ABSTRACT

Pyrroloindoline and unnatural tryptophan motifs are important targets for synthesis based on their incorporation into a diverse array of biologically active natural products. Both types of alkaloids have also found applications as chiral catalysts and tryptophan derivatives are commonly employed as biological probes. On account of their applications, these frameworks have inspired the development of numerous enantioselective, catalytic reactions. In particular, the past few years have witnessed an impressive number of novel approaches for pyrroloindoline formation.

The first project described herein involves our contribution to pyrroloindoline research. We have developed an (R)-BINOL•SnCl₄-catalyzed formal (3 + 2) cycloaddition reaction between 3-substituted indoles and 2-amidoacrylates that affords pyrroloindoline-2-carboxylates bearing an all-carbon quaternary center. Mechanistic studies have elucidated that the enantiodetermining step is a highly face-selective catalyst-controlled protonation reaction.

Second, application of this asymmetric protonation strategy to the synthesis of a variety of enantioenriched tryptophan derivatives is discussed. Finally, we found that these derivatives could undergo selective functionalization. More specifically, we were able to prepare novel hydroxypyrroloindolines that are currently the subject of a collaboration project with the Dougherty lab aimed at identifying novel positive allosteric modulators of ligand-gated ion channels.