Arsenous chloride-free synthesis of cyclic tertiary organoarsines from arylarsine oxides and di-Grignard reagents

Aaron M. Gregson  
*University of Wollongong, amg707@uowmail.edu.au*

Steven M. Wales  
*University of Wollongong, swales@uow.edu*

Stephen Bailey  
*University of Wollongong, sjb106@uowmail.edu.au*

Paul A. Keller  
*University of Wollongong, keller@uow.edu.au*

**Publication Details**
Arsenous chloride-free synthesis of cyclic tertiary organoarsines from arylarsine oxides and di-Grignard reagents

Abstract
The growing importance of triarylarsines as ligands for transition metal catalysis has sparked recent interest in new synthetic routes to tertiary arsines that avoid hazardous arsenous chloride reagents. However, safer methods for the synthesis of lesser explored arsine heterocycles, especially those containing As-C(sp3) bonds, remain lacking. We demonstrate for the first time that bench stable, less hazardous, arylarsine(III) oxides are effective substitutes for their corresponding chlorides in the one-pot construction of cyclic tertiary organoarsines from di-Grignard reagents. Several known and novel heterocycles have been prepared in reasonable yields, accommodating variations in both the diorganomagnesium reagent and electrophile, making this a modular approach to cyclic arsine assembly.

Disciplines
Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

This journal article is available at Research Online: http://ro.uow.edu.au/smhpapers/2664
Arsenous Chloride-Free Synthesis of Cyclic Tertiary Organoarsines from Arylar-sine Oxides and Di-Grignard Reagents

Aaron M. Gregson, Steven M. Wales, Stephen J. Bailey, and Paul A. Keller*

School of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia

* Corresponding author. Tel.: +61 2 4221 4692
E-mail address: keller@uow.edu.au (P. A. Keller)

Graphical Abstract

Abstract

The growing importance of triarylarsines as ligands for transition metal catalysis has sparked recent interest in new synthetic routes to tertiary arsines that avoid hazardous arsenous chloride reagents. However, safer methods for the synthesis of lesser explored arsine heterocycles, especially those containing As–C(sp³) bonds, remain lacking. We demonstrate for the first time that bench stable, less hazardous, arylarsine(III) oxides are effective substitutes for their corresponding chlorides in the one-pot construction of cyclic tertiary organoarsines from di-Grignard reagents. Several known and novel heterocycles have been prepared in reasonable yields, accommodating variations in both the diorgano-magnesium reagent and electrophile, making this a modular approach to cyclic arsine assembly.

Keywords: Arsine oxides, Grignard reagents, Heterocycles, Organoarsines, Ligands

Introduction

Organoarsines have found application in coordination chemistry [1], materials science [2] and recently in chemotherapy as potential drug delivery and anti-cancer agents [3]. Triaryl arsines in particular are now well established as valuable ligands for transition metal catalysis, demonstrating superiority to analogous phosphines in many cases [4]. Although tertiary organoarsines are traditionally prepared via the combination of arsenic chlorides (or other halides) with organometallic reagents or nucleophilic arenes, a major drawback to this approach is the inherent toxicity associated with the As–Cl bond [5]. It is well known that arsenic compounds (or metabolites thereof) generally exhibit toxicity [6], however, most arsenous chlorides are additionally characterized by alarming acute effects based on their rapid in vivo covalent binding to thiol-containing enzymes and proteins [7]. These hazards are exacerbated by the often semi-volatility of arsenous(III) chlorides, which have historically been exploited as blistering and vomiting agents in chemical warfare (e.g., Lewisite, Ph₂AsCl, PhAsCl₂ and Adamsite) [5]. As such, tertiary organoarsine syntheses that avoid this reagent class have received some interest [8], particularly for the construction of acyclic triarylarsines via As–C(sp³) cross-coupling [4d, 9].
In our own search for alternate methods of As–C bond formation, we turned our attention to seminal work by Blicke with arylarsine(III) oxides 1 (Scheme 1) [10]. In contrast to the noxious arsenous chlorides, oxides 1 are generally bench-stable, non-hygrophilic solids that can be safely handled in the laboratory and are resistant to atmospheric oxidation [11]. These compounds (arsenic acid anhydrides) were shown to react with aryl Grignard reagents at ambient temperature to yield dimers 2 after addition of the carbanion (Scheme 1a) [10a]. Attempts to achieve a second Grignard addition were carried out with phenylarsine oxide 3 at elevated temperature (Scheme 1b) [10a]. In the two examples reported (both shown), the product ratio was highly dependent on the concentration of the Grignard regent: a large excess (8 equiv) was required to favour the second addition, enabling triphenylarsine to be obtained in near quantitative yield.

Although anhydrous arylarsine oxides are often depicted as containing a π-bond (As=O), spectroscopic experiments have shown their existence in solid state and solution as well-defined oligomers: (ArAsO)n [12]. Thus, the formation of a tertiary organoarsine from 1 (or 3) likely involves the sequential cleavage of two As–O σ-bonds. In this way, arsenic oxides could be considered as direct synthetic equivalents of arsenous chlorides.

Encouraged by these findings, we became interested in investigating arsine oxides as safer substitutes for arsenous chlorides in the preparation of (semi)saturated arsine heterocycles 7 from di-Grignard reagents (Scheme 2). Analogous cyclic phosphines and their derived dimers have proven highly effective in ligand-assisted catalysis and asymmetric variants [13], and thus safer and wider access to molecular class 7 was of interest to expand the repertoire of useful arsine ligands beyond the standard triaryl species.

