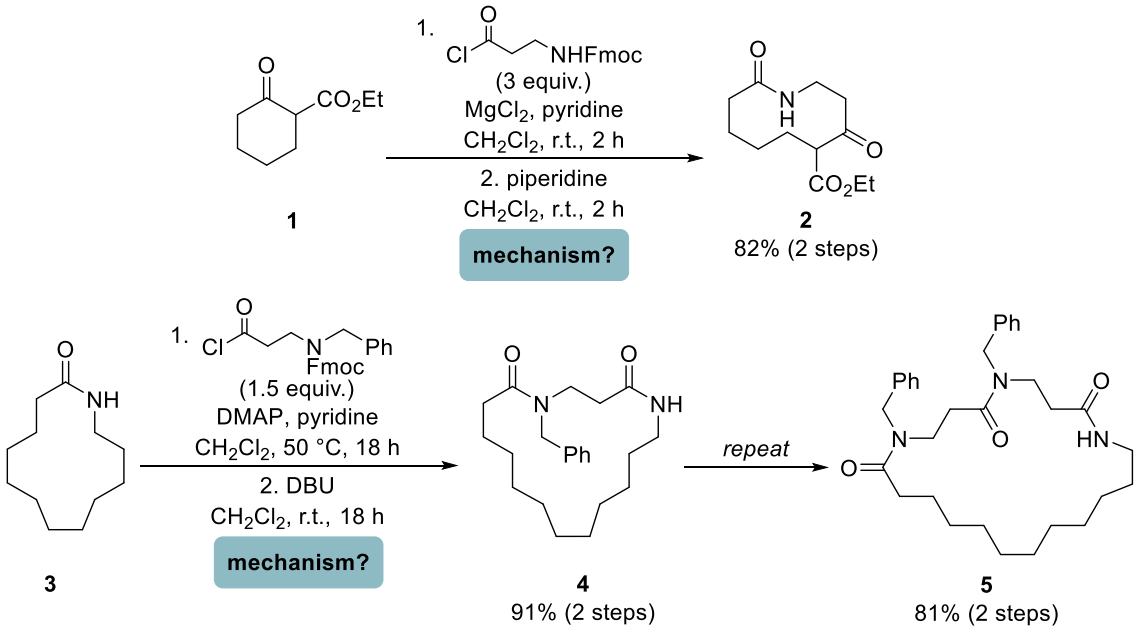
Early-Career Researchers

1. Will Unsworth [University of York]

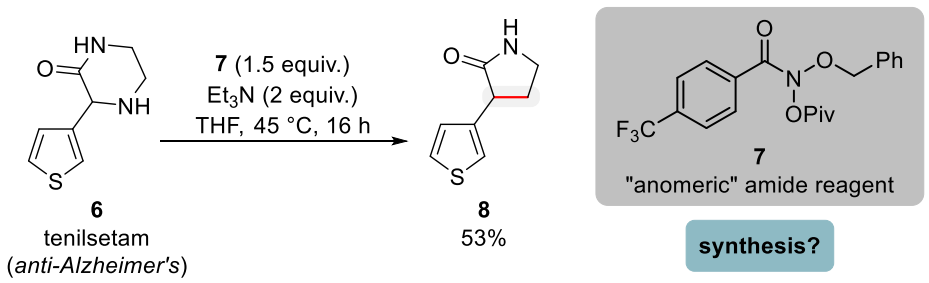
Macrocycles are an important class of compounds in drug discovery. The synthesis of medium and large-size rings presents a significant synthetic challenge. The Unsworth group's ongoing research into developing the Successive Ring Expansion (SuRE) protocol for the synthesis of medium/large rings and macrocyclic peptides attempts to challenge this paradigm by completely avoiding "end-to-end" macrocyclisation. Another key advantage of this new approach is that it can be repeated, and successive ring expansion steps allow access to larger and larger peptide-like macrocycles.

a. Outline some of the practical issues associated with conventional macrocyclisation reactions.
b. Provide mechanisms for the transformations shown below.



