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

Thesis by

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In Partial Fulfillment of the Requirements

For the Degree of

Doctor of Philosophy

CALIFORNIA INSTITUTE OF TECHNOLOGY

Pasadena, California

2015

(Defended May 21, 2015)

ACKNOWLEDGEMENTS

My time at Caltech has been truly enriched by all of the amazing people and scientists I have had the opportunity to meet.

Specifically, I need to thank my advisor, Professor Sarah Reisman, for allowing me to join a young and vibrant lab as well as for the opportunity to work on innovative research projects. Working with such a creative and ambitious advisor has encouraged me to grow as a scientist and reminds me to always strive for excellence. It is really Sarah's enthusiasm for science and for research that keeps our lab going.

I am also grateful for my thesis committee, Professors Brian Stoltz, Dennis Dougherty, and Jonas Peters, who have all offered invaluable advice over the years. In particular, Brian has been a constant source of encouragement for all members of the Reisman lab. His unconditional support and generosity with his time and resources has been instrumental in the success of our lab.

Dr. Scott Virgil does an amazing job running the Caltech Center for Catalysis and Chemical Synthesis. He is an outstanding chemist and has the incredible ability to fix everything that we manage to break. Beyond science, Scott is one of the most optimistic people I have ever met and definitely lifts the spirits of everyone on the 3rd floor of Schlinger.

Throughout my time at Caltech, I've had the opportunity to work with two amazing project partners. Dr. Lindsay "Czepka" Repka and Kangway Chuang are both incredible scientists. Their creativity and work ethic has pushed me to work harder and leave no questions unanswered. Although not an official project partner, Dr. Jake Cha,

has been an unbelievable resource, especially during my first two years. Jake taught me how to be a productive graduate student and kept our bay lively with music and jokes.

I must thank all other members of the Reisman lab, past and present, who are really some of the best chemists and people I know. Although the size and environment has changed dramatically in the past five years, it remains a fun and energetic place to conduct research. Specifically, Dr. Jake Cha, Dr. Raul Navarro, Dr. Lindsay Repka, Dr. John Yeoman, Dr. Jay Codelli, Kangway Chuang, Haoxuan Wang, Victor Mak, Lauren Chapman, and Alice Wong have all been wonderful friends and have made graduate school a more enjoyable experience.

Of course none of this research would be possible without the excellent support staff at Caltech. Agnes Tong, Dr. Dave Vandervelde, Rick Gerhart, Joe Drew, Tom Dunn, Leah Mentch, Lynne Martinez, and Silva Virgil keep our department running, fix all of the problems we create, and work very hard to make graduate life as happy as possible. Thank you!

I have also been very fortunate to come from an extremely nurturing undergraduate institution. I don't think I could have asked for better mentors than Professors David Haines and Don Elmore. Throughout my time at Wellesley and Caltech, they have encouraged me to not give up and treated me to more than my fair share of free lunches. I am extremely grateful for their mentorship and friendship.

I am also grateful for my friends outside of the Reisman lab. Zach Wickens, Nick O'Connor, Matt Griffin, Clint Reagan, Christopher Haley, Allen Hong, Hosea Nelson, Carson Mattier, Claire Droste, and Lena McCauley have all been great supports!

I would have never made it through my time here without my family. Thank you Mom, Dad, and Tony for loving me all of these years! I am thankful for your unconditional support and enthusiasm for everything I do. Although my visits home have been few and far between, I'm looking forward to more frequent trips home! During my time at Caltech, I've gained a little more family in the Chuangs. I feel very lucky to have gotten to know them over the past 4 years and have greatly enjoyed our trips up to Palo Alto.

Finally, I need to thank Kangway Chuang, who is really the biggest reason I ever made it through this place. Although he is the most talented chemist I have ever met, I think what makes him especially unique is his willingness to drop everything he's doing to help others. Beyond lab, I have really appreciated his love and patience these past five years, without which I don't think I would have made it! We've had five years of fun in southern California and I'm very excited to see what is to come in Boston!

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 trytophans 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 (+)-naseseazine 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

$[a]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
p-ABSA	*para*-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-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
C	cytosine

c	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: *confer*)
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane

de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMTS	dimethylthexylsilyl
DNA	deoxyribonucleic acid
DPPA	diphenylphosphorylazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTT	dithiothreitol
ee	enantiomeric excess
E	methyl carboxylate (CO_2CH_3)
E^+	electrophile
E	trans (entgegen) olefin geometry
EC_{50}	median effective concentration (50%)
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
eq	equation
ESI	electrospray ionization
Et	ethyl

et al.	and others (Latin: *et alii*)
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*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPT	hexamethylphosphoramide
hn	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: *id est*)
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)

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

n-Pr	propyl or *norm*-propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
R	rectus
REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
ref	reference
R_f	retention factor
RNA	ribonucleic acid
s	singlet or seconds
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
SOD	superoxide dismutase
Su	succinimide
t	triplet
T	thymine
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-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	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry