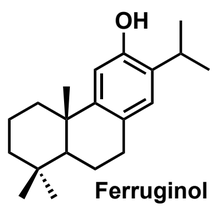
# ESR12: Rapid access to anticancer natural products and diverse derivatives

Philipp Schäfer†, Stephen P. Fletcher†*

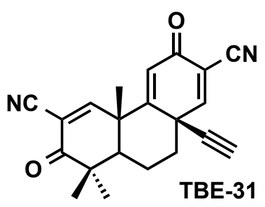
†*University of Oxford, Organic Chemistry, Chemistry Research Laboratory, 12 Mansfield Road, Oxford OX1 3TA, E-mail: philipp.schafer@chem.ox.ac.uk*

## 1 Introduction

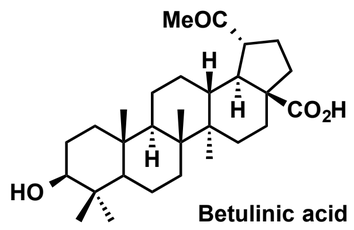
- Development of synthesis for natural products and various related synthetic derivatives
- Many natural products have anticancer activity, e.g. betulinic acid, ferruginol, CDDO, TBE-31[1,2]




Ferruginol

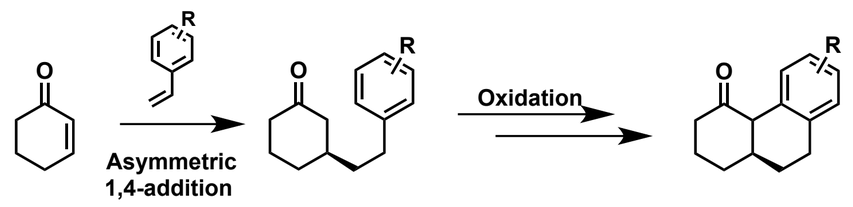



TBE-31



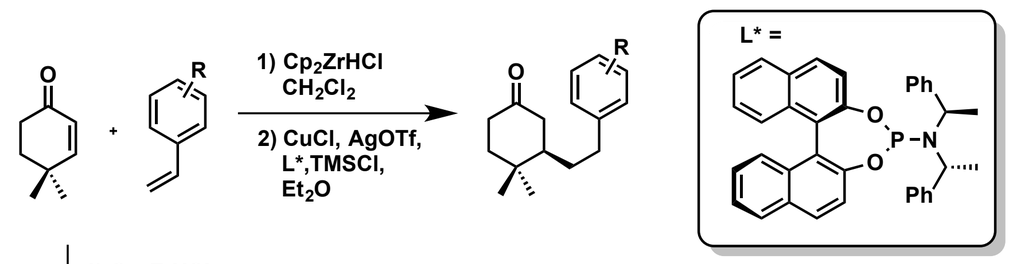

Betulinic acid

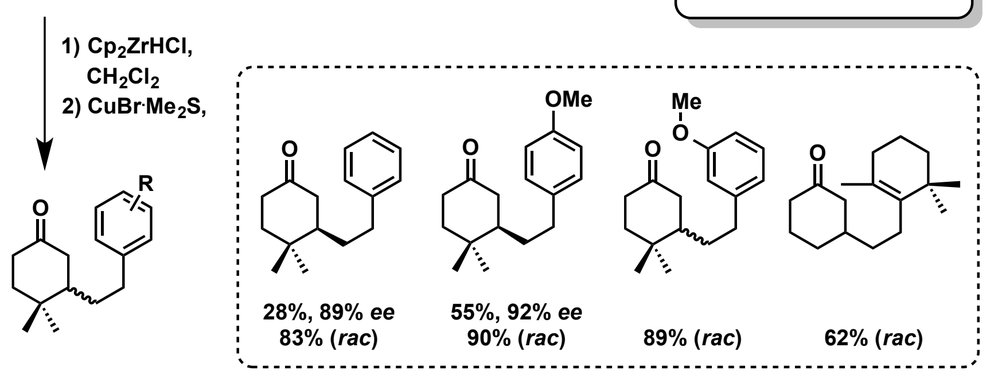
- Key steps of the synthesis involve asymmetric 1,4-addition[3] and $\alpha$-substitution of ketone to form the tricyclic core



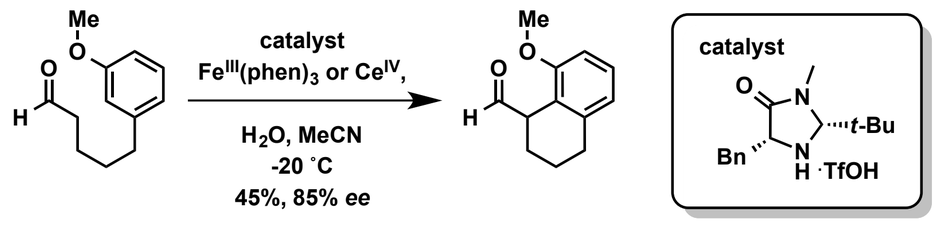

## 2 Results

- Enantioselective addition of styrene derivatives and dienes was successful



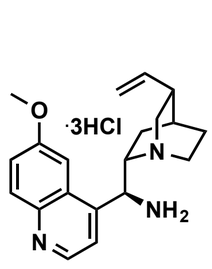




- SOMO catalysis as a template for $\alpha$-substitution
- Principle is iminium formation and radical addition at low temperatures[4]

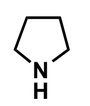



## 3 Challenges

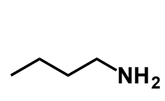
- Many catalysts did not work
- Solution: stable catalysts for $\alpha$-allylation of cyclic ketones[5]
- Application of SOMO-catalysis failed for ketones