Based on Blicke’s results (Scheme 1b) [10a], we proposed that di-Grignard reagents 6 would be ideal nucleophiles to react with oxides 1, given that the second (and evidently most challenging) As–C bond forming event could occur in an intramolecular mode (Scheme 2b). An additional advantage offered by this approach over stepwise processes was the ability to form the desired heterocycles in a single-pot, avoiding the isolation and purification of organoarsine intermediates.
Results and Discussion

The commercially available phenylarsine oxide 3 was selected as a model electrophile to begin our investigations. Although 3 is an oligomeric material, it dissolves readily in standard organic solvents ($x = 4$ in benzene, CCl$_4$ and camphor) [12a]. Arsenous chlorides have been used as electrophiles in previous syntheses of cyclic arsines from di-Grignard reagents (Scheme 2a) [14], therefore, by selecting known arsacycles 10 and 11 as initial targets for reaction optimization, a direct comparison could be made between the performance of (PhAsO)$_x$ and its corresponding dichloride (Table 1). Previous results from the literature using PhAsCl$_2$ are therefore included (entries 1−6) [15−19].

Our opening experiment was performed using an equimolar quantity of di-Grignard reagent 8 with a 20 h reaction time (entry 7). Following aqueous work-up, the desired arsolane 10 was isolated in 12% yield after elution through silica gel with hexanes. The remaining material consisted of a complex mixture of unidentified polar components. Encouraged by our immediate success in the formation of 10, we proceeded to examine the effect of temperature variations: mixing the reactants at −78 °C gave a similar yield (entry 8), while heating the reaction at reflux was detrimental (entry 9), possibly due to polymerization of the arsine oxide [12b]. An extension of the reaction time to 70 h did not result in an improvement (entry 10), establishing that the low yields were not merely a result of a slow Grignard addition.

Table 1. Reaction optimization for the synthesis of arsolane 10 and arsinane 11 from (PhAsO)$_x$.

<table>
<thead>
<tr>
<th>entry</th>
<th>[ref]</th>
<th>n equiv Grignard</th>
<th>electrophile</th>
<th>temp (°C)</th>
<th>prod</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [15]</td>
<td>1</td>
<td>1.0</td>
<td>PhAsCl$_2$</td>
<td>rt-reflux</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>2 [16]</td>
<td>1</td>
<td>1.1</td>
<td>PhAsCl$_2$</td>
<td>10−rt</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>3 [17]</td>
<td>1</td>
<td>3.2</td>
<td>PhAsCl$_2$</td>
<td>10−rt</td>
<td>10</td>
<td>66</td>
</tr>
<tr>
<td>4 [18]</td>
<td>2</td>
<td>1.3</td>
<td>PhAsCl$_2$</td>
<td>rt−reflux</td>
<td>11</td>
<td>32</td>
</tr>
<tr>
<td>5 [19]</td>
<td>2</td>
<td>1.4</td>
<td>PhAsCl$_2$</td>
<td>0−rt‡</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>6 [17]</td>
<td>2</td>
<td>3.2</td>
<td>PhAsCl$_2$</td>
<td>10−rt</td>
<td>11</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1.0</td>
<td>(PhAsO)$_x$</td>
<td>0−rt</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1.0</td>
<td>(PhAsO)$_x$</td>
<td>−78−rt</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>1.0</td>
<td>(PhAsO)$_x$</td>
<td>−78−reflux</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>1.0</td>
<td>(PhAsO)$_x$</td>
<td>−78−rt</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>3.0</td>
<td>(PhAsO)$_x$</td>
<td>−78−rt</td>
<td>10</td>
<td>39‡</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>5.0</td>
<td>(PhAsO)$_x$</td>
<td>−78−rt</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>5.0</td>
<td>(PhAsO)$_x$</td>
<td>−78−rt</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>5.0</td>
<td>(PhAsO)$_x$</td>
<td>0−rt</td>
<td>11</td>
<td>36</td>
</tr>
</tbody>
</table>

a Isolated yield based on electrophile. b Et$_2$O used as solvent. c Reaction time was 70 h. d Yield determined by 1H NMR with DMSO as internal standard.

Comparison of previous literature yields using PhAsCl$_2$ reveals a significant advantage from employing an excess of the di-Grignard reagent (entries 3 and 6) [17]. This also proved to be the case in our experiments when the equivalents of 8, relative to (PhAsO)$_x$, were increased 3- and 5-fold (entries 11 and 12). From the latter reaction (entry 12), 10 was isolated in an acceptable 42% yield. Translation to the six-membered homologue with an excess of di-Grignard reagent 9 occurred smoothly when the addition was performed at 0 °C, allowing 11 to be obtained in a similar yield (36%, entry 14).
Although it is evident that the previously optimized yields of 10 and 11 from the dichloride electrophile are higher than obtained here with \((\text{PhAsO})_x\) (entry 3 versus 12; entry 6 versus 14), we believe that the benefits of avoiding hazardous \(\text{PhAsCl}_2\) outweighs these current discrepancies. Importantly, the current reactions are also amenable to larger-scale preparations. The arsine oxide can be weighed in the air with no special precautions. As an example, we have prepared 0.8 g of 10 from the reaction between 1.5 g of 3 and the di-Grignard reagent 8 (42% yield, entry 12).

