

**NEW CATALYTIC METHODS FOR THE PREPARATION OF TRYPTOPHANS
AND PYRROLOINDOLINES: TOTAL SYNTHESIS OF (+)-NASESEAZINES A
AND B AND (-)-ASPERGILAZINE A**

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ABSTRACT

Tryptophan and unnatural tryptophan derivatives are important building blocks for the total synthesis of natural products, as well as the development of new drugs, biological probes, and chiral small molecule catalysts. This thesis describes various catalytic methods for the preparation of tryptophan derivatives as well as their functionalization and use in natural product total synthesis.

Herein, the tandem Friedel–Crafts conjugate addition/asymmetric protonation reaction between 2-substituted indoles and methyl 2-acetamidoacrylate to provide enantioenriched tryptophans is reported. This method inspired further work in the area of transition metal catalyzed arylation reactions. We report the development of the copper-catalyzed arylation of tryptamine and tryptophan derivatives. The utility of these transformations is highlighted in the five-step syntheses of the natural products (+)-naseezine A and B. Further work on the development of a mild and general Larock indolization protocol to access unnatural tryptophans is also discussed.

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LIST OF ABBREVIATIONS

[α] _D	angle of optical rotation of plane-polarized light
Å	angstrom(s)
<i>p</i> -ABSA	<i>para</i> -acetamidobenzenesulfonyl azide
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
At	benztriazolyl
atm	atmosphere(s)
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenol (“ <u>b</u> utylated <u>h</u> ydroxy <u>t</u> oluene”)
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
<i>i</i> -Bu	<i>iso</i> -butyl
<i>n</i> -Bu	butyl or <i>norm</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
C	cytosine

<i>c</i>	concentration of sample for measurement of optical rotation
¹³ C	carbon-13 isotope
¹⁴ C	carbon-14 isotope
/C	supported on activated carbon charcoal
°C	degrees Celcius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: <i>confer</i>)
cm ⁻¹	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
CSA	camphor sulfonic acid
d	doublet
<i>d</i>	dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane

<i>de</i>	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DMTS	dimethylhexylsilyl
DNA	deoxyribonucleic acid
DPPA	diphenylphosphorylazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTT	dithiothreitol
<i>ee</i>	enantiomeric excess
E	methyl carboxylate (CO ₂ CH ₃)
E ⁺	electrophile
<i>E</i>	trans (entgegen) olefin geometry
EC ₅₀	median effective concentration (50%)
e.g.	for example (Latin: <i>exempli gratia</i>)
EI	electron impact
eq	equation
ESI	electrospray ionization
Et	ethyl

<i>et al.</i>	and others (Latin: <i>et alii</i>)
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
G	guanine
h	hour(s)
¹ H	proton
² H	deuterium
³ H	tritium
[H]	reduction
HATU	2-(7-aza-1 <i>H</i> -benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPT	hexamethylphosphoramide
<i>hn</i>	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC ₅₀	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: <i>id est</i>)
IR	infrared spectroscopy
<i>J</i>	coupling constant
<i>k</i>	rate constant
kcal	kilocalorie(s)

kg	kilogram(s)
L	liter or neutral ligand
<i>l</i>	levorotatory
LA	Lewis acid
LD ₅₀	median lethal dose (50%)
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet or meter(s)
M	molar or molecular ion
<i>m</i>	meta
μ	micro
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)

MS	molecular sieves
m/z	mass-to-charge ratio
N	normal or molar
NBS	<i>N</i> -bromosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu ⁻	nucleophile
<i>o</i>	ortho
[O]	oxidation
<i>t</i> -Oct	<i>tert</i> -octyl (1,1,3,3-tetramethylbutyl)
<i>p</i>	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
pK_a	acid dissociation constant
PMB	<i>para</i> -methoxybenzyl
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
<i>i</i> -Pr	isopropyl

<i>n</i> -Pr	propyl or <i>norm</i> -propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
<i>R</i>	rectus
REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
ref	reference
<i>R_f</i>	retention factor
RNA	ribonucleic acid
s	singlet or seconds
<i>S</i>	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
SOD	superoxide dismutase
Su	succinimide
t	triplet
T	thymine
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAT	tetra- <i>n</i> -butylammonium difluorotriphenylsilicate
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TCA	trichloroacetic acid

temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
Troc	2,2,2-trichloroethoxycarbonyl
Ts	<i>para</i> -toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry