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Metal-Free Hydrogenation of *N*-Heterocycles with Trimethylamine Borane and TFA in Aqueous Solution
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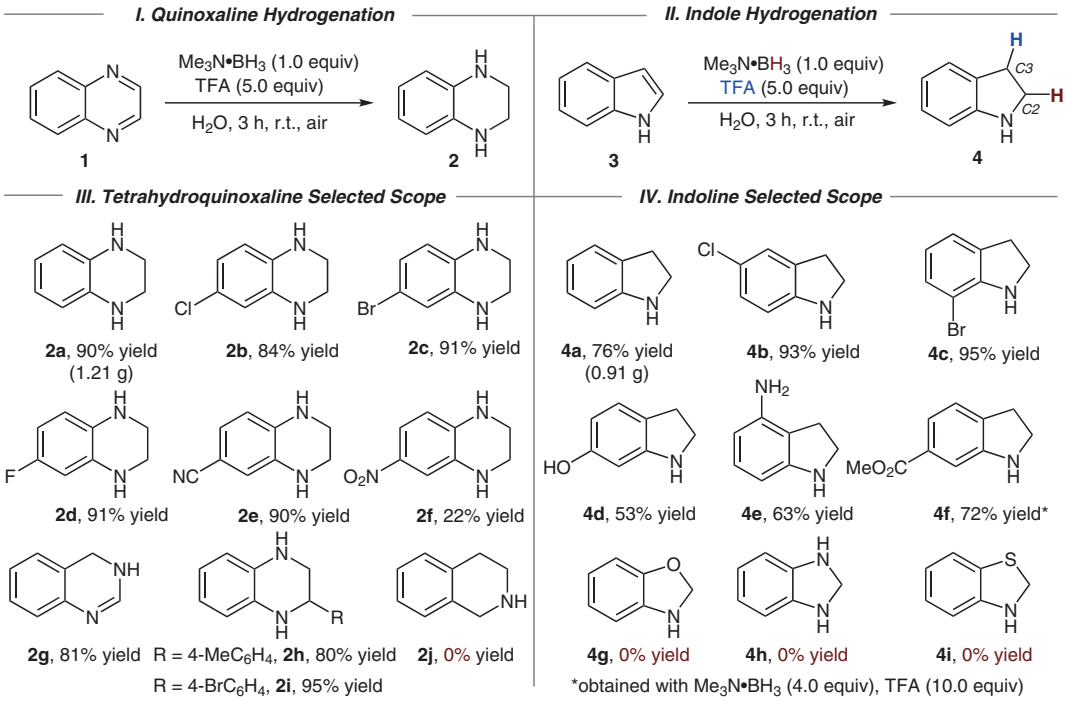
Room Temperature Metal-Free Heteroaryl Hydrogenation



Significance: Tetrahydroquinoxalines and indolines are important medicinal chemistry motifs that are currently being explored for treatment of a range of conditions, including cancer and diabetes (D. S. Millan et al. *ACS Med. Chem. Lett.* **2017**, *8*, 847). Synthetic strategies to access these groups from their quinoxaline and indole heteroaryl precursors, however, currently involve the use of flammable H_2 gas and/or excessive use of expensive metal catalysts, often with a limited substrate scope. This report details a simple and convenient method for hydrogenation of quinoxalines and indoles using TFA and $Me_3N{\cdot}BH_3$ in water at room temperature. The method offered a substantial substrate scope with wider functional group tolerance, including chloro and bromo groups that readily undergo hydrogenation in transition-metal-catalyzed hydrogenation, as well as sensitive cyano, ester and amino groups.

Comment: Optimized reaction conditions were found to be the following: 0.2 mmol of heteroaryl, one equivalent of $Me_3N{\cdot}BH_3$ and five equivalents of TFA stirred in water for three hours in air at room temperature. The reaction was also scalable on multi-gram scale, as demonstrated with both quinoxaline and indole to give 1.21 g and 0.91 g of **2a** and **4a**, respectively. Preliminary mechanistic studies suggest that TFA furnished the proton, while $Me_3N{\cdot}BH_3$ provided the hydride, with protonation occurring at the C3-position of the indole followed by C2-hydrogenation (***II.***). Structural motifs such as isoquinoline (**2j**), benzoxazole (**4g**), benzimidazole (**4h**), and benzothiazole (**4i**) were not well tolerated and gave 0% yields, setting guidelines to the applicability of this method. In summary, this method provides a safer and efficient alternative to the current hydrogenation strategies, with commercial reagents and mild reaction conditions, a wide substrate scope, and concrete scope limitations.

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