

Modular Access to Polycyclic N,O-heterocycles Using a Highly Functionalized Allylic Morpholinonate

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Abstract

The morpholine structural motif is prevalent in pharmaceuticals such as viloxazine and chiral ligands such as diphenylmorpholinol. Primarily due to their proneness to ring opening, stereoselective and atom-economical approaches to vicinally functionalized morpholines remain elusive. Here, we present a transitional metal-free, stereo- and regio-divergent approach to polycyclic morpholines starting from commodity chemicals such as amines, enals and diglycolic anhydride. The resplendent outcomes are accomplished through a stereocontrolled [4 + 2] cycloaddition between diglycolic anhydride and diversely substituted 1,3-azadienes to arrive at a densely functionalized morpholinonate, which previous work has shown to undergo palladium-mediated etherification to form cyclic enol ethers. We are proposing plans for iron-catalyzed pentannulation to make 6-, 5-polyheterocycles, as well as halolactonization/elimination to form dihydropyrones. It is anticipated that the divergent nature of the approach endear it to the synthesis and medicinal chemistry communities.

Background

Functionalized piperidines, morpholines and thiomorpholines are abundant structural motifs in natural products, pharmaceuticals, agrochemicals and amino acids (examples in figure 1). The biological application and structural complexity of these *N*-, *N,O*-, and *N,S*-heterocycles continue to endear them to the synthesis and medicinal communities, inspiring the development of increasingly more efficient strategies for their construction, functionalization, and evaluation of their structure-activity relationships. Previous approaches to saturated *N*-heterocycles, include those utilized by Aggarwal¹⁻⁴ (using α -phenylvinylsulfonium salts), Tiecco⁵ (using vinyl selenones), and Bode^{6, 7} (using SnAP reagents). Within these different types of azaheterocycles is a group which bears *vicinal stereocenters*. However, controlling the installation of vicinal and epimerizable stereocenters on the basic structure of the heterocycles is quite difficult, in part because sequential substitution of a 2- or 3-substituted cyclic amine derivative is rarely allowed in most of the existing C-2 or C-3 functionalization strategies. Furthermore, cyclizing the heterocycles with non-transition metals increases the novelty and applications of the approach.

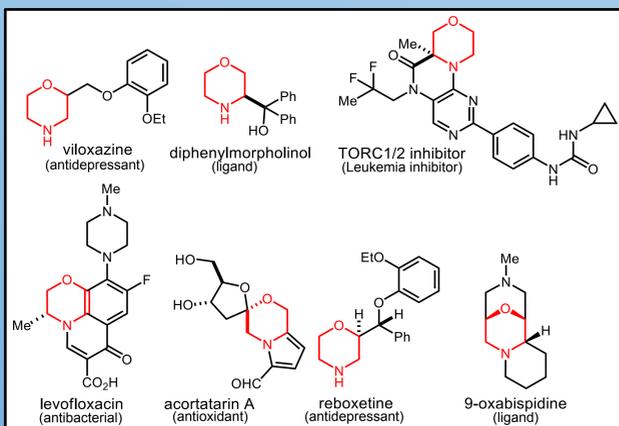


Figure 1. Examples of compounds containing morpholine motifs.

Overview

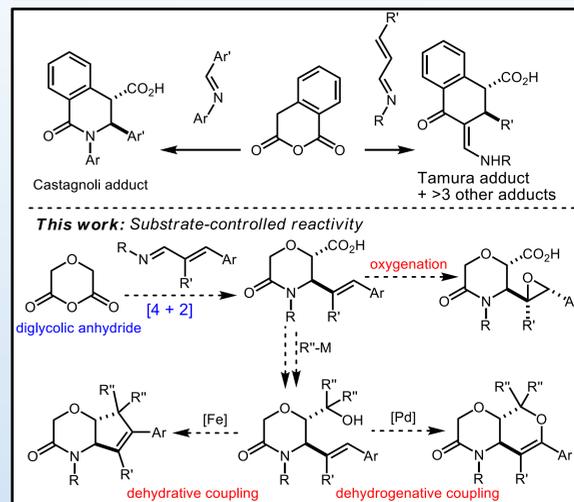


Figure 2. Homophthalic anhydride reacts efficiently with simple aromatic imines to produce Castagnoli-type cycloadducts, but reactions with α,β -unsaturated imines proceed through a Tamura mechanism. From the Castagnoli product, an oxygenation reaction as well as Pd and Fe catalyzed coupling reactions are proposed

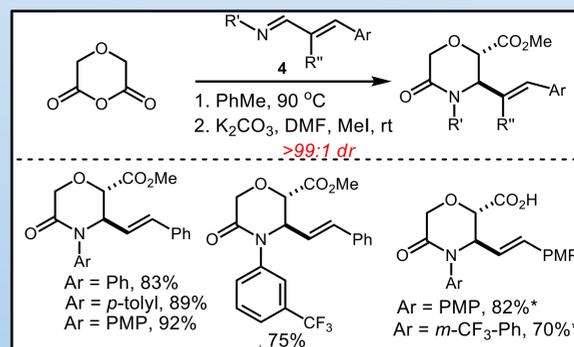


Figure 3. Annulation of 1,3-azadienes with diglycolic anhydride.

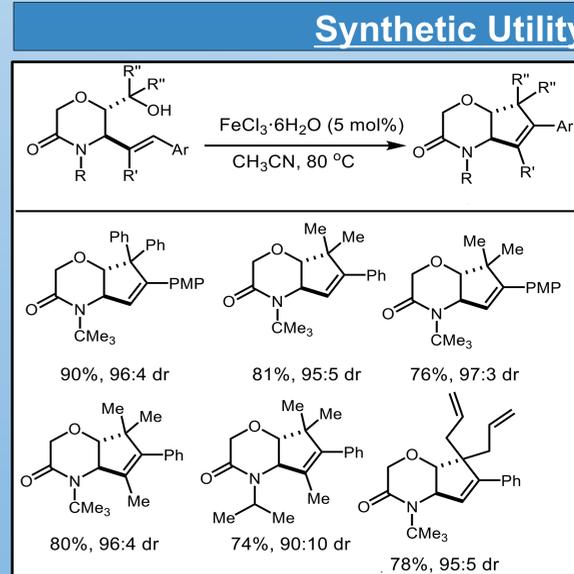


Figure 4. Fe-catalyzed dehydrative pentannulation with varying R-groups on the alcohol-bearing carbon. Percentages are recorded below and the high diastereomer ratios are to be noted.

Synthetic Utility: Pentannulation⁸

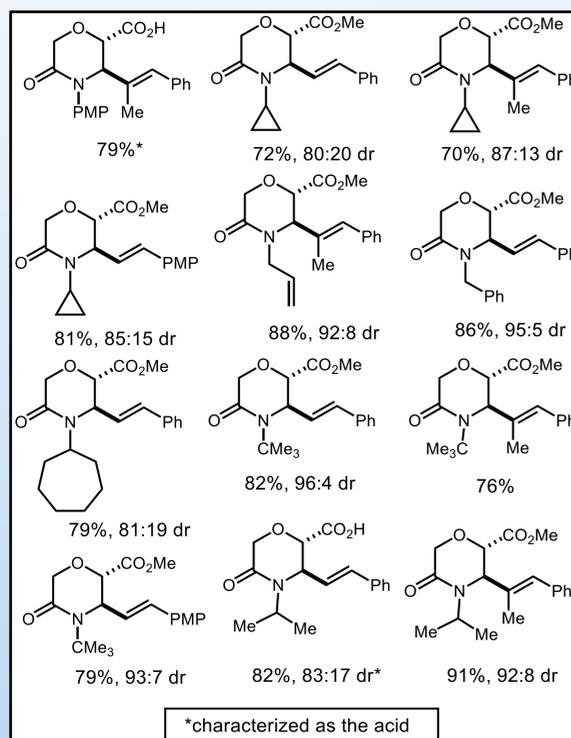


Figure 5. The mechanism through which the Fe-catalyzed dehydrative pentannulation goes through.

Synthetic Utility: Dihydropyranation⁸

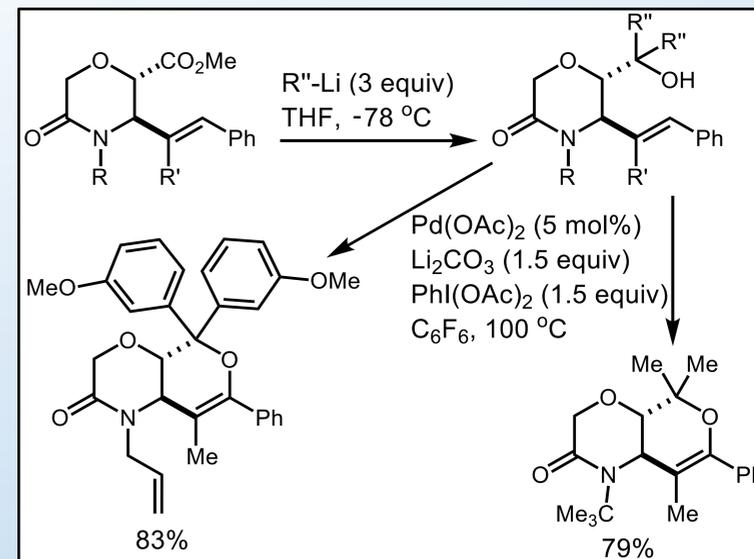


Figure 6. Pd-catalyzed dehydrative etherification using diverse R-groups adjacent to the ether and different protecting groups on the amide motif.

Synthetic Utility: Epoxidation⁸

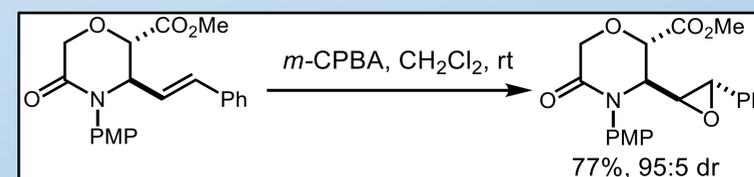


Figure 7. An epoxidation of the allylic lactamoyl ester.

Future Pursuits

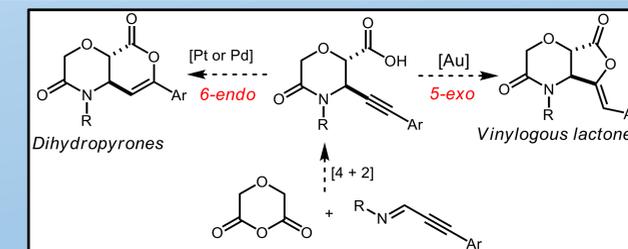


Figure 8. Addition of an alkyne-imine to diglycolic anhydride with the hopeful product coming from a Castagnoli-Cushman mechanism.

Acknowledgements

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