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Development of Nosyl Chemistry and its Application to Total Synthesis

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In 1993, we found a novel, radical-mediated methodology for 3-monosubstituted as well as 2,3-disubstituted indoles. For application of this methodology to total synthesis of indole alkaloids, we needed a highly versatile activating group for primary amines that could be used for Mitsunobu reaction. A daunting requirement for the activating group was that, after alkylation, it should be removed in the presence of an aldehyde and an α, β-unsaturated ester. There was no such an activating group known at that time. While reading a monograph on the Ullmann reactions, it occurred to me that a highly electron-deficient amide such as 2,4-dinitrobenzenesulfonamide would form a Meisenheimer complex upon treatment with a soft nucleophile. The Meisenheimer complex might collapse to form $RNHSO_2^-$ which, after protonation, should extrude sulfur dioxide to form a secondary amine. Upon treatment with a thiolate, 2,4-dinitrobenzenesulfonamide was immediately converted to the corresponding amine. For practical purposes, we found that either 2- or 4-nitrobenzenesulfonamides are more suited simply because they are more stable than 2,4-dinitrobenzenesulfonamides. A few examples of the application of the nosyl chemistry to total synthesis will be discussed in my lecture.