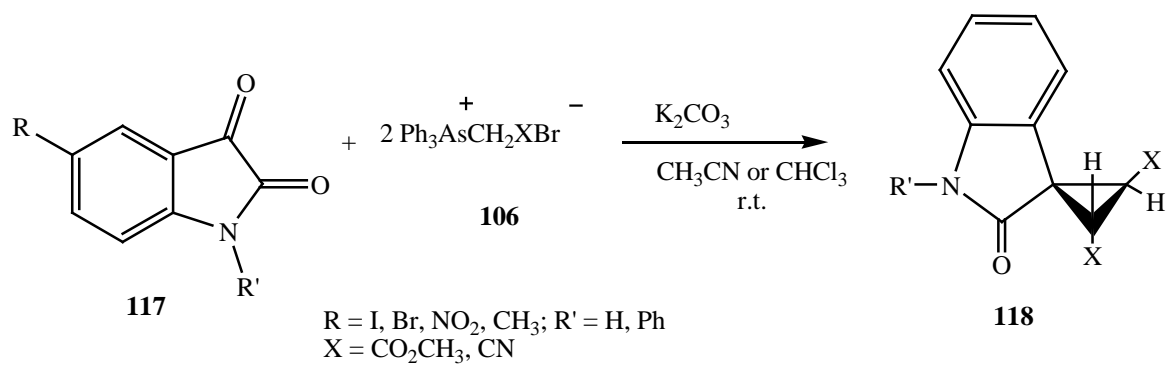
Scheme 36

Carbocycle synthesis

Silylcyclopropanes are useful intermediates in organic synthesis since they are capable of undergoing many synthetic transformations [61]. In this regard, Shen and Liao prepared **119**, which, when treated with enones, afforded the trimethylsilylethynylcyclopropanes **120** in 96–100% yield with high stereoselectivity (Scheme 37) [62]. Addition of methanol removed the silyl groups and afforded the terminal acetylenes **121** in a one-pot procedure in excellent yields (95-96%) [63].

R = Ph, C_6H_4-Cl, C_6H_4-p-Br, C_6H_4-m-Br,
      C_6H_4-p-Me, C_6H_4-p-OMe, C_6H_4-p-NO_2
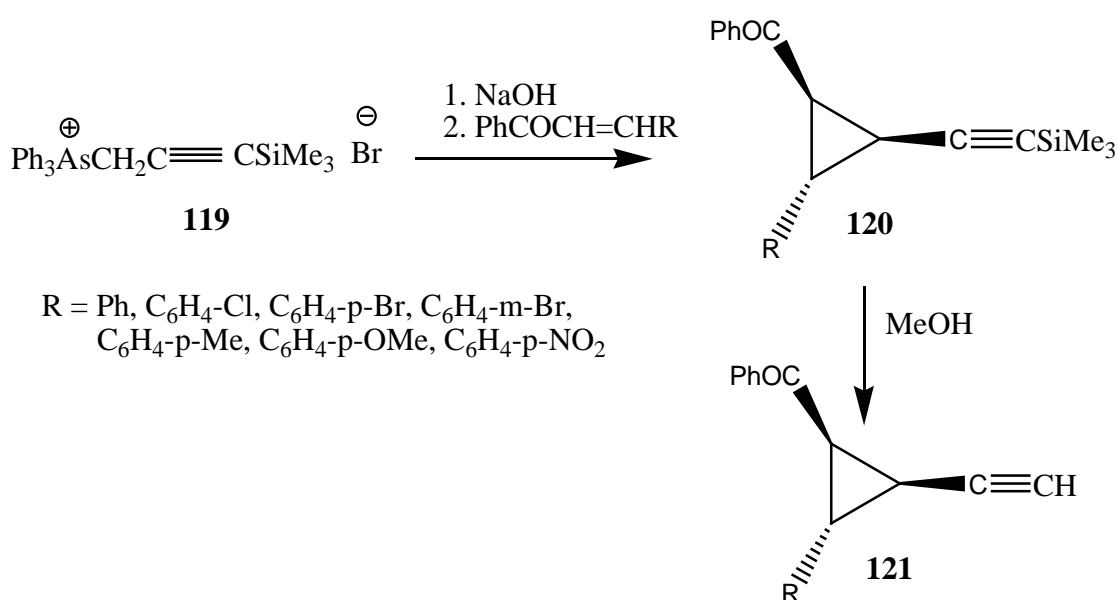
Scheme 37

A series of CF3-containing 2,3-dihydrofuran derivatives **123** were prepared *via* the reaction of arsonium bromides **34** with β,β-di(trifluoroacetyl)ethylene derivatives **122** in the presence of K_2CO_3, usually in a stereoselective manner with moderate yields. The trifluoromethyl containing 2,3-dihydrofuran derivatives **123** were obtained in moderate yield by the reaction of excess arsonium bromides **34** with β,β-di(trifluoroacetyl)ethylene derivatives **122** (Scheme 38) [64].
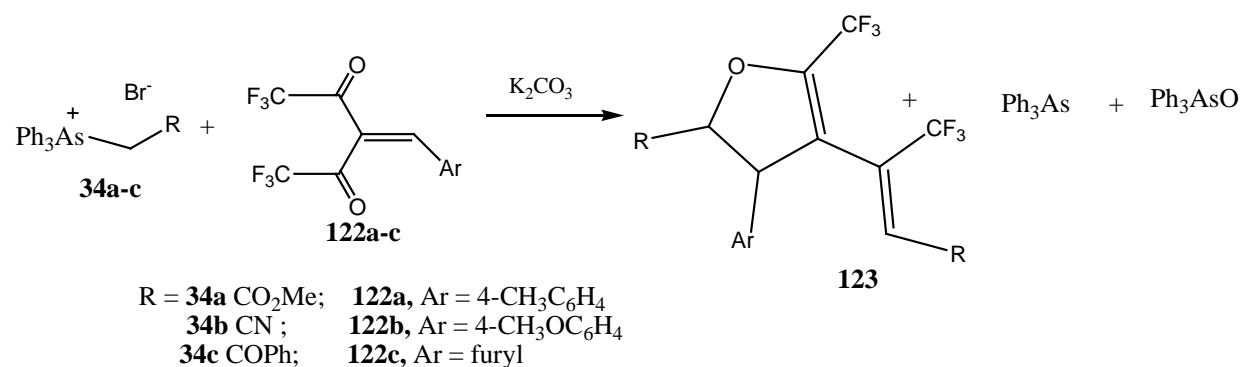
Scheme 38

trans-2,3-Dihydrofuran derivatives **126** and *trans*-1,2-cyclopropane derivatives **127** were prepared with high chemoselectivity and moderate overall chemical yield by the reaction of α,β-unsaturated sulfones **124** with arsonium bromides **125** in the presence of potassium carbonate (Scheme 39) [65].
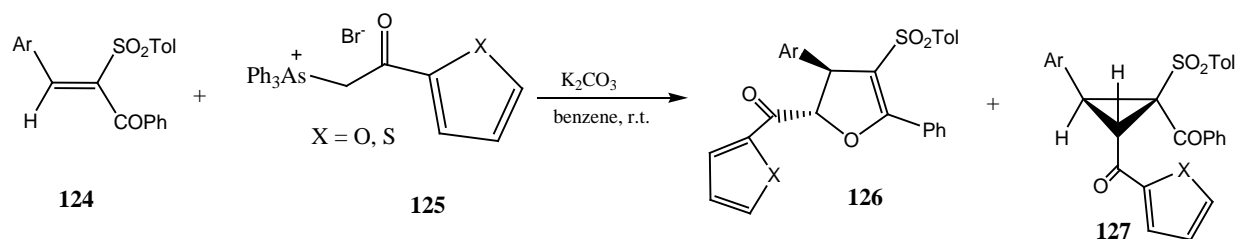
Scheme 39

A one-pot domino synthesis of photochromic 2,2-diarylphenanthro-(9,10)-[2*H*]-[1,4]-oxazines **129** in excellent yield is described starting with acrylic acid derivatives **128** (Scheme 40) [66].
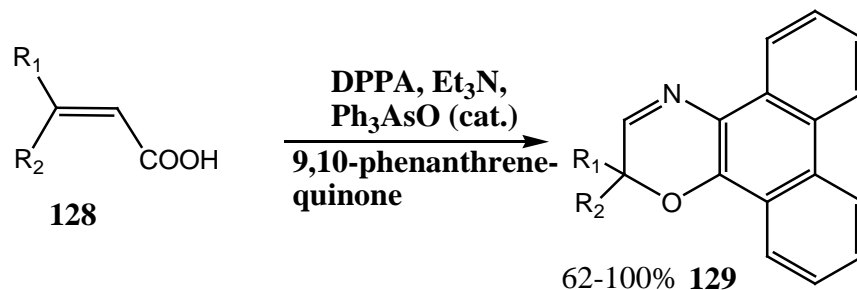
Scheme 40

An efficient approach for stereoselective synthesis of cyclopropyl indolyl ketone **131, 132** from

olefin **130** and arsonium ylied **34** was achieved. Its advantages are of mild condition, high yield,

and good stereoselectivity (Scheme 41) [67].
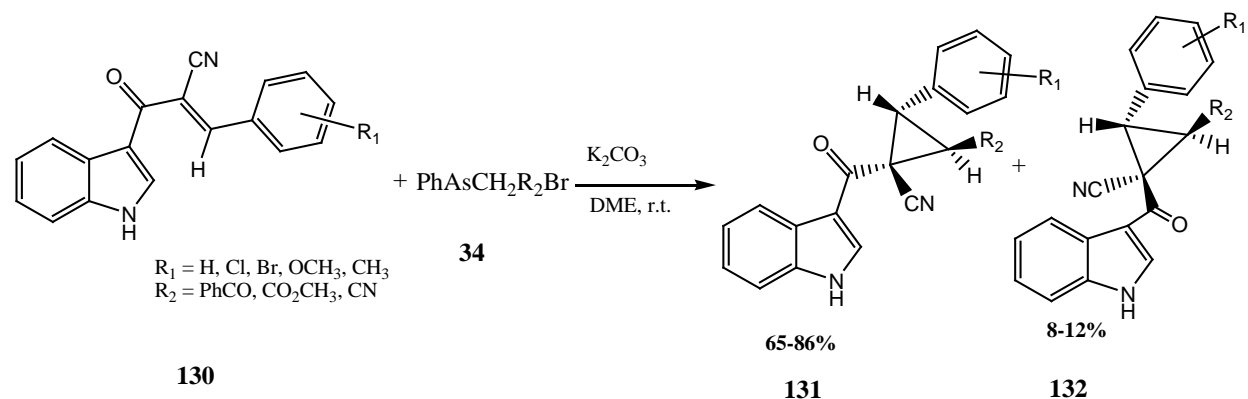
Scheme 41

trans-2-Thien-α-oyl-3-[(un)substituted phenyl]-4-acetyl-5-methyl-2,3-dihydrofurans **134** were

prepared in good yields with high stereoselectivity by the reaction of thien-α-

oylmethyltriphenylarsonium bromide **125** with 3-[(un)substituted benzylidene]-2,4-pentadione

133 in benzene in the presence of potassium carbonate at 55 °C (Scheme 42) [68].
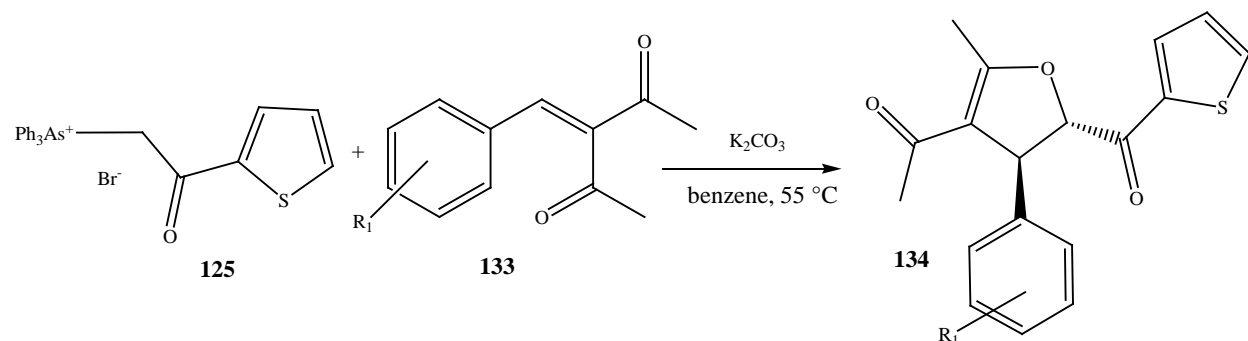
Scheme 42

Polymerization reactions

The photo-initiating ability of triphenylarsonium-*p*-nitrophenacylide **135** in the polymerization of methyl acrylate **136a** is studied [69] and methyl methacrylate **136b** [70]. They reported that the polymerization proceeded with low conversion when the reaction mixture was illuminated by visible light. Kinetic data and ESR spectroscopy confirmed that the photo-polymerization initiated by **135** proceeded *via* a radical mechanism. It was proposed that the origin of the radical initiator is from homolysis of one of the phenyl C–As bonds (Scheme 43).
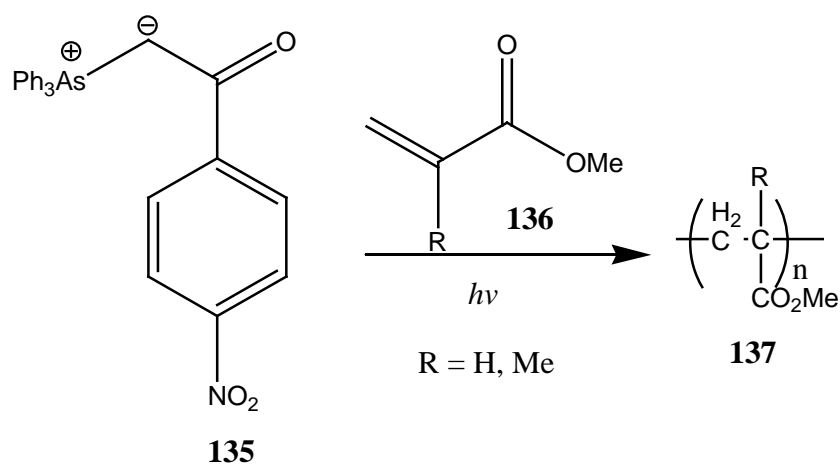
Scheme 43

