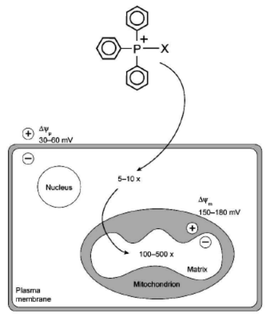
The Design and Synthesis of Triple Function Probes of Mitochondrial Disease

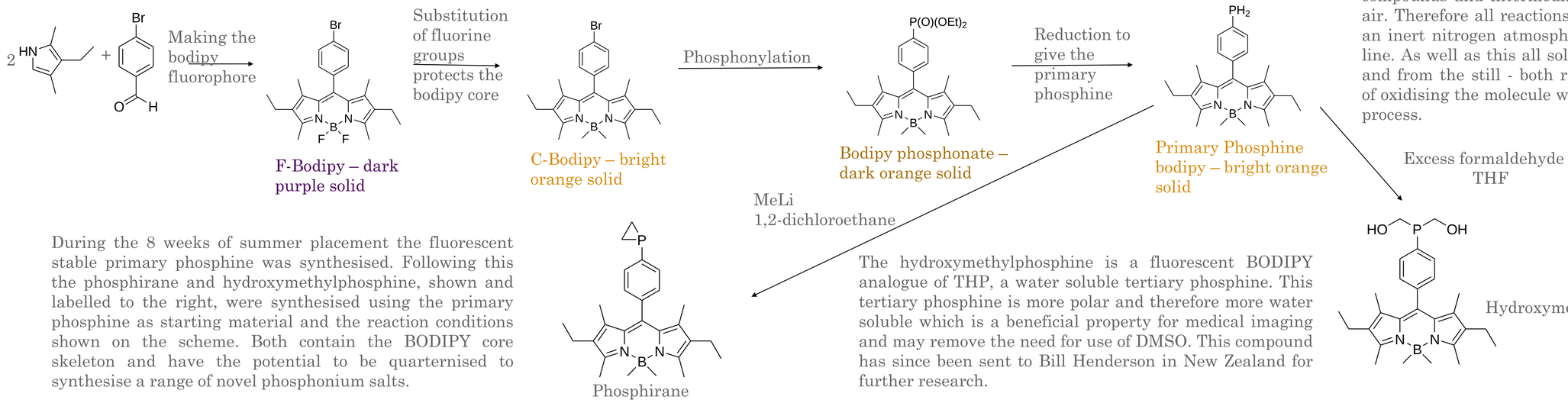
Investigating the synthesis of phosphonium salts used for medical imaging to identify dysfunctional mitochondria

The mitochondrial membrane potential (MMP) plays a key role in cardiac failure and cancer as the effected cells mitochondrial dysfunction can hugely disrupt the MMP. This change in charge potential results in an increase in the build up of MMP dependant compounds. Lipophilic cations, such as phosphonium salts, can pass through the lipid bilayer of the mitochondrion and increase proportionally with the increase of the gradient change of the MMP. Boron-dipyrromethene (BODIPY) type structures have regularly been used in optical biomedical imaging. The LJH group have previously developed fluorescent and air stable BODIPY phosphanes carrying dicyclohexyl and diphenyl substituents which were then methylated to form the phosphonium salts. Now the focus is on making new phosphines to improve the properties of the mitochondrial specific imaging agent.



Phosphonium salts are quarternary phosphines with a positive charge analogues to the molecule shown entering a mitochondria in the image the left.

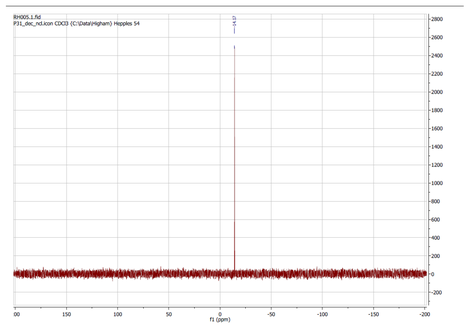
The bodipy primary phosphine is the starting material for the tertiary phosphines and phosphonium salts. The synthesis is shown below.



Although the bodipy primary phosphine is air stable as well as stable in chloroform, most compounds and intermediates are unstable in air. Therefore all reactions were carried out in an inert nitrogen atmosphere using a Schlenk line. As well as this all solvents used were dry and from the still - both reducing the chances of oxidising the molecule which is an unwanted process.

During the 8 weeks of summer placement the fluorescent stable primary phosphine was synthesised. Following this the phosphirane and hydroxymethylphosphine, shown and labelled to the right, were synthesised using the primary phosphine as starting material and the reaction conditions shown on the scheme. Both contain the BODIPY core skeleton and have the potential to be quarternised to synthesise a range of novel phosphonium salts.

The hydroxymethylphosphine is a fluorescent BODIPY analogue of THP, a water soluble tertiary phosphine. This tertiary phosphine is more polar and therefore more water soluble which is a beneficial property for medical imaging and may remove the need for use of DMSO. This compound has since been sent to Bill Henderson in New Zealand for further research.



Shown to the left is the phosphorus nuclear magnetic resonance (NMR) of the hydroxymethylphosphine. NMR is an analytical technique to help determine the structure of products made, the image shows one large peak at -14.17ppm with little noise. This is what we'd expect from this compound.

Future work will include the conversion of these tertiary phosphines into quarternary phosphonium salts by methylation. Once the salts have been synthesised they will be tested in cells, following this it would be interesting to see how they compare to the already used, diphenyl and dicyclohexyl, phosphonium salts as cell imaging agents. Research will also continue into other options of tertiary phosphines with the potential to be quarternised into a salt for medical imaging.

References:

- L. H. Davies (2013). 'Air-stable Fluorescent Primary Phosphines and their Potential Applications as Precursors for Disease Imaging Agents', PHD thesis, Newcastle University
- S. Nigam, B. P. Burke, L. H. Davies, J. Domarkas, J. F. Wallis, P. G. Waddell, J. S. Waby, D. M. Benoit, A.-M. Seymour, C. Cawthorne, L. J. Higham and S. J. Archibald, Chem. Commun., 2016, 52, 7114–7117.

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