Phosphine-based Fluorescent Switches

Can a Fluorescent Switch Help Identify Hard-to-Detect Intermediates in Medical Imaging?

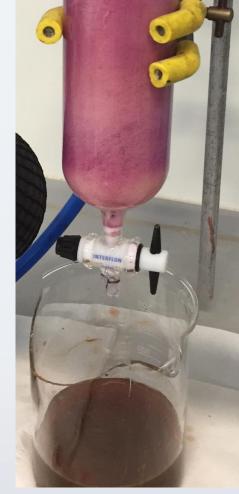
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Introduction & Aims

- During this project compounds were developed that were relevant in medical research. The production of these compounds has implications in cancer diagnostic imaging, i.e. radiology
- The aim was to build a precursor of a 'switch', to observe intermediates in reactions that are normally hard-to-detect - to better understand the chemical process
- The concept of the 'switch' would allow the prospective cancer agents to be tracked on a molecular level on its way to the target molecule

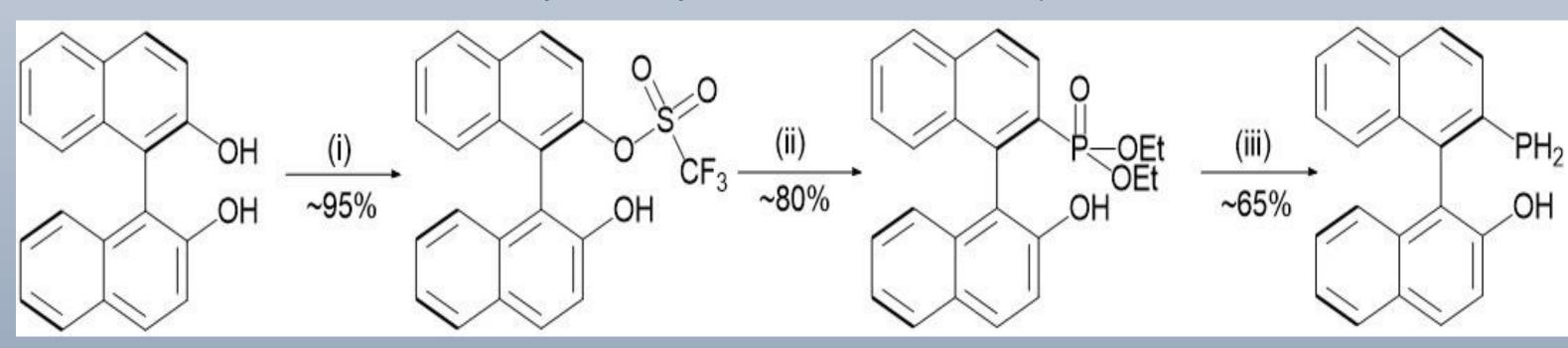






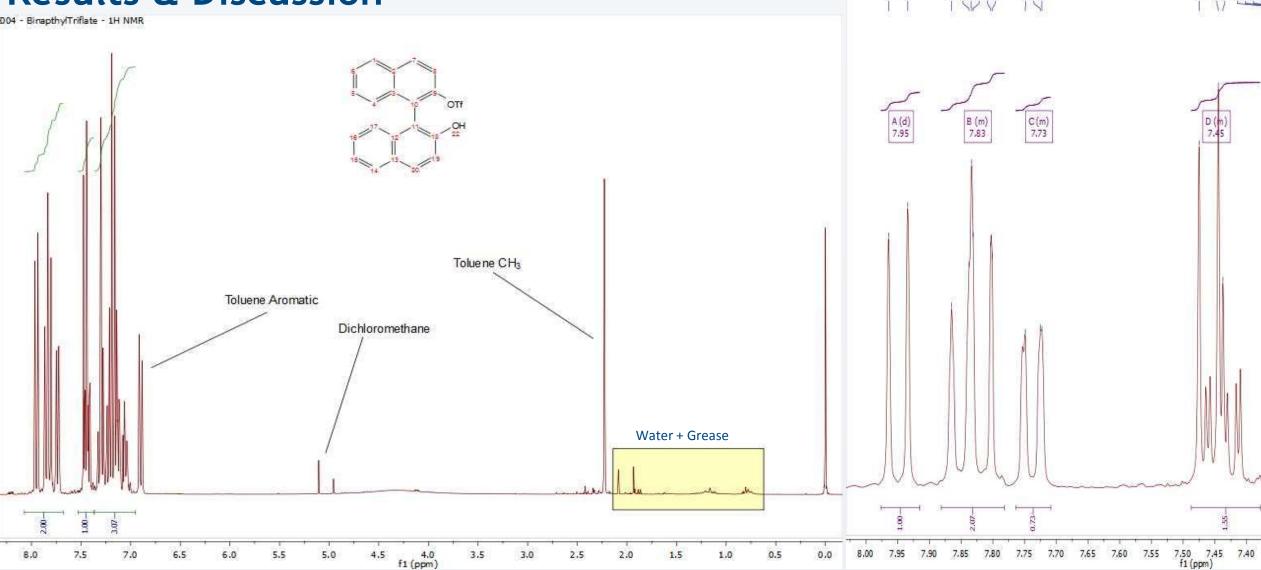
Method

- The final product was achieved by a several step synthesises, however this meant that it could be potentially difficult to produce a high yield
- The research project highlighted the fact that these phosphine compounds were unstable. Even with optimisation - using aromatic rings - they would decompose over 1-2 weeks. However, this is better than most primary phosphine systems which are often explosive and highly toxic
- This method would take about 2 weeks to the final product (phosphine), including all the reactions and their respective purifications and analysis



1. The primary reaction mechanism (above), with each individual percentage yield. (i) Tf₂O, DIPEA, DCM, 0°C (ii) Et₃N, HP(O)(OEt)₂, Pd(OAc)₂, DPPP, DMSO, 90°C (iii) LiAlH₄, TMSCl, THF, 78°C





The NMR (above left) shows the 2nd product within the reaction scheme, with the small amounts of impurity included

