

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

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For
Claire Weatherhead

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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, but rather 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 stoichiometric 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	<i>tert</i> -butyloxycarbonyl
bp	boiling point
br	broad
Bu	butyl
<i>i</i> -Bu	isobutyl
<i>n</i> -Bu	<i>n</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
<i>c</i>	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	<i>N,N</i> -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)
h ν	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
Imid.	Imidazole
IR	infrared
<i>J</i>	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	<i>N</i> -methylnmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhouser effect
[O]	oxidation
OKR	oxidative kinetic resolution
Ph	phenyl

PhH	benzene
p <i>K</i> _a	acidity constant
ppm	parts per million
<i>i</i> -Pr	isopropyl
q	quartet
ref	reference
R _F	retention factor
s	singlet or selectivity factor
sp	(-)-sparteine
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -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