DEVELOPMENT AND APPLICATIONS OF THE PALLADIUM-CATALYZED
ENANTIOSELECTIVE OXIDATION OF SECONDARY ALCOHOLS

Thesis by
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To my family
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ABSTRACT

The development of new methods for the preparation of chiral alcohols is vital due to the presence of alcohols in natural products, pharmaceuticals, and a variety of synthetic materials, as well as their versatility as synthetic intermediates. Until recently, oxidative kinetic resolution has been a relatively underdeveloped strategy for obtaining enantioenriched alcohols.

The development of a palladium-catalyzed aerobic system for the enantioselective oxidation of secondary alcohols is described. This mild method utilizes (–)-sparteine as a chiral ligand to resolve a wide range of benzylic, allylic, and cyclopropylcarbinyl alcohols to high enantiomeric excesses with excellent selectivity. The resolution of pharmaceutical intermediates and the Claisen rearrangement of resolved allylic alcohols demonstrate the utility of the method.

Mechanistic insights have driven further catalyst development. Anionic ligand modification has provided more efficient catalysts for the resolution of a broader array of substrates. Neutral ligand studies have led to an enantioselective alcohol oxidation system with a diamine pseudo-enantiomeric to (–)-sparteine, allowing access to enantioenriched alcohols in either enantiomeric series.

This methodology has been applied to the enantioselective total synthesis of (–)-amurensinine via a selective C–H insertion, an aryne C–C insertion, and an oxidative kinetic resolution with (–)-sparteine. Use of an alternative diamine in the resolution results in a formal synthesis of (+)-amurensinine.
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LIST OF ABBREVIATIONS

\[ \alpha \] \text{D} \quad \text{specific rotation at wavelength of sodium D line}

\text{Å} \quad \text{angstrom(s)}

\text{abs.} \quad \text{absolute}

\text{Ac} \quad \text{acetyl}

\text{app.} \quad \text{apparent}

\text{aq} \quad \text{aqueous}

\text{Ar} \quad \text{aryl, argon}

\text{atm} \quad \text{atmosphere(s)}

\text{B3LYP} \quad \text{Becke, three-parameter, Lee-Yang-Parr functional}

\text{BHT} \quad 2,6-di-\text{tert}-\text{butyl}-4-\text{methylphenol}

\text{BINAP} \quad 2,2'-\text{bis(diphenylphosphino)}-1,1'-\text{binaphthalene}

\text{BINOL} \quad 1,1'-\text{bi}(2-naphthol)

\text{Bn} \quad \text{benzyl}

\text{Boc} \quad \text{tert-butoxycarbonyl}

\text{br.} \quad \text{broad}

\text{Bu} \quad 1-\text{butyl}

\text{i-Bu} \quad 2-\text{methyl-1-propyl}

\text{s-Bu} \quad 2-\text{butyl}

\text{(S,S)-t-Bu-BOX} \quad 2,2'-\text{isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline]}

\text{c} \quad \text{concentration for optical rotation}

\text{calcd} \quad \text{calculated}

\text{CCDC} \quad \text{Cambridge Crystallographic Data Centre}

\text{cf.} \quad \text{compare}

\text{cm} \quad \text{centimeter(s)}

\text{COD} \quad \text{cis,cis-1,5-cyclooctadiene}

\text{comp.} \quad \text{complex}

\text{conc.} \quad \text{concentrated}

\text{conv} \quad \text{conversion}

\text{d} \quad \text{doublet}

\text{DABCO} \quad 1,4-diazabicyclo[2.2.2]octane

\text{dba} \quad \text{dibenzylideneacetone}

\text{DBU} \quad 1,8-diazabicyclo[5.4.0]undec-7-ene
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</tr>
<tr>
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<td>(−)-(4R,5R)-2,2-dimethyl-4,5-bis[(diphenylphosphino)-methyl]-1,3-dioxolane</td>
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<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<td>DMP</td>
<td>Dess-Martin periodinane</td>
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<tr>
<td>DPPA</td>
<td>diphenylphosphoryl azide</td>
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<tr>
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<tr>
<td>equiv</td>
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<tr>
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<td>electrospray ionization</td>
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<td>FAB</td>
<td>fast atom bombardment</td>
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<td>g</td>
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<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IR</td>
<td>infrared (spectroscopy)</td>
</tr>
<tr>
<td>$J$</td>
<td>coupling constant</td>
</tr>
<tr>
<td>$k$</td>
<td>reaction rate constant</td>
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<td>L</td>
<td>L-type ligand</td>
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<td>$\lambda$</td>
<td>wavelength</td>
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<td>lit.</td>
<td>literature</td>
</tr>
<tr>
<td>M</td>
<td>molar, metal, or molecular ion</td>
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</table>
m  meter(s), multiplet
m/z  mass to charge ratio
Me  methyl
mg  milligram(s)
MHz  megahertz
µL  microliter(s)
µm  micrometer(s)
min  minute(s)
mL  milliliter(s)
mm  millimeter(s)
mmol  millimole(s)
mol  mole(s)
mp  melting point
Ms  methanesulfonyl
MS  molecular sieves
MTBE  tert-butyl methyl ether
N  normal
nbd  norbornadiene
NBS  N-bromosuccinimide
p-Nbz  para-nitrobenzoyl
nm  nanometer(s)
NMR  nuclear magnetic resonance (spectroscopy)
[O]  oxidation
p  para
p-ABSA  para-acetamidobenzenesulfonyl azide
Ph  phenyl
pH  hydrogen ion concentration
PhH  benzene
(S,S)-Ph-PYBOX  2,6-bis[(S)-4-tert-butyl-2-oxazolinyl]pyridine
Piv  pivaloyl
pKₐ  acid dissociation constant
ppm  parts per million
i-Pr  2-propyl
n-Pr  n-propyl
psi  pounds per square inch
Py  pyridine
q  quartet  
ref  reference  
$R_f$  retention factor  
s  selectivity factor  
s  singlet  
$S_N1$  nucleophilic substitution, unimolecular  
$S_N2$  nucleophilic substitution, bimolecular  
Sub  substrate  
t  triplet  
TBAF  tetrabutylammonium fluoride  
TBS  tert-butyldimethylsilyl  
TEMPO  2,2,6,6-tetramethylpiperidine 1-oxyl  
Tf  trifluoromethanesulfonate  
TFA  trifluoroacetate  
THF  tetrahydrofuran  
TIPS  triisopropylsilyl  
TLC  thin-layer chromatography  
TMS  trimethylsilyl  
Ts  para-toluenesulfonyl  
UV  ultraviolet light  
Vis  visible light  
w/v  weight to volume ratio  
w/w  weight to weight ratio  
X  halide, anionic ligand