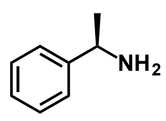

0%



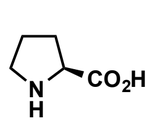

traces
*rac*



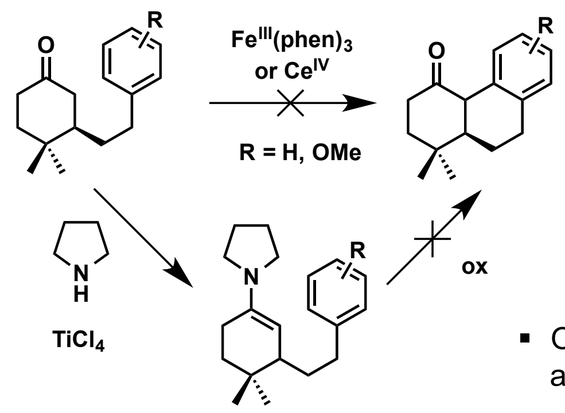

traces
*rac*

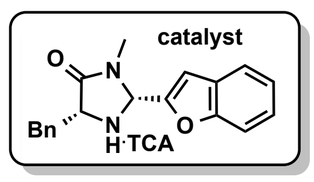



0%



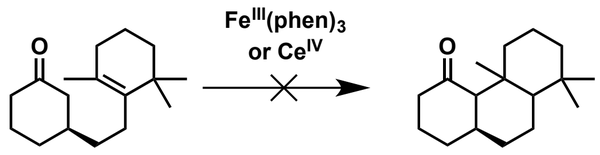

0%



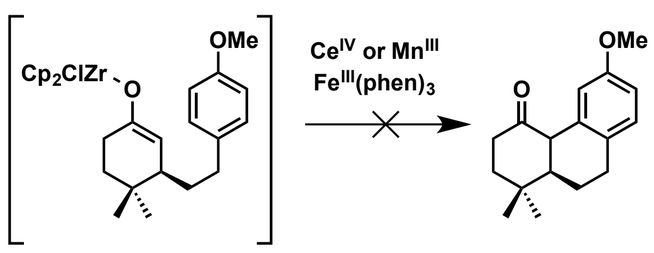




- Other secondary amines and amino acids were not successful

- Use of alkenes and SET oxidants did not gave the coupling product

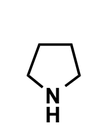



- *In situ* oxidation after 1,4-addition gave no result

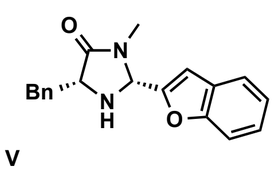



## 4 Electrochemical Approach

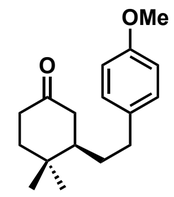
- Chemical approach failed
- Electrochemistry may achieve cyclisation reaction




*E* = + 1.3 V



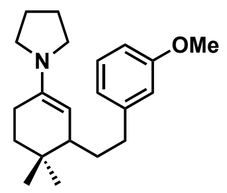

*E* = + 1.8 V



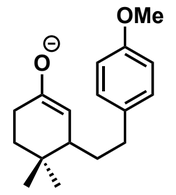

*E* = + 1.9 V

- Conditions:
  - Constant current experiments
  - 6 V battery/ C rod electrodes[6]
  - Substrate *c* = 0.01 M
  - $Et_4NOTs$, $Et_4NBF_4$ or $LiClO_4$
  - Solvent: MeCN or THF

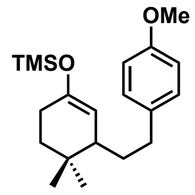
➪ No product obtained
➪ Complex mixture or
➪ Low conversion




*E* = + 0.7 V



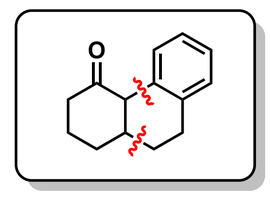

*E* = + 1.7 V




*E* = + 1.7 V

## 5 Conclusion and Future Work

- First key steps were made but require optimization
- SOMO catalysis not suitable for aromatic substrates
- Development of alternative method for C-C coupling
- Broaden the scope to access other structure motifs
- Once key step is established, focus on suitable derivatives of substrates for testing anticancer activity




The research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013) under REA grant agreement nº 316955. In addition, we would like to thank the EPSRC for research funding.

### ESR12 in summary:

A large number of drugs used in cancer treatment contain a common structure that comprises three rings of 6-carbon atoms each, fused together in a particular way. The aim of this project is to develop a fast and general way to construct this using chemical reactions of cheap and readily available starting materials. These methods will allow variations of the ring structure to be examined. At a later stage the molecules created will be tested in anti-cancer treatment.

### References

**(1)** Ferreira, C. V. *et al. Biochimie* **2008**, *90*, 843. **(2)** Gribble, G. W. *et al. J. Med. Chem.* **2011**, *54*, 1762. **(3)** Fletcher, S. P. *et al.*, *Nature Chem.* **2012**, *4*, 649. **(4)** Nicolaou, K. C. *et al., J. Am. Chem. Soc.* **2009**, *131*,1735; MacMillan, D. W. C. *et al.*, *J. Am. Chem. Soc.* **2009**, *131*, 11640. **(5)** MacMillan, D. W. C. *et al.*, *PNAS* **2010**, *107*, 20648. **(6)** Moeller, K. D. *et al.*, *Tetrahedron Lett.* **1996**, *7*, 8317; Moeller, K. D., *Tetrahedron* **2000**, *56,* 9527.