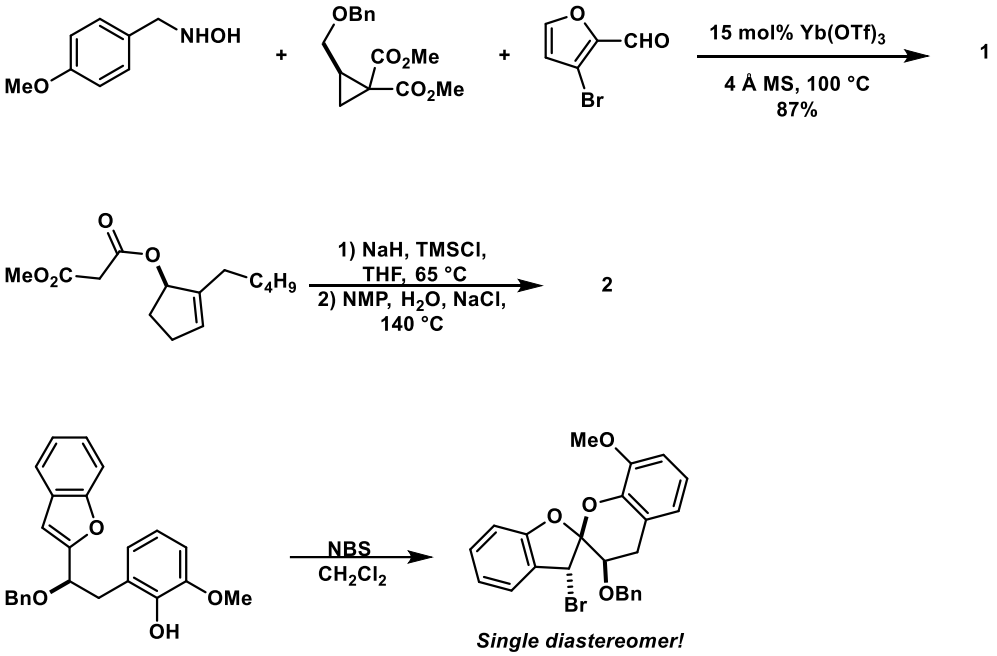
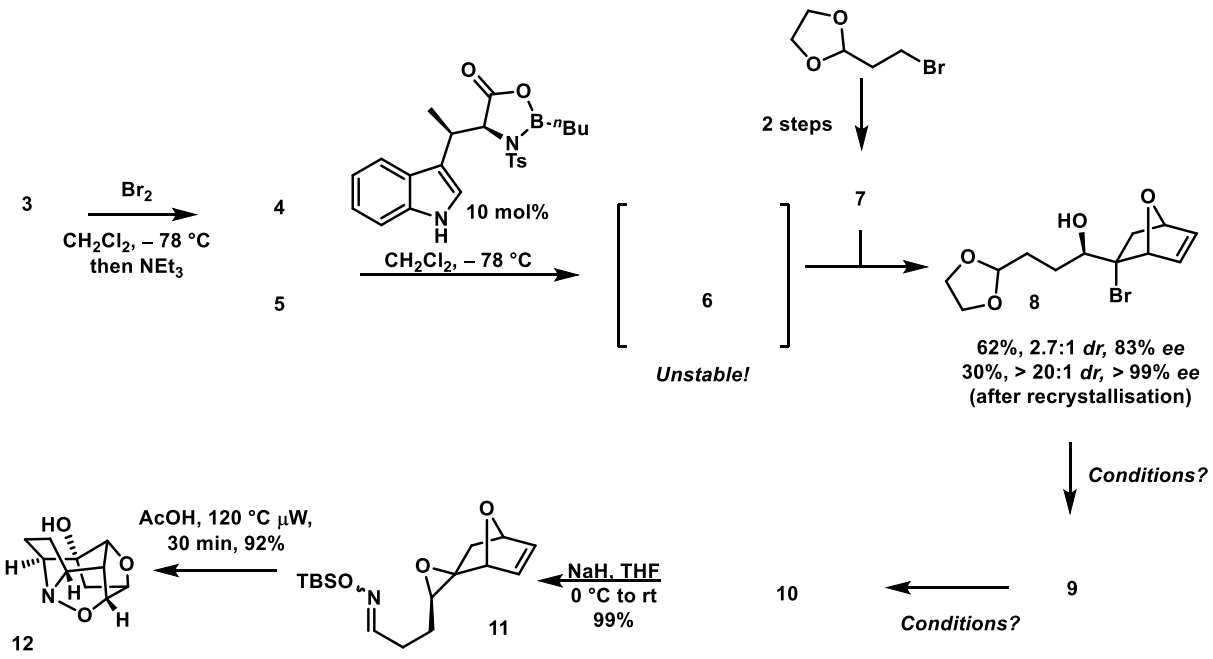
Spivey problem session 4/2018

