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Enantioselective Synthesis of Dihydrobenzofurans derivatives by Merging Intramolecular Heck-Matsuda Reactions from Anilines with Redox-Relay Process

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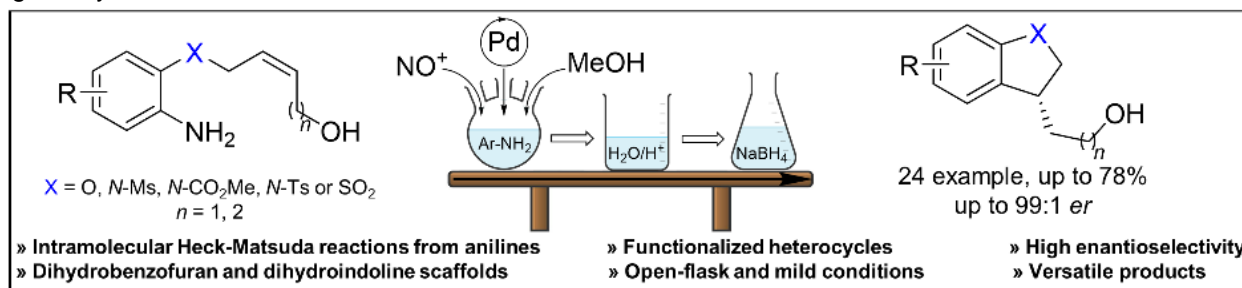
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ABSTRACT

Heteroaromatic compounds are scaffolds present in a variety of important natural products, and they are building blocks in the synthesis of several biologically active molecules, agrochemicals, and drugs. Dihydrobenzofuran and indolines are relevant heterocyclic compounds, and the literature lacks effective protocols for their enantioselective synthesis.¹ Since our first enantioselective Heck-Matsuda reaction in 2012,² we have been focusing on the expansion of the reaction to the construction of more complex heterocycles.³

Herein, we report the efficient and practical protocol for the homogeneous Pd-catalyzed synthesis of dihydrobenzofuran, dihydroindole, and dihydrobenzofuran scaffolds with high enantioselectivity in a Heck-Matsuda reaction with aryldiazonium salt generated *in situ* directly from anilines, or nitro compounds, in a tandem, one-pot, process. Derivatizations of the versatile acetal intermediate allowed the construction of more than 20 hydroxylated heterocycles and methyl esters in overall yields up to 78% over 5 steps, in an enantiomeric ratio of up to 99:1.⁴ Those functionalized heterocycles represent valuable building blocks in organic synthesis.



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