More recently, Mioskowski *et al*. developed a method that provided successive elongation by three carbon atoms using methallyltriphenylarsonium ylide **138** as the monomer in a boron-catalyzed process [71] to produce oligomers **139** (Scheme 44).
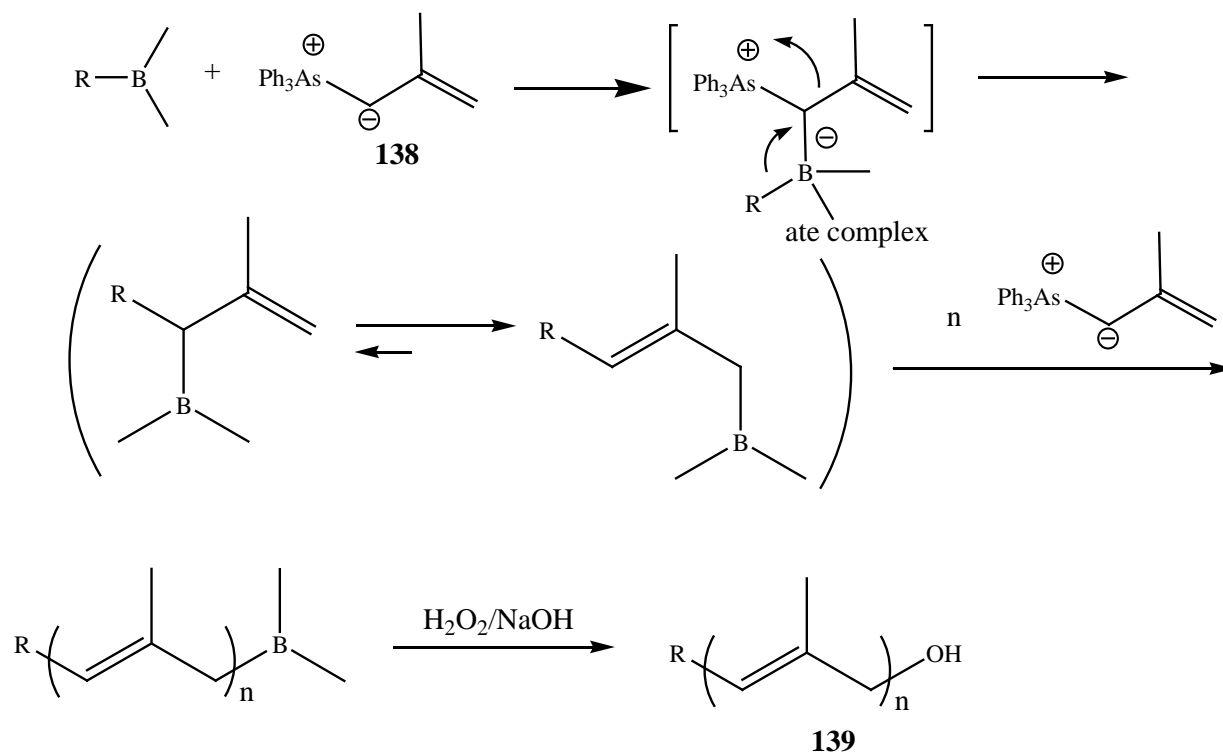
Scheme 44

The arsonium-substituted isocyanides, o-(I-R_3As–CH_2)$C_6H_4N{\equiv}C$ (As$R_{3¼}$AsPh$_3$, L1; AsMePh$_2$, L$_2$; AsMe$_2$Ph,L$_3$), **141** were prepared by reaction of o-(chloromethyl)phenyl isocyanide, o-(CH_2Cl)$C_6H_4N{\equiv}C$ **140** , with a slight molar stoichiometric amount of the arsine in the presence of a 3-fold excess of NaI in acetone at room temperature. The isocyanides L1–L3 coordinate to some Pt(II)complexes such as *trans*-[PtX{o-(I+R_3AsCH_2)C_6H_4NC}(PPh$_3$)$_2$] [BF$_4$] (As$R_{3¼}$AsPh$_3$, $_1$; AsMePh$_2$, 2; AsMe$_2$Ph,$_3$;X$_¼$Cl, I) and [PtX{o-(I +R3AsCH_2)C_6H_4NC}(Ph$_2$PCH=CHPPh$_2$)] [BF$_4$] (AsR_3¼AsMePh$_2$,4;X¼Cl, I) (Scheme 45) [72].
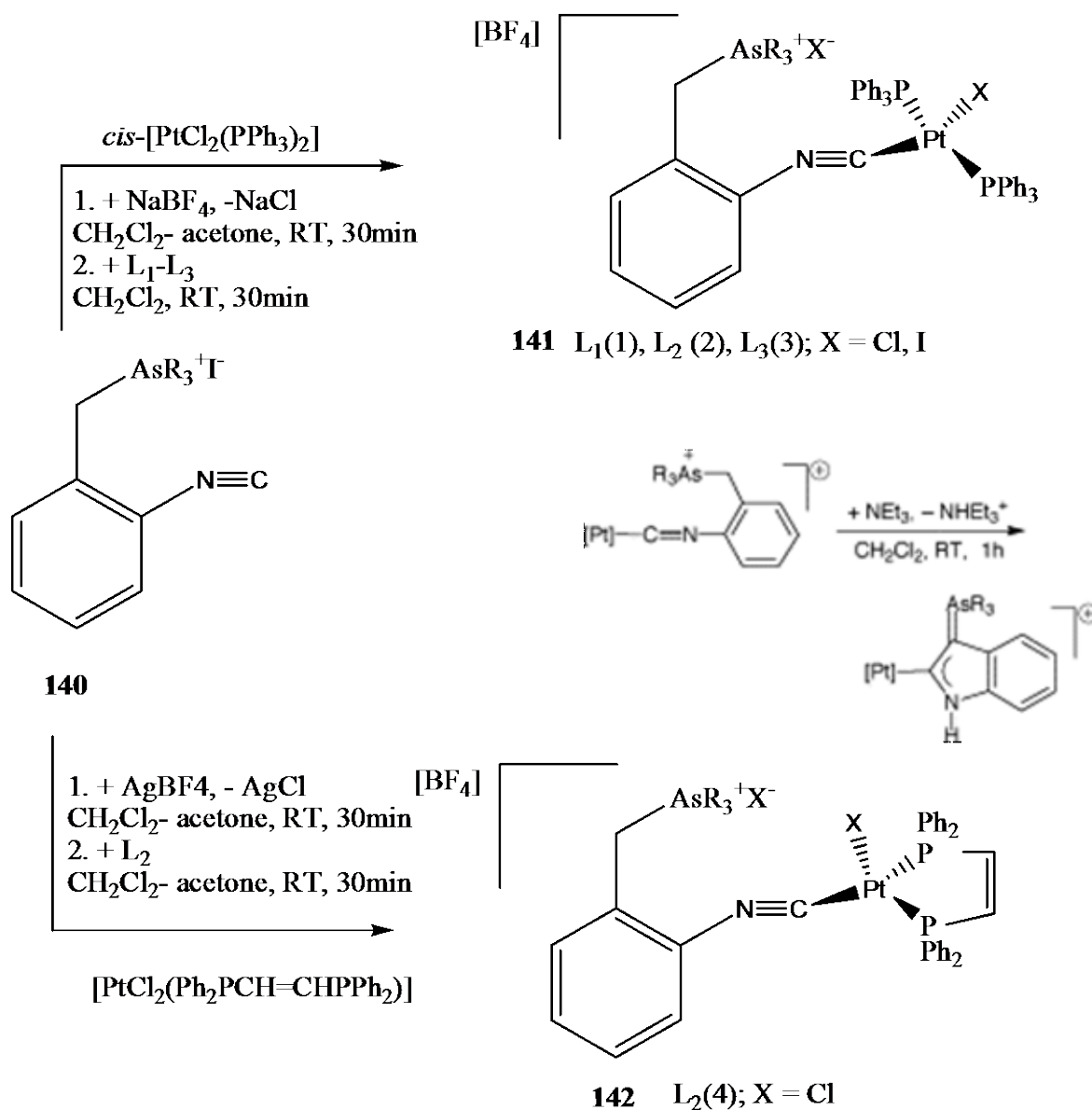
Scheme 45

Fundamental Organoarsenic Compounds and their applications

1. Cacodyl

Cacodyl, dicacodyl, tetramethyldiarsine, alkarsine or minor part of the "Cadet's fuming liquid" (after the French chemist Louis Claude Cadet de Gassicourt in 1760) $(CH_3)_2As$—$As(CH_3)_2$ is a

poisonous oily liquid with a garlicky odor. The first organometallic compound to be identified was tetramethyl-diarsine. It is obtained by heating arsenic oxide with potassium acetate (ethanoate) and then distilling out the product. Called 'kakodyl' (later cacodyl), from the Greek meaning 'evil-smelling liquid', its composition was established by Robert Wilhelm Bunsen in 1843 [73].

Bunsen began to study the chemistry of cacodyl in the late 1830s when he was at the University of Marburg. In the days before fume cupboards, this was a dangerous undertaking. Cacodyl is poisonous, flammable and has a nauseating odour, even at low concentrations. Bunsen wrote of cacodyl: [74] the smell of this body produces instantaneous tingling of the hands and feet and even giddiness and insensibility. He went on to observe that when one is exposed to the smell, the tongue becomes covered with a black coating [73].

While at Marburg, Bunsen was joined briefly by the young English chemist Edward Frankland [73]. In 1849 Frankland, by using gas handling techniques he had learnt from Bunsen, thought he had isolated ethyl radicals. Indeed, for a short while he was introduced to Marburg society as the 'discoverer of ethyl'. In fact, what he had done was to prepare butane by the action of water on diethylzinc. Working alongside Bunsen, Frankland focused his efforts on synthesizing organometallic compounds. In 1854 he published his results in the Journal of the Chemical Society [75]. Experimental details are sketchy, but appear to have involved heating the finely divided element - Main Group metals such as zinc, tin, arsenic, antimony and mercury - with excess of organic iodide. He sealed the reactants in a glass tube and heated them on an oil bath, or with light. In the latter case, he concentrated sunlight by using a parabolic reflector, and placed the sealed glass tube containing the reactants at its focus. Frankland had no way of

knowing the correct equivalent weight of carbon, so following the convention of the time, he took it to be six, and thus wrote methyl as C_2H_3. While it is possible to identify the compounds he synthesized, it is less clear for arsenic, but he seems to have prepared the tetra-alkyldiarsines for R = ethyl, propyl, butyl and pentyl. He also made tetraphenyldiarsine. He thus extended the range of known organoarsenic compounds beyond cacodyl (R = methyl).

This work was significant for two reasons. First, it was the earliest explicit recognition of the existence of organometallic compounds and, indeed, Frankland himself coined the word 'organometallic' to describe them [75]. Secondly, by noticing the number of organic groups that could be attached to individual metal atoms, Frankland was led towards the concept of valency [73, 76]. Towards the end of his 1854 paper, for instance, he notes a degree of similarity between formulae then used for compounds such as NO_3, NH_3, PO_3, $SbCl_3$ and AsH_3, suggesting that .the combining power of the attracting element, if I may be allowed the term, is always satisfied by the same number of these atoms' [74]. He was criticised by his peers because not all the formulae were correct but, to be fair, at the time there were many unresolved issues concerning the relative atomic mass. However, the essential concept that elements have specific 'combining power' was born and, without question, the concept first saw the light of day in Frankland's mind in the early 1850s.

a. Preparation

Cacodyl oxide is prepared by the reaction of potassium acetate with arsenic trioxide.

$$4 \; CH_3CO_2K + As_2O_3 \rightarrow As_2(CH_3)_4 + 2 \; K_2CO_3 + 2 \; CO_2$$
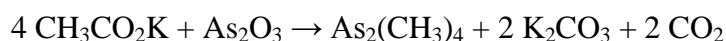
A subsequent reduction or disproportionation of the substance under the reaction conditions yields a mixture of several methylated arsenic compounds.

A far better synthesis was developed which started from the dimethyl arsine chloride and dimethyl arsine.

$$As(CH_3)_2Cl + As(CH_3)_2H \rightarrow As_2(CH_3)_4 + HCl$$
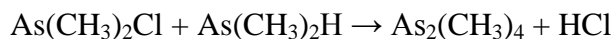
b. Use

Cacodyl was used to prove the radical theory of Berzelius, which resulted in a wide use of cacodyl in research laboratories. After the radical theory was established, the interest in the toxic substance with the literally evil smell decreased. During World War I the use of cacodyl as poison gas was considered, but it was never used in the war. The inorganic chemists discovered the properties of cacodyl as ligand for transition metals [74].

2. Salvarsan

Ehrlich's 'magic bullet: Paul Ehrlich (1854-1915) was a distinguished German bacteriologist who, early in his life, became fascinated with the fact that certain dyes were selectively taken up by blood cells and the cells of other tissues. He was particularly interested by the action of such compounds on parasites that caused disease, and in 1891 he reported the successful use of methylene blue as a novel treatment for malaria

Ehrlich continued to search for dyes which acted as bacterial toxins, which he called 'magic bullets' - *ie* individual compounds that would target and destroy the microorganisms responsible for diseases. He had little success with other dyes so he turned his attention to other compounds.

Spurred on by earlier work by Robert Koch, who pioneered tuberculin therapy for tuberculosis and Emil von Behring who developed therapies based on sera for the treatment of tetanus and diptheria, Ehrlich turned his attention to a treatment for syphilis [77].

The microorganism responsible for syphilis is the bacterium *Treponema pallidum*. Ehrlich brought together a team of scientists, including the chemist Alfred Bertheim and the microbiologist Sahachiro Hata, with the aim of developing a magic bullet that would kill this bacterium without affecting the human host. They chose an organoarsenic compound as their starting point, and Bertheim synthesised several hundred related compounds. Number 606 - arsphenamine (dioxydiamido-arsenobenzenol) - proved the most effective and a single dose completely cured rabbits infected with the bacterium. The compound was then tested on patients who had the disease at an advanced stage, when the dementia associated with its final phase had set in. To their surprise, several of these 'terminal' patients made a full recovery. Compound 606, prepared and tested in the autumn of 1909, was in clinical use under the name Salvarsan by 1910. Salvarsan remained the treatment of choice for syphilis until the development of antibiotics in the 1940s. Ehrlich received the Nobel Prize for medicine for this work in 1907 [77].
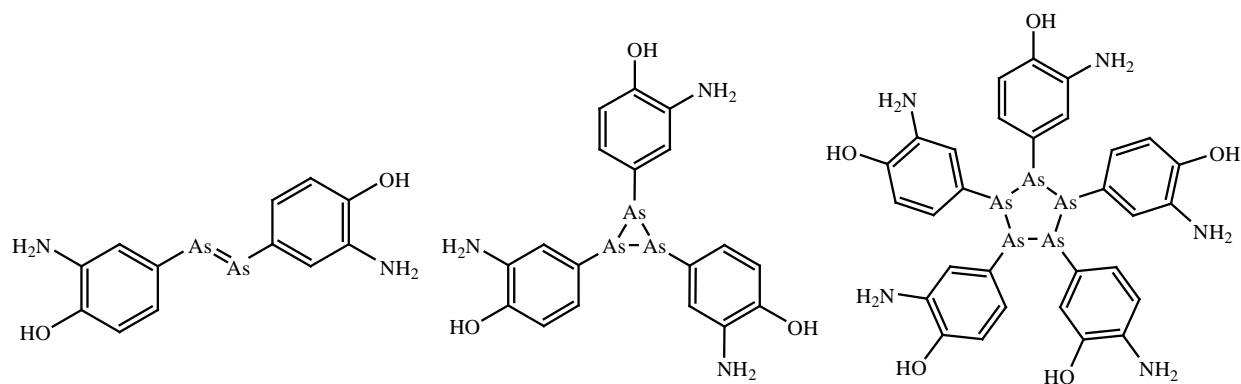
Salvarsan

Despite its clinical success, uncertainty remained over the structure of salvarsan. The original synthesis involved the reduction of 3-nitro-4-hydroxyphenylarsonic acid with dithionite, yielding a compound that could be written as $RAs.HCl.H_2O$ (R = 3-amino-4 hydroxyphenyl (**A**)). By analogy with azo compounds, Ehrlich and his team suggested that salvarsan contained an As=As double bond. In 2005 this was challenged. Bryan Nicholson and his team at the University of Waikato in New Zealand showed that salvarsan is a mixture of three- and five-membered ring structures based on As-As bonded species (see structures (**B**) and (**C**)) [78]. This mixture appears to undergo slow hydrolysis to yield $RAs(OH)_2$, and this, according to Nicholson, is the compound that is active against T. pallidum. Research continues to determine exactly what makes this compound quite so specific against this bacterium.

3. Lewisite

Lewisite (2-chloroethenylarsonous dichloride) is an organoarsenic compound, specifically an arsine. It was once manufactured in the U.S. and Japan as a chemical weapon, acting as a vesicant (blister agent) and lungirritant. Although colorless and odorless, impure samples of lewisite are a yellow or brown liquid with a distinctive odor that has been described as similar to scented geraniums or storks bills (flowering plant) [79].

a. Chemical Reactions

The compound is prepared by the addition of arsenic trichloride to acetylene in the presence of a suitable catalyst:

$$AsCl_3 + C_2H_2 \rightarrow ClCHCHAsCl_2$$
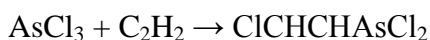
Lewisite, like other arsenous chlorides, hydrolyses in water to form hydrochloric acid:

$$ClCHCHAsCl_2 + 2\ H_2O \rightarrow ClCHCHAs(OH)_2 + 2\ HCl$$
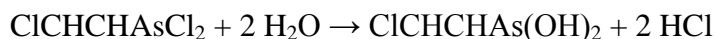
This reaction is accelerated in alkaline solutions, with poisonous (but non-volatile) sodium arsenite being the co product.

b. Mode of Actions as Chemical Weapon

Arsenite inhibits important biochemical pathways of the human body. Arsenite poisoning specifically targets the E_3 component of pyruvate dehydrogenase [61]. As an efficient method to produce ATP, pyruvate dehydrogenase is involved in the conversion of pyruvate to Acetyl-CoA. The latter subsequently enters the TCA cycle. Arsenite has a high affinity for dihydrolipoamide; E3 component of the pyruvate dehydrogenase. Binding results in inhibition of the enzyme and can lead to dire consequences. Nervous pathology usually arises from arsenite poisoning as the nervous system essentially relies on glucose as its only catabolic fuel [79].

It can easily penetrate ordinary clothing and even rubber; upon skin contact it causes immediate pain and itching with a rash and swelling. Large, fluid-filled blisters (similar to those caused by mustard gas exposure) develop after approximately 12 hours [79]. These are severe chemical burns. Sufficient absorption can cause systemic poisoning leading to liver necrosis or death.

Inhalation causes a burning pain, sneezing, coughing, vomiting, and possibly pulmonary edema [79]. Ingestion results in severe pain, nausea, vomiting, and tissue damage [79]. The results of eye exposure can range from stinging and strong irritation to blistering and scarring of the cornea [81]. Generalized symptoms also include restlessness, weakness, subnormal temperature and low blood pressure.

c. Chemical composition

Lewisite is usually found as a mixture, of 2-chlorovinylarsonous dichloride **(A)** as well as *bis*(2-chloroethenyl)arsinous chloride **(B)**("lewisite 2"), and *tris*(2-chlorovinyl)arsine **(C)** ("lewisite 3").

(A)   **(B)**   **(C)**
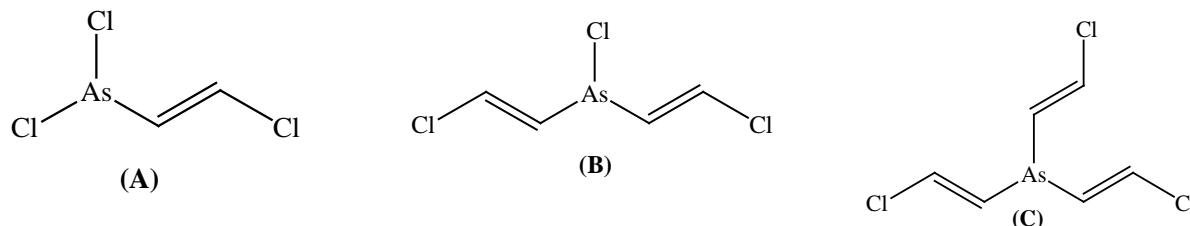
4.Roxarsone

Roxarsone **(**Nitrobenzenearsonic acid) is a controversial arsenic compound used as a nutritional supplement for chickens. The toxicity of arsenic to insects, bacteria and fungi led to its use as a wood preservative [82]. In the 1950s a process of treating wood with chromated copper arsenate (also known as CCA or Tanalith) was invented, and for decades this treatment was the most extensive industrial use of arsenic. An increased appreciation of the toxicity of arsenic resulted in a ban for the use of CCA in consumer products; the European Union and United States initiated this process in 2004 [83, 84]. CCA remains in heavy use in other countries however, e.g. Malaysian rubber plantations [85].
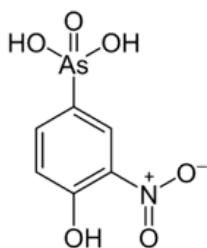
Arsenic was also used in various agricultural insecticides, termination and poisons. For example, lead hydrogen arsenate was a common insecticide on fruit trees [86], but contact with the compound sometimes resulted in brain damage among those working the sprayers. In the second half of the 20th century, monosodium methyl arsenate (MSMA) and disodium methyl arsenate (DSMA) – less toxic organic forms of arsenic – have replaced lead arsenate in agriculture.

Arsenic is still added to animal food, in particular in the U.S. as a method of disease prevention [87, 88] and growth stimulation. One example is Roxarsone, which is used as a broiler starter by about 70% of the broiler growers since 1995 [89]. The Poison-Free Poultry Act of 2009 proposes to ban the use of Roxarsone in industrial swine and poultry production [90].

Conclusion

Many of arsonium ylides have been investigated and regarded. These ylides have proven to be very effective reagents for converting carbonyl compounds into olefins and epoxides. These reactions are very useful synthetically, especially in the synthesis of biologically active natural products. As shown, diverse functional groups such as enynyl, trifluoromethyl, and organoselenium groups can be introduced using arsonium ylides. In addition, such ylides have also been used in the stereoselective synthesis of cyclopropane derivatives, which can easily be converted into other diverse and useful building blocks. On the other hand, the oldest known organoarsenic compound, the foul smelling cacodyl was classified as the first synthetic organometallic compound. The compound Salvarsan was one of the first pharmaceuticals, earning a Nobel Prize for Paul Ehrlich. Lewisit, especially those featuring As-Cl bonds, have

been used as chemical weapons during World War I. Organoarsenic compounds are produced industrially with uses as insecticides, herbicides, and fungicides.

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