Photochemical Approaches to the Bridge Functionalisation of Bicyclo[1.1.1]pentane Derivatives

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Bicyclo[1.1.1]pentane (BCP) derivatives represent valuable bioisosteres for *tert*-butyl groups, internal alkynes and arenes, facilitating "escape from flatland"[1] with ability to increase the solubility, metabolic stability, potency and target specificity of biologically-active compounds (e.g. **Scheme 1**, A).[2] In comparison to *bridgehead* (1,3)-substituted BCP derivatives, synthetic access to *bridge* (2,4,5)-functionalised derivatives remains limited.[2-5] This is partly due to challenges associated with synthesis of the strained BCP core, and partly because the chemistry of many functional groups and reactive intermediates do not translate to BCP systems due to orbital hybridisation and ring strain effects (**Scheme 1**, B).[2] Divergent and general platforms to access bridge-functionalised BCP derivatives are yet to be fully investigated. Although possessing attentuated properties compared to conventional alkyl radicals, BCP bridge *radicals* are kinetically stable and represent an appealing handle for late-stage derivatisation.[2,3] The ability of photoredox catalysis to provide access to such open-shell species under mild conditions[6] make it an ideal, scalable[7] technology to access these promising intermediates.

This presentation will discuss our synthesis of model substrate **3**, a rare example of a derivatisable 1,2,3-trisubstituted BCP derivative, and our findings from high-throughput investigation of its radical decarboxylation under photochemical conditions (**Scheme 1**, C). Owing to the ubiquity of nitrogen heterocycles in biologically-active compounds, our studies to date have focussed on engaging the desired radical in a Minisci-type reaction, providing entry to valuable bridge-heteroarylated BCP derivatives (e.g. **5**). Key results from these studies will be highlighted, along with their implications for future work and extension of our decarboxylative platform to more diverse reaction types. Since BCP derivatives frequently represent novel chemical and intellectual property space,[1] we expect this work to be of significant interest and utility to scientists across the agroscience and drug discovery industries.

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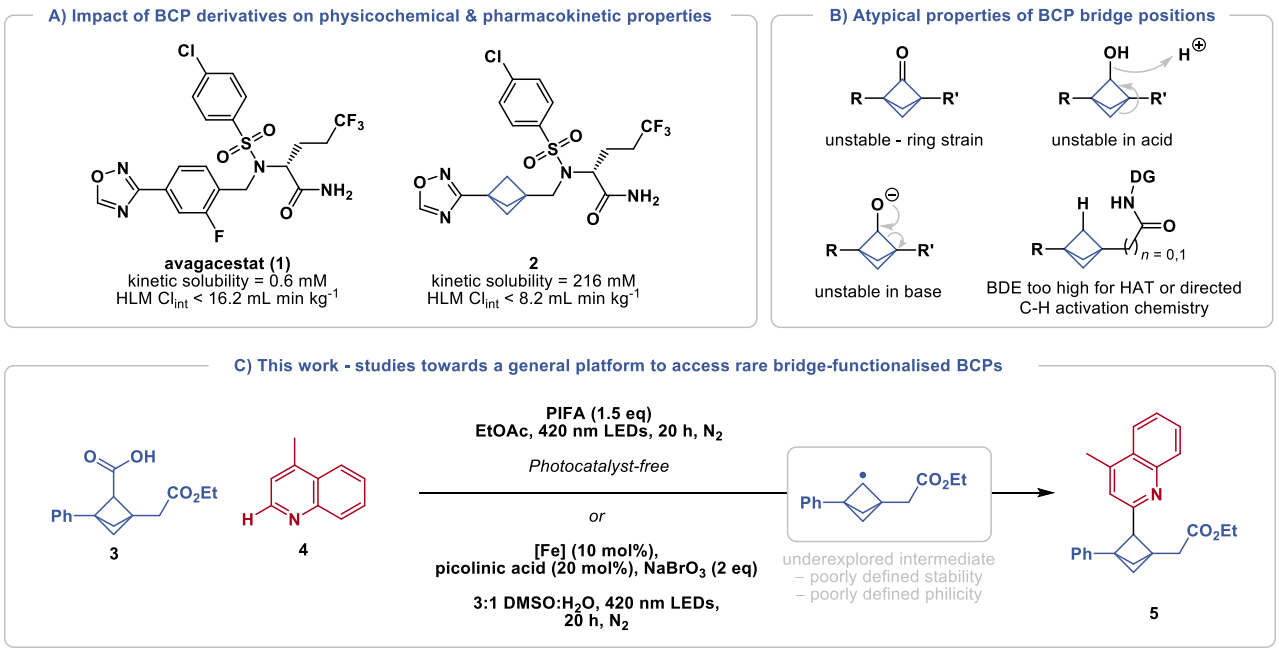
A) Impact of BCP derivatives on physicochemical & pharmacokinetic properties
avagacestat (1)
kinetic solubility = 0.6 mM
HLM Clint < 16.2 mL min kg-1
2
kinetic solubility = 216 mM
HLM Clint < 8.2 mL min kg-1
B) Atypical properties of BCP bridge positions
unstable - ring strain
unstable in acid
unstable in base
BDE too high for HAT or directed C-H activation chemistry
C) This work - studies towards a general platform to access rare bridge-functionalised BCPs
3
4
PIFA (1.5 eq)
EtOAc, 420 nm LEDs, 20 h, N2
Photocatalyst-free
or
[Fe] (10 mol%),
picolinic acid (20 mol%), NaBrO3 (2 eq)
3:1 DMSO:H2O, 420 nm LEDs,
20 h, N2
underexplored intermediate
– poorly defined stability
– poorly defined philicity
5