Air-Stable Primary Phosphines: Safer Routes to Industrially-Significant Chiral Catalysts

An investigation into whether novel air-stable phosphine ligands can be synthesised and developed into catalysts for safer and more efficient pharmaceutical drug syntheses

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Drug synthesis — medicines often required to be *enantiopure* in the body to work effectively and gain regulatory approval

Chirality is a key aspect of chemistry, and especially in drug design. A molecule is chiral if it is not superimposable on its mirror image. The chiral molecule and its mirror image are called *enantiomers*; although they only differ in their 3D structure, they have different chemical properties in a chiral environment, such as our bodies, which are built using chiral building blocks, due to binding differences.

Figure 1. The word chiral comes from the Greek word for hand, χειρ (kheir). Hands are the perfect example for chirality, as the right hand is the mirror image of the left one, but no matter the orientation, they cannot be superimposed. This picture of my hands should help demonstrate this!

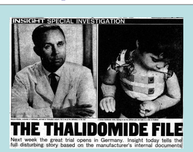
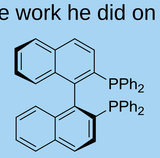
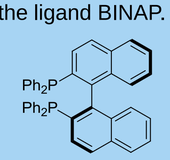


Figure 2, The drug from the 1950s, Thalidomide, was sold as a racemic mixture (a 50% mixture of each enantiomer). While the enantiomer *(R)*-Thalidomide helped pregnant women with their morning sickness, the (*S*) enantiomer caused some babies to be born with phocomelia (above).

To make these chiral drugs, a technique called asymmetric catalysis is used. For this, a chiral catalyst is needed, in order to form the stereospecific molecule; transition metal complexes with phosphorus ligands are often used as these chiral catalysts. Those molecules are a such an important part of current research that Noyori won a share of the 2001 Nobel Prize in Chemistry, for the work he did on the ligand BINAP.



(*S*)-BINAP



(*R*)-BINAP

Another interesting catalyst is the rhodium complex of DuPhos, which possesses chiral phosphine ligands. This phosphine was developed in 1991 by researchers at DuPont, and is now used in industry to synthesise stereospecific drugs.

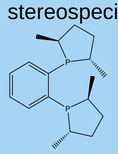


Figure 3. The chiral molecule (*S*,*S*)-DuPhos.

Figure 4. The anticoagulant drug Warfarin is synthesised using the DuPhos catalyst, and is formed with more than 98% enantioselectivity.

The synthetic route to DuPhos ligands employs the corresponding *bis*-primary phosphine. However, many problems emerge from the use of primary phosphines. These molecules can smell very unpleasant, have pyrophoric properties and are often highly toxic.

For example $PhPH_2$ presents the following hazards:
H225: Highly flammable liquid and vapour.
H250: Catches fire spontaneously if exposed to air.
H330: Fatal if inhaled.

Can we replace hazardous starting materials with safer alternatives that still perform in asymmetric catalysis?

On an industrial scale, using primary phosphines can prove to be quite challenging, due to the high risks involved. We are keen to tame this functional group, and reduce the hazardous properties. The LJH Research group (http://leejohnhighamresearch.co.uk/) has made remarkable advances in showing that adding extra conjugated rings (so more electron density) into the starting materials renders these molecules air-stable!

The target of this summer's research was to see if changing the backbone precursors could make air-stable, user friendly DuPhos analogues.

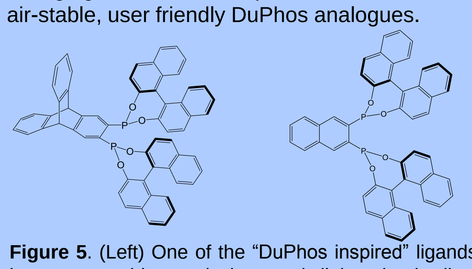


Figure 5. (Left) One of the "DuPhos inspired" ligands of interest was this novel triptycenyl diphosphonite ligand. (Right) Two modified backbones were studied, and the second one was this naphthalene based analogue.

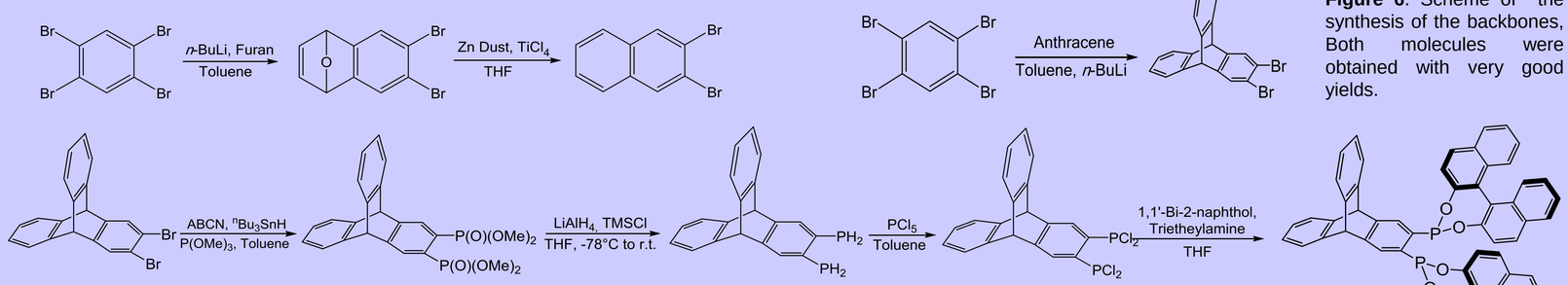
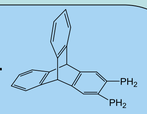


Figure 6. Scheme of the synthesis of the backbones, Both molecules were obtained with very good yields.

Figure 7. Scheme of the synthetic route to the air stable phosphine and the chiral ligand. The final reaction was done with both (*R*)- and (*S*)-equivalents of the 1,1-bi-2-naphthol. The reactions were also all carried out with the naphthalene backbone; both triptycene and naphthalene molecules reacted readily, and the synthesises worked in exactly the same way for both.

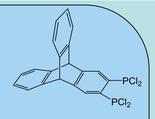
Results — (1) the target is air stable (2) a gateway compound was made and (3) a new chiral ligand has been developed

Result 1
Primary phosphine —



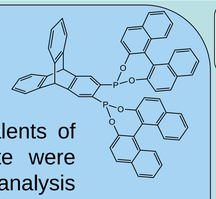
Both the triptycene and naphthalene-based primary phosphines can be synthesised, in more than 70% yield. The reaction can be done in relatively large scale (for chiral compounds); increasing the equivalents of each reagent did not alter the extent of success.
Those new phosphines are predicted to be air-stable: the work up and column chromatography were done in air!

Result 2
Dichlorophosphine —



This is a new gateway compound, again synthesised with both backbones, and obtained in very good yield. It is also air-stable, and does not have a nasty smell, therefore very user-friendly. The naphthalene species has not been tested for this compound yet.

Result 3
Chiral phosphonite —



Both (*R*)- and (*S*)- equivalents of the triptycene phosphonite were obtained. The NMR analysis proved that the compounds were synthesised, but quickly decomposed. However this is a completely novel compound, and a big discovery that will lead to further work in the world of asymmetric catalysis.

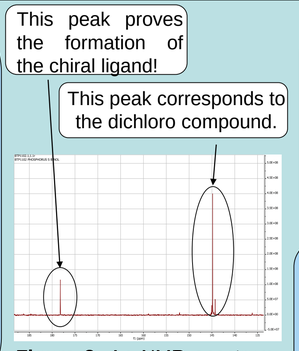


Figure 8. An NMR spectrum of the (*S*)-binol phosphorus ligand.

Conclusion and Further Work

The project was a success, with the synthesis of several novel chiral phosphorus compounds! The LJH group will now continue the research by exploring the stability of the dichloro- compound, and trying to synthesise the ligand again and finding a way to prevent its decomposition, but also by trying the last synthesis route with the naphthalene backbone. All this will then lead to further research to test this ligand on a Rhodium complex catalyst!

References

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