

DEVELOPMENT OF ASYMMETRIC PROTONATION REACTIONS
FOR THE SYNTHESIS OF INDOLINE ALKALOIDS

Thesis by

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To my teachers

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ABSTRACT

Nitrogen-containing heterocycles, such as indolines and pyrroloindolines, are prevalent in a variety of diverse natural products, many of which exhibit remarkable biological activities. These frameworks have inspired innovative research aimed at discovering novel methods for their stereoselective preparation.

We have developed an enantioselective synthesis of pyrroloindolines based on a formal (3 + 2) cycloaddition of indoles and 2-amidoacrylates. This reaction is promoted by (*R*)-BINOL•SnCl₄; this complex is a Lewis acid-assisted Brønsted acid that effects a highly face-selective catalyst-controlled protonation of an enolate. Mechanistic studies also determined that the initial product of this reaction is an indolinium ion, which upon aqueous workup undergoes cyclization to the pyrroloindoline.

Based on this result, we investigated alternative nucleophiles to trap the indolinium ion. First, addition of sodium borohydride to the optimized reaction conditions yields indoline-containing amino acid derivatives.

Next, carbon nucleophiles were explored. Indole substrates incorporating a tethered alkene were exposed to the conditions for the formal (3 + 2) cycloaddition, resulting in a conjugate addition/asymmetric protonation/Prins cyclization cascade. In this transformation, the indolinium ion is attacked by the olefin, and the resulting carbocation is quenched by a chloride ion. Zirconium tetrachloride was found to be the optimal Lewis acid. Stoichiometric proton and chloride sources were also found to be crucial for reactivity.

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LIST OF ABBREVIATIONS

A	alanine
AAA	Asymmetric Allylic Alkylation
Å	Ångstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
atm	atmosphere
BBN	borabicyclononane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi(2-naphthol)
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BOX	bisoxazoline
br	broad
BTF	benzotrifluoride
Bu	butyl
<i>n</i> -Bu	butyl
<i>t</i> -Bu	<i>tert</i> -Butyl
Bz	benzoyl
<i>c</i>	concentration for specific rotation measurements

°C	degrees Celsius
calc'd	calculated
Cbz	carbobenzyloxy
CCDC	Cambridge Crystallographic Data Centre
cm ⁻¹	wavenumber(s)
cod	1,5-cyclooctadiene
d	doublet
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DIC	diisopropyl carbodiimide
DM-BINAP	1,1'-Binaphthalene-2,2'-diy1)bis[bis(3,5-dimethylphenyl)phosphine]
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
E	electrophile

EC ₅₀	median effective concentration (50%)
ee	enantiomeric excess
EI	electron impact
e.g.	for example (Latin <i>exempli gratia</i>)
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
ETP	epidithiodiketopiperazine
FAB	fast atom bombardment
FID	flame ionization detector
FT	fourier transform
g	gram(s)
gCOSY	gradient-selected correlation spectroscopy
gHMBC	gradient-selected heteronuclear multiple bond correlation
h	hour(s)
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	Heteronuclear single quantum coherence
<i>hν</i>	light
Hz	hertz
IPA	isopropanol
IR	infrared (spectroscopy)
<i>J</i>	coupling constant
λ	wavelength
LA	Lewis acid

LAH	lithium aluminum hydride
LBA	Lewis acid-assisted Brønsted acid
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet; milli
<i>m</i>	meta
<i>m/z</i>	mass to charge ratio
M	metal; molar; molecular ion
Me	methyl
Mes	mesityl
MHz	megahertz
μ	micro
μwaves	microwave irradiation
min	minute(s)
MM	multimode
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
n	nano
N	normal
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect

NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
nr	no reaction
<i>o</i>	ortho
<i>p</i>	para
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
Phth	phthaloyl
PhMe	toluene
PMB	<i>p</i> -methoxybenzyl
PMP	<i>p</i> -methoxyphenyl
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
<i>i</i> -Pr	isopropyl
q	quartet
ref	reference
R	generic for any atom or functional group
Red-Al	sodium bis(2-methoxyethoxy)aluminum dihydride
R_f	retention factor
rt	room temperature
s	singlet
sat.	saturated
SFC	supercritical fluid chromatography
t	triplet
TBS	<i>tert</i> -butyldimethylsilyl

TES	triethylsilyl
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid; trifluoroacetyl
TfOH	triflic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOF	time-of-flight
t_R	retention time
Ts	<i>p</i> -toluenesulfonyl (tosyl)
<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
UV	ultraviolet
<i>v/v</i>	volume to volume
<i>w/v</i>	weight to volume
X	anionic ligand or halide