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Tunable Divergent Reactivity of Aziridinium Ylides in the Synthesis of Complex Piperidines and Azetidines

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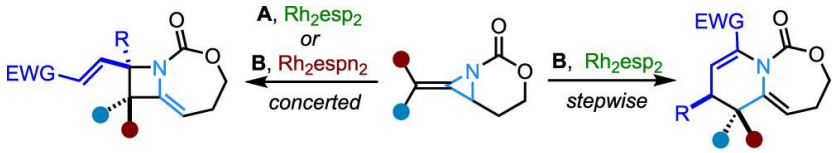
ABSTRACT

Nitrogenated heterocycles comprise the cores of several synthetically useful compounds, including pharmaceuticals, bioactive natural products, agrochemicals, and other drug-like molecules[1–4]. Currently, 84% of structurally unique and approved drugs contain at least one nitrogen atom, being 59% of then nitrogen-bearing heterocycles. The widespread interest in methods to increase the fraction of sp^3 carbon atoms (Fsp^3)[5] of drug-like scaffolds in a stereocontrolled manner, while enabling explorations of unusual amine chemical space, inspired our efforts to tune the reactivity of aziridinium ylides. A sequential nitrene–carbene transfer of simple allenes leads to divergent product outcomes depending on the nature of the carbene precursor, furnishing products of different ring sizes. Both products, four-membered heterocyclic azetidines, and the six-membered dehydropiperidine, are scaffolds of interest in medicinal chemistry[4]. In addition, the catalyst control over the ring size via proposed hydrogen-bonding interactions between the catalyst and substrate was explored. Computational studies were employed to gain insight into the major features of substrates and catalysts that influence the tunable reactivity of aziridinium ylide intermediates formed in this chemistry.



- both reagent and catalyst control of ring expansion
- flexible post-functionalizations
- DFT studies to elucidate pathways
- potential to telescope nitrene/carbene transfer

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