SYNTHESIS OF NOVEL 3-DIMENSIONAL BUILDING BLOCKS OF PHARMACEUTICAL INTEREST

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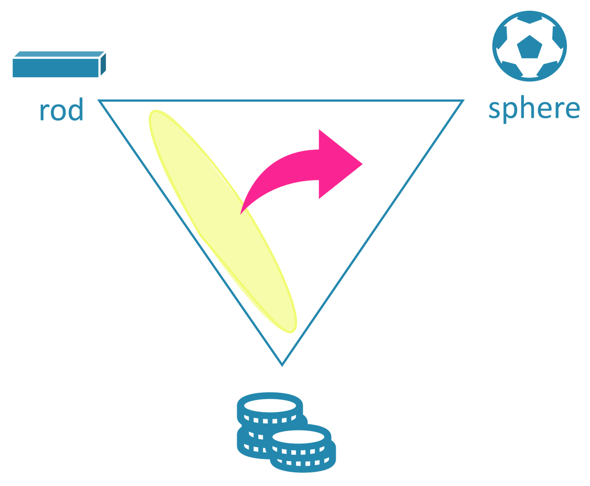
Introduction

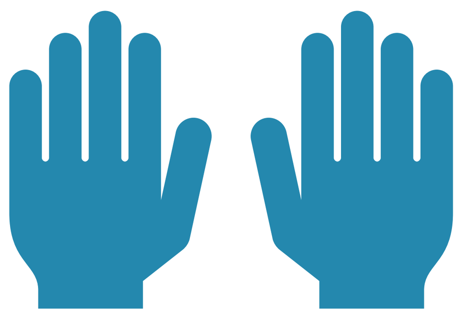
3-Dimensionality



Historically, drugs have been shaped like flat rods or discs. To access novel chemical space it is now desirable to find methods of introducing 3-dimensionality into drug molecules.

Chirality

Look at your hands.
Try and make it so that one looks exactly like the other.



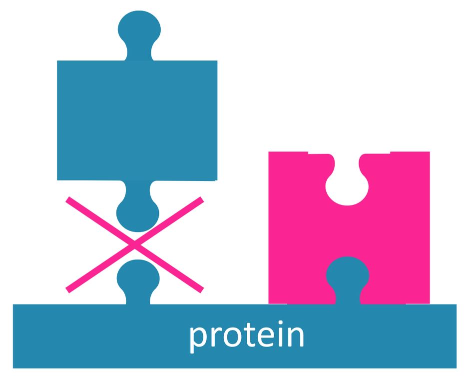
Struggling?
It is impossible!
That is because our hands are chiral.
This means they are non-superimposable on their mirror image. Molecules can be chiral, and the two "hands" of the molecule are called enantiomers.
Lots of things in life are chiral.

Why are we interested in chirality?

Have you ever gone to shake hands with someone who is opposite-handed to you (e.g. if you are right-handed and go to shake hands with someone who is left-handed) and the complementarity isn't quite there so the handshake doesn't proceed as smoothly?

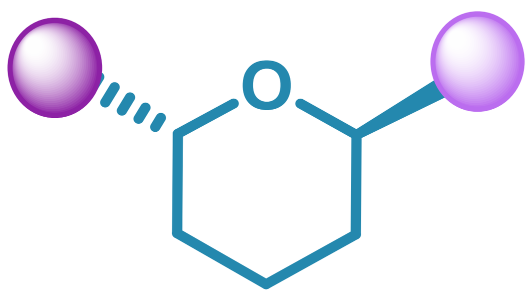
Chiral objects (like hands) interact with other chiral objects (someone else's hand) differently depending on which enantiomers (left or right hand) are interacting.

For chiral drug molecules, this may mean that one enantiomer exhibits better complementarity to a protein (which is also chiral) it needs to interact with in the body to work.
This can lead to a more potent medicine.



Tetrahydropyrans

What are they?