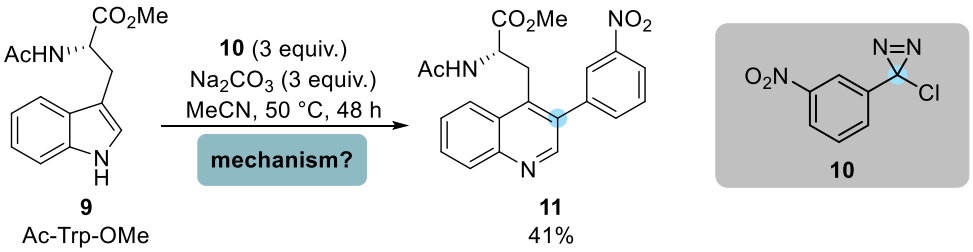
2. Mark Levin [University of Chicago]

a. Explain the terms 'skeletal editing' and 'peripheral editing'.
b. Propose a synthesis of the "anomeric" amide reagent, **7**, as used in the "nitrogen deletion" chemistry shown below.



-29 examples, 34-86%
-most reactions work without Et_3N

c. Propose a mechanism for the following carbon insertion reaction.

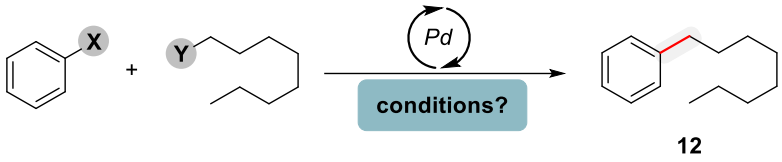


-37 substrate/aryl group combinations, 27-90%
-most reactions take only 16 h

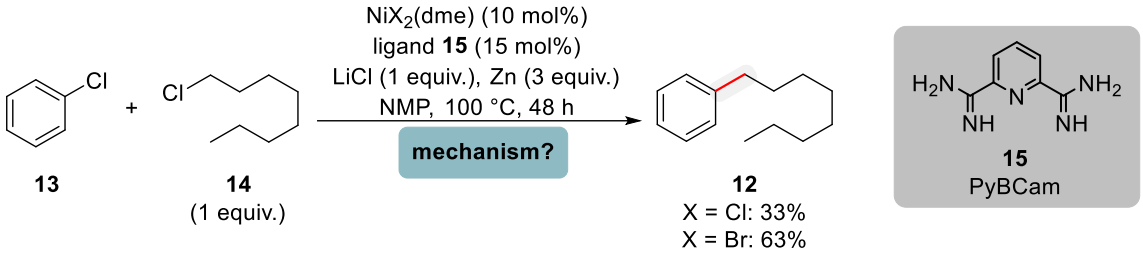
d. Give another example of skeletal editing.

3. Daniel Weix [University of Wisconsin-Madison]

a. Cross-coupling reactions at sp^3 carbon centres are a lot less common than those at sp^2 carbon centres. Explain why this is the case.
b. Suggest which classical cross-coupling reaction would be most suitable to accomplish the transformation shown below (assigning X and Y appropriately).



c. The Weix group has developed an alternative method for carrying out this kind of coupling, which uses alkyl and aryl chlorides – abundant and relatively stable starting materials. Provide a reasonable catalytic cycle for this reaction, as shown below. Note that the reaction proceeds *via* radical intermediates and Ni^{I}/Ni^{III} catalysis.

