

Design and Development of New Enantioselective Catalytic Reactions and  
Progress towards the Total Synthesis of Callipeltoside A

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John Jacob Moely Wiener

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This thesis is dedicated to David, Mommy, and Da with more love than I can express

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## Abstract

The development of a new enantioselective catalytic *anti* aldol reaction is described. In this Lewis acid-catalyzed process, a chiral metal-ligand enolate complex is accessed through soft-enolization and reacts with an aldehyde to form aldol adducts in good enantioselectivity and *anti* diastereoselection. Mechanistic studies confirm the non-Mukaiyama pathway involving a reactive metal enolate species. Investigations have shown that the choice of amine base has a remarkable effect on the mechanism and outcome of the reaction.

The development of the first enantioselective organocatalytic [1,3]-dipolar cycloaddition reaction is also reported. In this imidazolidinone-catalyzed process, nitrones react with  $\alpha,\beta$ -unsaturated aldehydes to form chiral isoxazolidines in excellent yield, enantioselectivity, and diastereoselection. The scope of this process appears quite general with respect to both the nitron and aldehyde components of the reaction. A second-generation imidazolidinone catalyst offers improved reaction rates and selectivities and has also facilitated the development of the first *exo* selective organocatalytic [1,3]-dipolar and Diels-Alder cycloaddition reactions.

A synthetic approach towards the marine natural product callipeltoside A is described. The synthesis relies upon rapid construction of the stereochemical backbone through a novel tandem amino-sulfide acyl-Claisen rearrangement. Subsequent elaboration towards the macrolide has involved a highly diastereoselective reductive opening of a spirocyclic intermediate, highly diastereoselective Ireland Claisen rearrangement, and synthesis of the tetrahydropyran moiety through a palladium catalyzed carbonylative cyclization. Completion of the synthesis has yet to be achieved due to difficulties in removal of a benzyl ether protecting group.



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