Diastereoselective Synthesis of *N*-Heterocycle Substituted Cyclobutanes *via* Michael Addition onto Cyclobutenes

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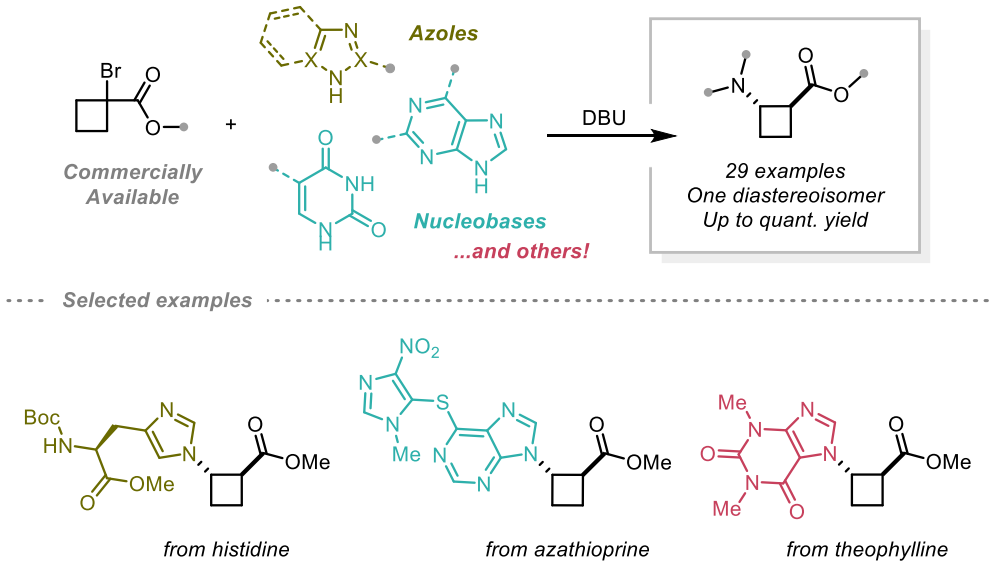
The incorporation of strained rings into drug candidates has become a widely used strategy among medicinal chemists, providing benefits such as increased molecular rigidity, improved solubility, and enhanced metabolic stability.[1] Additionally, *N*-heterocycles and carbonyl groups are fundamental motifs in the majority of small-molecule drugs.[2] However, existing synthetic approaches for functionalized cyclobutanes remain limited in both scope and efficiency, hampering their broader application.

We report a user-friendly diastereoselective method for the synthesis of *N*-heterocycle-substituted cyclobutanes starting from readily available bromocyclobutanes.[3] Using commercially available reagents, the desired compounds were obtained after dehydrobromination followed by Michael addition of diverse *N*-nucleophiles, including imidazoles, azoles, and nucleobase derivatives onto the cyclobutane ring. This approach enables the efficient preparation of various heterocyclic aminocyclobutane esters and amides in one step and significantly broadens the chemical space accessible to medicinal chemistry through a streamlined pathway to functionalized cyclobutanes.



[1] M. R. Bauer, P. D. Fruscia, S. C. C. Lucas, I. N. Michaelides, J. E. Nelson, R. I. Storer, B. C. Whitehurst, *RSC Med. Chem.* **2021**, *12*, 448–471.
[2] C. M. Marshall, J. G. Federice, C. N. Bell, P. B. Cox, J. T. Njardarson, *J. Med. Chem.* **2024**, *67*, 11622–11655.

[3] E. G. L. Robert, J. Waser, *Chem. Eur. J.* **2024**, *in press*.