The NMR (above right) demonstrates the H's that are within the aromatic backbone, consistent within all the products

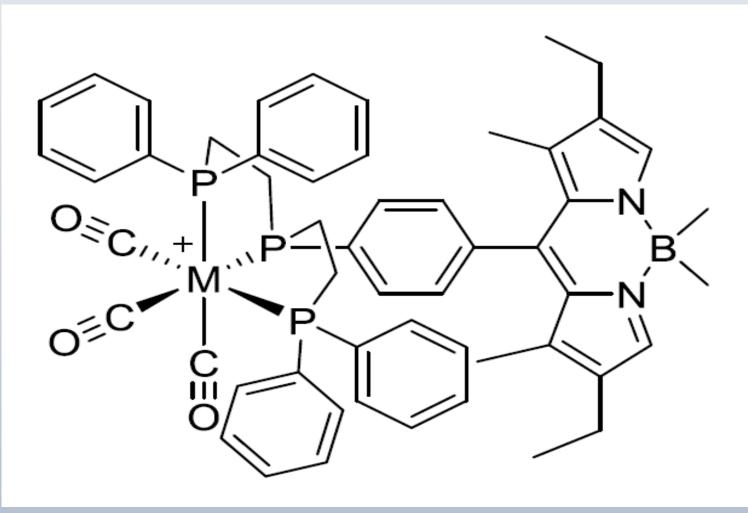
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• The different products could be produced in reasonably high purity, meaning that upon coordination to a metal (i.e. 99mTechnetium) there should be a high success rate

Conclusions & Further Work

- It was discovered that the final product can be produced in reasonable yield, in a high gram synthesis, and probably stored long enough to be coordinated to a 99mTechnetium complex
- This, as well as analogous complexes, can be utilised in cancer research. Certain complexes are taken into cervical and prostate cancer cells; and can be viewed due to their fluorescent nature



2. An example of a BODIPY based complex, using primary phosphines coordinated to a metal centre, where $M = {}^{99m}Tc$

• The aim is that these complexes will be chemically inert (therefore safe/unreactive) and stable to heat/water/light. Whilst also allowing for in vivo medical imaging using gamma scanning, and in in vitro fluorescence imaging. This would allow for more accurate diagnosis of certain aggressive tumours

References 1. REACTION SCHEME UTILISED AND EDITED FROM: Lee J. Higham; Efficient Multigram Syntheses of Air-Stable, Chiral Primary Phosphine Ligand Precursors via Palladium-Catalyzed Phosphonylation of Aryltriflates; Synthesis; 2012 2. EXAMPLE OF COMPLEX FROM: Laura Helen Davies; Air-Stable Fluorescent Primary Phosphines and their Potential Applications as Precursors for Disease Imaging Agents; 2013