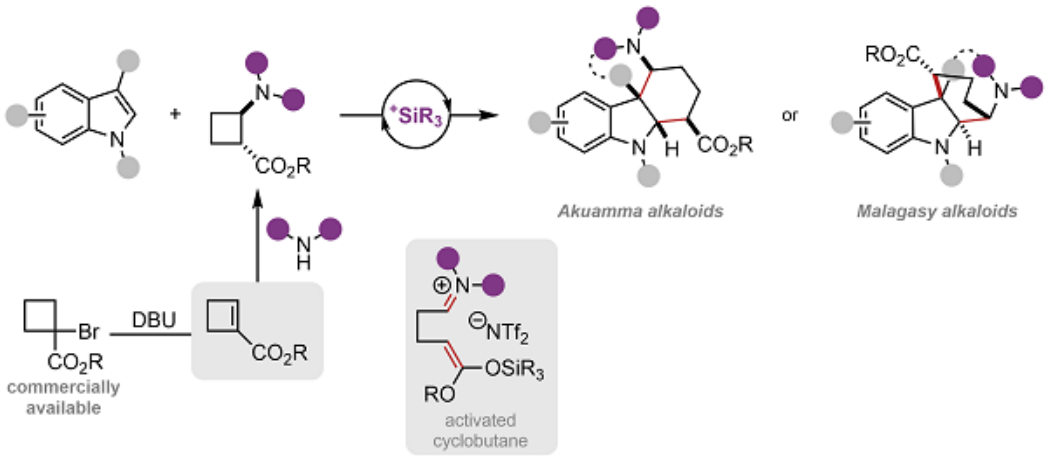
Donor-Acceptor Aminocyclobutane Monoesters: Synthesis and Silylium-Catalyzed (4+2) Annulation with Indoles.

E. G. Robert[1], V. Pirenne[1], M. D. Wodrich[1], J. Waser[1]*

[1] EPFL, Laboratory of Catalysis and Organic Synthesis, SB ISIC LCSO, BCH 4306, 1015 Lausanne, CH, Switzerland

Donor-acceptor (DA) cyclopropanes vicinally substituted with electron-donating and electron-accepting groups are among the most studied strained ring motifs.[1] The corresponding cyclobutanes have been considerably less studied, despite their similar ring strain energy. Progress in this area is highly desirable, as cyclobutanes stand out as advantageous precursors in the construction of saturated ring systems. In particular, (4+2) annulations between cyclobutanes and indoles have proved to be very effective to rapidly form complex alkaloid skeletons containing a 6-membered ring.[2] In that regard, the use of aminocyclobutanes would enable more convergent synthesis of alkaloid building blocks. However, only few methods for the synthesis and annulation of nitrogen substituted DA cyclobutanes have been reported so far.

Driven by the pursuit of efficiency and atom economy, we developed the first synthesis of bench stable donor-acceptor aminocyclobutane monoesters in one single step from commercially available building blocks.[3] We then disclose the first catalytic annulation reaction involving aminocyclobutane monoesters.[3] Activated by silylium catalysis, aminocyclobutane monoesters were able to perform (4+2) annulation with indoles providing valuable alkaloid scaffolds. Using this method, tetracyclic structure of either *akuamma* or *malagasy* alkaloids were obtained selectively depending on the temperature of the reaction.



[1] Hans-Ulrich Reissig, Reinhold Zimmer, *Chem. Rev.* **2003**, *103* (4), 1151–1196.
[2] a) Mizui Kawano, Takaaki Kiuchi, Shoko Negishi, Hiroyuki Tanaka, Takaya Hoshikawa, Jun-ichi Matsuo, Hiroyuki Ishibashi, *Angew. Chem. Int. Ed.* **2013**, *52* (3), 906–910. b) Liang-Wen Feng, Hai Ren, Hu Xiong, Pan Wang, Lijia Wang, Yong Tang, *Angew. Chem. Int. Ed.* **2017**, *56* (11), 3055–3058.
[3] Emma G. L. Robert, Vincent Pirenne, Matthew D. Wodrich, Jerome Waser, *Angew. Chem. Int. Ed.* **2023**, e202302420.