With phenylarsine oxide established as a viable synthon to cyclic arsines, we explored the synthesis of additional heterocycles using carbocyclic-fused di-Grignard reagents (Table 2). Phenyl- and naphthyl-fused bis-nucleophiles performed adequately in the cyclization, giving five-membered arsacycles 12 and 13 in 44% and 41% yields respectively (entries 1 and 2). These results compare well with that obtained for the non-aromatic analogue 10 (Table 1, entry 12). The standard flash chromatographic purification with hexanes was carried out to isolate the analogous six-membered arsine (deoxo)-14, (entry 3), however the product was found to be contaminated with non-volatile hydrocarbons derived from Grignard hydrolysis and Wurtz-coupling processes. Thus, subsequent treatment with \(\text{H}_2\text{O}_2\) [15] was performed to isolate the more polar oxide derivative 14 in an overall 26% yield. It should be noted that desymmetrized heterocycles 12–14 have been obtained as racemic mixtures due to the newly installed arsenic stereocentre. Additionally, both trans- and cis-cyclohexene-fused di-Grignard reagents reacted productively under the standard conditions (entries 4 and 5). The racemic trans product 15, which exhibits solely backbone chirality, was isolated in 36% yield, while its cis isomer 16, bearing an additional stereocentre at arsenic, was obtained after silica gel chromatography in 41% yield as a 1:1 mixture of the two meso compounds.

Table 2. Synthesis of arsine heterocycles 12–16 from carbocyclic-fused di-Grignard reagents.

<table>
<thead>
<tr>
<th>entry</th>
<th>di-Grignard precursor¹</th>
<th>product</th>
<th>yield (%)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>(12)</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>(13)</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>(14)</td>
<td>26d,e</td>
</tr>
<tr>
<td>4</td>
<td>(trans)</td>
<td>(15)</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>(cis)</td>
<td>(16)</td>
<td>41 (dr = 1:1)</td>
</tr>
</tbody>
</table>

¹ See the experimental section for Grignard formation conditions. ² Isolated yield based on 3. ³ Racemic mixture. ⁴ Reaction performed from 0 °C–rt. ⁵ Overall isolated yield after oxidation with \(\text{H}_2\text{O}_2\).
Although the yields obtained for known compounds 12 and (deoxo)-14 are modest (Table 2, entries 1 and 3), they are both superior to the previous three-step procedures (25% and 17% yields respectively) [20, 21], which involve Friedel-Crafts cyclization and again use hazardous PhAsCl₂ as starting material. Furthermore, we have fully characterized these compounds for the first time.

Importantly, this methodology can also be applied to arylarsine oxides of electronic and steric variability (Scheme 3). Utilizing di-Grignard reagent 8 under the established conditions, novel arsolanes 17−19, bearing 4-bromophenyl, 4-methoxyphenyl and 1-naphthyl substituents, were readily obtained in comparable yields (34−45%) to their phenyl analogue. The marginally lower yield of 18 was presumably a result of the electron-donating methoxy group, decreasing the reactivity of the electrophile.

Scheme 3. Preparation of novel arsolanes 17−19 from various arylarsine oxides.

As a first step to understanding why excess Grignard reagent is required for satisfactory double As–C bond formation, we carried out a control experiment to determine whether the cyclic arsine(III) products were sufficiently nucleophilic to react in situ with their oxide precursors (eq 1) [22]. Accordingly, exemplary substrate 11 was treated with 3 under the standard conditions of heterocycle formation. NMR spectroscopic analysis of the resultant mixture showed no reaction had occurred. This result clearly shows that the general requirement for excess Grignard reagent is not a consequence of a competing reaction between the formed heterocycle and the remaining (ArAsO)x. Given that we have also shown that longer reaction times do not increase the yield of the di-Grignard cyclization (Table 1, entry 10), we currently speculate that a higher concentration of the Grignard reagent activates the electrophile by Lewis acid coordination and/or affects the degree of (ArAsO)x association in solution. Further studies are required to validate these arguments.

In the course of this work, we found all arylarsine(III) heterocycles to be relatively stable compounds; no oxidation or decomposition was observed during work-up and chromatographic purification, without special precautions to exclude atmospheric oxygen and moisture. Selected compounds were nonetheless readily converted to their As(V) analogues by oxidation with H₂O₂ [15] (Scheme 4). No As–C(sp³) bond cleavage was detected in these reactions, as has been observed for some acyclic arsines [12c].
Previously reported in 96% yield but was not fully characterized [15].

Scheme 4. Oxidation of selected cyclic arsines.

Conclusion

In conclusion, we have demonstrated that arylarsine oxides can be utilized as synthetic equivalents to their dichloride counterparts in combination with di-Grignard reagents, allowing the preparation of cyclic tertiary organoarsines in a significantly less hazardous manner than previously possible. Extension to carbocyclic-fused di-Grignard reagents has enabled access to several novel arsacycles, including those with backbone and arsenic chirality, maintaining acceptable yields throughout. Modular electronic and steric alteration of the peripheral aryl substituent has also been shown to be possible. Conveniently, these arylarsine heterocycles are stable to air and moisture, but can be readily oxidized to their As(V) analogues, which offer potential opportunities for functionalization via α-lithiation chemistry [23], including oxidative dimerization [24] to novel bisarsines. Further studies in our laboratory will include the examination of solvent effects and/or Lewis acid additives on the cyclization efficiency, the resolution of chiral racemates 12–15 and potential applications of the cyclic arsines and derived dimers in transition metal catalysis.

Experimental

General Information: All reactions were carried out under an atmosphere of N₂ in oven-dried glassware with magnetic stirring. Thin layer chromatography (TLC) was performed on aluminum-backed 0.20 mm silica gel plates. Visualization was accomplished with UV light or an aqueous ceric ammonium molybdate solution. Flash chromatography was performed under positive air pressure using Silica Gel 60 of 230–400 mesh (40–63 μm). Infrared (IR) spectra were obtained with neat samples on a Shimadzu IRAffinity-1 FTIR Spectrometer. Proton and carbon magnetic resonance spectra (¹H NMR and ¹³C NMR) were recorded on a Varian Mercury 300 MHz spectrometer, a Varian Inova 500 MHz spectrometer or a Varian VNMRS PS54 500 MHz spectrometer. All spectra were acquired in CDCl₃ and are reported relative to tetramethylsilane (¹H: δ = 0.00 ppm) and solvent resonance (¹³C: δ = 77.0 ppm). ¹H NMR data are reported as follows: chemical shift, multiplicity (d = doublet, t = triplet, m = multiplet), coupling constant (Hz), integration and assignment. Low resolution mass spectrometry (MS) was performed on a Shimadzu LC-2010 Electrospray Ionization (ES) Mass Spectrometer or on a Shimadzu QP-5050 Electron Impact (EI) Spectrometer. High resolution mass spectrometry (HRMS) was performed on a Waters Quadrupole-Time of Flight (QTOF) Xevo ES Spectrometer with Leucine-Enkephalin as an internal standard or on a Fison/VG Autospec-TOF EI Spectrometer at 70 eV with a source temperature of 250 °C.

Nitrogen (N₂) was dried by passage through self-indicating silica gel (blue, 2–4 mm bead size). Known halogenated Grignard precursors unavailable commercially were prepared according to literature methods cited within. Grignard reagents were prepared from Mg turnings that were freshly washed with 1 M HCl, followed sequentially by water, EtOH, THF and Et₂O before being dried under high
vacuum. Phenylarsine oxide (PhAsO), and anhydrous tetrahydrofuran were purchased and used as received. The known 4-bromo-[25], 4-methoxy-[10b] and 1-napthylarsine oxides [10b] were prepared in two steps from the corresponding anilines via diazonium salt activation in the presence of arsenic trioxide [26], then reduction of the arsonic acids with an iodine/ascorbic acid system [12d]. All other reagents and solvents were purchased reagent grade and used without further purification.

Synthesis of 1-Phenylarsolane (10)

A suspension of Mg (2.215 g, 91.12 mmol) and 1,4-dibromobutane (9.838 g, 45.56 mmol) in THF (70 mL) was stirred at rt for 1 h. The resulting dark grey solution was added dropwise to a solution of (PhAsO)x (1.532 g, 9.11 mmol) in THF (70 mL) at −78 °C and the mixture was allowed to warm to rt and stirred for 20 h. Water (50 mL) was slowly added and the mixture was extracted with CH2Cl2 (3×50 mL). The combined extracts were dried (MgSO4), concentrated and subjected to column chromatography (hexanes) giving 10 [17] (803 mg, 42%) as a colorless oil. This compound has been fully characterized previously [17]. NMR data for the sample prepared herein was consistent with the published data, with the exception that the quaternary aromatic carbon [As–C(sp2)] was significantly further downfield than previously reported (lit: δ = 132.5 [17], our sample: δ = 143.3). 1H NMR (CDCl3, 500 MHz): δ 1.76-1.98 (m, 8H), 7.22-7.30 (m, 3H), 7.40-7.44 (m, 2H); 13C NMR (CDCl3, 125 MHz): δ 27.4, 30.4, 127.3, 128.3, 131.5, 143.3.

Synthesis of 1-Phenylarsinane (11)

A suspension of 1,5-dibromopentane (684 mg, 2.97 mmol) and Mg (145 mg, 5.97 mmol) in THF (6.3 mL) was stirred at rt for 1.5 h. The mixture, containing a small amount of unreacted Mg, was cooled to 0 °C and a solution of (PhAsO)x (100 mg, 0.595 mmol) in THF (4.2 mL) was added dropwise. The mixture was allowed to warm to rt and stirred for 20 h. The reaction was quenched with water (10 mL) and the product extracted with EtOAc (20 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO4), concentrated, and subjected to column chromatography (hexanes) affording 11 [17] (48 mg, 36%) as a colorless oil. This compound has been fully characterized previously [17]. NMR data for the sample prepared herein was consistent with the published data, with the exception that the quaternary aromatic carbon [As–C(sp2)] was significantly further downfield than previously reported (lit: δ = 132.5 [17], our sample: δ = 141.8). The identity of the sample prepared herein was also confirmed by high resolution mass spectrometry. 1H NMR (CDCl3, 500 MHz): δ 1.34-1.96 (m, 10H), 7.21-7.44 (m, 5H); 13C NMR (CDCl3, 125 MHz): δ 27.4, 30.4, 127.3, 128.3, 131.5, 143.3; MS (EI+): 222 (90%) [M]+, 152 (100%) [M–(CH2)5]+; HRMS (ES+): calcd for C11H16As 223.0463, found 223.0459.

Synthesis of 1-Phenyl-2,3-dihydro-1H-arsindole (12)

A suspension of 1-bromo-2-(2-chloroethyl)benzene [27] (5.00 g, 22.78 mmol) and Mg (1.108 g, 45.56 mmol) in THF (50 mL) was heated at reflux for 2 h. After cooling to rt, the resulting solution was added dropwise to a solution of (PhAsO)x (766 mg, 4.56 mmol) in THF (50 mL) at −78 °C and the mixture was allowed to warm to rt and stirred for 20 h. Water (50 mL) was slowly added and the mixture was extracted with Et2O (3×50 mL). The combined organic extracts were dried (MgSO4), concentrated and subjected to column chromatography (hexanes) giving 12 [20] (523 mg, 44%) as a colorless oil. This compound has not been fully characterized previously. FTIR: v 3384, 3046, 2360, 1435, 872, 765, 733, 696 cm⁻¹; 1H NMR (CDCl3, 300 MHz): δ 2.08-2.26 (m, 2H), 3.15-3.35 (m, 2H), 7.19-7.21 (m, 5H), 7.20-7.36 (m, 3H), 7.65 (d, J = 6.6 Hz, 1H); 13C NMR (CDCl3, 75 MHz): δ 26.7, 36.4, 125.0, 126.5, 127.7, 128.3, 128.6, 131.8, 131.9, 140.9, 142.7, 150.8; MS (EI+): 256 (77%) [M]+, 227 (40%), 179 (100%); HRMS (ES+): calcd for C14H14As 257.0311, found 257.0321.
Synthesis of 1-Bromo-2-(2-chloroethyl)naphthalene (novel precursor to 13)
A mixture of 2-(1-bromonaphthalen-2-yl)ethanol [28] (25.00 g, 99.55 mmol) and PCl₅ (31.10 g, 149.33 mmol) in CHCl₃ (200 mL) was heated at reflux for 4 h. Upon cooling to rt, water (100 mL) was added dropwise and the mixture was diluted with CH₂Cl₂ (200 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2×150 mL). The combined organic layers were dried (MgSO₄) then concentrated in vacuo and the residue subjected to silica gel chromatography. Elution with hexanes gave 1-bromo-2-(2-chloroethyl)naphthalene (25.50 g, 95%) as a pale yellow solid. mp: 42−43 °C; FTIR: ν 1321, 1259, 967, 817, 759, 706 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 3.44 (t, J = 7.5 Hz, 2H), 3.82 (t, J = 7.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 8.31 (d, J = 8.5 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 40.7, 43.3, 124.5, 126.5, 127.5, 127.7, 127.9, 128.2, 128.6, 132.7, 133.8, 135.7; MS (EI+): 270 (99%) [M, 81Br/35Cl]⁺, 268 (100%) [M, 79Br/35Cl]⁺; HRMS (EI+): calcd for C₁₂H₁₀Br⁷₉Cl³⁵ 267.9654, found 267.9657.

Synthesis of 1-Phenyl-2,3-dihydro-1H-benzo[g]arsindole (13)
A suspension of Mg (1.45 g, 59.5 mmol) and 1-bromo-2-(2-chloroethyl)naphthalene (8.02 g, 29.76 mmol) in THF (70 mL) was heated at reflux for 12 h. After cooling to rt, the dark grey/brown solution was added dropwise to a solution of (PhAsO)ₓ (1.00 g, 5.95 mmol) in THF (70 mL) at −78 °C and the mixture was allowed to warm to rt and stirred for 20 h. Water (50 mL) was slowly added and the mixture was extracted with Et₂O (3×50 mL). The combined extracts were dried (MgSO₄), concentrated and subjected to column chromatography (hexanes) giving 13 (746 mg, 41%) as a colorless oil. FTIR: ν 3047, 2961, 2916, 2849, 1432, 1023, 810, 773, 734, 693 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 2.21-2.27 (m, 1H), 2.32-2.38 (m, 1H), 3.48-3.51 (m, 2H), 7.14-7.19 (m, 5H), 7.41-7.49 (m, 3H), 7.81-7.86 (m, 2H), 7.93-7.94 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 26.1, 37.9, 123.6, 125.2, 126.7, 127.9, 128.27, 128.33, 128.7, 129.4, 132.1, 132.4, 135.3, 140.6, 140.7, 149.5; MS (ES+): 307 (30%) [M+H]⁺, 323 (100%) [M+NH₄]⁺; HRMS (ES+): calcd for C₁₈H₁₆As 307.0468, found 307.0481.

Synthesis of 1-Phenyl-1,2,3,4-tetrahydroarsinoline-1-oxide (14)
A suspension of Mg (785 mg, 32.31 mmol) and 1-bromo-2-(3-bromopropyl)benzene [29] (4.49 g, 16.15 mmol) in THF (10 mL) was stirred at rt for 12 h. The mixture was cooled to 0 °C and a solution of (PhAsO)ₓ (679 mg, 4.04 mmol) in THF (10 mL) was added dropwise. The mixture was allowed to warm to rt and stirred for 20 h. The reaction was quenched with water (10 mL) and the product extracted with Et₂O (3×50 mL). The combined extracts were washed with brine (10 mL), dried (MgSO₄), concentrated and subjected to column chromatography (petroleum ether) giving a mixture of 1-phenyl-1,2,3,4-tetrahydroarsinoline (deoxo-14) and a Wurtz coupling-derived Grignard hydrolysis side product: 1,6-diphenylhexane (387 mg total). The mixture was taken up in acetone (10 mL) and H₂O₂ (30% aqueous, 167 mg total, 1.43 mmol H₂O₂) was added and the solution was stirred at rt for 12 h. The solution was concentrated under reduced pressure and the residual solid was triturated with hexanes to provide 14 (340 mg, 26%) as a white foam. FTIR: ν 3363, 2930, 1697, 1438, 1269, 1262, 1087, 1066, 996, 874, 852, 802, 773, 743, 716 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 2.20-2.28 (m, 1H), 2.30-2.40 (m, 1H), 2.52-2.60 (m, 1H), 2.70-2.78 (m, 1H), 2.88-2.96 (m, 1H), 3.04-3.12 (m, 1H), 7.24-7.72 (m, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 22.1, 30.9, 32.2, 128.1, 129.3, 129.5, 130.0, 130.7, 132.2, 132.3, 132.5, 134.5, 145.2; MS (ES+): 287 (95%) [M+H⁺]⁺, 572 (100%) [2M+H⁺]; HRMS (ES+): calcd for C₁₅H₁₆AsO 287.0417, found 287.0405.
Synthesis of (rac)-Trans-4,5-bis(bromomethyl)cyclohex-1-ene (novel precursor to 15)

To a solution of (rac)-trans-4,5-bis(hydroxymethyl)cyclohex-1-ene [30] (13.25 g, 93.17 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added sequentially NEt₃ (32.3 mL, 232.91 mmol) and MsCl (15.9 mL, 204.97 mmol) and the resulting suspension was allowed to warm to rt and stirred for 3 h. Water (50 mL) was slowly added and the mixture was extracted with EtOAc (3×50 mL). The combined extracts were dried (MgSO₄) and concentrated. The crude dimesylate was taken up in THF (100 mL) and LiBr (37.00 g, 426.05 mmol) was added. The resulting solution was then heated between 40–50 °C for 48 h. Water (50 mL) was added and the mixture was extracted with EtOAc (3×50 mL). The combined extracts were dried (MgSO₄), concentrated and subjected to column chromatography (hexanes) giving (rac)-trans-4,5-bis(bromomethyl)cyclohex-1-ene (15.05 g, 60% over two steps) as a yellow oil. FTIR: ν 3027, 2898, 1430, 1276, 1223, 1034, 978, 924, 850, 768, 668, 607 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.98-2.25 (m, 6H), 3.45-3.53 (m, 2H), 3.60-3.67 (m, 2H), 5.64 (s, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 28.4, 36.2, 37.8, 125.0; MS (EI⁺): 270 (3%) [M⁺, 81Br⁺], 268 (6%) [M⁺, 81Br⁺/79Br⁺], 266 (3%) [M⁺, 79Br⁺], 189 (45%) [M⁺−Br, 81Br⁺], 187 (49%) [M⁺−Br, 79Br⁺], 107 (100%).

Synthesis of (rac)-Trans-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoarsindole (15)

A suspension of Mg (0.363 g, 14.93 mmol) and (rac)-trans-4,5-bis(bromomethyl)cyclohex-1-ene (1.000 g, 3.73 mmol) in THF (4 mL) was stirred at rt for 1 h. The supernatant liquid was added dropwise to a solution of (PhAsO)ₓ (0.125 g, 0.74 mmol) in THF (4 mL) at −78 °C and the mixture was allowed to warm to rt and stirred for 20 h. Water (5 mL) was slowly added and the mixture was extracted with CH₂Cl₂ (3×10 mL). The combined extracts were dried (MgSO₄), concentrated and subjected to column chromatography (hexanes) giving 15 (69 mg, 36%) as a colorless oil. FTIR: ν 3858, 3019, 2900, 1701, 1559, 1507, 1043, 774, 731, 694, 655 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 1.39-1.68 (m, 4H), 1.79-1.94 (m, 2H), 2.22-2.45 (m, 3H), 2.50-2.57 (m, 1H), 5.61 (s, 2H), 7.21-7.32 (m, 3H), 7.42-7.48 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz): δ 33.9, 34.4, 35.2, 35.3, 43.3, 44.0, 126.6, 126.7, 127.4, 128.4, 131.6, 143.5; MS (ES⁺): 261 (100%) [M⁺H⁺]; HRMS (ES⁺): calcd for C₁₄H₁₈As 261.0624, found 261.0634.

Synthesis of (meso)-(2r,3aR,7aS)-2-Phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoarsindole (16r) and (meso)-(2s,3aR,7aS)-2-Phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoarsindole (16s)

A suspension of Mg (0.308 g, 12.67 mmol) and (meso)-(4R,5S)-4,5-bis(bromomethyl)cyclohex-1-ene [31] (0.850 g, 3.17 mmol) in THF (3.4 mL) was stirred at rt for 1 h. The supernatant liquid was added dropwise to a solution of (PhAsO)ₓ (0.107 g, 0.64 mmol) in THF (3.4 mL) at −78 °C and the mixture was allowed to warm to rt and stirred for 20 h. Water (5 mL) was slowly added and the mixture was extracted with CH₂Cl₂ (3×10 mL). The combined extracts were dried (MgSO₄), concentrated and subjected to column chromatography (hexanes) giving 15 (69 mg, 36%) as a colorless oil. FTIR: ν 3741, 2915, 1653, 1540, 1038, 880, 732, 657 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 1.65-2.40 (m, 20H), 5.48 (s, 2H), 5.62 (s, 2H), 7.17-7.50 (m, 10H); ¹³C NMR (CDCl₃, 125 MHz): δ 33.9, 34.4, 35.2, 35.3, 43.3, 44.0, 126.6, 126.7, 127.4, 128.4, 131.6, 143.5; MS (ES⁺): 261 (100%) [M⁺H⁺]; HRMS (ES⁺): calcd for C₁₄H₁₈As 261.0624, found 261.0616.

Synthesis of 1-(4-Bromophenyl)arsolane (17)

A suspension of Mg (470 mg, 19.33 mmol) and 1,4-dibromobutane (1.386 g, 6.42 mmol) in THF (12.8 mL) was stirred at rt for 16 h. The supernatant liquid was added dropwise to a solution of (4-BrPhAsO), (406.7 mg, 1.65 mmol) in THF (16.5 mL) at −78 °C and the mixture was allowed to warm
to rt and stirred for 20 h. The reaction was quenched by the slow addition of saturated NH₄Cl (10 mL), then water (20 mL) was added and the product was extracted with Et₂O (2×20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄), concentrated and subjected to column chromatography (petroleum ether) giving 17 (211.5 mg, 45%) as a colorless oil. FTIR: \( \nu = 3331, 2917, 1653, 1479, 1377, 1043, 799, 704 \text{ cm}^{-1} \); \(^1\)H NMR (CDCl₃, 300 MHz): \( \delta = 1.72-2.04 \text{ (m, 8H)} \), 7.41 (d, \( J = 8.2 \text{ Hz, 2H} \)); \(^{13}\)C NMR (CDCl₃, 75 MHz): \( \delta = 27.5, 30.4, 121.6, 131.2, 133.1, 142.2 \); MS (EI+): 288 (11%) [M, \(^{81}\)Br]⁺, 286 (11%) [M, \(^{79}\)Br]⁺, 232 (15%), 230 (19%), 71 (100%); HRMS (EI+): calcd for C₁₀H₁₂As⁷⁹Br 285.9338, found 285.9349.

**Synthesis of 1-(4-Methoxyphenyl)arsolane (18)**

A suspension of Mg (245 mg, 10.10 mmol) and 1,4-dibromobutane (1.090 g, 5.05 mmol) in THF (5 mL) was stirred at rt for 1 h. The resulting dark grey solution was added dropwise to a solution of (4-OMePhAsO)₂ (200 mg, 1.01 mmol) in THF (9 mL) at \(-78 \text{ °C} \) and the mixture was allowed to warm to rt and stirred for 20 h. Water (5 mL) was slowly added and the mixture was extracted with EtOAc (2×10 mL). The combined extracts were washed with brine (10 mL), dried (MgSO₄), concentrated and subjected to column chromatography (hexanes) giving 18 (81.4 mg, 34%) as a colorless oil. FTIR: \( \nu = 3320, 2925, 2317, 1700, 1653, 1507, 1044, 668 \text{ cm}^{-1} \); \(^1\)H NMR (CDCl₃, 500 MHz): \( \delta = 1.73-1.95 \text{ (m, 8H)} \), 3.77 (s, 3H), 6.85 (d, \( J = 8.3 \text{ Hz, 2H} \)), 7.34 (d, \( J = 8.3 \text{ Hz, 2H} \)); \(^{13}\)C NMR (CDCl₃, 125 MHz): \( \delta = 27.7, 30.5, 55.2, 114.1, 132.9, 133.6, 159.4 \); MS (ES+): 239 (100%) [M+H]⁺; HRMS (ES+): calcd for C₁₁H₁₆AsO 239.0417, found 239.0424.

**Synthesis of 1-(Naphthalen-1-yl)arsolane (19)**

A suspension of Mg (223 mg, 9.17 mmol) and 1,4-dibromobutane (990 mg, 4.59 mmol) in THF (5 mL) was stirred at rt for 1 h. The resulting dark grey solution was added dropwise to a solution of (1-naphthylAsO)₂ (200 mg, 0.92 mmol) in THF (9 mL) at \(-78 \text{ °C} \) and the mixture was allowed to warm to rt and stirred for 20 h. Water (20 mL) was slowly added and the mixture was extracted with EtOAc (2×20 mL). The combined extracts were washed with brine (10 mL), dried (MgSO₄), concentrated and subjected to column chromatography (hexanes) giving 19 (87.6 mg, 37%) as a colorless oil. FTIR: \( \nu = 3741, 2927, 1701, 1255, 1022, 947, 787, 770, 649 \text{ cm}^{-1} \); \(^1\)H NMR (CDCl₃, 500 MHz): \( \delta = 1.73-1.86 \text{ (m, 4H)} \), 1.97-2.09 (m, 4H), 7.36 (t, \( J = 7.6 \text{ Hz, 1H} \)), 7.41-7.55 (m, 3H), 7.72 (d, \( J = 8.1 \text{ Hz, 1H} \)), 7.80 (d, \( J = 7.6 \text{ Hz, 1H} \)), 8.30 (d, \( J = 8.2 \text{ Hz, 1H} \)); \(^{13}\)C NMR (CDCl₃, 125 MHz): \( \delta = 26.3, 30.3, 125.2, 125.55, 125.57, 125.57, 125.57, 125.57, 126.7, 127.2, 127.9, 128.8, 133.9, 135.4, 140.5 \); MS (ES+): 259 (100%) [M+H]⁺; HRMS (ES+): calcd for C₁₄H₁₆As 259.0468, found 259.0468.

**Synthesis of 1-Phenylarsolane-1-oxide (20)**

Based on a literature procedure [15], to a solution of 10 (700 mg, 3.36 mmol) in acetone (10 mL) was added H₂O₂ (30% aqueous, 573 mg total, 5.05 mmol H₂O₂) and the solution was stirred at rt for 12 h. The solution was concentrated under reduced pressure and the residue subjected to column chromatography (EtOAc to 20% NEt₃/EtOAc) to afford 20 [15] (678 mg, 90%) as a colorless oil. This compound has not been fully characterized previously. FTIR: \( \nu = 3321, 2971, 1439, 1378, 1089, 1048, 879, 863, 740, 692 \text{ cm}^{-1} \); \(^1\)H NMR (CDCl₃, 300 MHz): \( \delta = 1.97-2.05 \text{ (m, 2H)} \), 2.13-2.28 (m, 6H), 7.50-7.60 (m, 3H), 7.72-7.78 (m, 2H); \(^{13}\)C NMR (CDCl₃, 125 MHz): \( \delta = 25.9, 29.2, 129.1, 129.5, 131.7, 134.8 \); MS (EI+): 224 (25%) [M]⁺, 169 (100%); HRMS (ES+): calcd for C₁₀H₁₄OAs 225.0261, found 225.0255.

**Synthesis of 1-Phenylarsinane-1-oxide (21)**

Based on a literature procedure [15], to a solution of 10 (700 mg, 3.36 mmol) in acetone (10 mL) was added H₂O₂ (30% aqueous, 573 mg total, 5.05 mmol H₂O₂) and the solution was stirred at rt for 12 h. The solution was concentrated under reduced pressure and the residue subjected to column chromatography (EtOAc to 20% NEt₃/EtOAc) to afford 20 [15] (678 mg, 90%) as a colorless oil. This compound has not been fully characterized previously. FTIR: \( \nu = 3321, 2971, 1439, 1378, 1089, 1048, 879, 863, 740, 692 \text{ cm}^{-1} \); \(^1\)H NMR (CDCl₃, 300 MHz): \( \delta = 1.97-2.05 \text{ (m, 2H)} \), 2.13-2.28 (m, 6H), 7.50-7.60 (m, 3H), 7.72-7.78 (m, 2H); \(^{13}\)C NMR (CDCl₃, 125 MHz): \( \delta = 25.9, 29.2, 129.1, 129.5, 131.7, 134.8 \); MS (EI+): 224 (25%) [M]⁺, 169 (100%); HRMS (ES+): calcd for C₁₀H₁₄OAs 225.0261, found 225.0255.
To a solution of 11 (220 mg, 0.99 mmol) in acetone (5 mL) was added H₂O₂ (30% aqueous, 112 mg total, 0.99 mmol H₂O₂) and the solution was stirred at rt for 12 h. The solution was concentrated under reduced pressure and the residue was subjected to column chromatography (10:20:70 MeOH:NEt₃:EtOAc to 20:20:60 MeOH:NEt₃:EtOAc) to give 21 (210 mg, 91%) as a yellow oil. FTIR: ν 3335, 2922, 2853, 1434, 1089, 1021, 930, 863, 809, 747, 740 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 1.58-2.42 (m, 10H), 7.50-7.58 (m, 3H), 7.76-7.82 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz): δ 23.3, 25.4, 29.5, 129.2, 129.9, 131.8, 133.6; MS (ES+): 239 (40%) [M+H]⁺, 477 (100%) [2M+H]⁺; HRMS (ES+): calcd for C₁₁H₁₆AsO, 239.0417 found 239.0420.

Synthesis of 1-Phenyl-2,3-dihydro-1H-arsindole-1-oxide (22)
To a solution of 12 (500 mg, 1.92 mmol) in acetone (10 mL) was added H₂O₂ (30% aqueous, 327 mg total, 2.88 mmol H₂O₂) and the solution was stirred at rt for 12 h. The solution was concentrated under reduced pressure and the residue subjected to column chromatography (EtOAc to 20% NEt₃/EtOAc) to give 22 (468 mg, 89%) as a colorless oil. FTIR: ν 3323, 3056, 1653, 1437, 1086, 866, 740, 691 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 2.50-2.62 (m, 2H), 3.36-3.42 (m, 1H), 3.55-3.61 (m, 1H), 7.39-7.57 (m, 5H), 7.65 (d, J = 7.5 Hz, 2H), 7.71 (d, J = 7.5 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): 27.5, 29.7, 127.2, 128.5, 129.4, 129.8, 130.3, 132.1, 132.6, 132.7, 143.4, 146.3; MS (ES+): 273 (100%) [M+H]⁺; HRMS (ES+): calcd for C₁₄H₁₄OAs 273.0261, found 273.0251.

Synthesis of 1-Phenyl-2,3-dihydro-1H-benzo[g]arsindole-1-oxide (23)
To a solution of 13 (400 mg, 1.31 mmol) in acetone (10 mL) was added H₂O₂ (30% aqueous, 222 mg total, 1.96 mmol H₂O₂) and the solution was stirred at rt for 12 h. The solution was concentrated under reduced pressure and the residual solid was triturated with cold CH₂Cl₂ providing 23 (394 mg, 94%) as a white solid. mp: 106−107 °C; FTIR: ν 3104, 2830, 845, 811, 744, 692 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 2.62-2.68 (m, 1H), 2.76-2.82 (m, 1H), 3.53-3.59 (m, 1H), 3.71-3.77 (m, 1H), 7.46-7.51 (m, 6H), 7.70 (d, J = 7.5 Hz, 2H), 7.90 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): 27.1, 30.2, 124.3, 126.0, 126.6, 128.1, 128.3, 128.7, 129.3, 129.9, 132.0, 132.1, 133.0, 133.5, 146.4; MS (ES+): 323 (100%) [M+H]⁺; HRMS (ES+): calcd for C₁₈H₁₆AsO 323.0417, found 323.0425.

Synthesis of 1-(4-Methoxyphenyl)arsolane-1-oxide (24)
To a solution of 18 (39.8 mg, 0.17 mmol) in acetone (1.2 mL) was added H₂O₂ (30% aqueous, 19.2 mg total, 0.17 mmol H₂O₂) and the solution was stirred at rt for 30 min. The solution was concentrated under reduced pressure and the residue subjected to column chromatography (CH₂Cl₂ to 10% MeOH/CH₂Cl₂) to give 24 (33 mg, 79%) as a colorless oil. FTIR: ν 3353, 2941, 1507, 1090, 1019, 884, 868, 821, 794, 752, 608 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 1.96-2.25 (m, 8H), 3.86 (s, 3H), 7.04 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz): δ 25.9, 29.3, 55.4, 114.9, 125.3, 131.2, 162.4; MS (ES+): 255 (100%) [M+H]⁺; HRMS (ES+): calcd for C₁₁H₁₆AsO₂ 255.0366, found 255.0360.

Acknowledgements
A.M.G. and S.J.B thank the University of Wollongong for the provision of a PhD scholarship.

Appendix A. Supplementary data
Supplementary data related to this article can be found at http.
References


