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Studies on Total Synthesis of Biologically Active Natural Products

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In 1994, we reported a novel, radical-mediated synthesis of 2,3-disubstituted indoles using 2-alkenylphenyl isocyanides as starting materials. This so-called first-generation protocol was successfully applied to total synthesis of aspidosperma-type indole alkaloids. The major drawback of the methodology, however, was a difficulty in introducing an sp^3 carbon to the 2-position of indoles. During the course of the total synthesis of catharanthine, an indole alkaloid with an sp^3 carbon at the 2-position, we were able to establish a powerful, radical-mediated indole synthesis starting from 2-alkenylthioanilides. The second-generation methodology was so versatile that we could achieve highly efficient total syntheses of a variety of indole alkaloids including (+)-vinblastine and (–)-strychnine. A common feature of our total synthesis of indole alkaloids is a mild activation of a primary amine with either 2,4-dinitrobenzenesulfonyl or 2-nitrobenzenesulfonyl groups for alkylation, which we developed during the total synthesis of vincadifformine. Both Mitsunobu protocol and conventional procedure with a base such as potassium carbonate could be employed for alkylation of the sulfonamides. Removal of the activating groups could be performed by treatment with a variety of thiolates under very mild conditions. The novel amination has been extensively used for conversion of primary amines to secondary amines. In this lecture, total synthesis of biologically active natural products using the aforementioned methodologies will be discussed.