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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Doctor of Philosophy

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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.

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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.

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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 (+)-nasesezaine 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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**A Mild and General Larock Indolization Protocol for the Synthesis of Natural Tryptophan Derivatives**

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<tr>
<td>[a]_D</td>
<td>angle of optical rotation of plane-polarized light</td>
</tr>
<tr>
<td>Å</td>
<td>angstrom(s)</td>
</tr>
<tr>
<td>p-ABSA</td>
<td>para-acetamidobenzenesulfonyl azide</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>APCI</td>
<td>atmospheric pressure chemical ionization</td>
</tr>
<tr>
<td>app</td>
<td>apparent</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl group</td>
</tr>
<tr>
<td>At</td>
<td>benztriazolyl</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere(s)</td>
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<tr>
<td>BHT</td>
<td>2,6-di-tert-butyl-4-methylphenol (“butylated hydroxytoluene”)</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
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<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>i-Bu</td>
<td>iso-butyl</td>
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<td>butyl or norm-butyl</td>
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<td>t-Bu</td>
<td>tert-butyl</td>
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<td>Bz</td>
<td>benzoyl</td>
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<td>C</td>
<td>cytosine</td>
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<td>Definition</td>
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<tr>
<td>$c$</td>
<td>concentration of sample for measurement of optical rotation</td>
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<td>$^{13}$C</td>
<td>carbon-13 isotope</td>
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<tr>
<td>$^{14}$C</td>
<td>carbon-14 isotope</td>
</tr>
<tr>
<td>/C</td>
<td>supported on activated carbon charcoal</td>
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<tr>
<td>°C</td>
<td>degrees Celcius</td>
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<td>calc’d</td>
<td>calculated</td>
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<tr>
<td>CAN</td>
<td>ceric ammonium nitrate</td>
</tr>
<tr>
<td>Cbz</td>
<td>benzyloxy carbonyl</td>
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<tr>
<td>CCDC</td>
<td>Cambridge Crystallographic Data Centre</td>
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<td>CDI</td>
<td>1,1’-carbonyldiimidazole</td>
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<tr>
<td>cf.</td>
<td>consult or compare to (Latin: confer)</td>
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<td>cm$^{-1}$</td>
<td>wavenumber(s)</td>
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<td>cod</td>
<td>1,5-cyclooctadiene</td>
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<td>comp</td>
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<td>CSA</td>
<td>camphor sulfonic acid</td>
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<tr>
<td>d</td>
<td>doublet</td>
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<td>$d$</td>
<td>dextrorotatory</td>
</tr>
<tr>
<td>D</td>
<td>deuterium</td>
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<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
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<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<td>DCE</td>
<td>1,2-dichloroethane</td>
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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$_2$CH$_3$)
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*)

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<td>FAB</td>
<td>fast atom bombardment</td>
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<td>Fmoc</td>
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<td>g</td>
<td>gram(s)</td>
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<tr>
<td>G</td>
<td>guanine</td>
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<tr>
<td>h</td>
<td>hour(s)</td>
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<tr>
<td>$^1\text{H}$</td>
<td>proton</td>
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<td>$^2\text{H}$</td>
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</tr>
<tr>
<td>$^3\text{H}$</td>
<td>tritium</td>
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<td>[H]</td>
<td>reduction</td>
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<td>HATU</td>
<td>2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate</td>
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<td>HMDS</td>
<td>hexamethyldisilamide or hexamethyldisilazide</td>
</tr>
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<td>HMPT</td>
<td>hexamethylphosphoramidé</td>
</tr>
<tr>
<td>$hn$</td>
<td>light</td>
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<td>HPLC</td>
<td>high performance liquid chromatography</td>
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<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
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<td>Hz</td>
<td>hertz</td>
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<tr>
<td>IC$_{50}$</td>
<td>half maximal inhibitory concentration (50%)</td>
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<tr>
<td>i.e.</td>
<td>that is (Latin: <em>id est</em>)</td>
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<td>IR</td>
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<tr>
<td>$J$</td>
<td>coupling constant</td>
</tr>
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<td>$k$</td>
<td>rate constant</td>
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<td>kcal</td>
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<tr>
<td>MS</td>
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<tr>
<td>m/z</td>
<td>mass-to-charge ratio</td>
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<tr>
<td>N</td>
<td>normal or molar</td>
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<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
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<td>nm</td>
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<td>NMR</td>
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<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
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<td>nuclear Overhauser enhancement spectroscopy</td>
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<tr>
<td>Nu−</td>
<td>nucleophile</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>[O]</td>
<td>oxidation</td>
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<td>t-Oct</td>
<td>tert-octyl (1,1,3,3-tetramethylbutyl)</td>
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<tr>
<td>p</td>
<td>para</td>
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<td>PCC</td>
<td>pyridinium chlorochromate</td>
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<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>pH</td>
<td>hydrogen ion concentration in aqueous solution</td>
</tr>
<tr>
<td>pKₐ</td>
<td>acid dissociation constant</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
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<td>ppm</td>
<td>parts per million</td>
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<tr>
<td>PPTS</td>
<td>pyridinium para-toluenesulfonate</td>
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<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
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$n$-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-butyldiphenyilsilyl
TBS  tert-butyldimethylsilyl
TCA  trichloroacetic acid
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<td>TES</td>
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<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
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<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
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<td>triisopropylsilyl</td>
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<td>TMEDA</td>
<td><em>N</em>,<em>N</em>,<em>N</em>,<em>N'</em>-tetramethylethylenediamine</td>
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<td>trimethylsilyl</td>
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<td>X</td>
<td>anionic ligand or halide</td>
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<tr>
<td>Z</td>
<td>cis (zusammen) olefin geometry</td>
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