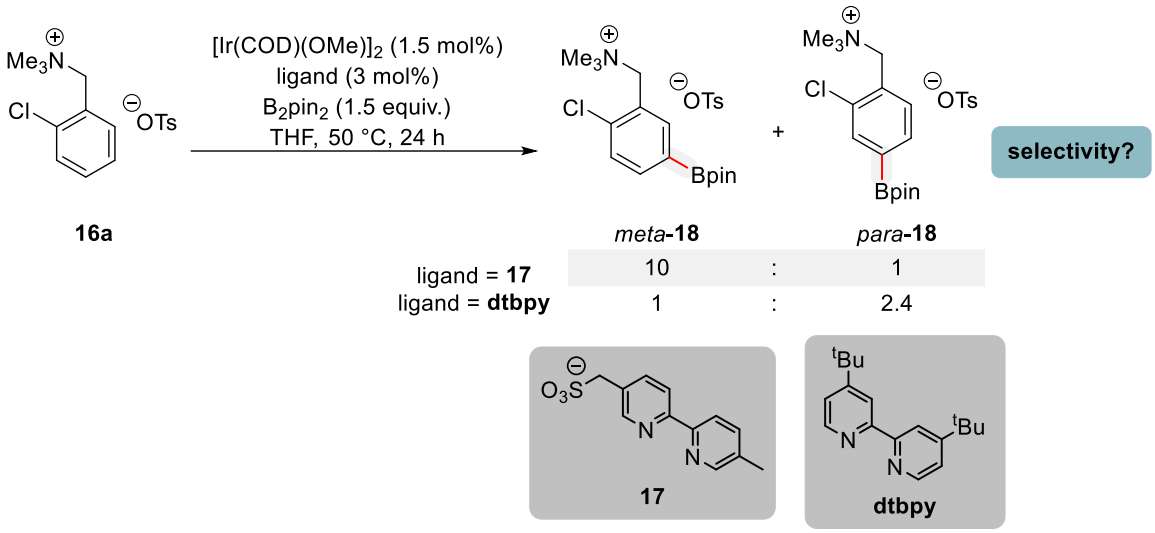


d. Why might nickel be more suitable than palladium for this type of coupling?
e. This reaction does not work as well with a nickel(II) chloride precatalyst. Rationalise this observation.

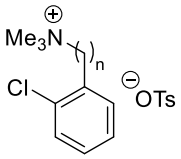
4. Robert Phipps [University of Cambridge]

Since its inception, the Phipps group has investigated the use of ionic interactions as a means of directing selectivity in chemical transformations. The following questions concern their earlier publications on the use of non-covalent interactions for the iridium-catalysed C-H borylation of arenes.

a. Consider the reaction shown overleaf. Draw a diagram to explain how, in the presence of the anionic bipyridine ligand **17**, high *meta* selectivity is observed. Suggest why using dtbpy instead led to poor selectivity.



b. Explain the change in observed regioselectivity for the borylation of quaternary ammonium substrates in the series shown below, as the chain length increases.

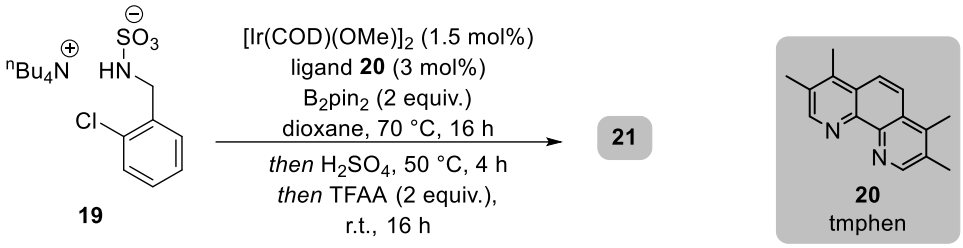


16a-d

	16a	16b	16c	16d
n	1	2	3	4
meta:*para*	11:1	12:1	7.5:1	4:1

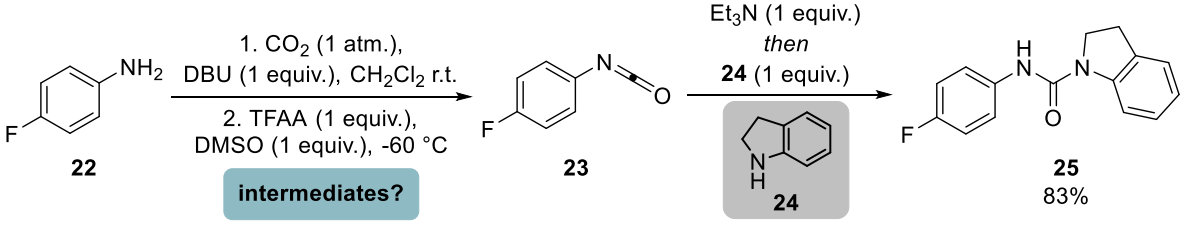
c. Suggest two ways to derivatise the quaternary ammonium functional handle (*e.g.*, FGIs, complete removal, *etc*.) in the borylated products.

d. In a subsequent publication, the system was modified such that the substrate now contained all of the ionic components, and the ligand was replaced with a more common phenanthroline (see below). Predict the major product for this reaction and explain this prediction.



5. Sophie Rousseaux [University of Toronto]

a. Consider the urea synthesis shown below. Identify the key intermediates involved in the formation of isocyanate **23**.

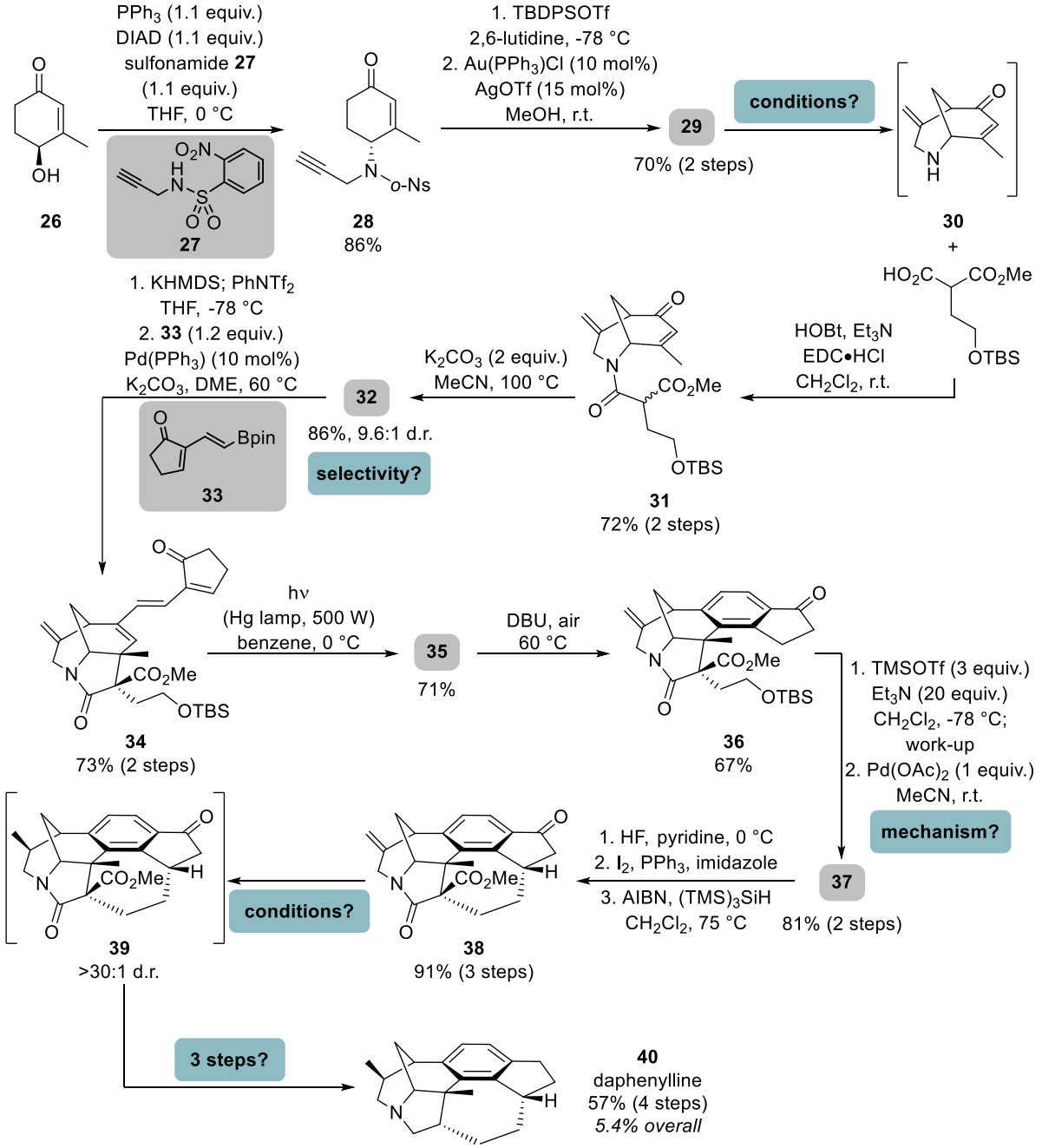


-15 aniline/amine combinations, 78-92%
-8 examples of carbamates, 67-98%

b. Suggest an appropriate spectroscopic method for monitoring the formation of the isocyanate *in situ*.
c. Suggest an alternative reagent that could be used instead of TFAA.

