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 α,β-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 α, β-unsaturated aldehydes toward a Friedel-Crafts reaction with a variety of indoles. This is the first and only example in the literature were an indole is alkylated by an α, β-unsaturated aldehyde enantioselectively and catalytically. This methodology allows for the rapid synthesis of this priviledged 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 enantioselectivive catalytic construction of the pyrroloindoline architecture. This direct route provides rapid access to this valuable core motif. This research has led to interesting observances in terms of indole facial selectivity that can be rationalized by an understanding of the cation-π 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

Ac_2O	acetic anhydride
AcOH	acetic acid
Boc	*tert*-butyl carbamate
Cbz	carbobenzyloxy
COSY	correlation spectroscopy
Cp	cyclopentadienyl
DERA	2-deoxyribose-5-phosphate aldolase
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyltartrate
DMF	dimethylformamide
DMPU	1,3-dimethyltetrahydro-2(1*H*)-pyrimidinone
DMSO	methylsulfoxide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EtOAc	ethyl acetate
GLC	gas liquid chromatography
h	hours
HOMO	highest occupied molecular orbital
HMQC	heteronuclear multiple quantum coherence
HPLC	high pressure liquid chromatography
HWE	Horner-Wadsworth-Emmons reaction
IC_{50}	concentration necessary for 50% inhibition
LA	Lewis acid
LiHMDS	lithium hexamethyldisilamide
LiTMP	lithium 2,2,6,6,-tetramethylpiperidine amide
LnLB	lanthanum (III) tris-lithium tris-binolate

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

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

To Erin