hashed line = pointing down
wedged line = pointing up

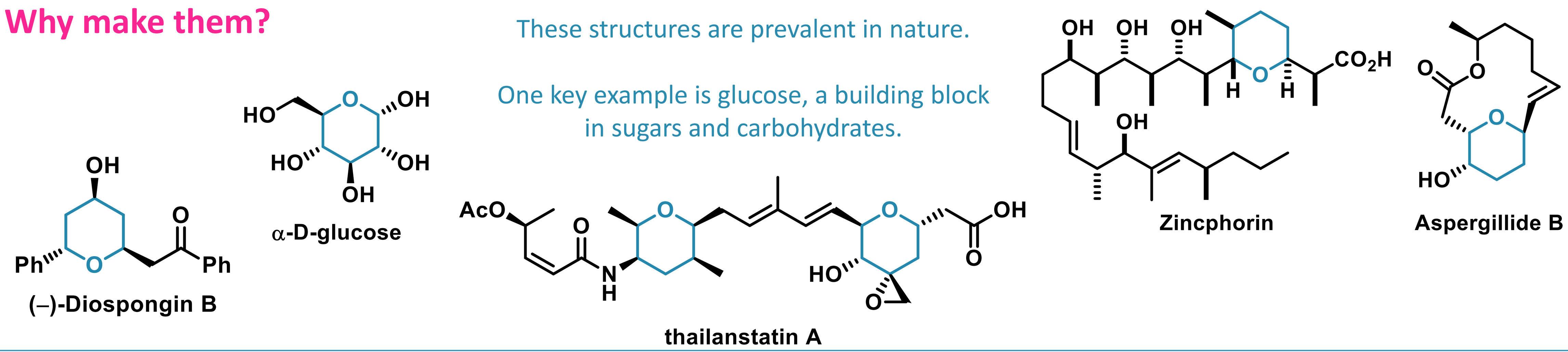
Tetrahydropyrans consist of a six-membered ring containing one oxygen atom.

2,6-*trans*-tetrahydropyrans have branches either side of the oxygen atom, which point in opposite directions.

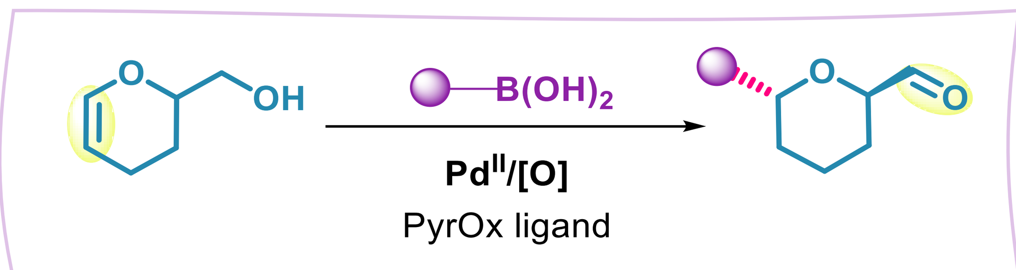
Why make them?

These structures are prevalent in nature.

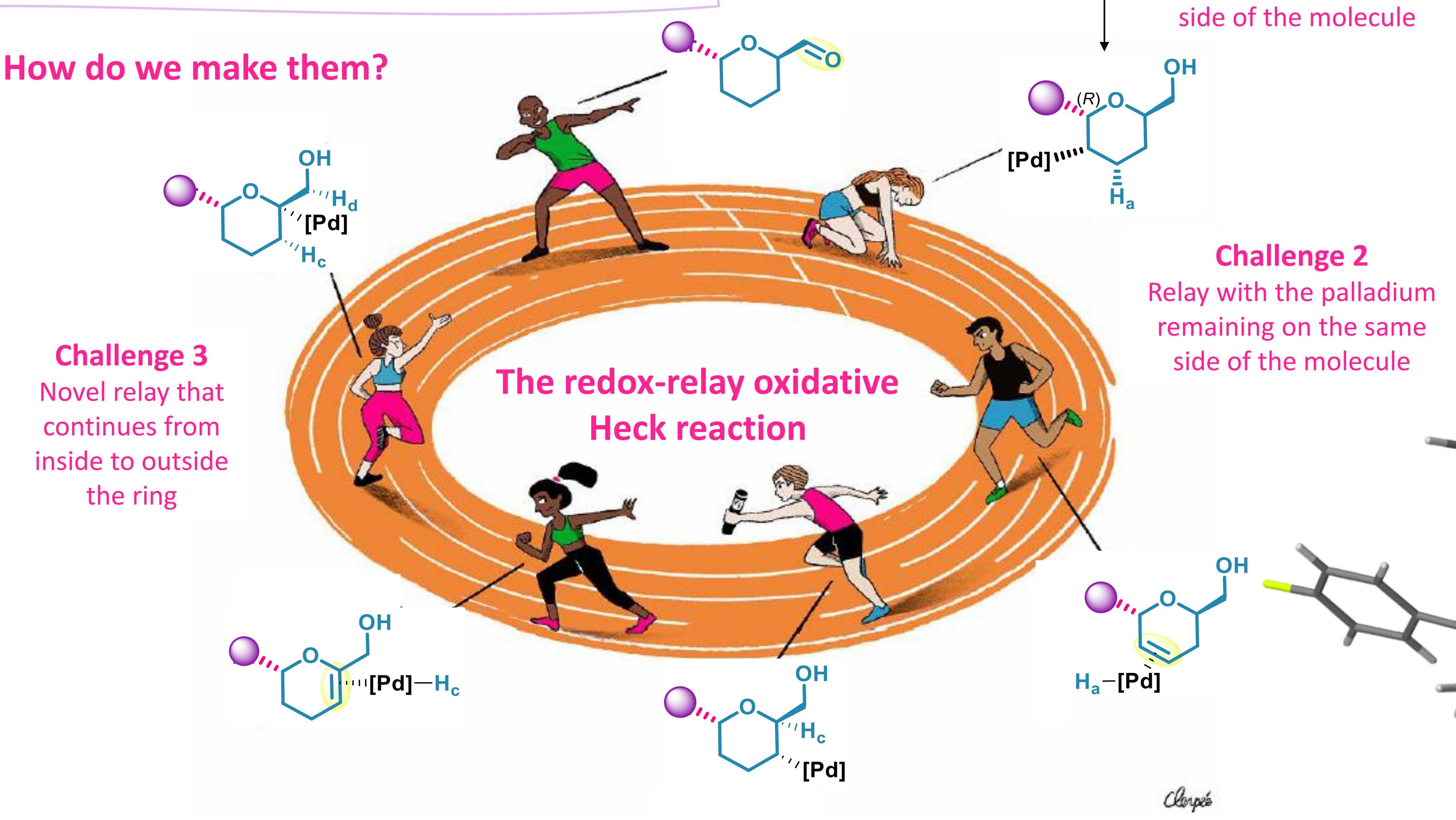
One key example is glucose, a building block in sugars and carbohydrates.



