Iminium and Enamine Activation:
Methods for Enantioselective Organocatalysis

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Florence Elizabeth Southall
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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 D-chiral esters.

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

Enamine activation of aldehydes has provided the first direct asymmetric D-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 D-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.
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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