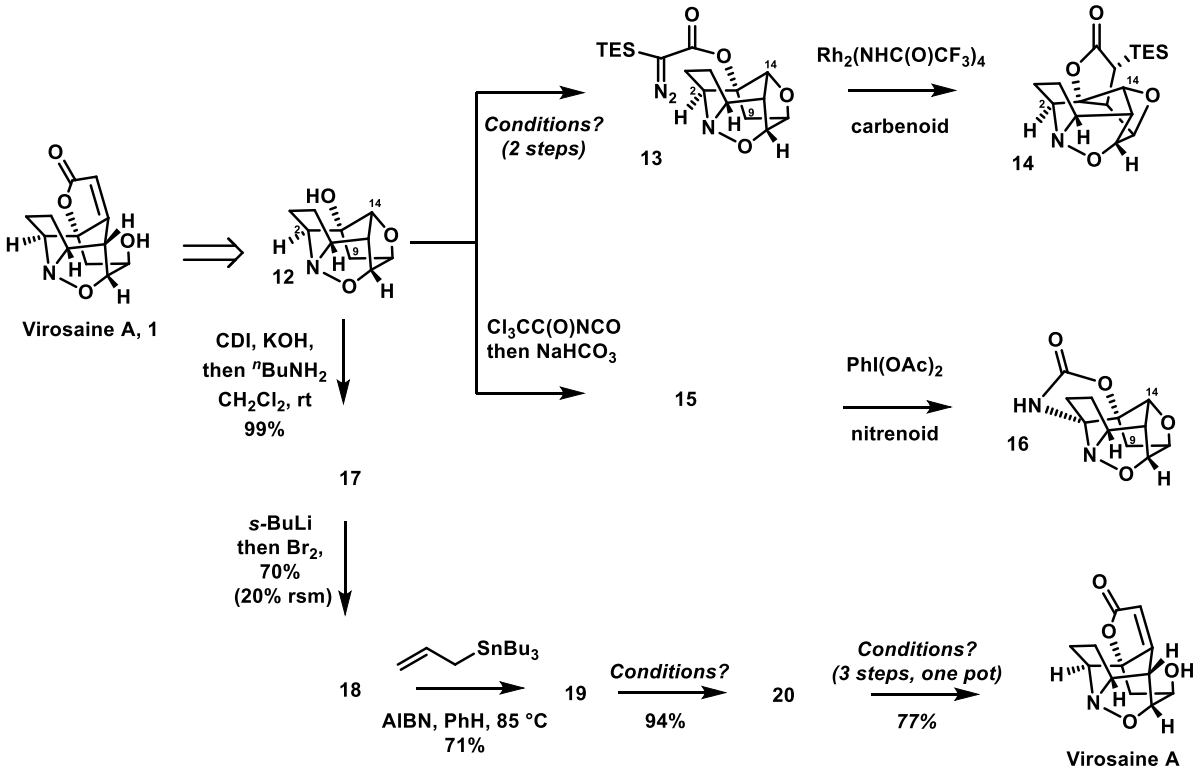
1. Please provide the products and mechanisms considering selectivity and stereochemistry…



2. Recently, the enantioselective total synthesis of virosane A was reported by Gleason. Please fill in the gaps with mechanisms. Key to access the 'birdcage' core was a nitrone [3+2] cycloaddition.

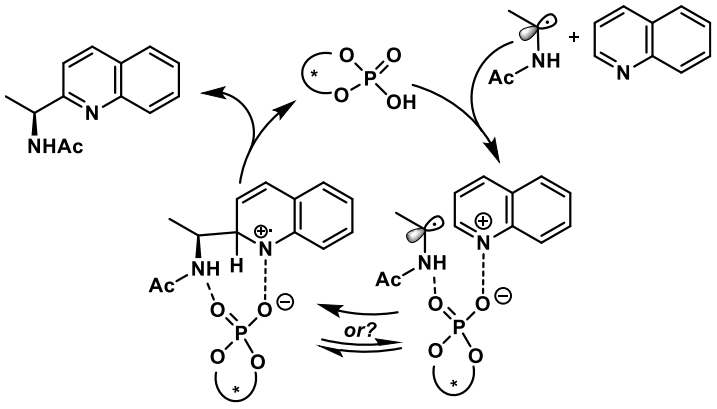


With a robust route to **12** (25% yield from **5**), the authors were primed to test late stage C-H functionalisation to furnish virosaine A. Key to the synthesis was the selective functionalisation of the bridgehead C14 methine, over the C2 methine and C9 methylene. More 'modern' C-H insertions failed to achieve selective functionalisation but a combined experimental and computational study suggested a directed lithiation may be feasible. What techniques could be employed to elucidate this reactivity?

