Development of the Enantioselective Oxidation of Secondary Alcohols and Natural Products Total Synthesis

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

2005

(Thesis Defended August 5, 2005)

For

Claire Weatherhead

Acknowledgements

The Stoltz group has collaborated to establish a work environment alive with creativity, based in mutual respect, and fortified with an amazing work ethic. It has been a truly rewarding experience to watch the lab grow from a group of friends, unsure of our common purpose but eager to find out, into a mature research force.

I'd like to first thank Brian for providing me with an excellent example of exactly what a successful, well-balanced scientist is. He has been a great motivator, mentor, teacher and friend over the years and I am constantly impressed at his ability to develop his students. That man knows what he is doing.

While every member of the group, past and present, has had an impact on me in my time here I would like to single out a few people. I'd like to thank all of my collaborators over the years, including Doug Behenna and, more recently, Jen Stockdill, for their diligent work on zoanthenol. While a number of people have contributed to various aspects of a rich palladium program, I'd like especially to thank Eric Ferriera, Raissa Trend, and Dave Ebner for keeping oxidation exciting and expanding my understanding of palladium catalysis. I'd like to thank Eric Ashley for pretending to not have a photographic memory and brightly outshining me during those early years as my baymate. (I was probably "in over my head" when I first got here.) I'd like to thank Uttam Tambar, Ryan Zeidan, Yeeman Ramtohul, and the Reverend Joel Austin for the many adventurous nights that made my last few years of bachelorhood here at Caltech memorable.

Which brings me to my bride-to-be. I need to thank Claire for standing by my side during the challenging times and lighting my way. I have the deepest gratitude for the love, patience and support she has given to me. I will work hard to return those gifts in our new life together.

Finally, I would like to thank my dad for setting the bar high, and my mom for helping my chin to reach it during my earliest years.

Abstract

Oxidation is a fundamental process in chemistry and biology. In synthetic chemistry, there are several methods for the asymmetric oxidation of organic substrates. Classically, these methods have focused on the delivery of a heteroatom from a reagent or catalyst to a prochiral substrate. What have historically been underdeveloped are enantioselective oxidation methods that do not involve the transfer of a heteroatom, butrather are defined by the enantioselective dehydrogenation of an organic substrate. This type of oxidative transformation was investigated using a palladium(II) catalyst system.

A palladium-catalyzed oxidative kinetic resolution of secondary alcohols was developed. Key features of the catalytic system include the use of (–)-sparteine as the source of chiral relay, and molecular oxygen as the sole stoicheometric oxidant. Under the described catalytic system, a number of benzylic and allylic alcohols have been oxidized in an enantioselective manner, to provide a ketone and residual alcohol in high enantiomeric excess and excellent yield.

Subsequent to the original system, the systematic investigation of a number of mechanistic hypotheses involving the role of exogenous bases and H-bonding additives prompted the discovery of new reaction conditions displaying greatly enhanced reactivity, selectivity, atom economy, and generality. The net result of these improvements was a catalytic system effective in oxidative desymmetrization of a number of complex *meso*-diols. Ultimately, these advances have permitted our method to be applied towards a number of synthetic endeavors, including the key step in the total synthesis of the natural product alkaloid (–)-lobeline.

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List of Abbreviations

$[\alpha]_D$	specific rotation at wavelength of sodium D line
aq.	aqueous
Ar	aryl
atm	atmosphere
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	isobutyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration for specific rotation measurements
° C	degrees Celsius
calc'd	calculated
cat.	catalytic
comp	complex
d	doublet
DCC	dicyclohexylcarbodiimide

DCE	1,2-dichloroethane
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electrospray ionization
equiv	equivalents
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
g	grams
GC	gas chromatography
[H]	reduction
h	hour(s)
hν	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
Imid.	Imidazole
IR	infrared
J	coupling constant

Kcal	kilocalories
L	liter
LAH	lithium aluminum hydride
M	metal or molar
m	milli or multiplet or meters
m/z	mass to charge ratio
μ	micro
Me	methyl
MHz	megahertz
min	minutes
mol	moles
mmol	millimoles
mp	melting point
MS	molecular sieves
Ms	methanesulfonyl
N	normal
nbd	norbornadiene
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhouser effect
[O]	oxidation
OKR	oxidative kinetic resolution
Ph	phenyl

PhH	benzene
p*K*a	acidity constant
ppm	parts per million
i-Pr	isopropyl
q	quartet
ref	reference
R_F	retention factor
s	singlet or selectivity factor
sp	(–)-sparteine
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
v/v	volume to volume
w/v	weight to volume