Investigations in Enantioselective Catalysis. Development of Novel Asymmetric Organocatalytic Reactions.

Thesis by

Christopher J. Borths

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For Liz, with more love and gratitude than words can express

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Abstract

A new strategy for the catalysis of organic transformations using iminium ion activation has been developed. Using this strategy, the first asymmetric organocatalytic Diels-Alder reaction has been developed. This methodology has demonstrated the possibility of an imidazolidinone salt to function as an effective asymmetric catalyst for a wide variety of chemical transformations.

The iminium ion activation strategy has also proved successful for conjugate additions, and an asymmetric organocatalytic Mukaiyama-Michael reaction has been developed using the principles of LUMO-lowering catalysis. A more reactive and selective chiral imidazolidinone catalyst was developed, and this secondary amine has extended the range of transformations possible with iminium ion catalysis.

Progress has been made towards the development of an enantioselective organocatalytic alpha-oxidation of ketones. Proline catalysis has been demonstrated to effectively catalyze the asymmetric alpha-oxidation of cyclohexanone, but extension of this methodology to other ketones has not been successful. These studies have further demonstrated the utility of proline as a catalyst, and provide a platform for the extension of HOMO-raising catalysis to other organic transformations.

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Abbreviations

Cbz: Benzyloxycarbonyl

CI: Chemical Ionization

DBA: DiBromoAcetic acid

DCA: DiChloroAcetic acid

DFA: DiFluoroAcetic acid

DME: 1,2-DiMethoxyEthane

DMSO: DiMethylSulfonyl Oxide

DNBA: 2,4-DiNitroBenzoic Acid

d.r.: Diastereomer Ratio

$\boldsymbol{E_T^N}$: Normalized empirical solvent polarity parameter; derived from the solvatochromism of a standard pyridinium-*N*-phenoxide betaine dye[a]

EDG: Electron-Donating Group

ee: Enantiomeric Excess

EI: Electrospray Ionization

EtOAc: Ethyl acetate

EWG: Electron-Withdrawing Group

FAB: Fast Atom Bombardment ionization

FMO: Frontier Molecular Orbital

GLC: Gas Liquid Chromatography

h: hour

Hex: hexanes

HOAc: Acetic acid

HOAcCN: Cyanoacetic acid

HOMO: Highest Occupied Molecular Orbital

HPLC: High Performance Liquid Chromatography

HRMS: High Resolution Mass Spectroscopy

Hz: Hertz

IR: Infrared

LUMO: Lowest Unoccupied Molecular Orbital

M: Molar

m**:** *meta*

mg: milligram

min: minute

mL: milliliter

mmol: millimole

MsOH: Methanesulfonic acid

mT: millitorr

NMR: Nuclear Magnetic Resonance spectroscopy

o**:** *ortho*

organocatalysis: Catalysis of a transformation by a wholly organic catalyst (not by an organometallic catalyst)

organocatalyst: A catalyst of wholly organic composition (not organometallic)

p**:** *para*

ppm: Parts Per Million

PTSA: *para*-Tolune Sulfonic Acid

TBS: *tert*-ButyldimethylSilyl

TIPS: TriIsopropylSilyl

TMS: TriMethylSilyl

TCA: TriChloroAcetic acid

TFA: TriFluoricAcetic acid

TfOH: Trifluoromethanesulfonic acid

THF: TetraHydroFuran

TLC: Thin Layer Chromatography

XRD: X-Ray Diffraction

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[a] Reichardt, C.; Harbusch-Görnert, E. *Liebigs. Ann. Chem.* **1983**, 721. Laurence, C.; Nicolet, P.; Lucon, M.; Reichardt, C. *Bull. Soc. Chim. Fr.* **1987**, 125. Laurence, C.; Nicolet, P.; Lucon, M.; Reichardt, C. *Bull. Soc. Chim. Fr.* **1987**, 1001.