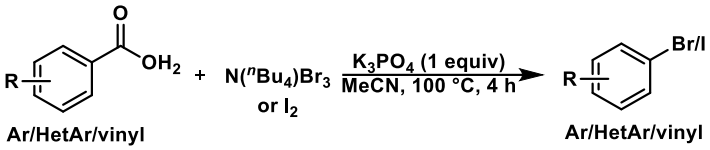


Kinetic isotope effects (KIEs) are powerful tools to assist in mechanism elucidation. The most commonly employed are H/D KIEs. However, ^{13}C can be utilised even at natural abundance to probe transition states (*JACS,* **1995***,* 117, 9357).

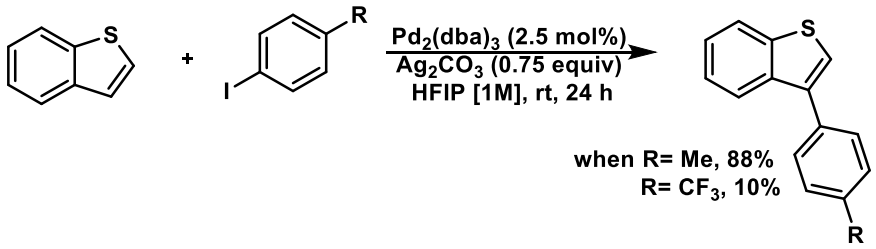
3. Consider this recent Minsci type reaction. What KIE experiment could you do to quickly suggest if the radical addition is reversible? What would also be implicated if such a process was reversible and what experiment could you do to confirm this?



4. Consider this useful decarboxylative bromination/iodination procedure. Traditional Hunsdiecker transformations have been suggested to be radical. How might you test if this process involves radicals? What KIE experiments would you conduct to interrogate its mechanism?

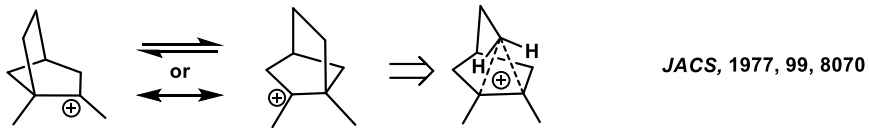


5. In the process of optimising the C3 selective arylation of benzothiophenes it was noticed a significant discrepancy in yields depending upon the electronic nature of the aryl iodide.

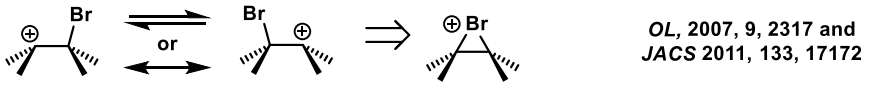


What experiments may you conduct to identify the nature of this discrepancy? How might you identify catalyst deactivation or even an induction period? How might KIEs be used to distinguish between 3 mechanistic paradigms (CMD, S_EAr and Heck)?

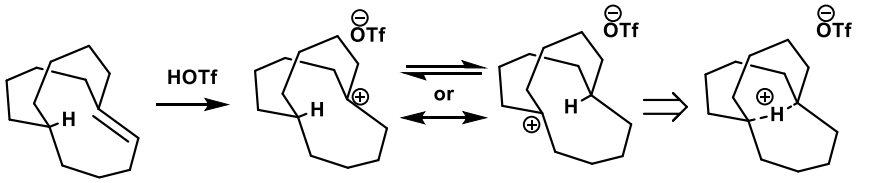
6. We are often comfortable with the concepts resonance and equilibration. If we can lower the temperature and the barrier to interconversion is large (>5 kcal/mol) we may be able to freeze out an intermediate and so 'prove' equilibration. But what if the barrier is <5 kcal/mol? How much equilibration constitutes resonance? Consider the below examples and reason how such a question may be answered.



JACS, 1977, 99, 8070



OL, 2007, 9, 2317 and
JACS 2011, 133, 17172



JACS, 1989, 111, 8867