Synthesis of substituted gamma-lactams through petasis-type addition of boronic acids to N-acyliminium ions

Substituted gamma-lactams are important heterocyclic motifs found in various biologically active compounds and marketed drugs, such as glimepiride, doxapram, and levetiracetam. Among available methods for the synthesis of substituted gamma-lactams, the addition of nucleophiles to N-acyliminium ions remains the most widely utilized approach. Even though hydroxylactams are important precursors of cyclic N-acyliminium ions, few approaches for their synthesis have been reported so far. By implementing a reductive cyclization reaction, linear L-malic acid derivatives were rapidly converted into cyclic N-acyliminium ions. Under the optimized conditions, entailing the use of HFIP as solvent, both electron-rich and electron-deficient boronic acids were successfully added to a range of cyclic N-acyliminium ions, thereby obtaining a collection of pharmaceutically relevant substituted gamma-lactams.