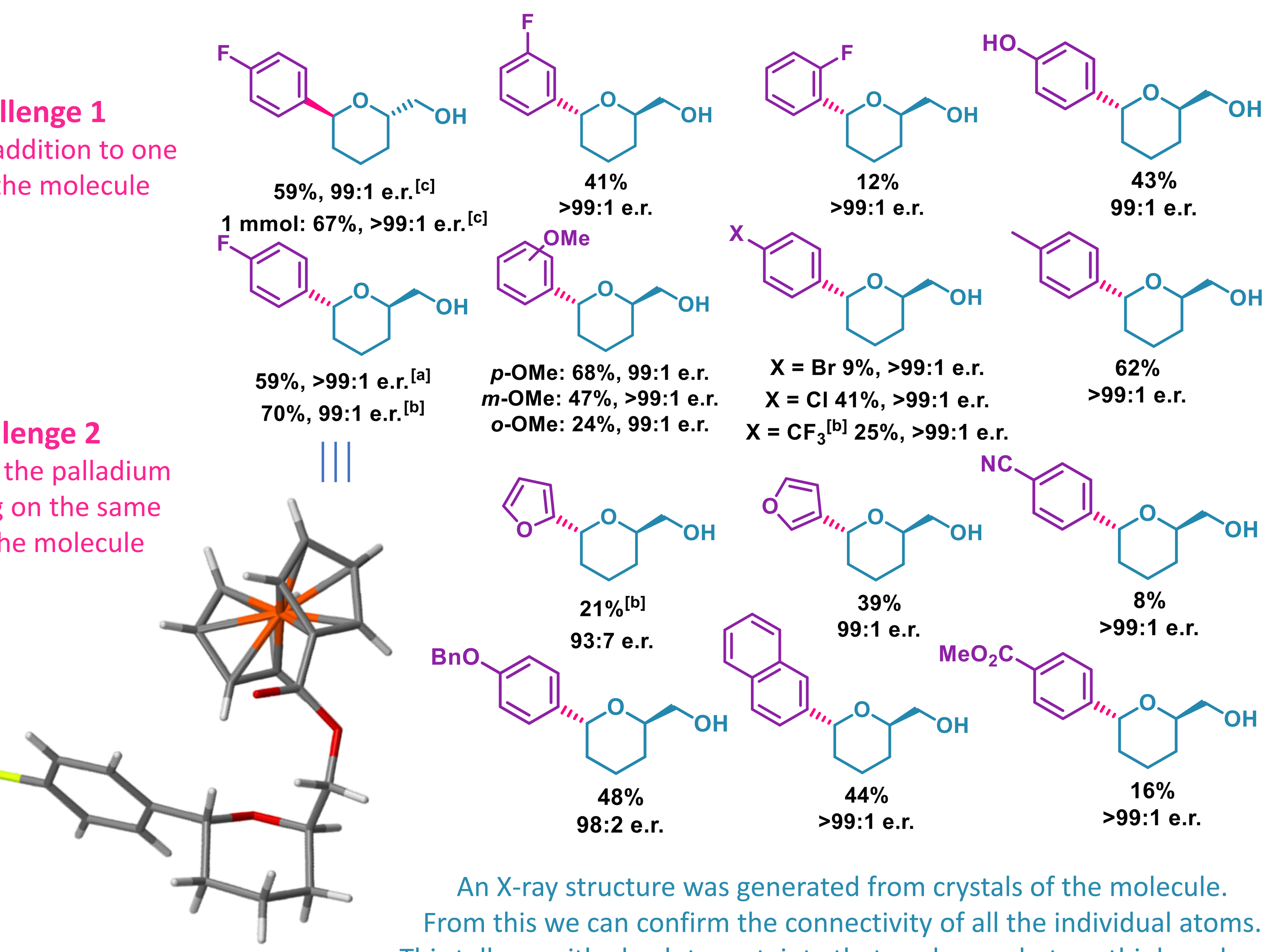
Results and Discussion



How do we make them?



What can we make?

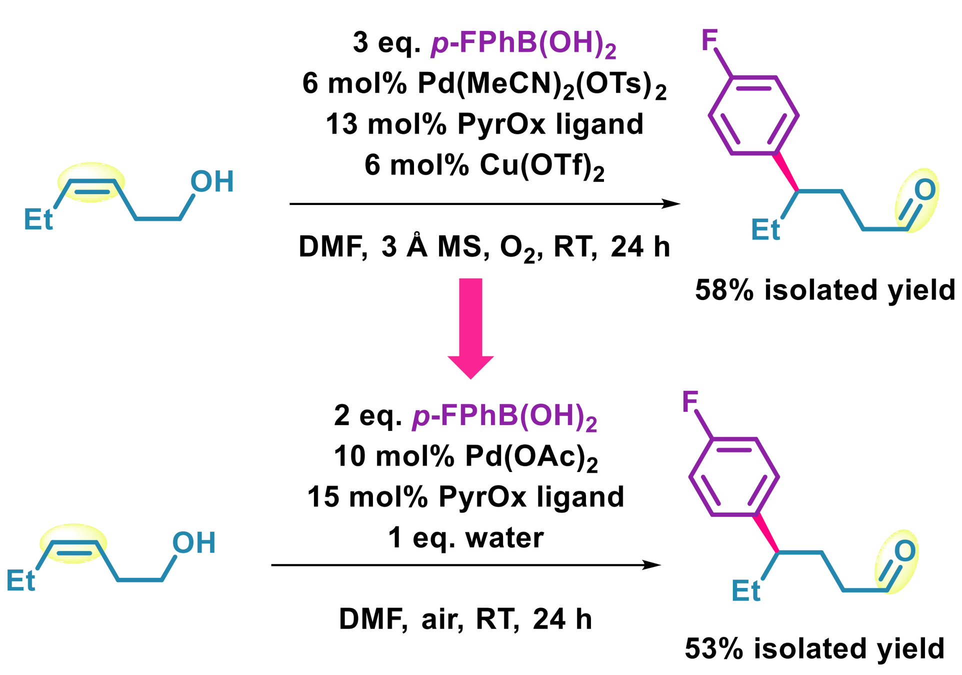


An X-ray structure was generated from crystals of the molecule.
From this we can confirm the connectivity of all the individual atoms.
This tells us with absolute certainty that we have what we think we have.

Scalability Assessment

The methodology has also been designed for incorporation at any point in the drug life-cycle – from small scale transformations in medicinal chemistry to large scale process chemistry. This will help to reduce the time it takes to bring new drugs to market and lower the cost of the developed medicine.

How did we improve it?



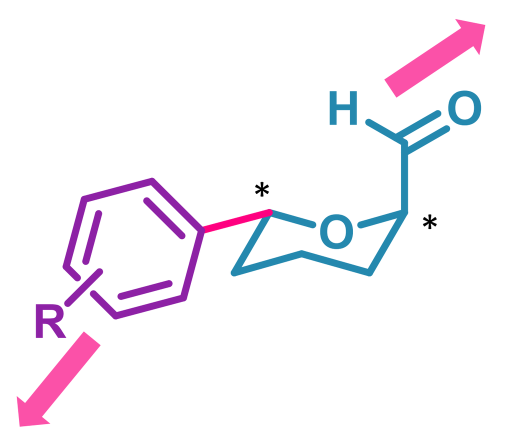
- Reduced the number of equivalents of reactants needed
- Changed to a more commercially available and cheaper palladium metal source
- Mitigated hazardous oxygen atmosphere with air
- Removed the need for a co-oxidant
- Removed the requirement for molecular sieves, which are problematic on scale

Conclusions

A relay methodology has been developed to access synthetically useful tetrahydropyran building blocks:

- In a single step
- From commercially available materials
- Generating a molecule with two points of chirality (*)
- And branch points for further functionalisation (➡)
- With a broad substrate scope

A set of scalable conditions, which show an improved safety and sustainability profile, whilst maintaining the yield and enantioselectivity have been developed.



Future Work

- Investigations into other ring systems are currently underway
- The scalability of reaction is also being explored further