

Heteroaromatic swapping *via* Claisen/retro-Claisen condensation

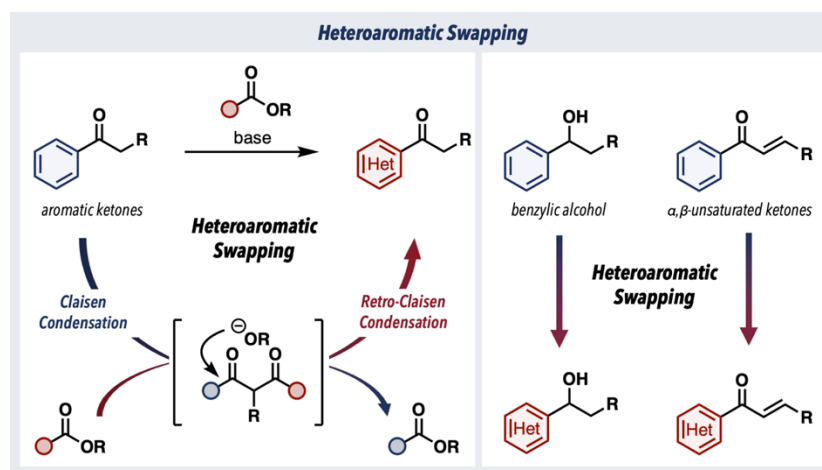
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Aromatic rings are fundamental structural motifs in organic chemistry, playing a central role in defining the structure and properties of numerous compounds. In bioactive molecules, they often function as key pharmacophores, where subtle modification can dramatically influence biological activity and selectivity. Replacing aromatic rings with heteroaromatic counterparts is a well-established strategy for optimizing pharmacokinetic properties, including metabolic stability and lipophilicity. A one-step, broadly applicable transformation that converts aromatic rings into diverse heteroaromatic rings—termed “heteroaromatic swapping”—would represent a significant advance in synthetic chemistry. Among few existing approaches, skeletal editing to introduce nitrogen atoms into aromatic framework has garnered particular attention. However, while numerous methods have been developed for nitrogen removal, general and efficient strategies for nitrogen incorporation remain limited. Similarly, transition-metal-catalyzed aromatic ring exchange reactions hold great promise, but successful applications to heteroaromatic rings construction are exceedingly rare.

We report a general and efficient method for heteroaromatic swapping of aromatic ketones, leveraging the classical Claisen/retro-Claisen mechanism. The reaction between aromatic ketones and heteroaromatic esters proceeds with high selectivity to afford the corresponding heteroaromatic ketones and aromatic esters. Notably, this transformation is also applicable to α,β -unsaturated ketones and benzylic alcohols. This discovery establishes a simple yet powerful strategy for heteroaromatic swapping, offering a versatile platform for late-stage molecular editing of bioactive molecules.



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