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A Ring Expansion Strategy towards Diverse Azaheterocycles
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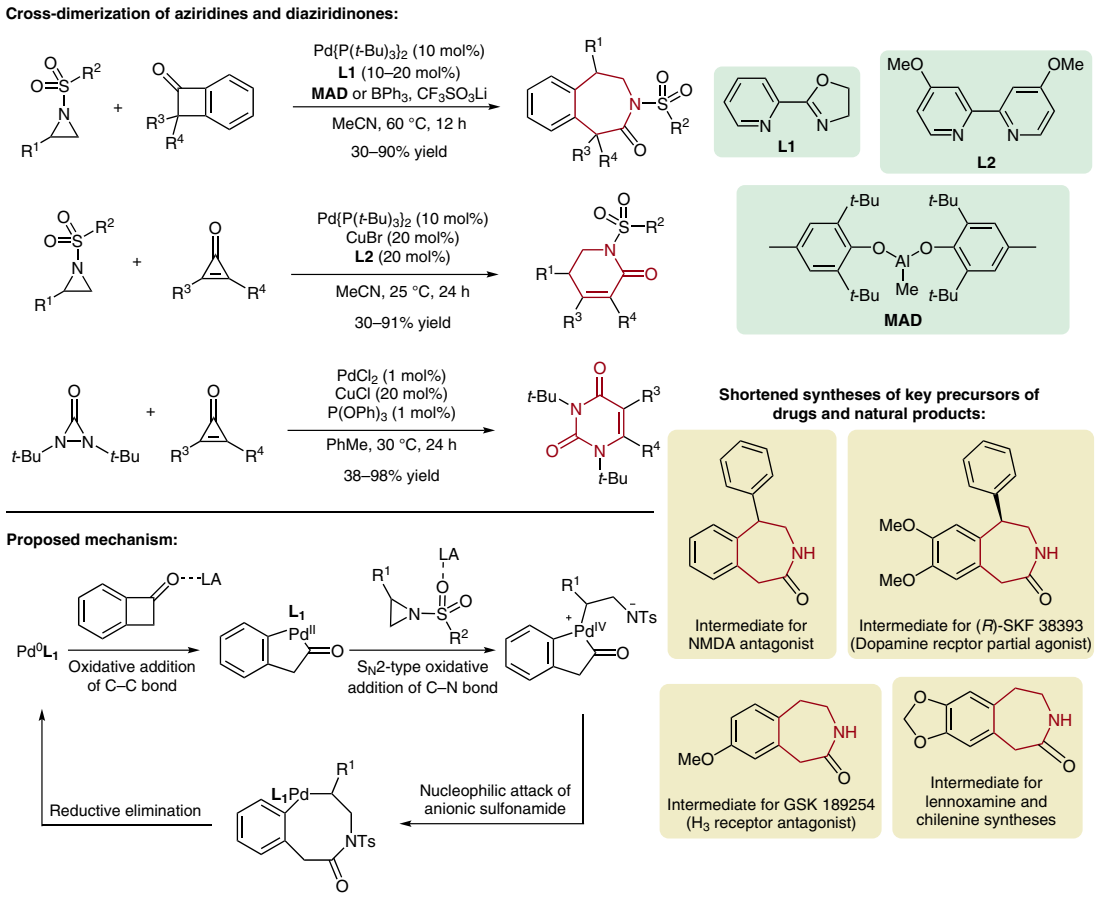
Aziridines Cross-Dimerize to Larger N-Heterocycles



Significance: Azepines, dihydropyridinone, and uracil are key N-heterocyclic motifs found in numerous drug molecules. However, syntheses of these rings often require multistep routes and suffer from poor efficiency. The authors present a robust catalytic method to access these azaheterocycles in an enantiospecific manner via cross-dimerization of aziridines or diaziridinones with cyclopropenones or cyclobutenones. This ring-expansion strategy enabled step-efficient syntheses of several pharmaceutical agents and natural products, underpinning the broader synthetic utility.

Comment: Lewis acid-mediated, Pd-catalyzed cross-dimerization of sulfonylated aziridines to benzacyclobutanone afforded the benzazepine skeleton. A synergistic Pd-Cu catalyst system was used to access the pyridinone and uracil motifs from cyclopropenone. A mechanistic study revealed a $Pd^{0/II/IV}$ cycle starting with an oxidative C–C cleavage of the strained carbocycle followed by oxidative aziridine opening to form a Pd^{IV} intermediate, which was supported by computational models. This protocol provided concise routes to useful drug precursors (e.g. SKF 38393, GSK 189254, ivabradine) with further synthetic modifications of the azepines, rendering this a potential retrosynthetic tool.

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Category
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Key words
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Pd-catalyzed ring expansion
azepine
uracil

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