

The Development of Organocatalytic Reactions  
Pertaining to Indoles

Thesis by  
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## Abstract

An improved imidazolidinone catalyst for the LUMO-lowering activation of  $\alpha,\beta$ -unsaturated aldehydes has been designed, synthesized and evaluated. This new catalyst allows hitherto infeasible reactions to proceed with high fidelity.

A new strategy for the synthesis of C-3 chiral indoles has been developed. This strategy employs the use of the aforementioned imidazolidinone catalyst to activate  $\alpha, \beta$ -unsaturated aldehydes toward a Friedel-Crafts reaction with a variety of indoles. This is the first and only example in the literature where an indole is alkylated by an  $\alpha, \beta$ -unsaturated aldehyde enantioselectively and catalytically. This methodology allows for the rapid synthesis of this privileged pharmacophore.

By exploiting the indolium ion intermediate produced during the asymmetric Friedel-Crafts alkylation of indoles, a cascade cyclization was found to occur in the first enantioselective catalytic construction of the pyrroloindoline architecture. This direct route provides rapid access to this valuable core motif. This research has led to interesting observations in terms of indole facial selectivity that can be rationalized by an understanding of the cation- $\pi$  interaction.

After numerous unsuccessful attempts to apply the direct pyrroloindoline construction to the synthesis of vicinally quaternary adducts, exploration of the higher reactivity of oxindoles was undertaken. This study has led to the first construction of vicinally quaternary stereogenic carbons via an organocatalyzed protocol.

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## Abbreviations

<b>Ac<sub>2</sub>O</b>	acetic anhydride
<b>AcOH</b>	acetic acid
<b>Boc</b>	<i>tert</i> -butyl carbamate
<b>Cbz</b>	carbobenzyloxy
<b>COSY</b>	correlation spectroscopy
<b>Cp</b>	cyclopentadienyl
<b>DERA</b>	2-deoxyribose-5-phosphate aldolase
<b>DDQ</b>	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
<b>DIBAL-H</b>	diisobutylaluminum hydride
<b>DIPT</b>	diisopropyltartrate
<b>DMF</b>	dimethylformamide
<b>DMPU</b>	1,3-dimethyltetrahydro-2(1 <i>H</i> )-pyrimidinone
<b>DMSO</b>	methylsulfoxide
<b>DTBMP</b>	2,6-di- <i>tert</i> -butyl-4-methylpyridine
<b>EtOAc</b>	ethyl acetate
<b>GLC</b>	gas liquid chromatography
<b>h</b>	hours
<b>HOMO</b>	highest occupied molecular orbital
<b>HMQC</b>	heteronuclear multiple quantum coherence
<b>HPLC</b>	high pressure liquid chromatography
<b>HWE</b>	Horner-Wadsworth-Emmons reaction
<b>IC<sub>50</sub></b>	concentration necessary for 50% inhibition
<b>LA</b>	Lewis acid
<b>LiHMDS</b>	lithium hexamethyldisilamide
<b>LiTMP</b>	lithium 2,2,6,6-tetramethylpiperidine amide
<b>LnLB</b>	lanthanum (III) tris-lithium tris-binolate

<b>LUMO</b>	lowest unoccupied molecular orbital
<b>MCA</b>	monochloroacetic acid
<b>MeOH</b>	methanol
<b>min</b>	minutes
<b>MOM</b>	methoxymethyl
<b>Ms</b>	methanesulfonyl
<b>MTPA</b>	$\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenyl acetyl
<b>NHK</b>	Nozaki-Hiyama-Kishi reaction
<b>NMO</b>	<i>N</i> -methylmorpholine-4-oxide
<b>NMP</b>	1-methyl pyrrolidin-2-one
<b>NMR</b>	nuclear magnetic resonance
<b>NOE</b>	Nuclear Overhauser effect
<b>Nu</b>	nucleophile
<b>Phth</b>	phthalimido
<b>Piv</b>	trimethylacetyl
<b>PMB</b>	<i>para</i> -methoxybenzyl
<b>PMP</b>	<i>para</i> -methoxyphenyl
<b><i>p</i>-TSA</b>	<i>para</i> -toluenesulfonic acid
<b>Pyr</b>	pyridine
<b>TBDPS</b>	<i>tert</i> -butyldiphenylsilyl
<b>TBDPSCI</b>	<i>tert</i> -butylchlorodiphenylsilane
<b>TBHP</b>	<i>tert</i> -butylhydroperoxide
<b>TBS</b>	<i>tert</i> -butyldimethylsilyl
<b>TBSCI</b>	<i>tert</i> -butylchlorodimethylsilane
<b>TBSOTf</b>	<i>tert</i> -butyldimethylsilyl trifluoromethanesulfonate
<b>TCA</b>	trichloroacetic acid
<b>TES</b>	triethylsilyl
<b>TESCI</b>	chlorotriethylsilane

<b>TFA</b>	trifluoroacetic acid
<b>TfOH</b>	trifluoromethanesulfonic acid
<b>THF</b>	tetrahydrofuran
<b>TIPS</b>	triisopropylsilyl
<b>TLC</b>	thin layer chromatography
<b>TMS</b>	trimethylsilyl
<b>TMSCl</b>	chlorotrimethylsilane
<b>TPAP</b>	tetrapropylammonium perruthenate
<b>TROC</b>	carbo-2,2,2-trichloroethoxy

*To Erin*