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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There are so many other people to thank, but this has already gotten way too long, and I know you are anxious to get to the actual chemistry that these people made possible, so I will end here. Okay, one more: thanks for reading!

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

$[\alpha]_D$	specific rotation at wavelength of sodium D line
Å	angstrom(s)
abs.	absolute
Ac	acetyl
app.	apparent
aq	aqueous
Ar	aryl, argon
atm	atmosphere(s)
B3LYP	Becke, three-parameter, Lee-Yang-Parr functional
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad
Bu	1-butyl
i-Bu	2-methyl-1-propyl
s-Bu	2-butyl
(*S*,*S*)-*t*-Bu-BOX	2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]
c	concentration for optical rotation
calcd	calculated
CCDC	Cambridge Crystallographic Data Centre
cf.	compare
cm	centimeter(s)
COD	*cis,cis*-1,5-cyclooctadiene
comp.	complex
conc.	concentrated
conv	conversion
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCE	1,2-dichloroethane
dec.	decomposition
°	degrees
°C	degrees Celsius
DFT	density functional theory
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
DIBAL-H	diisobutylaluminum hydride
(–)-DIOP	(–)-(4*R*,5*R*)-2,2-dimethyl-4,5-bis[(diphenylphosphino)-methyl]-1,3-dioxolane
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DPPA	diphenylphosphoryl azide
e	electron
ee	enantiomeric excess
EI	electron impact
equiv	equivalent(s)
ES	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
FID	flame ionization detector
g	gram(s)
GC	gas chromatography
h	hour(s)
$h\nu$	light
hNK-1	human neurokinin-1
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared (spectroscopy)
J	coupling constant
k	reaction rate constant
L	L-type ligand
λ	wavelength
lit.	literature
M	molar, metal, or molecular ion

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
pK_a	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