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

Thesis by
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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: \textit{tert}-butyloxycarbonyl
- bp: boiling point
- br: broad
- Bu: butyl
- \textit{i}-Bu: isobutyl
- \textit{n}-Bu: \textit{n}-butyl
- \textit{t}-Bu: \textit{tert}-butyl
- Bz: benzoyl
- \(c\): concentration for specific rotation measurements
- °C: degrees Celsius
- calc’d: calculated
- cat.: catalytic
- comp: complex
- d: doublet
- DCC: dicyclohexylcarbodiimide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
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</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
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</table>
PhH  benzene
pKa  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