

Iminium and Enamine Activation: Methods for Enantioselective Organocatalysis

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For
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 β -chiral esters.

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

Enamine activation of aldehydes has provided the first direct asymmetric β -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 β -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

Acknowledgements	iv
Abstract.....	vi
Table of Contents	vii
List of Schemes.....	xi
List of Figures.....	xii
List of Tables	xiii
Abbreviations.....	xv

Chapter 1 Enantioselective Organocatalysis

I. Introduction.....	1
II. Development of a General Approach to Enantioselective Organocatalysis.....	4
<i>LUMO-Lowering Catalysis</i>	<i>4</i>
<i>Chiral Imidazolidinone Catalysts</i>	<i>5</i>
<i>HOMO-Raising Catalysis.....</i>	<i>6</i>
III. Summary of Thesis Research.....	6
IV. References.....	8

Chapter 2 Enantioselective Organocatalytic Friedel-Crafts Alkylation of Furans

I. Introduction.....	11
<i>Enantioselective Friedel-Crafts Alkylations.....</i>	<i>11</i>
<i>Organocatalysis</i>	<i>12</i>

II.	Results and Discussion	12
	<i>First Generation Imidazolidinone Catalyst</i>	12
	<i>Second Generation Imidazolidinone Catalyst</i>	18
III.	Conclusion	21
IV.	Experimental Section	23
	<i>General Information</i>	23
	<i>Procedures</i>	24
	<i>Stereochemical Analysis</i>	34
V.	References	39
Chapter 3	Enantioselective Organocatalytic Mukaiyama-Michael Reaction	
I.	Introduction	40
	<i>The β-Butenolide Architecture</i>	40
	<i>The Mukaiyama-Michael Reaction</i>	41
	<i>Enantioselective Catalytic Mukaiyama-Michael Reactions</i>	41
	<i>Mukaiyama-Michael vs. Mukaiyama-Aldol</i>	42
	<i>Organocatalysis of the Michael Reaction</i>	43
	<i>Iminium Catalyzed Michael Reactions</i>	44
II.	Results and Discussion	44
	<i>Organocatalytic Access to the β-Butenolide Architecture</i>	44
	<i>Organocatalytic Access to β-amino acids</i>	48
III.	Conclusion	50
IV.	Experimental Section	51

	<i>General Information</i>	51
	<i>Procedures</i>	52
V.	References	64
Chapter 4	Enantioselective Organocatalytic α-Oxidation of Aldehydes	
I.	Introduction	66
	<i>α-Oxidation of Carbonyls</i>	66
	<i>Enantioselective Catalytic Approaches to the α-Oxidation of Carbonyls</i>	67
	<i>Proline Catalyzed Reactions</i>	68
II.	Results and Discussion	69
	<i>Organocatalyzed α-Oxidation of Carbonyls</i>	69
	<i>Other Approaches to Organocatalyzed α-Oxidation of Carbonyls</i>	73
	<i>Blackmond's α-Oxidation Mechanism</i>	74
	<i>The Role of Proline Solubility</i>	77
	<i>Soluble Proline Mimics</i>	79
III.	Conclusion	80
IV.	Experimental Section	82
	<i>General Information</i>	82
	<i>Procedures</i>	83
	<i>Stereochemical Analysis</i>	91
	<i>Procedure for Linearity Experiment</i>	92
	<i>Kinetics Experiment</i>	93
	<i>Visual Comparison Experiment</i>	93

V.	References.....	95
<i>Chapter 5</i>	Enantioselective Organocatalytic α-Chlorination of Aldehydes	
I.	Introduction.....	98
	<i>The Utility of Enantioenriched Halogen Stereocenters</i>	<i>98</i>
	<i>Asymmetric Construction of Halogen Stereocenters</i>	<i>98</i>
	<i>Enantioselective Catalytic Construction of Halogen Stereocenters.....</i>	<i>99</i>
	<i>Imidazolidinone Catalyzed Enamine Activation.....</i>	<i>100</i>
II.	Results and Discussion	100
	<i>First Generation Enantioselective Catalytic α-Chlorination.....</i>	<i>100</i>
	<i>Development of a Room Temperature Enantioselective α-Chlorination</i>	<i>105</i>
	<i>Second Generation Enantioselective Catalytic α-Chlorination.....</i>	<i>108</i>
	<i>Enantioselective Single operation Construction of Terminal Epoxides .</i>	<i>111</i>
III.	Conclusion	113
IV.	Experimental Section	115
	<i>General Information.....</i>	<i>115</i>
	<i>Procedures.....</i>	<i>116</i>
	<i>Stereochemical Analysis.....</i>	<i>123</i>
V.	References.....	125
<i>Appendix 1.</i>	X-Ray Crystallographic Data for (2<i>S</i>,3<i>R</i>)-5-(<i>N</i>-Methyl-<i>N</i>-((<i>S</i>)-1-phenylethyl)amino)-2-(benzamido)-2,3-dimethylpentanoic Acid•Hydrochloride	128

List of Schemes

Chapter 1 **Enantioselective Organocatalysis**

Scheme 1. Lewis acid catalysis 4

Chapter 2 **Enantioselective Organocatalytic Friedel-Crafts Alkylation of Furans**

Scheme 1. Catalytic cycle of the organocatalytic Friedel-Crafts alkylation of furans 15

Chapter 3 **Enantioselective Organocatalytic Mukaiyama-Michael Reaction**

Scheme 1. Butenolide containing natural products 40

Scheme 2. Catalytic cycle of the organocatalyzed Mukaiyama-Michael reaction..... 45

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

Scheme 1. Strategies for the preparation of α -oxy carbonyl compounds 67

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

Scheme 1. Pseudo C_2 symmetry 109

Scheme 2. Increased catalyst steric bulk leads to product configurational stability..... 109

List of Figures

Chapter 2	Enantioselective Organocatalytic Friedel-Crafts Alkylation of Furans	
Figure 1.	Mayr's study of the relative reactivity of nucleophilic π systems	13
Figure 1.	Computation model of amine catalysts.....	19
Figure 1.	Computation model of catalysts iminium ions.....	19
Chapter 4	Enantioselective Organocatalytic α-Oxidation of Aldehydes	
Figure 1.	Blackmond's reaction calorimetry data.....	74
Figure 2.	Blackmond's non-linear relationship data.....	75
Figure 3.	Enantiomeric excess of the product 6 vs. the enantiomeric excess of proline (5).....	77
Figure 4.	The percent initial rate of homogeneous reaction as a function of time.....	78
Figure 5.	Visual comparison of the homogeneous and heterogeneous reactions.....	79
Chapter 5	Enantioselective Organocatalytic α-Chlorination of Aldehydes	
Figure 1.	Secondary amine catalyst architecture.....	102
Figure 2.	Proposed transition states for organocatalyzed α -chlorination...	102
Figure 3.	Exposure of (<i>S</i>)-2-chlorooctanal (13) to catalyst 11	107
Figure 4.	Exposure of (<i>S</i>)-2-chlorooctanal (13) to catalyst 21	111

List of Tables

Chapter 2	Enantioselective Organocatalytic Friedel-Crafts Alkylation of Furans	
Table 1.	The effect of solvent on the alkylation of 2-methylfuran	14
Table 2.	The effect of imidazolidone architecture on the alkylation of 2-methylfuran	14
Table 3.	The effect of acid cocatalyst on the alkylation of 2-methylfuran .	15
Table 4.	The effect of water on the alkylation of 2-methylfuran.....	16
Table 5.	The effect of non-polar solvents on the alkylation of 2-methylfuran.....	17
Table 6.	The effect of cocatalyst on the alkylation of 2-methoxymethylfuran	18
Table 7.	Organocatalyzed conjugate addition of furans and thiophenes	20
Table 8.	Organocatalyzed conjugate addition of furans to α,β -unsaturated aldehydes.....	20
Chapter 3	Enantioselective Organocatalytic Mukaiyama-Michael Reaction	
Table 1.	The effect of protect nucleophiles on the organocatalyzed Mukaiyama-Michael.....	46
Table 2.	The effect of acid cocatalyst on the organocatalyzed Mukaiyama-Michael	46
Table 3.	Organocatalyzed Mukaiyama-Michael: aldehyde substrate scope	47

Table 4.	Organocatalyzed Mukaiyama-Michael: silyloxy furan substrate scope	48
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Chapter 4 Enantioselective Organocatalytic α -Oxidation of Aldehydes

Table 1.	Effect of Solvent on the Asymmetric α -Oxyamination.....	70
Table 2.	Effect of catalyst loading on organocatalyzed α -oxidation	71
Table 3.	Enantioselective α -oxyamination: substrate scope	72

Chapter 5 Enantioselective Organocatalytic α -Chlorination of Aldehydes

Table 1.	Effect of catalyst and chlorinating reagent on α -chlorination	102
Table 2.	Effect of solvent on the organocatalyzed α -chlorination	103
Table 3.	Enantioselective α -chlorination: substrate scope.....	104
Table 4.	Ambient temperature α -chlorination utilizing catalyst 11	106
Table 5.	Enantioselective α -chlorination: substrate scope.....	110
Table 6.	Effect of solvent on the organocatalyzed α -chlorination	112
Table 7.	Enantioselective α -chlorination: substrate scope.....	113

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