6. Ang Li [Shanghai Institute of Organic Chemistry]

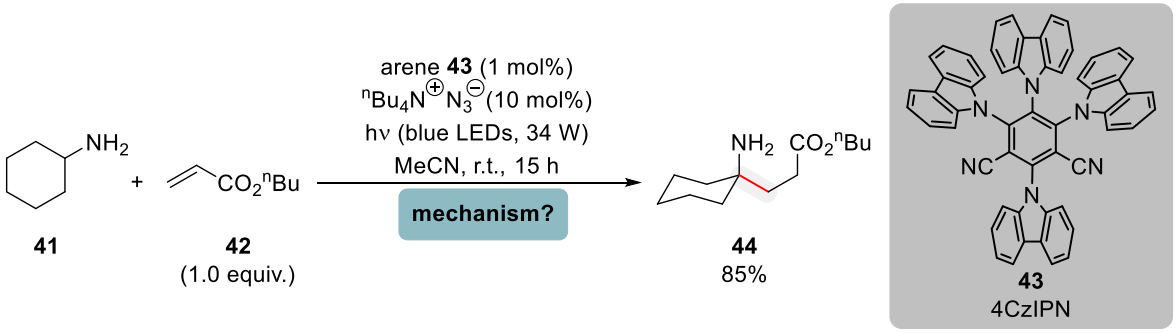
a. Consider the total synthesis of daphenylline (**40**) shown below. Identify compounds **29**, **32**, **35**, and **37**, indicating the major diastereoisomer(s) where appropriate.



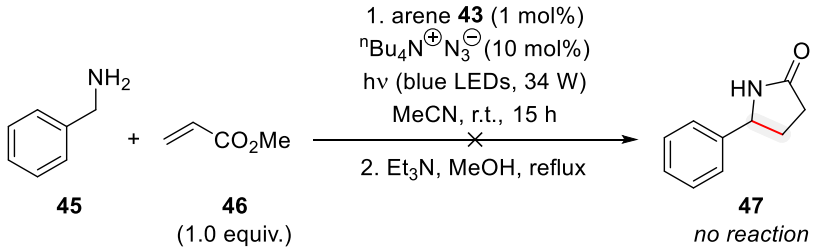
b. Suggest appropriate conditions for the formation of amine **30** from **29**.
c. Rationalise the diastereoselectivity observed in the transformation of **31** to **32**.
d. Propose a reasonable mechanism for the formation of **37** from ketone **36**.
e. Suggest appropriate conditions for the diastereoselective formation of **39** from **38**.
f. Outline the steps required to complete the synthesis of daphenylline, **40**, from intermediate **39**.

7. Alex Cresswell [University of Bath]

   a. Consider the amine α-functionalisation reaction shown below. Propose a reasonable mechanism for this transformation.

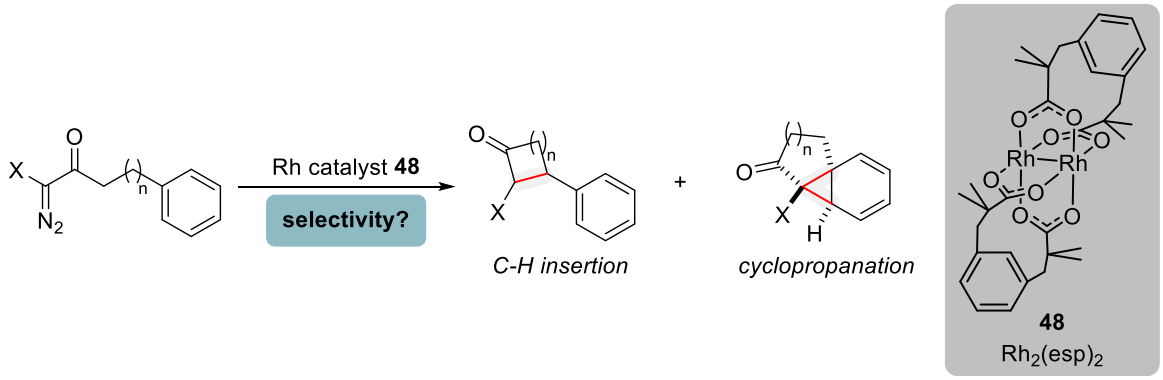


   b. What is the role of tetrabutylammonium azide in this system?
   c. Suggest suitable methods to analyse the quenching step of the catalytic cycle.
   d. An attempt to prepare 5-phenylpyrrolidin-2-one (**47**) *via* this method was unsuccessful. Rationalise this observation.

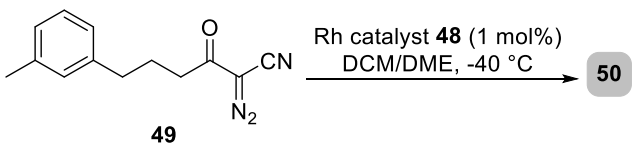


8. Sarah Reisman [California Institute of Technology]

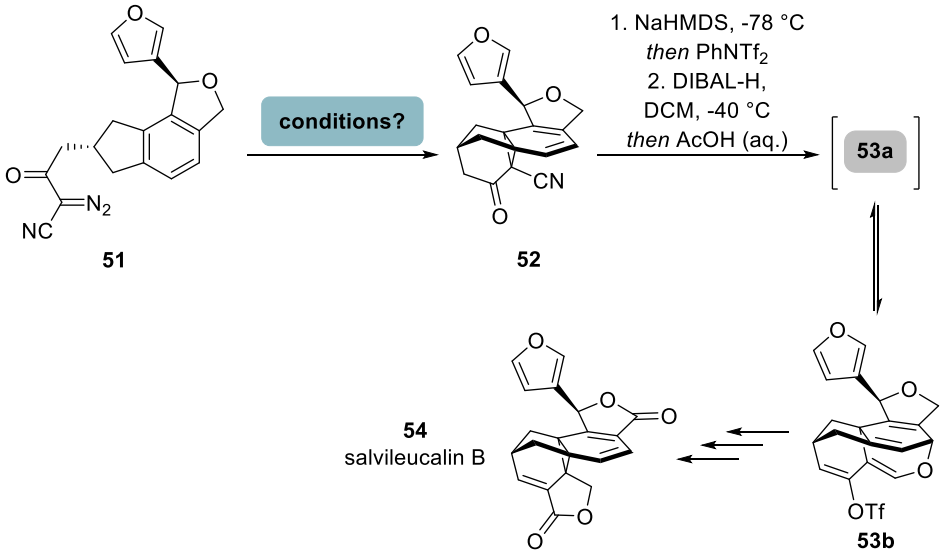
   a. Provide mechanisms accounting for the formation of C-H insertion and cyclopropanation products from diazo compounds of the type shown below. Discuss the effects of changing chain length (n) and substituent X on the product distribution.



   b. Predict the major product of the rhodium-catalysed reaction of **49**, as shown below.

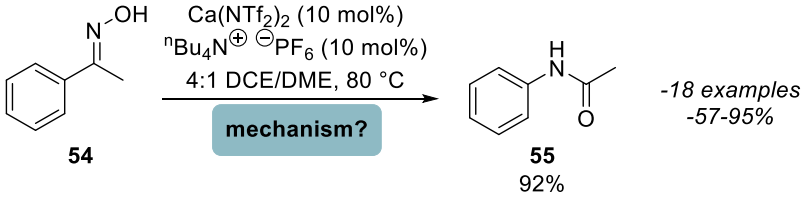


c. Consider the sequence shown below, from the total synthesis of salvileucalin B. Suggest appropriate conditions for the cyclopropanation step shown, identify intermediate **53a**, and explain its interconversion with **53b**.



