The Aza-Silyl-Prins Reaction:
Development and Application
to the Total Synthesis of
(±)-Pipecolic Acid and (±)-Cannabisativine

Submitted by
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Signed ________________________________”
Abstract

The focus of this thesis is to develop new methods towards the synthesis of nitrogen-containing heterocycles. Chapter one contains a brief introduction into previous work by the Dobbs group, involving the optimisation of the silyl-Prins reaction and aza-silyl-Prins reaction, which afford substituted dihydropyran and tetrahydropyridines respectively.

Chapter two initially provides a literature overview towards the synthesis of piperidines using this methodology. Following this, our results demonstrate that using different substitution patterns in the homoallylic amine precursors has quite a significant regiochemical effect on the reaction. These effects include the formation of pyrrolidine structures, which can be isolated and characterised.

Chapter three presents the utilisation of the previously optimised silyl-Prins and aza-silyl-Prins reaction to obtain oxa- and aza-cycles containing a trifluoromethyl group, a functionality known to have significant effects on the lipophilicity of drug molecules. Next in chapter four, again the advantages of using the aza-silyl-Prins reaction to obtain high functionality in a simple coupling reaction are presented, with the formation of pipecolate and pipecolic acid analogues. Chapter five includes attempts to use the aza-silyl-Prins to form tetrasubstituted tetrahydropyridines using precedent from studies in the silyl-Prins reaction. However, although the similarities between these two coupling reactions are obvious, the differences in heteroatom in the substrates and products have a significant effect. Following previous attempts in the group to form nitrogen heterocycles in high enantiopurity with little success, chapter six discusses the optimisation of a new Lewis acid mediated imine-vinylsilane cyclisation reaction. The formation of 2-substituted free amine tetrahydropyridines was successful for racemic examples, but the studies into utilising this methodology towards an asymmetric synthesis are yet to be finalised. Finally, chapter seven investigates the use of the aza-silyl-Prins reaction into forming more complex natural products such as cannabisativine.

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EXPERIMENTAL

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<tr>
<th>Abbreviation</th>
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<tr>
<td>Ac</td>
<td>Acetyl</td>
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<tr>
<td>acac</td>
<td>Acetylacetonate</td>
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<tr>
<td>BINOL</td>
<td>1,1'-Bi-2-naphthol</td>
</tr>
<tr>
<td>bpy</td>
<td>2,2'-Bipyridine</td>
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<tr>
<td>Boc</td>
<td>t-Butoxycarbonyl</td>
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<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Cbz</td>
<td>Benzyloxy carbonyl</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical ionisation</td>
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<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
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<tr>
<td>DAST</td>
<td>Diethylaminosulfur trifluoride</td>
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<td>DBU</td>
<td>1,8-Diazabicyclo[4.3.0]undec-7-ene</td>
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<td>(N,N')-Dicyclohexylcarbodiimide</td>
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<tr>
<td>DHQ</td>
<td>Hydroquinone</td>
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<td>DiBAL</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropyl azodicarboxylate</td>
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<tr>
<td>4-DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>Dimethoxyethane</td>
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<tr>
<td>DMF</td>
<td>(N,N)-Dimethylformamide</td>
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<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>DPPA</td>
<td>Diphenyl phosphorylazide</td>
</tr>
<tr>
<td>Ei</td>
<td>Electronic ionisation</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalent</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<td>HMDS</td>
<td>Hexamethyldisilazide</td>
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<td>Hmim</td>
<td>1-Hexyl-3-methylimidazolium</td>
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<td>HMPA</td>
<td>Hexamethylphosphoramidate</td>
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<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
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<td>Im</td>
<td>Imidazole</td>
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Abbreviations

IR  Infrared
LA  Lewis Acid
LAH Lithium aluminium hydride
LCMS Liquid chromatography-mass spectrometry
LDA Lithium diisopropylamide
LUMO Lowest unoccupied molecular orbital
m-CPBA meta-chloroperoxybenzoic acid
MEM methoxethoxymethyl
MHz  Mega-Hertz
MMPP Magnesium monoperoxyphthalate
MOM Methoxymethyl
M.p. Melting point
Ms Methanesulfonyl
MS Molecular sieves
m/z  Mass to charge ratio
NMO 4-Methylmorpholine N-oxide
NMR Nuclear magnetic resonance
nOe Nuclear Overhauser effect
NOESY Nuclear Overhauser enhancement spectroscopy
Nu Nucleophile
PCC Pyridinium chlorochromate
PDC Pyridinium dichromate
PG Protecting group
PhF 9-Phenylfluorene
PMP 1-Phenyl-3-methyl-5-pyrazolone
PYBOX 2,6-Bis(4,5-dihydro-1,3-oxazol-2-yl)pyridine
RCM Ring closing metathesis
rt Room temperature
SAR Structure activity relationship
TBAB Tetrabutylammonium bromide
TBS t-Butyldimethylsilyl
TBDPS t-Butyldiphenylsilyl
TCC trans-2-(α-Cumyl)cyclohexyl
<table>
<thead>
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<tr>
<td>Tf</td>
<td>Trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
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<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
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<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>Tetramethylethylenediamine</td>
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<td>TMS</td>
<td>Trimethylsilyl</td>
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<td>Tr</td>
<td>Triphenylmethyl (Trityl)</td>
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<td>Tp</td>
<td>Hydridotrispyrazolylborate</td>
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<td>Troc</td>
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<tr>
<td>Ts</td>
<td>para-Toluenesulfonyl</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra-violet</td>
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