Synthesis of 3-Nitroindoles via an Intramolecular α-Selective Heck Reaction

Significance: The Kurth group reports the intramolecular Heck reaction of N-aryl β-nitroenamines to provide 3-nitroindoles in moderate to high yield. The method described is an extension of their previous report exploring a palladium-catalyzed multi-component indole synthesis (Angew. Chem. Int. Ed. 2012, 51, 10588). The major advancement in the chemistry presented is the ability to generate 3-nitroindoles in a predictable manner from easily obtained N-aryl β-nitroenamine starting materials. Direct nitration methods of indoles typically use harsh conditions, which can lead to functional group compatibility concerns and regioselectivity issues. By taking advantage of an α-selective Heck strategy, the relatively mild reaction conditions diminish these issues. The work also illustrates extension of the method to the synthesis of 3-carboxaldehyde and 3-cyanoindoles from the respective enamine precursors.

Comment: In this study, a thorough solvent and catalyst screen was carried out to identify the optimal conditions for the formation of the 3-nitroindoles. The synthesis of the β-nitroenamine starting materials from o-bromoanilines and α-nitroketones is also described. Improved reaction efficiency (short reaction time and higher yields of isolated products) was achieved by using microwave irradiation as opposed to standard oil bath heating protocols. The yields of isolated products are good for a broad range of substrates, including electron-donating and electron-withdrawing substituents on the aryl ring. Indole substitution is modestly explored; however, the 2-position always possesses substituents (alkyl, aryl, heteroaryl) and no synthesis of 7-substituted indoles is given. Toleration of 3-ester and 3-nitrile functional groups broadens the utility of the described method.