9. Mark McLaughlin [Manchester Metropolitan University]

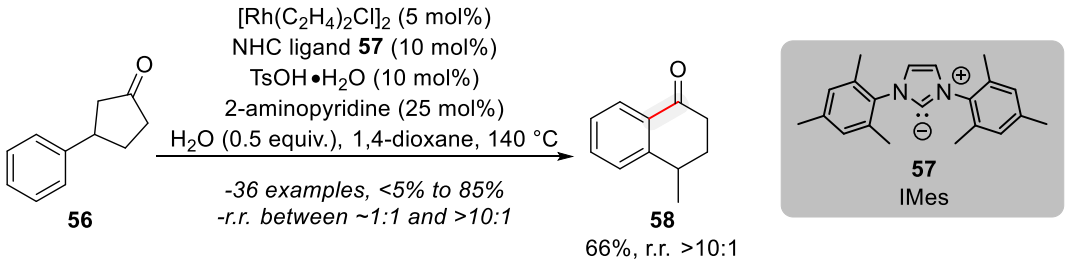
a. Propose a reasonable mechanism for the calcium-catalysed Beckmann rearrangement, as shown below.



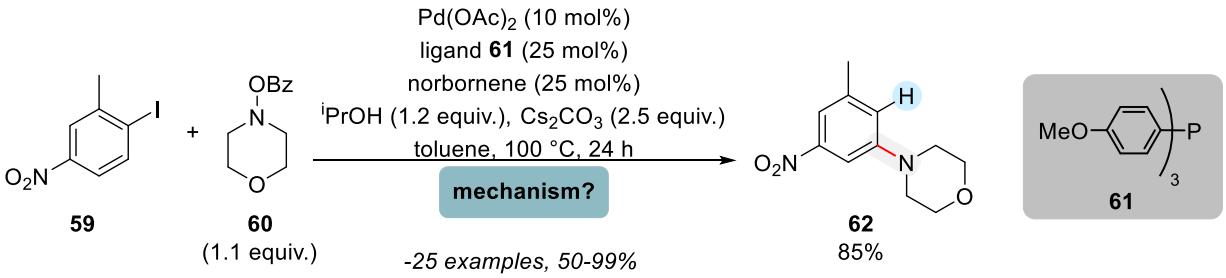
b. Comment on the long-term stability of the calcium catalyst.

10. Guangbin Dong [University of Chicago]

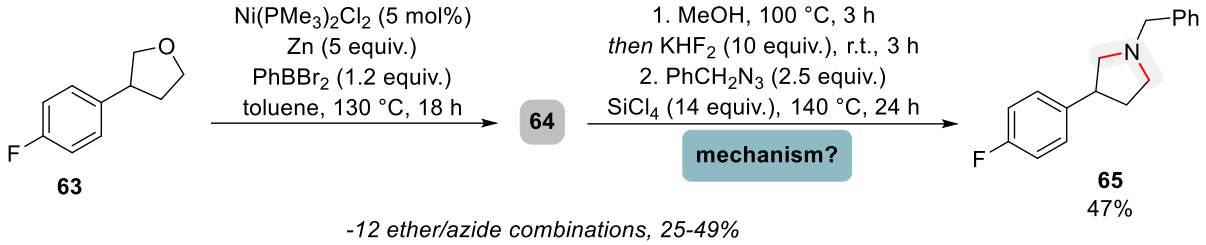
a. Consider the rearrangement shown below. What is the other regioisomeric product of this reaction? Explain how, using this chemistry, enantiomerically enriched **58** could be accessed.



b. Construct a catalytic cycle for the *ortho*-amination reaction shown overleaf. Propose an experiment to determine the source of the highlighted H-atom.



c. Consider the conversion of ether **63** to amine **65** shown below. Identify intermediate **64** and propose a reasonable mechanism for its transformation to **65**.



d. Identify all oxidative addition events that take place during the reactions discussed above. Explain why, in each case, the oxidative addition is favourable and productive.

The above questions were written by the following indiviuals:

1. Jozef Park
2. Thomas Barber
3. James Wilson
4. Nicholas Atkinson
5. Jamie Crooks
6. Li Zhai
7. Jaffer Zaidi
8. Amelia Stoneley
9. Oska Pugh
10. Ben Scrafield