Iminium and Enamine Activation: Methods for Enantioselective Organocatalysis

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Abstract

Further development of an organocatalytic LUMO-lowering activation strategy utilizing chiral imidazolidinone salts has been described. Enantioselective catalytic Friedel-Crafts alkylations of furans and thiophenes have been achieved with good yields and high levels of enantioselectivity. Furthermore, this methodology has been utilized to access enantioenriched □-chiral esters.

The organocatalytic iminium activation strategy has been applied to the development of an enantioselective Mukaiyama-Michael reaction for the construction of the □-butenolide architecture. This reaction is viable due to imidazolidinone catalysts' ability to partition silyloxyfurans to react through an unprecedented 1,4-addition manifold to □,□-unstaturated aldehydes. This Mukaiyama-Michael methodology has also been extended to provide access to □-amino acids by use of silyloxyoxazoles.

Enamine activation of aldehydes has provided the first direct asymmetric □-oxidation of carbonyls. This proline catalyzed HOMO-raising activation strategy affords high levels of reaction efficiency and enantioselectivity. Moreover, the function of proline solubility has been investigated to explain an unusual kinetic and enantioselective profile.

The imidazolidinone framework, developed for iminium activation, was also demonstrated to participate in enamine activation of aldehydes to perform the enantioselective □-chlorination of aldehydes. A first generation catalyst provided good yields and high enantioselectivities at –30 °C. Design of a second generation catalyst afforded high levels of reaction efficiency and enantioselectivity at ambient temperature.

Table of Contents

List of Schemes

List of Figures

List of Tables

Chapter 4 **Enantioselective Organocatalytic α-Oxidation of Aldehydes**

Chapter 5 **Enantioselective Organocatalytic α-Chlorination of Aldehydes**

Abbreviations

Cbz: Benzyloxycarbonyl

CI: Chemical Ionization

CNAcOH: Cyanoacetic acid

DBA: Dibromoacetic acid

DCA: Dichloroacetic acid

DFA: Difluoroacetic acid

DME: 1,2-Dimethoxyethane

DMSO: Dimethylsulfonyl Oxide

DNBA: 2,4-Dinitrobenzoic acid

dr: diastereomeric ratio

ee: Enantiomeric excess

EI: Electrospray Ionization

EtOAc: Ethyl Acetate

FAB: Fast Atom Bombardment ionization

GLC: Gas Liquid Chromatography

h: Hour

HOAc: Acetic 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

p: para

ppm: Parts per million

PTSA: *p*-Toluene sulfonic acid

TBS: *tert*-Butyldimethylsilyl

tert: tertiary

TIPS: Triisopropylsilyl

TMS: Trimethylsilyl

TCA: Trichloroacetic acid

TfOH: Trifluoromethanesulfonic acid

THF: Tetrahydrofuran

TLC: Thin layer chromatography

XRD: X-ray diffraction