

ENANTIOSELECTIVE BENZOIN REACTION CATALYZED BY N-HETEROCYCLIC CARBENE BORONIC ESTERS (NHC-BE)

Vasudevan Dhayalan, Santosh C. Gadekar, Zayed Alassad, and Anat Milo*

Department of Chemistry, Ben-Gurion University of the Negev,
Beer Sheva 84105, Israel

Synthetic protocols to modify the steric and electronic properties of *N*-heterocyclic carbene (NHC) structures serve to tune selectivity, catalytic activity and basicity in organocatalytic reactions [1]. Recently, we reported a practical method for the preparation of functionalized chiral NHC triazolium salts containing a hydroxy handle from readily accessible chiral (*S*)-pyroglutamic acid in eight steps [2]. The resulting NHCs can be further functionalized at the hydroxy handle to extend the library of catalysts by covalent and non-covalent modifiers. For example, we introduced an approach for modifying these organocatalysts *in-situ* by dynamic-covalent binding with molecular modifiers, in this case boronic acids (BA). As a proof-of concept, we selected to focus on the benzoin reaction because the highest enantioselectivity afforded by an NHC organocatalyst was the result of installing a hydroxy group in proximity to the catalytic center [3]. We were able to harness this approach to regulate the stability and reproducibility of the NHC-catalyzed benzoin condensation for a challenging substrate class containing electron-withdrawing groups. We also demonstrated the ability of our approach to streamline the optimization of reactivity and enantioselectivity through a gram scale reaction with the lowest NHC catalyst and base loading for this benzoin reaction to date [4].

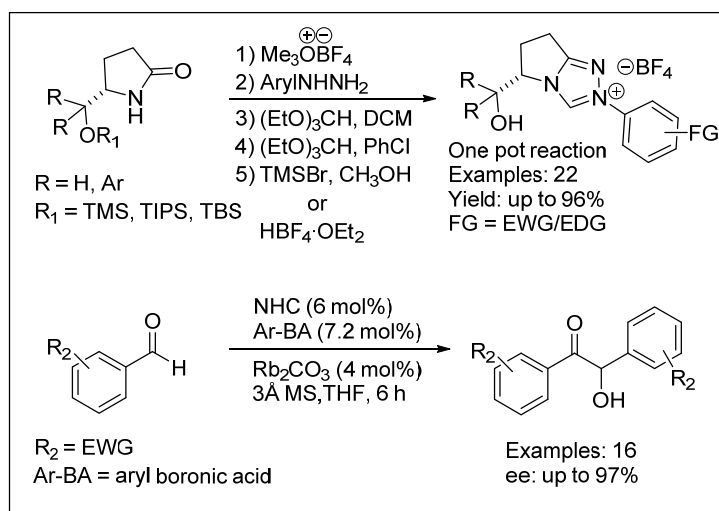


Figure 1. Enantioselective benzoin reaction catalyzed by NHC-BE

[1] Flanigan, D. M.; Michailidis, F.-R.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307-9387.

[2] Dhayalan, V.; Mal, K.; Milo, A. *Synthesis*, **2019** (DOI: 10.1055/s-0037-1611786).

[3] Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214-9217.

[4] Dhayalan, V.; Gadekar, S. C.; Alassad, Z.; Milo, A. *Nature Chemistry* **2019** (DOI: 10.1038/s41557-019-0258-1).