Copper-Catalysed C–H Activation: A Sustainable, Efficient and Inexpensive Way To Prepare Medicinally Important Structures

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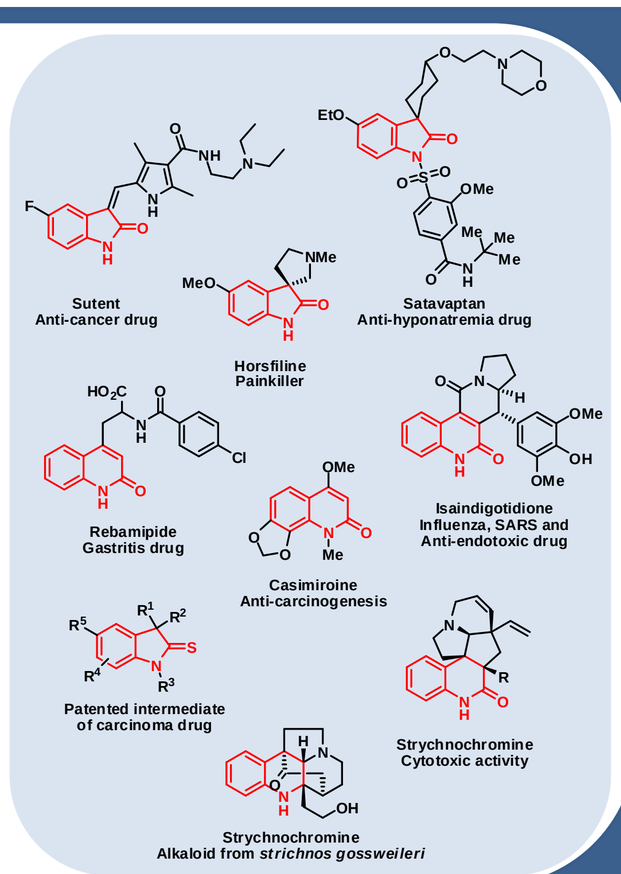
1. The Importance of Drugs

Modern medicine is arguably one of mankind's greatest discoveries and plays a large role in society and has a major impact on the economy.

The combined contribution of the pharmaceutical and chemical industries to the UK's national income was £15.5 billion in 2013.[1]

Despite the importance of these two industries the manufacture of drugs and chemicals can be expensive, inefficient and produce toxic or harmful waste.

The procedures used to prepare drugs is often environmentally unfriendly.

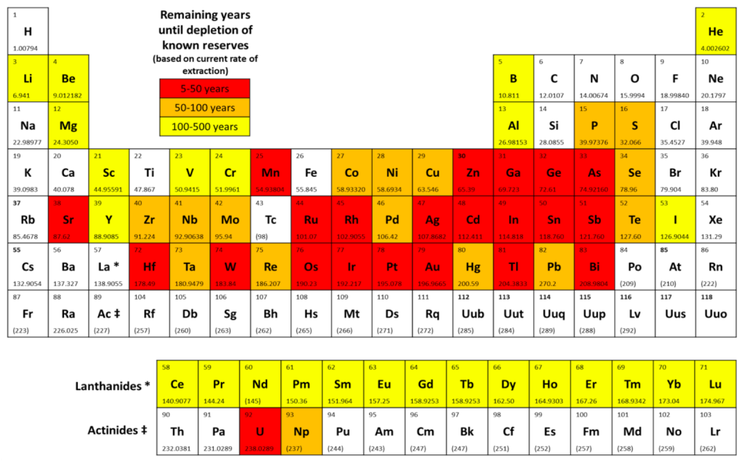


2. Greener Chemistry for a Sustainable Future

Green chemistry focusses on making chemical processes more environmentally friendly, efficient and safe.

The synthesis of many crucial medicines involve the use of toxic solvents, rare earth metals, expensive chemicals and very tailored conditions.

Quite often, however, the most environmentally friendly methods are not the cheapest.



The rate of extraction of earth metals is unsustainable.[2] Precious metals are in low abundance with the majority of reserves based in the East and Africa.

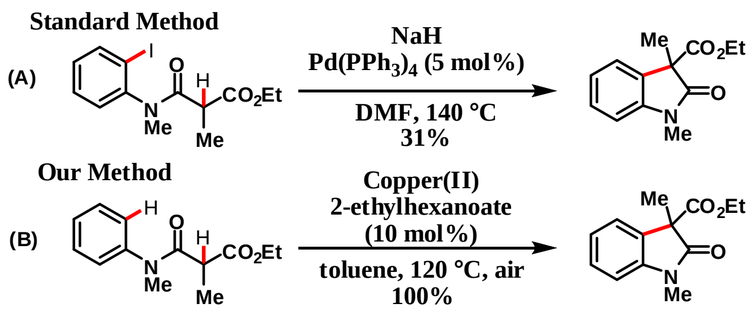
It is therefore of utmost importance to develop green methods which are also financially attractive yet sustainable.

3. Our Method

We have developed a new way of making many of the structures at the core of drug molecules using a cutting edge method called C–H activation. This is an extremely efficient process which provides almost no waste on a molecular level, illustrated by atom economy values (AE) of over 99%.

Other known methods produce toxic halogenated waste and suffer from poor atom economies.[3] Procedures that contain elements which are of low global abundance are deemed elementally unsustainable; this is reflected in the cost of reagents.

Our method utilises the inexpensive and elementally sustainable copper(II) 2-ethylhexanoate catalyst and produces no halogenated waste at all.

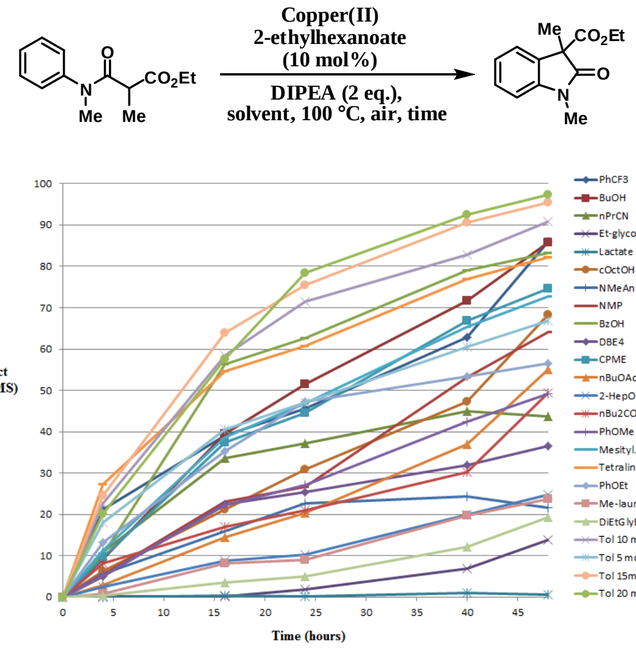


Method	Yield (%)	AE (%)	Waste	Solvent	Cat. Cost (per g)
A	31	65	Halogenated	DMF	£ 45.30
B	100	>99	Non-halogenated	Toluene	£ 2.86

Standard methods often require an unreactive atmosphere of argon to succeed. This can be expensive and operationally tedious. Our method works in an atmosphere of air and is moisture insensitive making this method extremely simple to carry out.

Geopolitics can effect the cost of chemicals and reagents. To emphasise the versatility of our method we showed that the reaction can be carried out successfully in a wide range of solvents including numerous green alternatives.

Our method also works using other cheap metal catalysts including nine copper catalysts and one manganese catalyst.



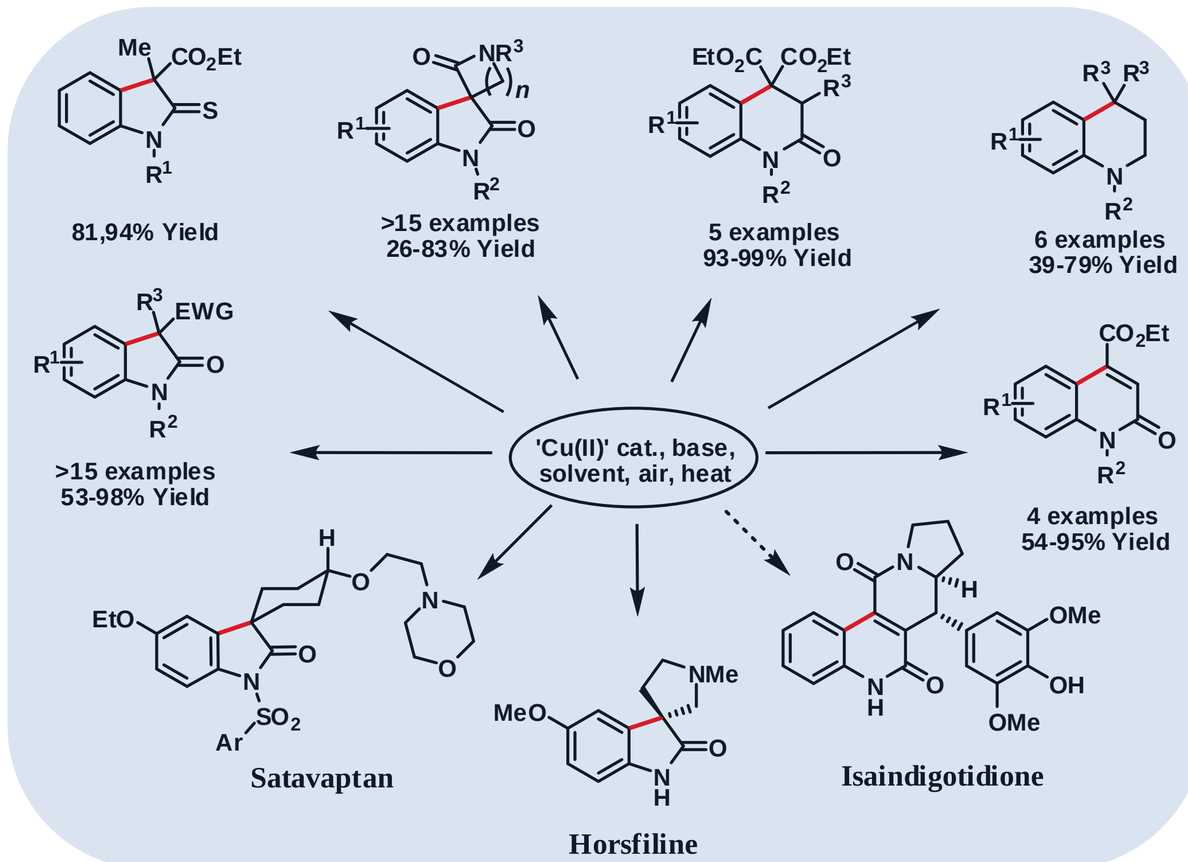
A graph of desired product formed over time in various solvents exemplifying the versatility of the method.

4. Application Of Our Method

We were able to make several different types of structures found in drug molecules using our method.[4]

The ability to make so many medicinally useful scaffolds using just one method makes this approach very powerful and versatile, which is attractive to the pharmaceutical industry.

We have successfully made Horsfiline and the drug Sataveptan utilising this methodology and work has begun on the synthesis of Isaindigotidione, exemplifying this method's application to complex drug molecules.



5. Summary of our Method

- Numerous drug molecule cores are accessible by our method
- Low environmental impact
- Low cost
- High yielding
- Highly efficient
- Operationally simple
- Elementally sustainable
- Highly attractive to the pharmaceutical industry

6. Acknowledgements

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7. References

1. ONS Annual Business Survey 2013, Section C Manufacturing. Release date 13th Nov 2014
2. A. J. Hunt *et al.*, Element Recovery and Sustainability, RSC: Cambridge, **2013**, ch. 1, pp 1.
3. M. A. Ciufolini *et al.*, *J. Org. Chem.*, **1988**, *53*, 4149.
4. (a) R. M. Gorman, *et al.*, *Chem. Eur. J.*, **2014**, *20*, 14063. (b) A. Perry, *et al.*, *Chem. Commun.*, **2009**, 3249. (c) C. L. Moody *et al.*, *Tetrahedron Lett.* **2012**, *53*, 1897.