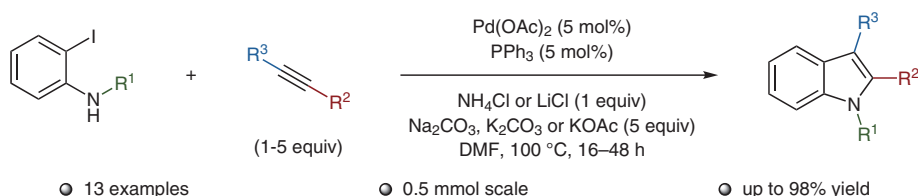
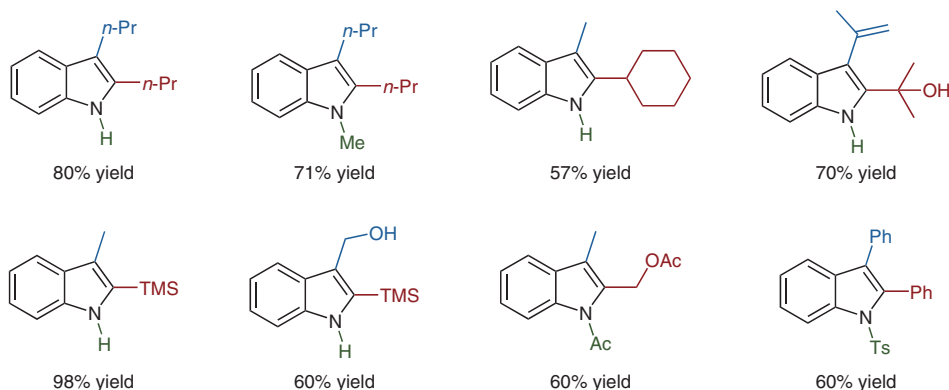


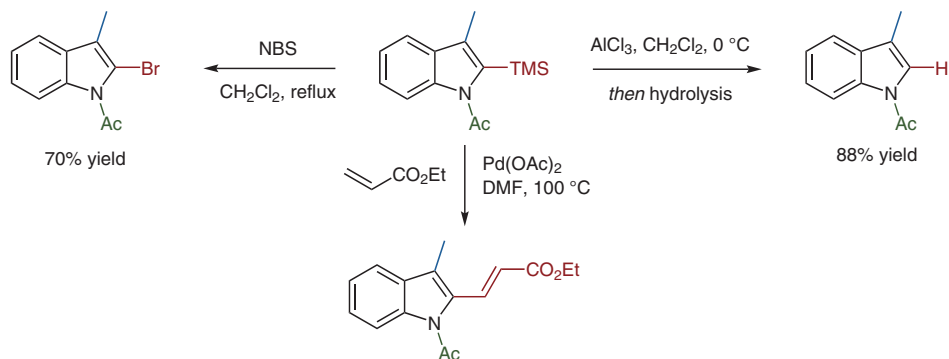
The Larock Indole Synthesis: Pd-Catalyzed Annulation of 2-Iodoaniline and Internal Alkyne Derivatives



Selected examples:



Derivatizations harnessing the reactivity of a TMS group:



Significance: The indole ring is one of the most prevalent scaffolds in natural products and bioactive molecules. In 1991, Larock reported a new methodology to access this scaffold via a cyclization reaction between 2-iodoaniline and alkyne moieties. The concept was subsequently applied to the synthesis of analogous heterocycles and has been used in various total syntheses.

Book Chapter: J. Herraiz-Cobo, F. Albericio, M. Álvarez, In *Adv. Heterocycl. Chem.*, E. F. V. Scriven, C. A. Ramsden, Eds., Academic Press, **2015**, 1–35.

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Comment: The reaction proceeds regioselectively when unsymmetrical alkynes are used, as the bulkier group ends up on the indole's 2-position, i.e., closer to the nitrogen atom. It was observed that the reaction can be run in the absence of triphenylphosphine, resulting in higher yields in some instances. Reactions run with LiCl were found to be more effective and reproducible than with NH₄Cl. Furthermore, adding more than one equivalent of LiCl resulted in lower yields of indole and instead gave rise to multiple insertion products.